References

Abdel-Malek, Z. A., Swope, V. B., Starner, R. J., Koikov, L., Cassidy, P., & Leachman, S. (2014). Melanocortins and the melanocortin 1 receptor, moving translationally towards melanoma prevention. *Archives of Biochemistry and Biophysics,*

Beginning in the last decade of the twentieth century, the fields of pigment cell research and melanoma have witnessed major breakthroughs in the understanding of the role of melanocortins in human pigmentation and the DNA damage response of human melanocytes to solar ultraviolet radiation (UV). This began with the cloning of the melanocortin 1 receptor (MC1R) gene from human melanocytes and the demonstration that the encoded receptor is functional. Subsequently, population studies found that the MC1R gene is highly polymorphic, and that some of its variants are associated with red hair phenotype, fair skin and poor tanning ability. Using human melanocytes cultured from donors with different MC1R genotypes revealed that the alleles associated with red hair color encode fro 1 non-functional receptor. Epidemiological studies linked the MC1R red hair color variants to increased melanoma risk. Investigating the impact of different MC1R variants on the response of human melanocytes to UV led to the important discovery that the MC1R signaling activates antioxidant, DNA repair and survival pathways, in addition to stimulation of eumelanin synthesis. These effects of MC1R were absent in melanocytes expressing 2 MC1R red hair color variants that result in loss of function of the receptor. The importance of the MC1R in reducing UV-induced genotoxicity in melanocytes led us to design small peptide analogs of the physiological MC1R agonist alpha-melanocortin (alpha-melanocyte stimulating hormone; alpha-MSH) for the goal of utilizing them for melanoma chemoprevention.

Abraham, J., Nunez-Alvarez, Y., Hettmer, S., Carrio, E., Chen, H. I., Nishijo, K., et al. (2014). Lineage of origin in rhabdomyosarcoma informs pharmacological response. *Genes & Development, 28*(14), 1578-1591.

Lineage or cell of origin of cancers is often unknown and thus is not a consideration in therapeutic approaches. Alveolar rhabdomyosarcoma (aRMS) is an aggressive childhood cancer for which the cell of origin remains debated. We used conditional genetic mouse models of aRMS to activate the pathognomonic Pax3:Foxo1 fusion oncogene and inactivate p53 in several stages of prenatal and postnatal muscle development. We reveal that lineage of origin significantly influences tumor

histomorphology and sensitivity to targeted therapeutics. Furthermore, we uncovered differential transcriptional regulation of the Pax3:Foxo1 locus by tumor lineage of origin, which led us to identify the histone deacetylase inhibitor entinostat as a pharmacological agent for the potential conversion of Pax3:Foxo1-positive aRMS to a state akin to fusion-negative RMS through direct transcriptional suppression of Pax3:Foxo1.

Ahluwalia, S. C., Bekelman, D. B., Huynh, A. K., Prendergast, T. J., Shreve, S., & Lorenz, K. A. (2014). Barriers and strategies to an iterative model of advance care planning communication. *The American Journal of Hospice & Palliative Care,*

BACKGROUND: Early and repeated patient-provider conversations about advance care planning (ACP) are now widely recommended. We sought to characterize barriers and strategies for realizing an iterative model of ACP patient-provider communication. METHODS: A total of 2 multidisciplinary focus groups and 3 semistructured interviews with 20 providers at a large Veterans Affairs medical center. Thematic analysis was employed to identify salient themes. RESULTS: Barriers included variation among providers in approaches to ACP, lack of useful information about patient values to guide decision making, and ineffective communication between providers across settings. Strategies included eliciting patient values rather than specific treatment choices and an increased role for primary care in the ACP process. CONCLUSIONS: Greater attention to connecting providers across the continuum, maximizing the potential of the electronic health record, and linking patient experiences to their values may help to connect ACP communication across the continuum.

Albers, M. W., Gilmore, G. C., Kaye, J., Murphy, C., Wingfield, A., Bennett, D. A., et al. (2014). At the interface of sensory and motor dysfunctions and alzheimer's disease. *Alzheimer's and Dementia,*

Recent evidence indicates that sensory and motor changes may precede the cognitive symptoms of Alzheimer's disease (AD) by several years and may signify increased risk of developing AD. Traditionally, sensory and motor dysfunctions in aging and AD have been studied separately. To ascertain the evidence supporting the relationship between age-related changes in sensory and motor systems and the development of AD and to facilitate communication between several disciplines, the National Institute on Aging held an exploratory workshop titled "Sensory and

Motor Dysfunctions in Aging and AD." The scientific sessions of the workshop focused on age-related and neuropathologic changes in the olfactory, visual, auditory, and motor systems, followed by extensive discussion and hypothesis generation related to the possible links among sensory, cognitive, and motor domains in aging and AD. Based on the data presented and discussed at this workshop, it is clear that sensory and motor regions of the central nervous system are affected by AD pathology and that interventions targeting amelioration of sensory-motor deficits in AD may enhance patient function as AD progresses. © 2014 The Alzheimers Association.

Albrecht, J. S., Gruber-Baldini, A. L., Hirshon, J. M., Brown, C. H., Goldberg, R., Rosenberg, J. H., et al. (2014). Hospital discharge instructions: Comprehension and compliance among older adults. *Journal of General Internal Medicine,*

BACKGROUND Little is known regarding the prevalence or risk factors for non-comprehension and non-compliance with discharge instructions among older adults. OBJECTIVE To quantify the prevalence of non-comprehension and non-compliance with discharge instructions and to identify associated patient characteristics. RESEARCH DESIGN Prospective cohort study. SUBJECTS Four hundred and fifty adults aged ≥ 65 admitted to medical and surgical units of a tertiary care facility and meeting inclusion criteria. MEASURES We collected information on demographics, psycho-social factors, discharge diagnoses, and medications using surveys and patient medical records. Domains within discharge instructions included medications, follow-up appointments, diet, and exercise. At 5 days post-discharge, we assessed comprehension by asking patients about their discharge instructions, and compared responses to written instructions from medical charts. We assessed compliance among patients who understood their instructions. RESULTS Prevalence of non-comprehension was 5 % for follow-up appointments, 27 % for medications, 48 % for exercise and 50 % for diet recommendations. Age was associated with non-comprehension of medication [odds ratio (OR) 1.07; 95 % confidence interval (CI) 1.04, 1.12] and follow-up appointment (OR 1.08; 95 % CI 1.00, 1.17) instructions. Male sex was associated with non-comprehension of diet instructions (OR 1.91; 95 % CI 1.10, 3.31). Social isolation was associated with non-comprehension of exercise instructions (OR 9.42; 95 % CI 1.50, 59.11) Depression was associated with non-compliance with medication (OR 2.29; 95 % CI 1.02, 5.10) and diet

instructions (OR 3.30; 95 % CI 1.24, 8.83). CONCLUSIONS Non-comprehension of discharge instructions among older adults is prevalent, multi-factorial, and varies by domain. © 2014 Society of General Internal Medicine.

Anderson, K., Williams, E. M., Kaplan, J., Matsumura, L., & Troxell, M. L. (2014). Utility of immunohistochemical markers in irradiated breast tissue: An analysis of the role of myoepithelial markers, p53, and ki-67. *The American Journal of Surgical Pathology, 38*(8), 1128-1137. Radiation therapy is an important adjunct to breast-conserving surgery, but the diagnosis of recurrent/de novo carcinoma in a background of radiation atypia can be difficult, especially on small biopsies. Immunostaining for myoepithelial cell proteins is often used to assess invasion in nonirradiated breast tissue, yet these stains have not been investigated specifically in irradiated breast. We studied 29 irradiated breast resection specimens, some with carcinoma in situ (CIS, n=13) and/or invasive carcinoma (n=13). Representative blocks were stained for the myoepithelial proteins p63, smooth muscle myosin heavy chain (SMM), calponin, CK5/6, the proliferative marker Ki-67, and the tumor-suppressor p53. Nonirradiated control tissue was also stained with Ki-67 and p53 (CIS, normal, contralateral). Areas of radiation atypia/atrophy and nearly all CIS in irradiated breast tissue had abundant myoepithelial cells as evidenced by SMM, calponin, and p63 stains, with focal staining attenuation or gaps with SMM and calponin and frequently absent CK5/6 staining. As predicted, myoepithelial cell staining was absent in invasive carcinoma. p63 staining revealed postradiation myoepithelial nuclear morphologic changes. p53 staining was increased, although weak, in irradiated non-neoplastic breast (12% irradiated; 4% nonirradiated); however, irradiated CIS had less p53 staining when compared with control CIS (3% irradiated; 38% nonirradiated). As expected, Ki-67 was increased in carcinoma as compared with non-neoplastic irradiated tissue. Thus, myoepithelial immunostaining is a useful diagnostic adjunct in irradiated breast, with caveats similar to nonirradiated breast. Ki-67 may be helpful in some postradiation specimens; however, p53 staining is not reliable in this setting.

Anderson, R. R., & Kulesz-Martin, M. F. (2014). Montagna symposium 2013-light and skin: How light sustains, damages, treats, images and modifies skin biology. *The Journal of Investigative Dermatology, 134*(8), 2064-2067.

Apostolides, P. F., & Trussell, L. O. (2014). Control of interneuron firing by subthreshold synaptic potentials in principal cells of the dorsal cochlear nucleus. *Neuron, 83*(2), 324-330.

Voltage-gated ion channels amplify, compartmentalize, and normalize synaptic signals received by neurons. We show that voltage-gated channels activated during subthreshold glutamatergic synaptic potentials in a principal cell generate an excitatory-->inhibitory synaptic sequence that excites electrically coupled interneurons. In fusiform cells of the dorsal cochlear nucleus, excitatory synapses activate a TTX-sensitive Na(+) conductance and deactivate a resting Ih conductance, leading to a striking reshaping of the synaptic potential. Subthreshold voltage changes resulting from activation/deactivation of these channels subsequently propagate through gap junctions, causing slow excitation followed by inhibition in GABAergic stellate interneurons. Gap-junction-mediated transmission of voltage-gated signals accounts for the majority of glutamatergic signaling to interneurons, such that subthreshold synaptic events from a single principal cell are sufficient to drive spikes in coupled interneurons. Thus, the interaction between a principal cell's synaptic and voltage-gated channels may determine the spike activity of networks without firing a single action potential.

Arao, R. F., Rosenberg, K. D., McWeeney, S., & Hedberg, K. (2014). Influenza vaccination of pregnant women: Attitudes and behaviors of oregon physician prenatal care providers. *Maternal and Child Health Journal,*

In spite of increased risk of influenza complications during pregnancy, only half of US pregnant women get influenza vaccination. We surveyed physician prenatal care providers in Oregon to assess their knowledge and behaviors regarding vaccination of pregnant women. From September through November 2011, a state-wide survey was mailed to a simple random sample (n = 1,114) of Oregon obstetricians and family physicians. The response rate was 44.5 %. Of 496 survey respondents, 187 (37.7 %) had provided prenatal care within the last 12 months. Of these, 88.5 % reported that they routinely recommended influenza vaccine to healthy pregnant patients. No significant differences in vaccine recommendation were found by specialty, practice location, number of providers in their practice, physician gender or years in practice. In multivariable regression analysis, routinely recommending influenza vaccine was significantly associated with younger physician age [adjusted odds ratio (AOR) 2.01, 95 % confidence interval

(CI) 1.29-3.13] and greater number of pregnant patients seen per week (AOR 1.95, 95 % CI 1.25-3.06). Among rural physicians, fewer obstetricians (90.3 %) than family physicians (98.5 %) had vaccine-appropriate storage units (p = 0.001). Most physician prenatal care providers understand the importance of influenza vaccination during pregnancy. To increase influenza vaccine coverage among pregnant women, it will be necessary to identify and address patient barriers to receiving influenza vaccination during pregnancy.

Azimipour, M., Baumgartner, R., Liu, Y., Jacques, S. L., Eliceiri, K., & Pashaie, R. (2014). Extraction of optical properties and prediction of light distribution in rat brain tissue. *Journal of Biomedical Optics, 19*(7), 75001.

Azuma, M., Yabuta, C., Fraunfelder, F. W., & Shearer, T. R. (2014). Dry eye in LASIK patients. *BMC Research Notes, 7*(1), 420-0500-7-420.

BACKGROUND: Increasing age is a known risk factor for developing dry eye. The specific aims of the present study were to determine the prevalence of dry eye syndrome (DES) and use of post-operative dry eye medications in a relatively young population presenting for LASIK surgery at an academic ophthalmology clinic. FINDINGS: A retrospective, analysis of 948 de-identified patient charts (median age 39 years, not age stratified) was performed to extract pre-LASIK diagnoses and post-LASIK medication lists. Clinical evaluation for DES and the results of Schirmer's reflex tear flow test were used to assign LASIK patients into Normal, Pre-dry eye (Pre-DES), and Dry Eye Syndrome (DES) groups; which were then compared for use of dry eye medications.Based on pre-operative diagnoses, only 2% (CI: 1.3 - 3.1) of LASIK patients presented with overt DES. Unexpectantly, 25% (CI: 22.2 - 27.6) of LASIK patients labeled Pre-DES were not classified by the clinician as having overt DES, yet they showed poor reflex tear flow rates </= 5 mm before surgery, and frequently used post-operative lubricant dry eye medications. CONCLUSIONS: Although the number of patients with pre-existing eye conditions was unknown, a sizable portion of relatively young LASIK patients displays poor reflex tear flow without overt DES. Such patients could go on to develop more serious consequences of poor tear flow, such as corneal abrasion and erosion. More specific, dry eye medications may be needed for ideal treatment.

Bailit, J. L., Grobman, W., Zhao, Y., Wapner, R. J., Reddy, U. M., Varner, M. W., et al. (2014). Nonmedically indicated induction vs expectant treatment in term nulliparous women. *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: The purpose of this study was to compare maternal and neonatal outcomes in nulliparous women with nonmedically indicated inductions at term vs those expectantly treated. STUDY DESIGN: Data were obtained from maternal and neonatal charts for all deliveries on randomly selected days across 25 US hospitals over a 3-year period. A low-risk subset of nulliparous women with vertex nonanomalous singleton gestations who delivered 38 0/7 to 41 6/7 weeks were selected. Maternal and neonatal outcomes for nonmedically indicated induction within each week were compared with women who did not undergo nonmedically indicated induction during that week. Multivariable analysis was used to adjust for hospital, maternal age, race/ethnicity, body mass index, cigarette use, and insurance status. RESULTS: We found 31,169 women who met our criteria. Neonatal complications were either less frequent with nonmedically indicated induction or no different between groups. Nonmedically indicated induction was associated with less frequent peripartum infections (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.16-0.98) at 38 weeks of gestation and less frequent third- and fourth-degree lacerations (OR, 0.60; 95% CI, 0.42-0.86) and less frequent peripartum infections (OR, 0.66; 95% CI, 0.49-0.90) at 39 weeks of gestation. Nonmedically indicated induction was associated with a longer admission-to-delivery time by approximately 3-4 hours and increased odds of cesarean delivery at 38 (OR, 1.50; 95% CI, 1.08-2.08) and 40 weeks (OR, 1.30; 95% CI, 1.15-1.46) of gestation. CONCLUSION: At 39 weeks of gestation, nonmedically indicated induction is associated with lower maternal and neonatal morbidity than women who are expectantly treated.

Baldwin, M. K., & Edelman, A. B. (2014). Development of a training model for estimation of uterine size in early pregnancy. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics,*

Baquero, A. F., de Solis, A. J., Lindsley, S. R., Kirigiti, M. A., Smith, M. S., Cowley, M. A., et al. (2014). Developmental switch of leptin signaling in arcuate nucleus neurons. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(30), 9982-9994.

Leptin is well known for its role in the regulation of energy homeostasis in adults, a mechanism that at least partially results from the inhibition of the activity of NPY/AgRP/GABA neurons (NAG) in the arcuate nucleus of the hypothalamus (ARH). During early postnatal development in the rodent, leptin promotes axonal outgrowth from ARH neurons, and preautonomic NAG neurons are particularly responsive to leptin's trophic effects. To begin to understand how leptin could simultaneously promote axonal outgrowth from and inhibit the activity of NAG neurons, we characterized the electrochemical effects of leptin on NAG neurons in mice during early development. Here, we show that NAG neurons do indeed express a functional leptin receptor throughout the early postnatal period in the mouse; however, at postnatal days 13-15, leptin causes membrane depolarization in NAG neurons, rather than the expected hyperpolarization. Leptin action on NAG neurons transitions from stimulatory to inhibitory in the periweaning period, in parallel with the acquisition of functional ATP-sensitive potassium channels. These findings are consistent with the idea that leptin provides an orexigenic drive through the NAG system to help rapidly growing pups meet their energy requirements.

Baraniuk, S., Tilley, B. C., Del Junco, D. J., Fox, E. E., van Belle, G., Wade, C. E., et al. (2014). Pragmatic randomized optimal platelet and plasma ratios (PROPPR) trial: Design, rationale and implementation. *Injury,*

BACKGROUND: Forty percent of in-hospital deaths among injured patients involve massive truncal haemorrhage. These deaths may be prevented with rapid haemorrhage control and improved resuscitation techniques. The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial was designed to determine if there is a difference in mortality between subjects who received different ratios of FDA approved blood products. This report describes the design and implementation of PROPPR. STUDY DESIGN: PROPPR was designed as a randomized, two-group, Phase III trial conducted in subjects with the highest level of trauma activation and predicted to have a massive transfusion. Subjects at 12 North American level 1 trauma centres were randomized into one of two standard transfusion ratio interventions: 1:1:1 or 1:1:2, (plasma, platelets, and red blood cells). Clinical data and serial blood samples were collected under Exception from Informed Consent (EFIC) regulations. Co-primary mortality endpoints of 24h and 30 days were evaluated. RESULTS: Between August 2012 and December 2013, 680

patients were randomized. The overall median time from admission to randomization was 26min. PROPPR enrolled at higher than expected rates with fewer than expected protocol deviations. CONCLUSION: PROPPR is the largest randomized study to enrol severely bleeding patients. This study showed that rapidly enrolling and successfully providing randomized blood products to severely injured patients in an EFIC study is feasible. PROPPR was able to achieve these goals by utilizing a collaborative structure and developing successful procedures and design elements that can be part of future trauma studies.

Barnett, C. M., Heinrich, M. C., Lim, J., Nelson, D., Beadling, C., Warrick, A., et al. (2014). Genetic profiling to determine risk of relapse-free survival in high-risk localized prostate cancer. *Clinical Cancer Research, 20*(5), 1306-1312.

Purpose: The characterization of actionable mutations in human tumors is a prerequisite for the development of individualized, targeted therapy.Weexamined the prevalence of potentially therapeutically actionable mutations in patients with high-risk clinically localized prostate cancer. Experimental Design: Forty-eight samples of formalin-fixed paraffin-embedded prostatectomy tissue from a neoadjuvant chemotherapy trial were analyzed. DNA extracted from microdissected tumor was analyzed for 643 common solid tumor mutations in 53 genes using mass spectroscopy-based sequencing. In addition, PTEN loss and erythroblast transformation-specific-related gene (ERC) translocations were examined using immunohistochemistry (IHC) in associated tissue microarrays. Association with relapse during 5 years of follow-up was examined in exploratory analyses of the potential clinical relevance of the genetic alterations. Results: Of the 40 tumors evaluable for mutations, 10% had point mutations in potentially actionable cancer genes. Of the 47 tumors evaluable for IHC, 36% had PTEN loss and 40% had ERG rearrangement. Individual mutations were not frequent enough to determine associations with relapse. Using Kaplan- Meier analysis with a log-rank test, the 16 patients who had PTEN loss had a significantly shorter median relapse-free survival, 19 versus 106 months (P = 0.01). Conclusions: This study confirms that point mutations in the most common cancer regulatory genes in prostate cancer are rare. However, the PIK3CA/AKT pathway was mutated in 10% of our samples. Although point mutations alone did not have a statistically significant association with

relapse, PTEN loss was associated with an increased relapse in high-risk prostate cancer treated with chemotherapy followed by surgery. © 2013 AACR.

Barrett, C. M. F., Troxell, M. L., Larse, C. P., & Houghton, D. C. (2014). Membranous glomerulonephritis with crescents. *International Urology and Nephrology, 46*(5), 963-971.

Purpose: The coexistence of membranous glomerulonephritis (MGN) and necrotizing and crescentic glomerulonephritis (NCGN) is an unusual finding in a renal biopsy except in lupus nephritis. Little is known about whether these lesions are causally related in any clinical setting. Methods: We reviewed the pathology, presentation, and clinical course of 13 non-lupus patients with combined MGN and NCGN in native kidney biopsies (nine females, four males; median age 69 years), with particular attention to evidence of secondary MGN. Additional IgG subclass and phospholipase A2 receptor (PLA2R) immunofluorescence studies were conducted in seven cases. Results: Eight biopsies were pauci-immune other than the capillary wall deposits of MGN; one patient had a non-lupus immune complex disease, and four had mesangial deposits, including one with rare subendothelial deposits. None had anti-glomerular basement membrane disease. IgG4 was dominant or codominant in the capillary wall deposits in three cases and virtually absent in four; PLA2R was positive in two cases, and negative in five. Seven patients were judged to have secondary MGN, including five of eight ANCA+ patients. Twelve patients were treated with combinations of steroids, cyclophosphamide, rituximab, followed by durable response in seven and relentless progression to end stage renal disease in four. Conclusions: Secondary MGN occurs with higher frequency in ANCA-positive NCGN than in the general MGN population. A causal relationship between MGN and NCGN was not established in any patient, but circumstances suggest a common cause in several, including immune complex disease, drug reaction and paraneoplastic syndrome. © Springer Science+Business Media 2013.

Bas, E., Erdogmus, D., Ozertem, U., & Pavel, M. (2008). Towards fish-eye camera based in-home activity assessment. *Conference Proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference,* , 2558-2561.

Indoors localization, activity classification, and behavioral modeling are increasingly important for

surveillance applications including independent living and remote health monitoring. In this paper, we study the suitability of fish-eye cameras (high-resolution CCD sensors with very-wide-angle lenses) for the purpose of monitoring people in indoors environments. The results indicate that these sensors are very useful for automatic activity monitoring and people tracking. We identify practical and mathematical problems related to information extraction from these video sequences and identify future directions to solve these issues.

Beck, L. A., Thaci, D., Hamilton, J. D., Graham, N. M., Bieber, T., Rocklin, R., et al. (2014). Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *The New England Journal of Medicine, 371*(2), 130-139.

BACKGROUND: Dupilumab, a fully human monoclonal antibody that blocks interleukin-4 and interleukin-13, has shown efficacy in patients with asthma and elevated eosinophil levels. The blockade by dupilumab of these key drivers of type 2 helper T-cell (Th2)-mediated inflammation could help in the treatment of related diseases, including atopic dermatitis. METHODS: We performed randomized, double-blind, placebo-controlled trials involving adults who had moderate-to-severe atopic dermatitis despite treatment with topical glucocorticoids and calcineurin inhibitors. Dupilumab was evaluated as monotherapy in two 4-week trials and in one 12-week trial and in combination with topical glucocorticoids in another 4-week study. End points included the Eczema Area and Severity Index (EASI) score, the investigator's global assessment score, pruritus, safety assessments, serum biomarker levels, and disease transcriptome. RESULTS: In the 4-week monotherapy studies, dupilumab resulted in rapid and dose-dependent improvements in clinical indexes, biomarker levels, and the transcriptome. The results of the 12-week study of dupilumab monotherapy reproduced and extended the 4-week findings: 85% of patients in the dupilumab group, as compared with 35% of those in the placebo group, had a 50% reduction in the EASI score (EASI-50, with higher scores in the EASI indicating greater severity of eczema) ($P<0.001$); 40% of patients in the dupilumab group, as compared with 7% in the placebo group, had a score of 0 to 1 (indicating clearing or near-clearing of skin lesions) on the investigator's global assessment ($P<0.001$); and pruritus scores decreased (indicating a reduction in itch) by 55.7% in the dupilumab group versus 15.1% in the placebo group ($P<0.001$). In the combination study, 100% of the patients in the dupilumab group, as compared

with 50% of those who received topical glucocorticoids with placebo injection, met the criterion for EASI-50 (P=0.002), despite the fact that patients who received dupilumab plus glucocorticoids used less than half the amount of topical glucocorticoids used by those who received placebo plus the topical medication (P=0.16). Adverse events, such as skin infection, occurred more frequently with placebo; nasopharyngitis and headache were the most frequent adverse events with dupilumab. CONCLUSIONS: Patients treated with dupilumab had marked and rapid improvement in all the evaluated measures of atopic dermatitis disease activity. Side-effect profiles were not dose-limiting. (Funded by Regeneron Pharmaceuticals and Sanofi; ClinicalTrials.gov numbers, NCT01259323, NCT01385657, NCT01639040, and NCT01548404.).

Benedek, G., Zhu, W., Libal, N., Casper, A., Yu, X., Meza-Romero, R., et al. (2014). A novel HLA-DRα1-MOG-35-55 construct treats experimental stroke. *Metabolic Brain Disease, 29*(1), 37-45. Chemoattraction of leukocytes into the brain after induction of middle cerebral artery occlusion (MCAO) increases the lesion size and worsens disease outcome. Our previous studies demonstrated that partial MHC class II constructs can reverse this process. However, the potential application of pMHC to human stroke is limited by the need to rapidly match recipient MHC class II with the β1 domain of the pMHC construct. We designed a novel recombinant protein comprised of the HLA-DRα1 domain linked to MOG-35-55 peptide but lacking the β1 domain found in pMHC and treated MCAO after 4 h reperfusion in humanized DR2 mice. Infarct volumes were quantified after 96 h reperfusion and immune cells from the periphery and CNS were evaluated for expression of CD74 and other cell surface, cytokine and pathway markers. This study demonstrates that four daily treatments with DRα1-MOG-35-55 reduced infarct size by 40 % in the cortex, striatum and hemisphere, inhibited the migration of activated CD11b+CD45high cells from the periphery to the brain and reversed splenic atrophy. Furthermore, DRα1-MOG-35-55 bound to CD74 on monocytes and blocked both binding and downstream signaling of macrophage migration inhibition factor (MIF) that may play a key role in infarct development. The novel DRα1-MOG-35-55 construct is highly therapeutic in experimental stroke and could be given to all patients at least 4 h after stroke onset without the need for tissue typing due to universal expression of DRα1 in humans.

Berman, B., Goldenberg, G., Hanke, C. W., Tyring, S. K., Werschler, W. P., Knudsen, K. M., et al. (2014). Efficacy and safety of ingenol mebutate 0.015% gel after cryosurgery of actinic keratosis: 12-month results. *Journal of Drugs in Dermatology, 13*(6), 741-747.

Introduction: Recurrence rates of actinic keratosis (AK) lesions after cryosurgery are high, and this treatment does not address field cancerization. We investigated the efficacy and safety of field treatment of AKs with ingenol mebutate gel following cryosurgery. Methods: In this phase 3, randomized, double-blind, vehicle-controlled study (NCT01541553), patients =18 years with four to eight clinically typical, visible, discrete AKs within a contiguous 25-cm2 treatment area on the face or scalp underwent cryosurgery followed 3 weeks later by once-daily ingenol mebutate 0.015% or vehicle gel for 3 consecutive days. Endpoints included complete clearance at week 11 and safety and efficacy over 12 months. Results: In 329 randomized patients, complete clearance rates were greater with ingenol mebutate than vehicle (week 11: 60.5% vs 49.4%; P=.04; month 12: 30.5% vs 18.5%; P=.01). Fewer patients experienced the emergence of new lesions with ingenol mebutate than with vehicle (38.9% vs 51.9%; P=.02). At month 12, mean percentage reduction of AKs was higher with ingenol mebutate than with vehicle (68.2% vs 54.1%; P=.002). The probability of remaining free of lesions was sustained longer with ingenol mebutate compared with vehicle gel: 78% vs 68% at 6 months; 64% vs 57% at 9 months; 55% vs 40% at month 12, respectively. Ingenol mebutate 0.015% gel was well tolerated and no unexpected adverse events occurred; all adverse events resolved within 2 weeks of starting treatment. Conclusions: Field treatment with ingenol mebutate 0.015% gel following cryosurgery significantly enhanced clearance of baseline lesions, and was well tolerated. Furthermore, ingenol mebutate 0.015% gel following cryosurgery reduced development of new lesions in the treated field. Copyright © 2014.

Bernier, R., Golzio, C., Xiong, B., Stessman, H. A., Coe, B. P., Penn, O., et al. (2014). Disruptive CHD8 mutations define a subtype of autism early in development. *Cell, 158*(2), 263-276.

Autism spectrum disorder (ASD) is a heterogeneous disease in which efforts to define subtypes behaviorally have met with limited success. Hypothesizing that genetically based subtype identification may prove more productive, we resequenced the ASD-associated gene CHD8 in 3,730 children with developmental delay or ASD. We identified a total of 15 independent

mutations; no truncating events were identified in 8,792 controls, including 2,289 unaffected siblings. In addition to a high likelihood of an ASD diagnosis among patients bearing CHD8 mutations, characteristics enriched in this group included macrocephaly, distinct faces, and gastrointestinal complaints. chd8 disruption in zebrafish recapitulates features of the human phenotype, including increased head size as a result of expansion of the forebrain/midbrain and impairment of gastrointestinal motility due to a reduction in postmitotic enteric neurons. Our findings indicate that CHD8 disruptions define a distinct ASD subtype and reveal unexpected comorbidities between brain development and enteric innervation.

Berns, J. S., Ellison, D. H., Linas, S. L., & Rosner, M. H. (2014). Training the next generation's nephrology workforce. *Clinical Journal of the American Society of Nephrology : CJASN,*
The subspecialty of nephrology faces several critical challenges, including declining interest among medical students and internal medicine residents and worrisome declines in the number of applicants for nephrology fellowships. There is an urgent need to more clearly define the subspecialty and its scope of practice, reinvigorate meaningful research training and activities among trainees, and ensure that fellows who complete training and enter the practice of nephrology are experts in the broad scope of nephrology. This need requires a critical look at fellowship training programs and training requirements. A new workforce analysis is also needed that is not focused on primarily meeting estimated future clinical needs but rather, ensuring that there is alignment of supply and demand for nephrology trainees, which will ensure that those entering nephrology fellowships are highly qualified and capable of becoming outstanding nephrologists and that there are desirable employment opportunities for them when they complete their training.

Bhaskaran, H., Taniguchi, T., Suzuki, T., Suzuki, T., & Perona, J. J. (2014). Structural dynamics of a mitochondrial tRNA possessing weak thermodynamic stability. *Biochemistry, 53*(9), 1456-1465.
Folding dynamics are ubiquitously involved in controlling the multivariate functions of RNAs. While the high thermodynamic stabilities of some RNAs favor purely native states at equilibrium, it is unclear whether weakly stable RNAs exist in random, partially folded states or sample well-defined, globally folded conformations. Using a folding assay that precisely tracks the formation

of native aminoacylable tRNA, we show that the folding of a weakly stable human mitochondrial (hmt) leucine tRNA is hierarchical with a distinct kinetic folding intermediate. The stabilities of the native and intermediate conformers are separated by only about 1.2 kcal/mol, and the species are readily interconvertible. Comparison of folding dynamics between unmodified and fully modified tRNAs reveals that post-transcriptional modifications produce a more constrained native structure that does not sample intermediate conformations. These structural dynamics may thus be crucial for recognition by some modifying enzymes in vivo, especially those targeting the globular core region, by allowing access to pretransition state conformers. Reduced conformational sampling of the native, modified tRNAs could then permit improved performance in downstream processes of translation. More generally, weak stabilities of small RNAs that fold in the absence of chaperone proteins may facilitate conformational switching that is central to biological function.

Bilyk, O. O., Pande, N. T., Pejovic, T., & Buchinska, L. G. (2014). The frequency of human papilloma virus types 16, 18 in upper genital tract of women at high risk of developing ovarian cancer. *Experimental Oncology, 36*(2), 121-124.

Aim: To investigate the incidence of human papilloma virus (HPV) types 16, 18 in upper genital tract of women considered at a high risk (HR) of developing epithelial ovarian cancer (EOC). Methods: HPV 16 and 18 E6 ORF specific semiquantitative PCR was used to screen the incidence of HPV in 20 women at HR of developing EOC and 10 women with no ovarian disease (control). Results: The HR subset of fallopian tubes and ovarian tissues showed greater positivity for HPV E6 ORF (40%) as compared to control (10%) tissues. Of all the samples, two (10%) were positive for HPV 16, two (10%) were positive for HPV 18, and four (20%) showed positivity for mixed HPV 16/18 infection. The presence of HPV E6 ORF was found both in the fallopian tubes and ovarian DNA from 6 (30%) patients. In two cases (10%) we detected HPV ORF only in the fallopian tube derived genomic DNA. Conclusion: It has been shown the presence of HPV in the upper genital tract in women at HR of developing EOC in close proximity of HPV susceptible tissue cervix.

Block, M. S., Charbonneau, B., Vierkant, R. A., Fogarty, Z., Bamlet, W. R., Pharoah, P. D. P., et al. (2014). Variation in NF-κB signaling pathways and survival in invasive epithelial ovarian cancer. *Cancer Epidemiology Biomarkers and Prevention, 23*(7), 1421-1427.

Survival in epithelial ovarian cancer (EOC) is influenced by the host immune response, yet the key genetic determinants of inflammation and immunity that affect prognosis are not known. The nuclear factor-kB (NF-kB) transcription factor family plays an important role in many immune and inflammatory responses, including the response to cancer. We studied common inherited variation in 210 genes in the NF-kB family in 10,084 patients with invasive EOC (5,248 high-grade serous, 1,452 endometrioid, 795 clear cell, and 661 mucinous) from the Ovarian Cancer Association Consortium. Associations between genotype and overall survival were assessed using Cox regression for all patients and by major histology, adjusting for known prognostic factors and correcting for multiple testing (threshold for statistical significance, P < 2.5 × 10-5). Results were statistically significant when assessed for patients of a single histology. Key associations were with caspase recruitment domain family, member 11 (CARD11) rs41324349 in patients with mucinous EOC [HR, 1.82; 95% confidence interval (CI), 1.41-2.35; P = 4.13 × 10-6] and tumor necrosis factor receptor superfamily, member 13B (TNFRSF13B) rs7501462 in patients with endometrioid EOC (HR, 0.68; 95% CI, 0.56-0.82; P = 2.33 × 10-5). Other associations of note included TNF receptor-associated factor 2 (TRAF2) rs17250239 in patients with high-grade serous EOC (HR, 0.84; 95% CI, 0.77-0.92; P = 6.49 ± 10-5) and phospholipase C, gamma 1 (PLCG1) rs11696662 in patients with clear cell EOC (HR, 0.43; 95% CI, 0.26-0.73; P = 4.56 × 10-4). These associations highlight the potential importance of genes associated with host inflammation and immunity in modulating clinical outcomes in distinct EOC histologies. © 2014 American Association for Cancer Research.

Bloomfield, H. E., Olson, A., Greer, N., Cantor, A., MacDonald, R., Rutks, I., et al. (2014). Screening pelvic examinations in asymptomatic, average-risk adult women: An evidence report for a clinical practice guideline from the american college of physicians. *Annals of Internal Medicine, 161*(1), 46-53.

Background: Pelvic examination is often included in well-woman visits even when cervical cancer screening is not required. Purpose: To evaluate the diagnostic accuracy, benefits, and harms of

pelvic examination in asymptomatic, nonpregnant, average-risk adult women. Cervical cancer screening was not included. Data Sources: MEDLINE and Cochrane databases through January 2014 and reference lists from identified studies. Study Selection: 52 English-language studies, 32 of which included primary data. Data Extraction: Data were extracted on study and sample characteristics, interventions, and outcomes. Quality of the diagnostic accuracy studies was evaluated using a published instrument, and quality of the survey studies was evaluated with metrics assessing population representativeness, instrument development, and response rates. Data Synthesis: The positive predictive value of pelvic examination for detecting ovarian cancer was less than 4% in the 2 studies that reported this metric. No studies that investigated the morbidity or mortality benefits of screening pelvic examination for any condition were identified. The percentage of women reporting pelvic examination-related pain or discomfort ranged from 11% to 60% (median, 35%; 8 studies [n = 4576]). Corresponding figures for fear, embarrassment, or anxiety ranged from 10% to 80% (median, 34%; 7 studies [n = 10 702]). Limitation: Only English-language publications were included; the evidence on diagnostic accuracy, morbidity, and mortality was scant; and the studies reporting harms were generally low quality. Conclusion: No data supporting the use of pelvic examination in asymptomatic, average-risk women were found. Low-quality data suggest that pelvic examinations may cause pain, discomfort, fear, anxiety, or embarrassment in about 30% of women. © 2014 American College of Physicians.

Blum, M., Schweickert, A., Vick, P., Wright, C. V., & Danilchik, M. V. (2014). Symmetry breakage in the vertebrate embryo: When does it happen and how does it work? *Developmental Biology,* Asymmetric development of the vertebrate embryo has fascinated embryologists for over a century. Much has been learned since the asymmetric Nodal signaling cascade in the left lateral plate mesoderm was detected, and began to be unraveled over the past decade or two. When and how symmetry is initially broken, however, has remained a matter of debate. Two essentially mutually exclusive models prevail. Cilia-driven leftward flow of extracellular fluids occurs in mammalian, fish and amphibian embryos. A great deal of experimental evidence indicates that this flow is indeed required for symmetry breaking. An alternative model has argued, however, that flow simply acts as an amplification step for early asymmetric cues generated by ion flux

during the first cleavage divisions. In this review we critically evaluate the experimental basis of both models. Although a number of open questions persist, the available evidence is best compatible with flow-based symmetry breakage as the archetypical mode of symmetry breakage.

Bodhankar, S., Chen, Y., Vandenbark, A. A., Murphy, S. J., & Offner, H. (2014). Treatment of experimental stroke with IL-10-producing B-cells reduces infarct size and peripheral and CNS inflammation in wild-type B-cell-sufficient mice. *Metabolic Brain Disease, 29*(1), 59-73. Clinical stroke induces inflammatory processes leading to cerebral and splenic injury and profound peripheral immunosuppression. IL-10 expression is elevated during major CNS diseases and limits inflammation in the brain. Recent evidence demonstrated that absence of B-cells led to larger infarct volumes and CNS damage after middle cerebral artery occlusion (MCAO) that could be prevented by transfer of IL-10+ B-cells. The purpose of this study was to determine if the beneficial immunoregulatory effects on MCAO of the IL-10 + B-cell subpopulation also extends to B-cell-sufficient mice that would better represent stroke subjects. CNS inflammation and infarct volumes were evaluated in male C57BL/6J (WT) mice that received either RPMI or IL-10+ B-cells and underwent 60 min of middle cerebral artery occlusion (MCAO) followed by 96 h of reperfusion. Transfer of IL-10+ B-cells markedly reduced infarct volume in WT recipient mice when given 24 h prior to or 4 h after MCAO. B-cell protected (24 h pre-MCAO) mice had increased regulatory subpopulations in the periphery, reduced numbers of activated, inflammatory T-cells, decreased infiltration of T-cells and a less inflammatory milieu in the ischemic hemispheres of the IL-10+ B-cell-treated group. Moreover, transfer of IL-10+ B-cells 24 h before MCAO led to a significant preservation of regulatory immune subsets in the IL-10+ B-cell protected group presumably indicating their role in immunomodulatory mechanisms, post-stroke. Our studies are the first to demonstrate a major immunoregulatory role for IL-10+ regulatory B-cells in preventing and treating MCAO in WT mice and also implicating their potential role in attenuating complications due to post-stroke immunosuppression. © 2013 Springer Science+Business Media.

Bogdanov, A., & Wan, E. (2003). SDRE control with nonlinear feedforward compensation for a small unmanned helicopter. *2nd AIAA "Unmanned Unlimited" Conference and Workshop and Exhibit*

2003, San Diego, CA.

In this paper we report on the state-dependent Riccati equation (SDRE) control of a small unmanned helicopter for autonomous agile maneuvering. SDRE control requires reformulation of the vehicle dynamics into a pseudo-linear form. For a helicopter application, however, this results in a number of terms not accounted in the SDRE design. To overcome this problem, we employ a nonlinear feedforward compensator that is designed to match the vehicle response to the model used in the SDRE design. This paper provides new control results and additonal details based on work described previously by Bogdanov, et al. © 2003 by the American Institute of Aeronautics and Astronautics, Inc.

Boscaro, M., Bertherat, J., Findling, J., Fleseriu, M., Atkinson, A. B., Petersenn, S., et al. (2014). Extended treatment of cushing's disease with pasireotide: Results from a 2-year, phase II study. *Pituitary, 17*(4), 320-326.

In a previous 15-day, Phase II study of patients with de novo or persistent/recurrent Cushing's disease (core study), treatment with pasireotide 600 μg sc bid reduced urinary free cortisol (UFC) levels in 76 % of patients and normalized UFC in 17 %. The objective of this study was to evaluate the efficacy and safety of extended treatment with pasireotide. This was a planned, open-ended, single-arm, multicenter extension study (primary endpoint: 6 months). Patients aged ≥18 years with Cushing's disease who completed the core study could enter the extension if they achieved UFC normalization at core study end and/or obtained significant clinical benefit. Of the 38 patients who completed the core study, 19 entered the extension and 18 were included in the efficacy analyses (three responders, 11 reducers, four non-reducers in the core study). At data cut-off, median treatment duration in the extension was 9.7 months (range: 2 months to 4.8 years). At extension month 6, 56 % of the 18 patients had lower UFC than at core baseline and 22 % had normalized UFC. Of the four patients who remained on study drug at month 24, one had normalized UFC. Reductions in serum cortisol, plasma adrenocorticotropic hormone, body weight and diastolic blood pressure were observed. The most common adverse events were mild-to-moderate gastrointestinal disorders and hyperglycemia. Pasireotide offers a tumor-directed medical therapy that may be effective for the extended treatment of some patients with Cushing's disease. © 2013 The Author(s).

Bourdette, D. N., & Cohen, J. A. (2014). Venous angioplasty for "CCSVI" in multiple sclerosis: Ending a therapeutic misadventure. *Neurology, 83*(5), 388-389.

Brace, R. A., & Cheung, C. Y. (2014). Regulation of amniotic fluid volume: Evolving concepts. *Advances in Experimental Medicine and Biology, 814*, 49-68.

Studies in late gestation fetal sheep have provided several new insights into the regulation of amniotic fluid (AF) volume (AFV): There are four quantitatively important amniotic inflows and outflows that include fetal urine production, lung liquid secretion, swallowing, and intramembranous absorption. Of these, AFV is regulated primarily by modulating the rate of intramembranous absorption of AF water and solutes across the amniotic epithelial cells into the underlying fetal vasculature. Modulation of the rate of intramembranous absorption depends on the presence of stimulators and inhibitors present in the AF. A stimulator of intramembranous absorption is present in fetal urine. In addition, AF contains a non-renal, non-pulmonary inhibitor of intramembranous absorption presumably secreted by the fetal membranes. Although passive bidirectional movements of water and solutes occur across the intramembranous pathway, intramembranous absorption is primarily a unidirectional, vesicular, bulk transport process mediated through VEGF activation of transcytotic transport via caveolae. Further, the stimulators and inhibitors of intramembranous absorption alter only the active, unidirectional component of intramembranous absorption while the passive components are not altered under experimental conditions studied thus far. Future progress depends on identifying the cellular and molecular mechanisms that regulate active and passive intramembranous absorption as well as their regulatory components.

Brzana, J., Yedinak, C. G., Hameed, N., & Fleseriu, M. (2014). FRAX score in acromegaly: Does it tell the whole story? *Clinical Endocrinology, 80*(4), 614-616.

Burchill, L. J., Edwards, L. B., Dipchand, A. I., Stehlik, J., & Ross, H. J. (2014). Impact of adult congenital heart disease on survival and mortality after heart transplantation. *The Journal of Heart and Lung Transplantation : The Official Publication of the International Society for Heart Transplantation,*

BACKGROUND: Reduced early survival has been reported in adult congenital heart disease

(ACHD) heart transplant (HTx) recipients, but little is known about late outcomes after HTx. The aim of this study was to examine survival; causes of death; and predictors of early (5 years) mortality in ACHD HTx recipients. METHODS: ACHD patients undergoing HTx between 1985 and 2010 were identified in the transplant registry of the International Society for Heart and Lung Transplantation (ISHLT). Survival was compared between ACHD and other adult HTx recipients ("controls") using the Kaplan-Meier method. Factors associated with survival beyond 1 year were assessed using multivariable proportional hazards regression analysis. RESULTS: Of 85,647 adults who underwent HTx, 1,851 (2.2%) were transplanted for ACHD. Early death secondary due to technical reasons was high among ACHD HTx recipients: 10% vs. 4% in controls ($p < 0.0001$). However, long-term survival of ACHD recipients who survived the early hazard phase was superior compared with controls ($p < 0.0001$). This was in part due to a lower infection ($p < 0.0001$) and malignancy-related ($p < 0.01$) mortality. Cardiac re-transplantation in ACHD HTx recipients was associated with a 2.75-fold increase in mortality. CONCLUSION: A "survival paradox" exists among ACHD recipients, whose high early mortality is balanced by better long-term survival in those who survive the early hazard phase after HTx. A high mortality risk after cardiac re-transplantation in this group of patients suggests that this treatment option should only be considered in carefully selected ACHD HTx recipients.

Burrows, G. G., Maziarz, R. T., Hunady, K., Lehman, N., Raber, A., Deans, R. J., et al. (2014). Human multipotent adult progenitor cells transcriptionally regulate fucosyltransferase VII. *Cytotherapy, 16*(4), 566-575.

Background aims: Targeted recruitment of leukocytes to sites of inflammation is a crucial event in normal host defense against pathogens, and attachment to and rolling on activated endothelial cells is a prerequisite first step for eventual leukocyte extravasation into sites of inflammation. These key events are mediated by interactions between glycosylated ligands expressed on leukocytes and selectins expressed on activated endothelium. Cell surface expression of selectin ligands on leukocytes is regulated by the rate-limiting enzyme fucosyltransferase VII (Fut7), and in its absence extravasation of leukocytes is severely inhibited. Multipotent adult progenitor cells (MAPCs) are an adherent cell population isolated from adult bone marrow. Intravenous administration of MAPCs provided functional improvement in multiple pre-clinical models of injury

or disease, but the mechanisms by which these outcomes were achieved remain poorly understood. Methods: In vitro cell analysis studies including fluorescence-activated cell sorting, messenger RNA analysis, T-cell proliferation assays and endothelial cell binding assays were performed. Results: The in vitro cell analysis studies characterized the ability of MAPCs to secrete factors that transcriptionally attenuate expression of Fut7 in T cells, blocking the terminal fucosylation event in the biosynthesis of selectin ligands and reducing T-cell binding to endothelial cells. Conclusions: This study presents the first example of a distinct regulatory mechanism involving transcriptional down-regulation of Fut7 by MAPCs that could modulate the trafficking behavior of T cells in vivo. © 2014 International Society for Cellular Therapy.

Calonge, N., Klein, R. D., Berg, A. O., Berg, J. S., Armstrong, K., Botkin, J., et al. (2014). The EGAPP initiative: Lessons learned. *Genetics in Medicine, 16*(3), 217-224.

The Evaluation of Genomic Applications in Practice and Prevention Working Group was first convened in 2005 to develop and test evidence-based methods for the evaluation of genomic tests in transition from research to clinical and public health practice. Over the ensuing years, the Working Group has met 26 times, publishing eight recommendation statements, two methods papers, and one outcomes paper, as well as planning and serving as technical experts on numerous associated systematic reviews. Evaluation of Genomic Applications in Practice and Prevention methods have evolved to address implications of the proliferation of genome-wide association studies and are currently expanding to face challenges expected from clinical implementation of whole-genome sequencing tests. In this article, we review the work of the Evaluation of Genomic Applications in Practice and Prevention Working Group over the first 8 years of its existence with an emphasis on lessons learned throughout the process. It is hoped that in addition to the published methods of the Working Group, the lessons we have learned along the way will be informative to others who are producers and consumers of evidence-based guidelines in the field of genomic medicine. © American College of Medical Genetics and Genomics.

Cannady, S. B., Rosenthal, E. L., Knott, P. D., Fritz, M., & Wax, M. K. (2014). Free tissue transfer for head and neck reconstruction: A contemporary review. *JAMA Facial Plastic Surgery,*

Microvascular free tissue transfer is used for complex composite tissue defects in previously treated fields, in particular after treatment of malignant disease. The increasing incidence of skin cancer in the general population has increased the number of patients with massive tumors that require the expertise of the free flap reconstructive surgeon. We herein examine a number of the recent advances in the field that use free tissue transfer for orbitomaxillary and scalp reconstruction, including maxillary reconstruction, virtual surgical planning in head and neck reconstruction, and scalp reconstruction. Advanced computer algorithms allow planning of these procedures at a savings of time and cost. Free tissue transfer is a reconstructive modality that is often at the top of the reconstructive ladder and, in some instances, is the reconstructive method of choice. The ability to harvest composite tissue that matches the tissue defect in composition, surface area, and volume makes free tissue transfer a versatile modality.

Cannell, M. B., Manini, T., Spence-Almaguer, E., Maldonado-Molina, M., & Andresen, E. M. (2014). U.S. population estimates and correlates of sexual abuse of community-dwelling older adults. *Journal of Elder Abuse and Neglect, 26*(4), 398-413.

We describe the annual prevalence of sexual abuse among community-dwelling older adults in the United States. We also describe factors associated with experiencing sexual abuse. We used data from 24,343 older adults from the 2005 Behavioral Risk Factor Surveillance System pooled across 18 states. We estimated prevalence of sexual abuse, bivariate distributions, and odds ratio associations across demographic, health, and contextual factors. Our results show that 0.9% of older adults reported experiencing sexual abuse in the previous year. This represents approximately 90,289 community-dwelling older adults. We also report on factors associated with experiencing recent sexual abuse. There was a significant gender by binge drinking interaction, with a stronger association among women. There is a need for health promotion efforts targeted specifically toward older adults, encouraging them to seek services, if possible, after exposure to sexual abuse.

Cannon, R. B., Gurgel, R. K., Warren, F. M., & Shelton, C. (2014). Facial nerve outcomes after middle fossa decompression for bell's palsy. *Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and*

Neurotology,

OBJECTIVE: Evaluate the long-term outcomes of facial nerve decompression via the middle fossa approach for Bell's palsy patients with poor prognosis based on clinical and electrodiagnostic testing. STUDY DESIGN: Retrospective case series. SETTING: Tertiary-care, academic medical center. PATIENTS: Fourteen patients underwent surgical decompression for Bell's palsy within 14 days of symptom onset from 2000 to 2012. Surgical criteria included greater than 90% degeneration on ENoG testing and no voluntary EMG potentials. INTERVENTION: Middle cranial fossa (MCF) bony decompression of the facial nerve, including the meatal foramen, labyrinthine segment, and geniculate ganglion. MAIN OUTCOME MEASURES: Long-term facial function, hearing results, and surgical complications. RESULTS: After MCF decompression, 10 patients (71.4%) regained normal or near-normal facial function (House-Brackmann [HB] I or II) within 1 year after surgery, and 5 of those patients (35.7%) improved to HB I. The remaining 4 patients (28.6%) improved to HB III. Patients older than 60 years (n = 3) had an HB III outcome and did significantly worse than the younger-than-60-years group (p = 0.002). The difference in preoperative and postoperative pure tone average and word recognition score was 2.1 dB and 0.9%, respectively. There were no major complications. Minor, transient complications occurred in 22.2% of patients. CONCLUSION: In patients with severe Bell's palsy at risk for a poor facial nerve outcome, MCF decompression of the facial nerve within 14 days of symptom onset provides good facial nerve outcomes with minimal morbidity.

Carbonaro, T. M., Eshleman, A. J., Forster, M. J., Cheng, K., Rice, K. C., & Gatch, M. B. (2014). The role of 5-HT2A, 5-HT2C and mGlu2 receptors in the behavioral effects of tryptamine hallucinogens N,N-dimethyltryptamine and N,N-diisopropyltryptamine in rats and mice. *Psychopharmacology,*

Rationale Serotonin 5-HT2A and 5-HT2C receptors are thought to be the primary pharmacological mechanisms for serotonin-mediated hallucinogenic drugs, but recently there has been interest in metabotropic glutamate (mGluR2) receptors as contributors to the mechanism of hallucinogens. Objective The present study assesses the role of these 5-HT and glutamate receptors as molecular targets for two tryptamine hallucinogens, N,N-dimethyltryptamine (DMT) and N,N-diisopropyltryptamine (DiPT). Methods Drug discrimination, head twitch, and radioligand binding

assays were used. A 5-HT2AR inverse agonist (MDL100907), 5-HT2CR antagonist (SB242084), and mGluR2/3 agonist (LY379268) were tested for their ability to attenuate the discriminative stimulus effects of DMT and DiPT; an mGluR2/3 antagonist (LY341495) was tested for potentiation. MDL100907 was used to attenuate head twitches induced by DMT and DiPT. Radioligand binding studies and inosital-1-phosphate (IP-1) accumulation were performed at the 5-HT2CR for DiPT. Results MDL100907 fully blocked the discriminative stimulus effects of DMT, but only partially blocked DiPT. SB242084 partially attenuated the discriminative stimulus effects of DiPT, but produced minimal attenuation of DMT's effects. LY379268 produced potent, but only partial blockade of the discriminative stimulus effects of DMT. LY341495 facilitated DMT- and DiPT-like effects. Both compounds elicited head twitches (DiPT>DMT) which were blocked by MDL1000907. DiPT was a low-potency full agonist at 5-HT2CR in vitro. Conclusions The 5-HT2AR likely plays a major role in mediating the effects of both compounds. 5-HT2C and mGluR2 receptors likely modulate the discriminative stimulus effects of both compounds to some degree.

Carney, N., Ghajar, J., Jagoda, A., Bedrick, S., Davis-O'Reilly, C., du Coudray, H., et al. (2014). Concussion guidelines step 1: Systematic review of prevalent indicators. *Neurosurgery, 75 Suppl 1*, S3-S15.

BACKGROUND: Currently, there is no evidence-based definition for concussion that is being uniformly applied in clinical and research settings. OBJECTIVE: To conduct a systematic review of the highest-quality literature about concussion and to assemble evidence about the prevalence and associations of key indicators of concussion. The goal was to establish an evidence-based foundation from which to derive, in future work, a definition, diagnostic criteria, and prognostic indicators for concussion. METHODS: Key questions were developed, and an electronic literature search from 1980 to 2012 was conducted to acquire evidence about the prevalence of and associations among signs, symptoms, and neurologic and cognitive deficits in samples of individuals exposed to potential concussive events. Included studies were assessed for potential for bias and confound and rated as high, medium, or low potential for bias and confound. Those rated as high were excluded from the analysis. Studies were further triaged on the basis of whether the definition of a case of concussion was exclusive or inclusive; only those with wide,

inclusive case definitions were used in the analysis. Finally, only studies reporting data collected at fixed time points were used. For a study to be included in the conclusions, it was required that the presence of any particular sign, symptom, or deficit be reported in at least 2 independent samples. RESULTS: From 5437 abstracts, 1362 full-text publications were reviewed, of which 231 studies were included in the final library. Twenty-six met all criteria required to be used in the analysis, and of those, 11 independent samples from 8 publications directly contributed data to conclusions. Prevalent and consistent indicators of concussion are (1) observed and documented disorientation or confusion immediately after the event, (2) impaired balance within 1 day after injury, (3) slower reaction time within 2 days after injury, and/or (4) impaired verbal learning and memory within 2 days after injury. CONCLUSION: The results of this systematic review identify the consistent and prevalent indicators of concussion and their associations, derived from the strongest evidence in the published literature. The product is an evidence-based foundation from which to develop diagnostic criteria and prognostic indicators. ABBREVIATIONS: GCS, Glasgow Coma ScaleLOC, loss of consciousnessPCE, potential concussive eventPTA, posttraumatic amnesiaSOT, Sensory Organization TestSSD, signs, symptoms, neurologic deficits, and cognitive deficits.

Cawthon, P. M., Haslam, J., Fullman, R., Peters, K. W., Black, D., Ensrud, K. E., et al. (2014). Methods and reliability of radiographic vertebral fracture detection in older men: The osteoporotic fractures in men study. *Bone, 67C*, 152-155.

We describe the methods and reliability of radiographic vertebral fracture assessment in MrOS, a cohort of community dwelling men aged >/=65yrs. Lateral spine radiographs were obtained at Visit 1 (2000-2) and 4.6years later (Visit 2). Using a workflow tool (SpineAnalyzer, Optasia Medical), a physician reader completed semi-quantitative (SQ) scoring. Prior to SQ scoring, technicians performed "triage" to reduce physician reader workload, whereby clearly normal spine images were eliminated from SQ scoring with all levels assumed to be SQ=0 (no fracture, "triage negative"); spine images with any possible fracture or abnormality were passed to the physician reader as "triage positive" images. Using a quality assurance sample of images (n=20 participants; 8 with baseline only and 12 with baseline and follow-up images) read multiple times, we calculated intra-reader kappa statistics and percent agreement for SQ scores. A subset

of 494 participants' images was read regardless of triage classification to calculate the specificity and sensitivity of triage. Technically adequate images were available for 5958 of 5994 participants at Visit 1, and 4399 of 4423 participants at Visit 2. Triage identified 3215 (53.9%) participants with radiographs that required further evaluation by the physician reader. For prevalent fractures at Visit 1 (SQ>/=1), intra-reader kappa statistics ranged from 0.79 to 0.92; percent agreement ranged from 96.9% to 98.9%; sensitivity of the triage was 96.8% and specificity of triage was 46.3%. In conclusion, SQ scoring had excellent intra-rater reliability in our study. The triage process reduces expert reader workload without hindering the ability to identify vertebral fractures.

Cefalu, W. T., Boulton, A. J. M., Tamborlane, W. V., Moses, R. G., LeRoith, D., Greene, E. L., et al. (2014). Status of diabetes care: "it just doesn't get any better... or does it?". *Diabetes Care, 37*(7), 1782-1785.

Cetnar, J. P., & Beer, T. M. (2014). Personalizing prostate cancer therapy: The way forward. *Drug Discovery Today,*

Advances in genomic sequencing and molecular characterization are improving our understanding of the biology of prostate cancer and challenging us to translate emerging data into meaningful clinical outcomes. Several recently approved treatments for advanced prostate cancer extend survival; however, these therapies are not personalized based on predictive biomarkers. Innovative strategies for early phase drug testing that harness our growing knowledge of important prognostic markers and emerging predictive biomarkers are needed. In this review we discuss new strategies to assess drug response in early phase clinical trial testing.

Chaste, P., Sanders, S. J., Mohan, K. N., Klei, L., Song, Y., Murtha, M. T., et al. (2014). Modest impact on risk for autism spectrum disorder of rare copy number variants at 15q11.2, specifically breakpoints 1 to 2. *Autism Research, 7*(3), 355-362.

The proximal region of chromosome 15 is one of the genomic hotspots for copy number variants (CNVs). Among the rearrangements observed in this region, CNVs from the interval between the common breakpoints 1 and 2 (BP1 and BP2) have been reported cosegregating with autism spectrum disorder (ASD). Although evidence supporting an association between BP1-BP2 CNVs

and autism accumulates, the magnitude of the effect of BP1-BP2 CNVs remains elusive, posing a great challenge to recurrence-risk counseling. To gain further insight into their pathogenicity for ASD, we estimated the penetrance of the BP1-BP2 CNVs for ASD as well as their effects on ASD-related phenotypes in a well-characterized ASD sample (n=2525 families). Transmission disequilibrium test revealed significant preferential transmission only for the duplicated chromosome in probands (20T:9NT). The penetrance of the BP1-BP2 CNVs for ASD was low, conferring additional risks of 0.3% (deletion) and 0.8% (duplication). Stepwise regression analyses suggest a greater effect of the CNVs on ASD-related phenotype in males and when maternally inherited. Taken together, the results are consistent with BP1-BP2 CNVs as risk factors for autism. However, their effect is modest, more akin to that seen for common variants. To be consistent with the current American College of Medical Genetics guidelines for interpretation of postnatal CNV, the BP1-BP2 deletion and duplication CNVs would probably best be classified as variants of uncertain significance (VOUS): they appear to have an impact on risk, but one so modest that these CNVs do not merit pathogenic status. Autism Res 2014, 7: 355-362.

Cheng, Y. W., Shaffer, B. L., Nicholson, J. M., & Caughey, A. B. (2014). In reply. *Obstetrics and Gynecology, 123*(6), 1359.

Cheng, Y. W., Snowden, J. M., Handler, S., Tager, I. B., Hubbard, A., & Caughey, A. B. (2014). Clinicians' practice environment is associated with a higher likelihood of recommending cesarean deliveries. *Journal of Maternal-Fetal and Neonatal Medicine, 27*(12), 1220-1227.
Objective: Little data exist regarding clinicians' role in the rising annual incidence rate of cesarean delivery in the US. We aimed to examine if clinicians' practice environment is associated with recommending cesarean deliveries. Study design: This is a survey study of clinicians who practice obstetrics in the US. This survey included eight clinical vignettes and 27 questions regarding clinicians' practice environment. Chi-square test and multivariable logistic regression were used for statistical comparison. Results: Of 27675 survey links sent, 3646 clinicians received and opened the survey electronically, and 1555 (43%) participated and 1486 (94%) completed the survey. Clinicians were categorized into three groups based on eight common

obstetric vignettes as: more likely (n=215), average likelihood (n=1099), and less likely (n=168) to recommend cesarean. Clinician environment factors associated with a higher likelihood of recommending cesarean included Laborists/Hospitalists practice model (p<0.001), as-needed anesthesia support (p=0.003), and rural/suburban practice setting (p<0.001). Conclusion: We identified factors in clinicians' environment associated with their likelihood of recommending cesarean delivery. The decision to recommend cesarean delivery is a complicated one and is likely not solely based on patient factors.

Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., Ratnapriya, R., Edwards, A. O., et al. (2014). No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS report number 38. *Ophthalmology,*

OBJECTIVE: To determine whether genotypes at 2 major loci associated with late age-related macular degeneration (AMD), complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2), influence the relative benefits of Age-Related Eye Disease Study (AREDS) supplements. DESIGN: Unplanned retrospective evaluation of a prospective, randomized, placebo-controlled clinical trial of vitamins and minerals for the treatment of AMD. SUBJECTS: AREDS participants (mean age, 69 years) who were at risk of developing late AMD and who were randomized to the 4 arms of AREDS supplement treatment. METHODS: Analyses were performed using the Cox proportional hazards model to predict progression to late AMD (neovascular or central geographic atrophy). Statistical models, adjusted for age, gender, smoking status, and baseline AMD severity, were used to examine the influence of genotypes on the response to therapy with 4 randomly assigned arms of AREDS supplement components: placebo, antioxidants (vitamin C, vitamin E, beta-carotene), zinc or a combination. MAIN OUTCOME MEASURES: The influence of the genotype on the relative treatment response to the randomized components of the AREDS supplement, measured as progression to late AMD. RESULTS: Of the 1237 genotyped AREDS participants of white ethnicity, late AMD developed in 385 (31.1%) during the mean follow-up of 6.6 years. As previously demonstrated, CFH genotype (P = 0.005), ARMS2 (P< 0.0001), and supplement were associated individually with progression to late AMD. An interaction analysis found no evidence that the relative benefits of AREDS

supplementation varied by genotype. Analysis of (1) CFH rs1061170 and rs1410996 combined with ARMS2 rs10490924 with the 4 randomly assigned arms of AREDS supplement and (2) analysis of the combination of CFH rs412852 and rs3766405 with ARMS2 c.372_815del443ins54 with the AREDS components resulted in no interaction (P = 0.06 and P = 0.45, respectively, before multiplicity adjustment). CONCLUSIONS: The AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes at the CFH and ARMS2 loci did not statistically significantly alter the benefits of AREDS supplements. Genetic testing remains a valuable research tool, but these analyses suggest it provides no benefits in managing nutritional supplementation for patients at risk of late AMD.

Childers, R. E., Eluri, S., Vazquez, C., Weise, R. M., Bayless, T. M., & Hutfless, S. (2014). Family history of inflammatory bowel disease among patients with ulcerative colitis: A systematic review and meta-analysis. *Journal of Crohn's & Colitis,*

BACKGROUND AND AIMS: Despite numerous shared susceptibility loci between Crohn's disease and ulcerative colitis, the prevalence of family history among ulcerative colitis patients is not well-established and considered to be less prevalent. A systemic review and meta-analysis were conducted to estimate the prevalence of family history of inflammatory bowel disease in ulcerative colitis patients, and its effect on disease outcomes. METHODS: PubMED was searched to identify studies reporting the prevalence of family history of inflammatory bowel disease among ulcerative colitis patients. Definitions of family history, study type, and subtypes of family history prevalence were abstracted, as were disease outcomes including age at ulcerative colitis diagnosis, disease location, surgery and extraintestinal manifestations. Pooled prevalence estimates were calculated using random effects models. RESULTS: Seventy-one studies (86,824 patients) were included. The prevalence of a family history of inflammatory bowel disease in ulcerative colitis patients was 12% (95% confidence interval [CI] 11 to 13%; range 0-39%). Family history of ulcerative colitis (9%; 22 studies) was more prevalent than Crohn's disease (2%; 18 studies). Patients younger than 18years of age at time of diagnosis had a greater family history of inflammatory bowel disease (prevalence 15%, 95% CI: 11-20%; 13 studies). There were no differences in disease location, need for surgery, or extraintestinal manifestations among those with a family history, although very few studies reported on these outcomes.

CONCLUSIONS: Overall, 12% of ulcerative colitis patients have a family history of inflammatory bowel disease, and were more likely to have a family history of ulcerative colitis than Crohn's disease. Pediatric-onset ulcerative colitis patients were more likely to have a family history of inflammatory bowel disease.

Chiovaro, J. C. (2014). Capsule commentary on ryan et al., does it get easier to use an EHR? report from an urban regional extension center. *Journal of General Internal Medicine,*

Chou, R., Dana, T., Bougatsos, C., Blazina, I., Khangura, J., & Zakher, B. (2014). Screening for hepatitis B virus infection in adolescents and adults: A systematic review to update the U.S. preventive services task force recommendation. *Annals of Internal Medicine, 161*(1), 31-45. Background: In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against screening for hepatitis B virus (HBV) infection. Purpose: To update the 2004 USPSTF review on screening for HBV infection in adolescents and adults. Data Sources: MEDLINE (through January 2014), the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO. Study Selection: Randomized trials of screening and treatment and observational studies of screening or the association between intermediate and clinical outcomes after antiviral therapy. Data Extraction: One investigator abstracted data, and a second investigator checked them; 2 investigators independently assessed study quality. Data Synthesis: No study directly evaluated the effects of screening for HBV infection versus no screening on clinical outcomes. Vaccination against HBV infection was associated with decreased risk in high-risk populations. On the basis of 11 primarily fairquality trials, antiviral therapy may be more effective than placebo for reducing the risk for clinical outcomes associated with HBV infection. However, differences were not statistically significant. On the basis of 22 primarily fair-quality trials, antiviral therapy was more effective than placebo for various intermediate outcomes, with limited evidence that first-line antiviral agents are superior to lamivudine. Antiviral therapy was associated with a higher risk for withdrawal due to adverse events than placebo, but risk for serious adverse events did not differ. Limitation: Only English-language articles were included, clinical outcome data for antiviral therapies were limited, and several studies were done in countries where the prevalence and natural history of HBV infection differ from those of the

United States. Conclusion: Antiviral treatment for chronic HBV infection is associated with improved intermediate outcomes, but more research is needed to understand the effects of screening and subsequent interventions on clinical outcomes and to identify optimal screening strategies. © 2014 American College of Physicians.

Colao, A., Bronstein, M. D., Freda, P., Gu, F., Shen, C. C., Gadelha, M., et al. (2014). Pasireotide versus octreotide in acromegaly: A head-to-head superiority study. *The Journal of Clinical Endocrinology and Metabolism, 99*(3), 791-799.

CONTEXT: Biochemical control reduces morbidity and increases life expectancy in patients with acromegaly. With current medical therapies, including the gold standard octreotide long-acting-release (LAR), many patients do not achieve biochemical control. OBJECTIVE: Our objective was to demonstrate the superiority of pasireotide LAR over octreotide LAR in medically naive patients with acromegaly. DESIGN AND SETTING: We conducted a prospective, randomized, double-blind study at 84 sites in 27 countries. PATIENTS: A total of 358 patients with medically naive acromegaly (GH >5 mug/L or GH nadir >/=1 mug/L after an oral glucose tolerance test (OGTT) and IGF-1 above the upper limit of normal) were enrolled. Patients either had previous pituitary surgery but no medical treatment or were de novo with a visible pituitary adenoma on magnetic resonance imaging. INTERVENTIONS: Patients received pasireotide LAR 40 mg/28 days (n = 176) or octreotide LAR 20 mg/28 days (n = 182) for 12 months. At months 3 and 7, titration to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted, but not mandatory, if GH >/=2.5mug/L and/or IGF-1 was above the upper limit of normal. MAIN OUTCOME MEASURE: The main outcome measure was the proportion of patients in each treatment arm with biochemical control (GH <2.5 mug/L and normal IGF-1) at month 12. RESULTS: Biochemical control was achieved by significantly more pasireotide LAR patients than octreotide LAR patients (31.3% vs 19.2%; P = .007; 35.8% vs 20.9% when including patients with IGF-1 below the lower normal limit). In pasireotide LAR and octreotide LAR patients, respectively, 38.6% and 23.6% (P = .002) achieved normal IGF-1, and 48.3% and 51.6% achieved GH <2.5 mug/L. 31.0% of pasireotide LAR and 22.2% of octreotide LAR patients who did not achieve biochemical control did not receive the recommended dose increase. Hyperglycemia-related adverse events were more

common with pasireotide LAR (57.3% vs 21.7%). CONCLUSIONS: Pasireotide LAR demonstrated superior efficacy over octreotide LAR and is a viable new treatment option for acromegaly.

Corless, C. L. (2015). *Molecular pathology* Elsevier Inc.

Cottrell, E. K., O'Brien, K., Curry, M., Meckler, G. D., Engle, P. P., Jui, J., et al. (2014). Understanding safety in prehospital emergency medical services for children. *Prehospital Emergency Care, 18*(3), 350-358.

Objective. For over a decade, the field of medicine has recognized the importance of studying and designing strategies to prevent safety issues in hospitals and clinics. However, there has been less focus on understanding safety in prehospital emergency medical services (EMS), particularly in regard to children. Roughly 27.7 million (or 27%) of the annual emergency department visits are by children under the age of 19, and about 2 million of these children reach the hospital via EMS. This paper adds to our qualitative understanding of the nature and contributors to safety events in the prehospital emergency care of children. Methods. We conducted four 8- to 12-person focus groups among paid and volunteer EMS providers to understand 1) patient safety issues that occur in the prehospital care of children, and 2) factors that contribute to these safety issues (e.g., patient, family, systems, environmental, or individual provider factors). Focus groups were conducted in rural and urban settings. Interview transcripts were coded for overarching themes. Results. Key factors and themes identified in the analysis were grouped into categories using an ecological approach that distinguishes between systems, team, child and family, and individual provider level contributors. At the systems level, focus group participants cited challenges such as lack of appropriately sized equipment or standardized pediatric medication dosages, insufficient human resources, limited pediatric training and experience, and aspects of emergency medical services culture. EMS team level factors centered on communication with other EMS providers (both prehospital and hospital). Family and child factors included communication barriers and challenging clinical situations or scene characteristics. Finally, focus group participants highlighted a range of provider level factors, including heightened levels of anxiety, insufficient experience and training with children, and errors in assessment and decision making. Conclusions. The findings of our study suggest that, just as in

hospital medicine, factors at the systems, team, child/family, and individual provider level system contribute to errors in prehospital emergency care. These factors may be modifiable through interventions and systems improvements. Future studies are needed to ascertain the generalizability of these findings and further refine the underlying mechanisms.

Cowburn, S., Carlson, M., Lapidus, J., Heintzman, J., Bailey, S., & DeVoe, J. (2014). Insurance continuity and human papillomavirus vaccine uptake in oregon and california federally qualified health centers. *American Journal of Public Health,* , e1-e9.
Objectives. We examined the association between insurance continuity and human papillomavirus (HPV) vaccine uptake in a network of federally qualified health clinics (FQHCs). Methods. We analyzed retrospective electronic health record data for females, aged 9-26 years in 2008 through 2010. Based on electronic health record insurance coverage information, patients were categorized by percent of time insured during the study period (0%, 1%-32%, 33%-65%, 66%-99%, or 100%). We used bilevel multivariable Poisson regression to compare vaccine-initiation prevalence between insurance groups, stratified by race/ethnicity and age. We also examined vaccine series completion among initiators who had at least 12 months to complete all 3 doses. Results. Significant interactions were observed between insurance category, age, and race/ethnicity. Juxtaposed with their continuously insured peers, patients were less likely to initiate the HPV vaccine if they were insured for less than 66% of the study period, aged 13 years or older, and identified as a racial/ethnic minority. Insurance coverage was not associated with vaccine series completion. Conclusions. Disparities in vaccine uptake by insurance status were present in the FQHCs studied here, despite the fact that HPV vaccines are available to many patients regardless of ability to pay. (Am J Public Health. Published online ahead of print July 17, 2014: e1-e9. doi:10.2105/AJPH.2014.302007).

Curtis, J. R., Yang, S., Patkar, N. M., Chen, L., Singh, J. A., Cannon, G. W., et al. (2014). Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. *Arthritis Care and Research, 66*(7), 990-997.
Objective The comparative risk of infection associated with non-anti-tumor necrosis factor (anti-TNF) biologic agents is not well established. Our objective was to compare risk for hospitalized

infections between anti-TNF and non-anti-TNF biologic agents in US veterans with rheumatoid arthritis (RA). Methods Using 1998-2011 data from the US Veterans Health Administration, we studied RA patients initiating rituximab, abatacept, or anti-TNF therapy. Exposure was based upon days supplied (injections) or usual dosing intervals (infusions). Treatment episodes were defined as new biologic agent use. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for hospitalization for a bacterial infection were estimated from Cox proportional hazards models, adjusting for potential confounders. Results Among 3,152 unique RA patients contributing 4,158 biologic treatment episodes to rituximab (n = 596), abatacept (n = 451), and anti-TNF agents (n = 3,111), the patient mean age was 60 years and 87% were male. The most common infections were pneumonia (37%), skin/soft tissue (22%), urinary tract (9%), and bacteremia/sepsis (7%). Hospitalized infection rates per 100 person-years were 4.4 (95% CI 3.1-6.4) for rituximab, 2.8 (95% CI 1.7-4.7) for abatacept, and 3.0 (95% CI 2.5-3.5) for anti-TNF. Compared to etanercept, the adjusted rate of hospitalized infection was not different for adalimumab (HR 1.4, 95% CI 0.9-2.2), abatacept (HR 1.1, 95% CI 0.6-2.1), or rituximab (HR 1.4, 0.8-2.6), although it was increased for infliximab (HR 2.3, 95% CI 1.3-4.0). Infection risk was greater for those taking prednisone >7.5 mg/day (HR 1.8, 95% CI 1.3-2.7) and in the highest quartile of C-reactive protein (HR 2.3, 95% CI 1.4-3.8) and erythrocyte sedimentation rate (HR 4.1, 95% CI 2.3-7.2) compared to the lowest quartile. Conclusion In older, predominantly male US veterans with RA, the risk of hospitalized bacterial infections associated with rituximab or abatacept was similar to etanercept.

Danve, A., Perry, L., & Deodhar, A. (2014). Use of belimumab throughout pregnancy to treat active systemic lupus erythematosus-A case report. *Seminars in Arthritis and Rheumatism,* 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 Ebsteins 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.

Davenport, A. T., Grant, K. A., Szeliga, K. T., Friedman, D. P., & Daunais, J. B. (2014). Standardized method for the harvest of nonhuman primate tissue optimized for multiple modes of analyses. *Cell and Tissue Banking, 15*(1), 99-110.

Appropriate animal models are critical to conduct translational studies of human disorders without variables that can confound clinical studies. Such analytic methods as patch-clamp electrophysiological and voltammetric recordings of neurons in brain slices require living brain tissue. In order to obtain viable tissue from nonhuman primate brains, tissue collection methods must be designed to preserve cardiovascular and respiratory functions for as long as possible. This paper describes a method of necropsy that has been used in three species of monkeys that satisfies this requirement. At necropsy, animals were maintained under a deep surgical plane of anesthesia while a craniotomy was conducted to expose the brain. Following the craniotomy, animals were perfused with ice-cold, oxygenated artificial cerebrospinal fluid to displace blood and to reduce the temperature of the entire brain. The brain was removed within minutes of death and specific brain regions were immediately dissected for subsequent in vitro electrophysiology or voltammetry experiments. This necropsy method also provided for the collection of tissue blocks containing all brain regions that were immediately frozen and stored for subsequent genomic, proteomic, autoradiographic and histological studies. An added benefit from the design of this necropsy method is that all major peripheral tissues were also collected and are now being utilized in a wide range of genomic, biochemical and histological assays. This necropsy method has resulted in the establishment and growth of a nonhuman primate alcohol tissue bank

designed to distribute central nervous system and peripheral tissues to the larger scientific community. © 2013 Springer Science+Business Media Dordrecht.

Davis, S. J., Lauer, A. K., & Flaxel, C. J. (2014). Polypoidal choroidal vasculopathy in white patients. *Retina (Philadelphia, Pa.),*

PURPOSE:: To report on a series of white patients in the United States with polypoidal choroidal vasculopathy (PCV). METHODS:: This is a retrospective chart review of 27 patients at a single center with PCV. RESULTS:: The mean age was 74.3 with 48% being male. The most common presenting diagnosis was exudative age-related macular degeneration in 59%, and it took 17.5 months to diagnose PCV. During this time, patients received one antivascular endothelial growth factor injection every 1.3 months. The most common reason for suspecting PCV was a large retinal pigment epithelial detachment or a poor response to antivascular endothelial growth factor therapy. Once PCV was diagnosed, most underwent photodynamic therapy. In those who received photodynamic therapy, the fluid and/or age-related macular degeneration decreased in 86%. The vision improved in 41% with 36% maintaining stable vision. Patients received only one additional injection every 3.95 months after photodynamic therapy. CONCLUSION:: This is one of the larger series of PCV in an entirely white population. It emphasizes the importance of diagnosis in whites as PCV can masquerade as recalcitrant exudative age-related macular degeneration. Common findings were a temporal or peripapillary location and the presence of lipid. After photodynamic therapy, the patients still required antivascular endothelial growth factor therapy, but the injection burden was decreased by 67% and vision was found to be improved or maintained in 77% of patients.

DeConde, A. S., Mace, J. C., Alt, J. A., Schlosser, R. J., Smith, T. L., & Soler, Z. M. (2014). Comparative effectiveness of medical and surgical therapy on olfaction in chronic rhinosinusitis: A prospective, multi-institutional study. *International Forum of Allergy & Rhinology,*

BACKGROUND: Evidence comparing the impact of medical and surgical management of chronic rhinosinusitis on olfactory function is limited. This study evaluates olfactory outcomes in patients who failed initial medical management and elect either continued medical management or endoscopic sinus surgery (ESS) followed by medical management. METHODS: Adult subjects

were prospectively enrolled into a nonrandomized, multi-institutional cohort. Baseline characteristics, quality-of-life and objective clinical findings were collected along with 2 quality-of-life disease-specific measures, the Rhinosinusitis Disability Index (RSDI) and Sinonasal Outcome Test (SNOT-22). The primary outcome measure was the posttreatment change (>/=6 months) in the Brief Smell Identification Test (B-SIT). Bivariate and multivariate analyses compared B-SIT changes by treatment type while controlling for baseline cofactors. RESULTS: Subjects (n = 280) were enrolled between March 2011 and May 2013. Baseline B-SIT scores (mean +/- standard deviation) were comparable between medical and surgical treatment groups (8.8 +/- 3.2 vs 9.0 +/- 3.2; p = 0.703). Subjects with baseline impaired olfaction (n = 83; 29.6%) experienced B-SIT improvement in both the medical (n = 17; 2.3 +/- 2.8; p = 0.005) and surgical (n = 66; 2.1 +/- 3.0; p 0.050). CONCLUSION: Subjects electing ESS experienced gains in olfaction comparable to subjects electing continued medical management. Further study with larger sample size and more sensitive measures of olfaction are needed to determine differences between treatment groups.

Denfeld, Q. E., Mudd, J. O., Gelow, J. M., Chien, C., Hiatt, S. O., & Lee, C. S. (2014). Physical and psychological symptom biomechanics in moderate to advanced heart failure. *The Journal of Cardiovascular Nursing,*

BACKGROUND:: There is a common dissociation between objective measures and patient symptomatology in heart failure (HF). OBJECTIVE:: The aim of this study was to explore the relationship between cardiac biomechanics and physical and psychological symptoms in adults with moderate to advanced HF. METHODS:: We performed a secondary analysis of data from 2 studies of symptoms among adults with HF. Stepwise regression modeling was performed to examine the influence of cardiac biomechanics (left ventricular internal diastolic diameter, right atrial pressure [RAP], and cardiac index) on symptoms. RESULTS:: The average age of the sample (n = 273) was 57 +/- 16 years, 61% were men, and 61% had class III or IV HF. Left ventricular internal diastolic diameter (beta = 4.22 +/- 1.63, P = .011), RAP (beta = 0.71 +/- 0.28, P = .013), and cardiac index (beta = 7.11 +/- 3.19, P = .028) were significantly associated with physical symptoms. Left ventricular internal diastolic diameter (beta = 0.10 +/- 0.05, P = .038) and RAP (beta = 0.03 +/- 0.01, P = .039) were significantly associated with anxiety. There

were no significant biomechanical determinants of depression. CONCLUSION:: Cardiac biomechanics were related to physical symptoms and anxiety, providing preliminary evidence of the biological underpinnings of symptomatology among adults with HF.

Detwiller, K. Y., Schindler, J. S., Schneider, D. S., & Lindau, R. (2013). Complex adult laryngotracheal reconstruction with a prefabricated flap: A case series. *Head & Neck, 35*(12), E376-80. BACKGROUND: Laryngotracheal stenosis (LTS) can cause persistent or recurrent airway obstruction. Although there is extensive literature on surgical techniques to treat LTS at onset, there are few techniques described for complex adult LTS after failed prior airway surgery. We describe a procedure used successfully in 3 patients who required structural augmentation for complex LTS. METHODS: Patients were treated with staged reconstruction using a prefabricated composite graft consisting of auricular cartilage and a radial forearm free flap. RESULTS: All patients underwent successful reconstruction with good wound healing and are tolerating oral diets. Two patients have been successfully decannulated. CONCLUSION: A delayed prefabricated graft using auricular cartilage in a radial forearm free flap is a viable surgical intervention in patients with complex adult LTS who are not candidates for conventional approaches.

Deville, C., Chapman, C. H., Burgos, R., Hwang, W. T., Both, S., & Thomas, C. R.,Jr. (2014). Diversity by race, hispanic ethnicity, and sex of the united states medical oncology physician workforce over the past quarter century. *Journal of Oncology Practice / American Society of Clinical Oncology,*

PURPOSE: To assess the medical oncology (MO) physician workforce diversity by race, Hispanic ethnicity, and sex, with attention to trainees. METHODS: Public registries were used to assess 2010 differences among MO practicing physicians, academic faculty, and fellows; internal medicine (IM) residents; and the US population, using binomial tests with $P < .001$ significance adjusting for multiple comparisons. Significant changes in fellow representation from 1986 to 2011 were assessed. RESULTS: Female representation as MO fellows (45.0%) was significantly increased compared with faculty (22.4%) and practicing physicians (27.4%); was no different than IM residents (44.7%, $P = .853$); and increased significantly, by 1.0% per year. Women were significantly underrepresented as practicing physicians, faculty, and fellows compared with

the US population (50.8%). Traditionally underrepresented minorities in medicine (URM) were significantly underrepresented as practicing physicians (7.8%), faculty (5.7%), and fellows (10.9%), versus US population (30.0%). Hispanic MO fellows (7.5%) were increased compared with faculty (3.9%) and practicing physicians (4.1%); Black fellows (3.1%) were no different than faculty (1.8%, P = .0283) or practicing physicians (3.5%, P = .443). When comparing MO fellows versus IM residents, there were no differences for American Indians/Alaska Natives/Native Hawaiians/Pacific Islanders (0.3%, 0.6%, respectively, P = .137) and Hispanics (7.5%, 8.7%, P = .139), unlike Blacks (3.1%, 5.6%, P < .001). There has been no significant change in URM representation, with negligible changes every 5 years for American Indians/Alaska Natives/Native Hawaiians/Pacific Islanders (-0.1%), Blacks (-0.3%), and Hispanics (0.3%). CONCLUSIONS: Female fellow representation increased 1% per year over the quarter century indicating historical gains, whereas URM diversity remains unchanged. For Blacks alone, representation as MO fellows is decreased compared with IM residents, suggesting greater disparity in MO training.

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2014). Focus article report of the NIH task force on research standards for chronic low back pain. *The Clinical Journal of Pain, 30*(8), 701-712.

BACKGROUND: Despite rapidly increasing intervention, functional disability due to chronic low back pain (cLBP) has increased in recent decades. We often cannot identify mechanisms to explain the major negative impact cLBP has on patients' lives. Such cLBP is often termed non-specific and may be due to multiple biologic and behavioral etiologies. Researchers use varied inclusion criteria, definitions, baseline assessments, and outcome measures, which impede comparisons and consensus. METHODS: The NIH Pain Consortium therefore charged a Research Task Force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel developed a 3-stage process, each with a 2-day meeting. RESULTS: The panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimum dataset to describe research participants (drawing heavily on the PROMIS methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain

Consortium has approved the recommendations, which investigators should incorporate into NIH grant proposals. CONCLUSIONS: The RTF believes these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of chronic low back pain. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes. We expect that the RTF recommendations will become a dynamic document and undergo continual improvement.

Deyo, R. A., Jarvik, J. G., & Chou, R. (2014). Low back pain in primary care. *BMJ (Clinical Research Ed.), 349*, g4266.

Dhar, M., Wayman, G. A., Zhu, M., Lambert, T. J., Davare, M. A., & Appleyard, S. M. (2014). Leptin-induced spine formation requires TrpC channels and the CaM kinase cascade in the hippocampus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(30), 10022-10033.

Leptin is a critical neurotrophic factor for the development of neuronal pathways and synaptogenesis in the hypothalamus. Leptin receptors are also found in other brain regions, including the hippocampus, and a postnatal surge in leptin correlates with a time of rapid growth of dendritic spines and synapses in the hippocampus. Leptin is critical for normal hippocampal dendritic spine formation as db/db mice, which lack normal leptin receptor signaling, have a reduced number of dendritic spines in vivo. Leptin also positively influences hippocampal behaviors, such as cognition, anxiety, and depression, which are critically dependent on dendritic spine number. What is not known are the signaling mechanisms by which leptin initiates spine formation. Here we show leptin induces the formation of dendritic protrusions (thin headless, stubby and mushroom shaped spines), through trafficking and activation of TrpC channels in cultured hippocampal neurons. Leptin-activation of the TrpC current is dose dependent and blocked by targeted knockdown of the leptin receptor. The nonselective TrpC channel inhibitors SKF96365 and 2-APB or targeted knockdown of TrpC1 or 3, but not TrpC5, channels also eliminate the leptin-induced current. Leptin stimulates the phosphorylation of CaMKIgamma and beta-Pix within 5 min and their activation is required for leptin-induced trafficking of TrpC1 subunits to the membrane. Furthermore, we show that CaMKIgamma, CaMKK, beta-Pix, Rac1,

and TrpC1/3 channels are all required for both the leptin-sensitive current and leptin-induced spine formation. These results elucidate a critical pathway underlying leptin's induction of dendritic morphological changes that initiate spine and excitatory synapse formation.

Dhar, M., Zhu, M., Impey, S., Lambert, T. J., Bland, T., Karatsoreos, I. N., et al. (2014). Leptin induces hippocampal synaptogenesis via CREB-regulated MicroRNA-132 suppression of p250GAP. *Molecular Endocrinology, 28*(7), 1073-1087.

Leptin acts in the hippocampus to enhance cognition and reduce depression and anxiety. Cognitive and emotional disorders are associated with abnormal hippocampal dendritic spine formation and synaptogenesis. Although leptin has been shown to induce synaptogenesis in the hypothalamus, its effects on hippocampal synaptogenesis and the mechanism(s) involved are not well understood. Here we show that leptin receptors (LepRs) are critical for hippocampal dendritic spine formation in vivo because db/db mice lacking the long form of the leptin receptor (LepRb) have reduced spine density on CA1 and CA3 neurons. Leptin promotes the formation of mature spines and functional glutamate synapses on hippocampal pyramidal neurons in both dissociated and slice cultures. These effects are blocked by short hairpin RNAs specifically targeting the LepRb and are absent in cultures from db/db mice. Activation of the LepR leads to cAMP response element-binding protein (CREB) phosphorylation and initiation of CREB-dependent transcription via the MAPK kinase/Erk pathway. Furthermore, both Mek/Erk and CREB activation are required for leptin-induced synaptogenesis. Leptin also increases expression of microRNA-132 (miR132), a well-known CREB target, which is also required for leptin-induced synaptogenesis. Last, leptin suppresses the expression of p250GAP, a miR132 target, and this suppression is obligatory for leptin's effects as is the downstream target of p250GAP, Rac1. LepRs appear to be critical in vivo as db/db mice have lowered hippocampal miR132 levels and elevated p250GAP expression. In conclusion, we identify a novel signaling pathway by which leptin increases synaptogenesis through inducing CREB transcription and increasing microRNA-mediated suppression of p250GAP activity, thus removing a known inhibitor of Rac1-stimulated synaptogenesis.

Didier, R. A., Vajtai, P. L., & Hopkins, K. L. (2014). Iterative reconstruction technique with reduced volume CT dose index: Diagnostic accuracy in pediatric acute appendicitis. *Pediatric Radiology,* BACKGROUND: Iterative reconstruction technique has been proposed as a means of reducing patient radiation dose in pediatric CT. Yet, the effect of such reductions on diagnostic accuracy has not been thoroughly evaluated. OBJECTIVE: This study compares accuracy of diagnosing pediatric acute appendicitis using contrast-enhanced abdominopelvic CT scans performed with traditional pediatric weight-based protocols and filtered back projection reconstruction vs. a filtered back projection/iterative reconstruction technique blend with reduced volume CT dose index (CTDIvol). MATERIALS AND METHODS: Results of pediatric contrast-enhanced abdominopelvic CT scans done for pain and/or suspected appendicitis were reviewed in two groups: A, 192 scans performed with the hospital's established weight-based CT protocols and filtered back projection reconstruction; B, 194 scans performed with iterative reconstruction technique and reduced CTDIvol. Reduced CTDIvol was achieved primarily by reductions in effective tube current-time product (mAseff) and tube peak kilovoltage (kVp). CT interpretation was correlated with clinical follow-up and/or surgical pathology. CTDIvol, size-specific dose estimates (SSDE) and performance characteristics of the two CT techniques were then compared. RESULTS: Between groups A and B, mean CTDIvol was reduced by 45%, and mean SSDE was reduced by 46%. Sensitivity, specificity and diagnostic accuracy were 96%, 97% and 96% in group A vs. 100%, 99% and 99% in group B. CONCLUSION: Accuracy in diagnosing pediatric acute appendicitis was maintained in contrast-enhanced abdominopelvic CT scans that incorporated iterative reconstruction technique, despite reductions in mean CTDIvol and SSDE by nearly half as compared to the hospital's traditional weight-based protocols.

Dietz, M., Kram, D., & Burton, C. (2014). Newborn with bleeding left hand mass. *Neoreviews, 15*(7), e308-e310.

Dodge, H. H., Zhu, J., Harvey, D., Saito, N., Silbert, L. C., Kaye, J. A., et al. (2014). Biomarker progressions explain higher variability in stage-specific cognitive decline than baseline values in alzheimer disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association,* BACKGROUND: It is unknown which commonly used Alzheimer disease (AD) biomarker values-

baseline or progression-best predict longitudinal cognitive decline. METHODS: 526 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI composite memory and executive scores were the primary outcomes. Individual-specific slope of the longitudinal trajectory of each biomarker was first estimated. These estimates and observed baseline biomarker values were used as predictors of cognitive declines. Variability in cognitive declines explained by baseline biomarker values was compared with variability explained by biomarker progression values. RESULTS: About 40% of variability in memory and executive function declines was explained by ventricular volume progression among mild cognitive impairment patients. A total of 84% of memory and 65% of executive function declines were explained by fluorodeoxyglucose positron emission tomography (FDG-PET) score progression and ventricular volume progression, respectively, among AD patients. CONCLUSIONS: For most biomarkers, biomarker progressions explained higher variability in cognitive decline than biomarker baseline values. This has important implications for clinical trials targeted to modify AD biomarkers.

Donahue, J. J., Goranson, A. C., McClure, K. S., & Van Male, L. M. (2014). Emotion dysregulation, negative affect, and aggression: A moderated, multiple mediator analysis. *Personality and Individual Differences, 70*, 23-28.

Research on violence has highlighted the role of trait negative affect in reactive aggressive behavior. Emotion dysregulation is a multidimensional construct reflecting maladaptive ways in which a person experiences and responds to emotional states, and has also been empirically linked to aggression. This study sought to test the hypothesis that multiple facets of emotion dysregulation would mediate the relationship between negative affect and physical aggression in a nonclinical sample. An additional aim was to examine the moderating effect of sex in the relationship between negative affect and aggression, and whether mediators differ as a function of sex. Three-hundred and eighteen participants completed measures of physical aggression, difficulties in emotion regulation, and negative affect. Results showed that sex moderated the relationship between negative affect and physical aggression, and emotion dysregulation fully mediated the relationship between these variables in both males and females. While difficulty inhibiting impulsive behavior when distressed was a significant mediator across sexes, difficulties with emotional awareness demonstrated a mediation effect only in males. Findings provide

preliminary support for the facets of emotion dysregulation that are important in understanding the negative affect - physical aggression association in males and females. © 2014.

Doss, A., & Pereira, L. (2014). Strip of the month: July 2014. *Neoreviews, 15*(7), e299-e307.

Duke, J. W., Elliott, J. E., Laurie, S. S., Beasley, K. M., Mangum, T. S., Hawn, J. A., et al. (2014). Pulmonary gas exchange efficiency during exercise breathing normoxic and hypoxic gas in adults born very preterm with low diffusion capacity. *Journal of Applied Physiology (Bethesda, Md.: 1985),*

Adults with a history of very preterm birth (<32 weeks gestational age; PRET) have reduced lung function and significantly lower lung diffusion capacity for carbon monoxide (DLCO) relative to individuals born at term (CONT). Low DLCO may predispose PRET to diffusion limitation during exercise, particularly while breathing hypoxic gas because a of reduced O2 driving gradient and pulmonary capillary transit time. We hypothesized that PRET would have significantly worse pulmonary gas exchange efficiency [i.e. increased alveolar-to-arterial PO2 difference (AaDO2)] during exercise breathing room air or hypoxic gas (FIO2 = 0.12) compared to CONT. To test this hypothesis, we compared the AaDO2 in PRET (n = 13) with a clinically mild reduction in DLCO (72 +/- 7% of predicted) and CONT (n = 14) with normal DLCO (105 +/- 10% of predicted) pre- and during exercise breathing room air and hypoxic gas. Measurements of temperature-corrected arterial blood gases, and direct measure of O2 saturation (SaO2) were made prior to and during exercise at 25, 50, and 75% of VO2peak while breathing room air and hypoxic gas. In addition to DLCO, pulmonary function, and exercise capacity were significantly less in PRET. Despite PRET having low DLCO, no differences were observed in the AaDO2 or SaO2 pre- or during exercise breathing room air or hypoxic gas compared to CONT. Although our findings were unexpected, we conclude that reduced pulmonary function and low DLCO resulting from very preterm birth does not cause a measureable reduction in pulmonary gas exchange efficiency.

Durham, C. F., Cato, M. L., & Lasater, K. (2014). NLN/Jeffries simulation framework state of the science project: Participant construct. *Clinical Simulation in Nursing, 10*(7), 363-372.

Background: The initial Jeffries Simulation Framework was developed by Jeffries and Rogers in 2007 to guide the evolving simulation-based education. This framework identified five constructs:

student, teacher, educational practices, simulation design characteristics, and outcomes. In 2011, the International Nursing Association for Clinical Simulation and Learning assembled a panel of simulation experts to review the literature to establish evidence for each of the framework constructs. This report summarizes the findings of the research about the simulation student construct and the rationale for expanding the label from student to participant. Method: A database was used to collate literature citations and findings to identify who participates in simulation and their associated characteristics. Preliminary findings were presented at the 2012 International Nursing Association for Clinical Simulation and Learning (INACSL) annual conference and feedback from attendees was solicited. The team then summarized the findings and considered the attendee comments. Results: Findings from the literature suggest that the construct be changed from student to participant. This article used current literature and expertise to expand the original participant descriptors to four elements: demographics, roles/responsibilities, attributes, and values. The paper further presents characteristics for each element. Conclusion: It was notable that the participants in simulation were seldom the focus of the literature. Early on, it became evident that there was no consistency about what the participants in the simulation were called or what their roles were. The broadening of the term from student to participant allowed for the inclusion of the range of individuals involved in simulation. Standardization of terminology will provide more consistency, improving descriptions, and reporting of simulation activities in the literature.

Eastwood, E. C., Barkley-Levenson, A. M., & Phillips, T. J. (2014). Methamphetamine drinking microstructure in mice bred to drink high or low amounts of methamphetamine. *Behavioural Brain Research, 272C*, 111-120.

Genetic factors likely influence individual sensitivity to positive and negative effects of methamphetamine (MA) and risk for MA dependence. Genetic influence on MA consumption has been confirmed by selectively breeding mouse lines to consume high (MAHDR) or low (MALDR) amounts of MA, using a two-bottle choice MA drinking (MADR) procedure. Here, we employed a lickometer system to characterize the microstructure of MA (20, 40, and 80mg/l) and water intake in MAHDR and MALDR mice in 4-h limited access sessions, during the initial 4hours of the

dark phase of their 12:12h light:dark cycle. Licks at one-minute intervals and total volume consumed were recorded, and bout analysis was performed. MAHDR and MALDR mice consumed similar amounts of MA in mg/kg on the first day of access, but MAHDR mice consumed significantly more MA than MALDR mice during all subsequent sessions. The higher MA intake of MAHDR mice was associated with a larger number of MA bouts, longer bout duration, shorter interbout interval, and shorter latency to the first bout. In a separate 4-h limited access MA drinking study, MALDR and MAHDR mice had similar blood MA levels on the first day MA was offered, but MAHDR mice had higher blood MA levels on all subsequent days, which corresponded with MA intake. These data provide insight into the microstructure of MA intake in an animal model of differential genetic risk for MA consumption, which may be pertinent to MA use patterns relevant to genetic risk for MA dependence.

Eichenfield, L. F., Tom, W. L., Berger, T. G., Krol, A., Paller, A. S., Schwarzenberger, K., et al. (2014). Guidelines of care for the management of atopic dermatitis: Section 2. management and treatment of atopic dermatitis with topical therapies. *Journal of the American Academy of Dermatology, 71*(1), 116-132.

Atopic dermatitis is a common and chronic, pruritic inflammatory skin condition that can affect all age groups. This evidence-based guideline addresses important clinical questions that arise in its management. In this second of 4 sections, treatment of atopic dermatitis with nonpharmacologic interventions and pharmacologic topical therapies are reviewed. Where possible, suggestions on dosing and monitoring are given based on available evidence.

Elbogen, E. B., Cueva, M., Wagner, H. R., Sreenivasan, S., Brancu, M., Beckham, J. C., et al. (2014). Screening for violence risk in military veterans: Predictive validity of a brief clinical tool. *American Journal of Psychiatry, 171*(7), 749-757.

Objective: Violence toward others is a serious problem among a subset of military veterans. The authors evaluated the predictive validity of a brief decision support tool to screen veterans for problems with violence and identify potential candidates for a comprehensive risk assessment. Method: Data on risk factors at an initial wave and on violent behavior at 1-year follow-up were

collected in two independent sampling frames: a national randomsample survey of 1,090 Iraq and Afghanistan veterans and in-depth assessments of 197 dyads of veterans and collateral informants. Risk factors (lacking money for basic needs, combat experience, alcohol misuse, history of violence and arrests, and anger associated with posttraumatic stress disorder) were chosen based on empirical support in published research. Scales measuring these risk factors were examined, and items with the most robust statistical association with outcomeswere selected for the screening tool. Regression analyses were used to derive receiver operating characteristic curves of sensitivities and specificities, with area under the curve providing an index of predictive validity. Results: The resultant 5-item screening tool, called the Violence Screening and Assessment of Needs (VIO-SCAN), yielded area-under-the-curve statistics ranging from 0.74 to 0.78 for the national survey and from 0.74 to 0.80 for the in-depth assessments, depending on level of violence analyzed. Conclusions: Although the VIO-SCAN does not constitute a comprehensive violence risk assessment and cannot replace fully informed clinical decision making, it is hoped that the screen will provide clinicians with a rapid, systematic method for identifying veterans at higher risk of violence, prioritizing those in need a full clinical workup, structuring review of empirically supported risk factors, and developing plans collaboratively with veterans to reduce risk and increase successful reintegration in the community.

Ensrud, K. E., Taylor, B. C., Peters, K. W., Gourlay, M. L., Donaldson, M. G., Leslie, W. D., et al. (2014). Implications of expanding indications for drug treatment to prevent fracture in older men in united states: Cross sectional and longitudinal analysis of prospective cohort study. *BMJ (Clinical Research Ed.), 349*, g4120.

OBJECTIVES: To quantify incremental effects of applying different criteria to identify men who are candidates for drug treatment to prevent fracture and to examine the extent to which fracture probabilities vary across distinct categories of men defined by these criteria. DESIGN: Cross sectional and longitudinal analysis of a prospective cohort study. SETTING: Multicenter Osteoporotic Fractures in Men (MrOS) study in the United States. PARTICIPANTS: 5880 untreated community dwelling men aged 65 years or over classified into four distinct groups: osteoporosis by World Health Organization criteria alone; osteoporosis by National Osteoporosis Foundation (NOF) but not WHO criteria; no osteoporosis but at high fracture risk (at or above NOF derived

FRAX intervention thresholds recommended for US); and no osteoporosis and at low fracture risk (below NOF derived FRAX intervention thresholds recommended for US). MAIN OUTCOME MEASURES: Proportion of men identified for drug treatment; predicted 10 year probabilities of hip and major osteoporotic fracture calculated using FRAX algorithm with femoral neck bone mineral density; observed 10 year probabilities for confirmed incident hip and major osteoporotic (hip, clinical vertebral, wrist, or humerus) fracture events calculated using cumulative incidence estimation, accounting for competing risk of mortality. RESULTS: 130 (2.2%) men were identified as having osteoporosis by using the WHO definition, and an additional 422 were identified by applying the NOF definition (total osteoporosis prevalence 9.4%). Application of NOF derived FRAX intervention thresholds led to 936 (15.9%) additional men without osteoporosis being identified as at high fracture risk, raising the total prevalence of men potentially eligible for drug treatment to 25.3%. Observed 10 year hip fracture probabilities were 20.6% for men with osteoporosis by WHO criteria alone, 6.8% for men with osteoporosis by NOF (but not WHO) criteria, 6.4% for men without osteoporosis but classified as at high fracture risk, and 1.5% for men without osteoporosis and classified as at low fracture risk. A similar pattern was noted in observed fracture probabilities for major osteoporotic fracture. Among men with osteoporosis by WHO criteria, observed fracture probabilities were greater than FRAX predicted probabilities (20.6% v 9.5% for hip fracture and 30.0% v 17.4% for major osteoporotic fracture). CONCLUSIONS AND RELEVANCE: Choice of definition of osteoporosis and use of NOF derived FRAX intervention thresholds have major effects on the proportion of older men identified as warranting drug treatment to prevent fracture. Among men identified with osteoporosis by WHO criteria, who comprised 2% of the study population, actual observed fracture probabilities during 10 years of follow-up were highest and exceeded FRAX predicted fracture probabilities. On the basis of findings from randomized trials in women, these men are most likely to benefit from treatment. Expanding indications for treatment beyond this small group has uncertain value owing to lower observed fracture probabilities and uncertain benefits of treatment among men not selected on the basis of WHO criteria.

Estep, R. D., Rawlings, S. D., Li, H., Manoharan, M., Blaine, E. T., O'Connor, M. A., et al. (2014). The rhesus rhadinovirus CD200 homologue affects immune responses and viral loads during in vivo

infection. *Journal of Virology,*

Rhesus macaque rhadinovirus (RRV) is a gamma-herpesvirus of rhesus macaque (RM) monkeys that is closely related to human herpesvirus 8 (HHV-8)/Kaposi's Sarcoma-associated herpesvirus (KSHV), and is capable of inducing diseases in SIV-infected RM that are similar to those seen in humans co-infected with HIV and HHV-8. Both HHV-8 and RRV encode viral CD200 molecules that are homologues of cellular CD200, a membrane glycoprotein that regulates immune responses and helps maintain immune homeostasis via interactions with CD200 receptor (CD200R). Though the functions of RRV and HHV-8 vCD200 molecules have been examined in vitro, the precise roles that these viral proteins play during in vivo infection remain unknown. Thus, to address the contributions of RRV vCD200 to immune regulation and disease in vivo, we generated a form of RRV lacking expression of vCD200 for use in infection studies in RM. Our data indicate that RRV vCD200 expression limits immune responses against RRV at early times post-infection and also impacts viral loads, but does not appear to have significant effects on disease development. Further, examination of the distribution pattern of CD200R in RM indicates that this receptor is expressed on a majority of cells in PBMC, including B and T cells, suggesting potentially wider regulatory capabilities for both vCD200 and CD200 that are not strictly limited to myeloid lineage cells. In addition, we also demonstrate that RRV infection affects CD200R expression levels in vivo, although vCD200 expression does not play a role in this phenomenon. IMPORTANCE: Cellular CD200 and its receptor CD200R compose a pathway that is important in regulating immune responses, and is known to play a role in a variety of human diseases. A number of pathogens have been found to modulate the CD200-CD200R pathway during infection, including human herpesvirus 8 (HHV-8), the causative agent of Kaposi's sarcoma and B cell neoplasms in AIDS patients, and a closely related primate virus, rhesus macaque rhadinovirus (RRV), which infects and induces disease in rhesus macaque monkeys. HHV-8 and RRV encode homologues of CD200, termed vCD200, which are thought to play a role in preventing immune responses against these viruses. However, neither molecule has been studied in an in vivo model of infection to address their actual contributions to immunoregulation and disease. Here we report findings from our studies analyzing the properties of a mutant form of RRV lacking vCD200 expression in infected rhesus macaques.

Feeny, A., Han, L., & Tereshchenko, L. G. (2014). Repolarization lability measured on 10-second ECG by spatial TT' angle: Reproducibility and agreement with QT variability. *Journal of Electrocardiology,*

BACKGROUND: Reproducibility of spatial TT' angle on the 10-second ECG and its agreement with QT variability has not been previously studied. METHODS: We analyzed 2 randomly selected 10-second segments within 3-minute resting orthogonal ECG in 172 healthy IDEAL study participants (age 38.1+/-15.2years, 50% male, 94% white). Repolarization lability was measured by the QT variance (QTV), short-term QT variability (STV(QT)), and spatial TT' angle. Bland-Altman analysis was used to assess the agreement between different log-transformed metrics of repolarization lability, and to assess the reproducibility. RESULTS: The heart rate showed a very high reproducibility (bias 0.14%, Lin's rho_c=0.99). As expected, noise suppression by averaging improves reproducibility. Agreement between two 10-second LogQTV was poor (bias -0.04; 95% limits of agreement [-1.89; 1.81]), while LogSTV(QT) (0.04 [-1.01; 1.10]), and especially LogTT' angle (-0.009 [-0.84; 0.82]) was better. CONCLUSION: TT' angle is a satisfactory reproducible metric of repolarization lability on the 10-second ECG.

Feng, S., Weaver, D. L., Carney, P. A., M Reisch, L., M Geller, B., Goodwin, A., et al. (2014). A framework for evaluating diagnostic discordance in pathology discovered during research studies. *Archives of Pathology & Laboratory Medicine, 138*(7), 955-961.

Context.-Little is known about the frequency of discordant diagnoses identified during research. Objective.-To describe diagnostic discordance identified during research and apply a newly designed research framework for investigating discordance. Design.-Breast biopsy cases (N = 407) from registries in Vermont and New Hampshire were independently reviewed by a breast pathology expert. The following research framework was developed to assess those cases: (1) compare the expert review and study database diagnoses, (2) determine the clinical significance of diagnostic discordance, (3) identify and correct data errors and verify the existence of true diagnostic discrepancies, (4) consider the impact of borderline cases, and (5) determine the notification approach for verified disagreements. Results.-Initial overall discordance between the original diagnosis recorded in our research database and a breast pathology expert was 32.2% (131 of 407). This was reduced to less than 10% after following the 5-step research framework.

Detailed review identified 12 cases (2.9%) with data errors (2 in the underlying pathology registry, 3 with incomplete slides sent for expert review, and 7 with data abstraction errors). After excluding the cases with data errors, 38 cases (9.6%) among the remaining 395 had clinically meaningful discordant diagnoses (kappa = 0.82; SE, 0.04; 95% confidence interval, 0.76-0.87). Among these 38 cases, 20 (53%) were considered borderline between 2 diagnoses by either the original pathologist or the expert. We elected to notify the pathology registries and facilities regarding discordant diagnoses. Conclusions.-Understanding the types and sources of diagnostic discordance uncovered in research studies may lead to improved scientific data and better patient care.

Fleseriu, M. (2014). Advances in the pharmacotherapy of patients with acromegaly. *Discovery Medicine, 17*(96), 329-338.

Acromegaly is a disease characterized by growth hormone (GH) excess originating, in approximately 95% of cases, from a somatotroph pituitary adenoma. Symptomatology and clinical features are due to GH and insulin-like growth factor 1 excess; unfortunately, for most patients diagnosis is delayed by several years. Acromegaly patients' morbidity and mortality are higher than those of the normal population. However, with adequate biochemical control mortality rates can be restored to normal. Tumor size and location, symptoms, comorbidities, and lastly, but not least, patient preference, are all important aspects in treatment decision making, and treatment approach should be individualized. Current therapy includes medical, surgical, and radiation. This review focuses on recent significant developments in medical therapy. There are three major therapeutic drug classes: somatostatin receptor ligands (SRLs), which represent the mainstay of medical therapy, GH receptor blockers, and dopamine agonists. Multi-ligand receptor SRLs such as pasireotide, should increase therapeutic choices for acromegaly patients currently uncontrolled on available SRLs. Furthermore, significant research has been focused in the development of novel delivery modalities (e.g., oral and long acting subcutaneous administration).

Fleseriu, M., Findling, J. W., Koch, C. A., Schlaffer, S. M., Buchfelder, M., & Gross, C. (2014). Changes in plasma ACTH levels and corticotroph tumor size in patients with cushing's disease during long-

term treatment with the glucocorticoid receptor antagonist mifepristone. *The Journal of Clinical Endocrinology and Metabolism,* , jc20141843.

Context: Pituitary effects of long-term therapy with mifepristone, a glucocorticoid receptor antagonist, in Cushing's disease (CD) patients are not well understood. Objective: Report changes in adrenocorticotropic hormone (ACTH) and pituitary magnetic resonance imaging (MRI) findings during long-term use of mifepristone in CD patients. Design and Setting: SEISMIC, a 24-week, open-label study of mifepristone and its long-term extension (LTE) multicenter US study. Patients: Forty-three CD patients (mean age 45.3y) who were enrolled in SEISMIC with 27 continuing into the LTE study. Interventions: Mifepristone 300-1200mg once daily. Main outcome measures: ACTH and pituitary MRI were assessed at baseline and at regular intervals during treatment. Results: A >/=2-fold increase in ACTH was observed in 72% of patients treated for median duration of 11.3 months. The mean peak increase in ACTH was 2.76+/-1.65 fold during SEISMIC and mean ACTH concentrations remained stable during the LTE. ACTH was directly correlated with mifepristone dose and declined to near baseline levels after mifepristone discontinuation. Tumor regressed in 2 patients, and progressed in 3 patients with macroadenomas. An additional microadenoma was identified after 25 months of treatment following a baseline tumor-negative MRI. Conclusions: In the largest prospective study to date, long-term mifepristone treatment increased ACTH in approximately 2/3 of patients with CD. ACTH elevations were observed within the first few weeks of treatment, were dose-dependent, and generally remained stable over time. Corticotroph tumor progression and regression may occur over time, but patients may have significant increases in ACTH levels without evidence of tumor growth.

Fornetti, J., Martinson, H. A., Betts, C. B., Lyons, T. R., Jindal, S., Guo, Q., et al. (2014). Mammary gland involution as an immunotherapeutic target for postpartum breast cancer. *Journal of Mammary Gland Biology and Neoplasia,*

Postpartum mammary gland involution has been identified as tumor-promotional and is proposed to contribute to the increased rates of metastasis and poor survival observed in postpartum breast cancer patients. In rodent models, the involuting mammary gland microenvironment is sufficient to induce enhanced tumor cell growth, local invasion, and metastasis. Postpartum

involution shares many attributes with wound healing, including upregulation of genes involved in immune responsiveness and infiltration of tissue by immune cells. In rodent models, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) ameliorates the tumor-promotional effects of involution, consistent with the immune milieu of the involuting gland contributing to tumor promotion. Currently, immunotherapy is being investigated as a means of breast cancer treatment with the purpose of identifying ways to enhance anti-tumor immune responses. Here we review evidence for postpartum mammary gland involution being a uniquely defined 'hot-spot' of pro-tumorigenic immune cell infiltration, and propose that immunotherapy should be explored for prevention and treatment of breast cancers that arise in this environment. © 2014 Springer Science+Business Media New York.

Franasiak, J. M., Burns, K. A., Slayden, O., Yuan, L., Fritz, M. A., Korach, K. S., et al. (2014). Endometrial CXCL13 expression is cycle regulated in humans and aberrantly expressed in humans and rhesus macaques with endometriosis. *Reproductive Sciences (Thousand Oaks, Calif.),*

C-X-C ligand 13 (CXCL13), a regulator of mucosal immunity, is secreted by human endometrial epithelium and may be involved in embryo implantation. However, cyclic expression of human endometrial CXCL13 in health and disease is not well studied. This study examines cycle stage-specific endometrial CXCL13 expression in normal humans when compared to those with biopsy-confirmed, stage 1 to 4 endometriosis using real-time reverse transcriptase, real-time polymerase chain reaction and immunohistochemistry. Eutopic endometrial CXCL13 expression was also compared between normal, control Rhesus macaques, and macaques with advanced endometriosis. In healthy women, CXLC13 messenger RNA expression was minimal in the proliferative phase and maximal in the secretory phase. However, in the presence of endometriosis, proliferative-phase endometrial expression markedly increased in both humans and rhesus subjects ($P < .05$). The cross-species and cross-stage concordance suggests a pathophysiologic role for CXCL13 in endometriosis and its use as a biomarker for disease.

Friedly, J. L., Comstock, B. A., Turner, J. A., Heagerty, P. J., Deyo, R. A., Sullivan, S. D., et al. (2014). A randomized trial of epidural glucocorticoid injections for spinal stenosis. *New England Journal of*

Medicine, 371(1), 11-21.

BACKGROUND: Epidural glucocorticoid injections are widely used to treat symptoms of lumbar spinal stenosis, a common cause of pain and disability in older adults. However, rigorous data are lacking regarding the effectiveness and safety of these injections. METHODS: In a double-blind, multisite trial, we randomly assigned 400 patients who had lumbar central spinal stenosis and moderate-to-severe leg pain and disability to receive epidural injections of glucocorticoids plus lidocaine or lidocaine alone. The patients received one or two injections before the primary outcome evaluation, performed 6 weeks after randomization and the first injection. The primary outcomes were the score on the Roland-Morris Disability Questionnaire (RMDQ, in which scores range from 0 to 24, with higher scores indicating greater physical disability) and the rating of the intensity of leg pain (on a scale from 0 to 10, with 0 indicating no pain and 10 indicating "pain as bad as you can imagine"). RESULTS: At 6 weeks, there were no significant between-group differences in the RMDQ score (adjusted difference in the average treatment effect between the glucocorticoid-lidocaine group and the lidocaine-alone group, -1.0 points; 95% confidence interval [CI], -2.1 to 0.1; P = 0.07) or the intensity of leg pain (adjusted difference in the average treatment effect, -0.2 points; 95% CI, -0.8 to 0.4; P = 0.48). A prespecified secondary subgroup analysis with stratification according to type of injection (interlaminar vs. transforaminal) likewise showed no significant differences at 6 weeks. CONCLUSIONS: In the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone. Copyright © 2014 Massachusetts Medical Society.

Furuno, J. P., Noble, B. N., Horne, K. N., McGregor, J. C., Elman, M. R., Bearden, D. T., et al. (2014). Frequency of outpatient antibiotic prescription on discharge to hospice care. *Antimicrobial Agents and Chemotherapy,*

Antibiotic use is common in hospice care despite limited evidence that it improves symptoms or quality of life. Patients receiving antibiotics on hospital discharge may be more likely to continue use following transition to hospice care despite a shift in goals of care. We quantified the frequency and characteristics for receiving a prescription for antibiotics on discharge from acute care to hospice care. This was a cross-sectional study among adult (age>/=18 years) inpatients

discharged to hospice care from Oregon Health & Science University (OHSU) from 1/1/2010-12/31/2012. Data were collected from an electronic data repository and from the Department of Care Management. Among 62,792 discharges, 845 (1.3%) patients were discharged directly to hospice care (60.0% home and 40.0% inpatient). Most patients discharged to hospice were >65 years old (50.9%), male (54.6%), and had a length of hospital stay </=7 days (56.6%). Prevalence of antibiotic prescription upon discharge to hospice was 21.1%. Among patients discharged with an antibiotic prescription, 71.8% had a documented infection during their index admission. Among documented infections, 40.3% were bloodstream infections, septicemia, or endocarditis and 38.9% were pneumonia. Independent risk factors for receiving an antibiotic prescription were documented infection during the index admission (adjusted odds ratio (AOR)=7.00, 95% confidence interval (CI)=4.68 to 10.46), discharge to home hospice care (AOR=2.86, 95% CI=1.92 to 4.28), and having a cancer diagnosis (AOR=2.19, 95% CI=1.48 to 3.23). These data suggest that a high proportion of patients discharged from acute care to hospice care receive an antibiotic prescription upon discharge.

Gallun, F. J., McMillan, G. P., Molis, M. R., Kampel, S. D., Dann, S. M., & Konrad-Martin, D. L. (2014). Relating age and hearing loss to monaural, bilateral, and binaural temporal sensitivity. *Frontiers in Neuroscience, 8*, 172.

Older listeners are more likely than younger listeners to have difficulties in making temporal discriminations among auditory stimuli presented to one or both ears. In addition, the performance of older listeners is often observed to be more variable than that of younger listeners. The aim of this work was to relate age and hearing loss to temporal processing ability in a group of younger and older listeners with a range of hearing thresholds. Seventy-eight listeners were tested on a set of three temporal discrimination tasks (monaural gap discrimination, bilateral gap discrimination, and binaural discrimination of interaural differences in time). To examine the role of temporal fine structure in these tasks, four types of brief stimuli were used: tone bursts, broad-frequency chirps with rising or falling frequency contours, and random-phase noise bursts. Between-subject group analyses conducted separately for each task revealed substantial increases in temporal thresholds for the older listeners across all three tasks, regardless of stimulus type, as well as significant correlations among the performance of

individual listeners across most combinations of tasks and stimuli. Differences in performance were associated with the stimuli in the monaural and binaural tasks, but not the bilateral task. Temporal fine structure differences among the stimuli had the greatest impact on monaural thresholds. Threshold estimate values across all tasks and stimuli did not show any greater variability for the older listeners as compared to the younger listeners. A linear mixed model applied to the data suggested that age and hearing loss are independent factors responsible for temporal processing ability, thus supporting the increasingly accepted hypothesis that temporal processing can be impaired for older compared to younger listeners with similar hearing and/or amounts of hearing loss.

Gangopadhyay, N., Shah, M., Skolnick, G. B., Patel, K. B., Naidoo, S. D., & Woo, A. S. (2014). Point of maximum width: A new measure for anthropometric outcomes in patients with sagittal synostosis. *The Journal of Craniofacial Surgery, 25*(4), 1226-1229.

The esthetic success of sagittal synostosis reconstruction is measured by cephalic index (CI). This limited measure does not fully account for the abnormal head shape in sagittal synostosis. In this retrospective study, we investigate a new objective measure, point of maximum width (PMW) of the skull from a vertex view, to determine where the head is widest for children with sagittal synostosis as compared with normal controls. Preoperative computed tomography (CT) scans of 27 children with sagittal synostosis and 14 postoperative CT scans at least 8 months after surgery were obtained. Normal CT scans were matched for age, sex, and race. Three-dimensional renderings were standardized for orientation. Mean (SE) PMW in patients with sagittal synostosis was 53% (1%) compared with 57% (1%) in controls ($P < 0.001$). Mean (SE) CI in patients with sagittal synostosis was 66.8% (0.8%) compared with 83.3% (1.0%) in controls ($P < 0.001$). The correlation between PMW and CI was weak in both controls ($r = 0.002$, $P = 0.824$) and uncorrected cases ($r = 0.083$, $P = 0.145$). After surgical correction, both CI and PMW significantly improved. Mean (SE) PMW in patients after surgical release of sagittal synostosis was 58% (1%) compared with 58% (1%) in controls ($P = 0.986$). The PMW is not a surrogate for CI but is a novel, valid measure of skull shape, which aids in quantifying the widest region of the skull. It is significantly more anterior in children with sagittal synostosis and exhibits a consistent posterior shift along the cranium after surgery, showing no difference compared with healthy children.

Garimella, P. S., Ix, J. H., Katz, R., Shlipak, M. G., Criqui, M. H., Siscovick, D. S., et al. (2014). Association of albumin-creatinine ratio and cystatin C with change in ankle-brachial index: The multi-ethnic study of atherosclerosis (MESA). *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation,*

BACKGROUND: Low ankle-brachial index (ABI) is a reflection of atherosclerotic disease, and high ABI is an indicator of calcified vessels. The associations of albuminuria and cystatin C level with incidence of either low or high ABI are unknown. STUDY DESIGN: Prospective longitudinal cohort study. SETTING & PARTICIPANTS: MESA (Multi-Ethnic Study of Atherosclerosis) enrolled community-dwelling adults (N=6,814) aged 45-84 years who were free of clinical cardiovascular disease at baseline. PREDICTORS: Baseline albumin-creatinine ratio (ACR) and serum cystatin C level. OUTCOMES: Development of low (1.40) ABI using multinomial regression among persons with ABI of 0.90-1.40 at baseline. RESULTS: During 9.8 years of follow-up, 221 and 89 participants progressed to low and high ABIs, respectively. Baseline ACR and cystatin C level were higher among progressors compared with nonprogressors. In multivariable analyses, doubling of ACR was associated with increased risk of progression to low (OR, 1.08; 95% CI, 0.99-1.20) and high (OR, 1.16; 95% CI, 1.01-1.32) ABIs. Compared to the lowest quintile, the highest quintile of ACR had a significantly increased risk of progression to low (OR, 1.79; 95% CI, 1.03-3.12) and high (OR, 2.76; 95% CI, 1.32-5.77) ABIs. Higher cystatin C levels were associated with progression to low (OR per 1-SD greater, 1.12; 95% CI, 1.00-1.26) but not high (OR per 1-SD greater, 1.01; 95% CI, 0.81-1.25) ABI, but the highest quintile of cystatin C was not associated independently with either outcome. LIMITATIONS: Single measure of albuminuria and low number of progressors to high ABI. CONCLUSIONS: In adults free of clinical cardiovascular disease, albuminuria was a strong independent risk factor for the development of both high and low ABIs, important and different measures of peripheral artery disease.

Geller, B. M., Nelson, H. D., Carney, P. A., Weaver, D. L., Onega, T., Allison, K. H., et al. (2014). Second opinion in breast pathology: Policy, practice and perception. *Journal of Clinical Pathology,*

AIMS: To assess the laboratory policies, pathologists' clinical practice and perceptions about the value of second opinions for breast pathology cases among pathologists practising in the USA. METHODS: Cross-sectional data were collected from 252 pathologists who interpret breast

specimens in eight states using a web-based survey. Descriptive statistics were used to characterise findings. RESULTS: Most participants had >10 years of experience interpreting breast specimens (64%), were not affiliated with academic centres (73%) and were not considered experts by their peers (79%). Laboratory policies mandating second opinions varied by diagnosis: invasive cancer 65%; ductal carcinoma in situ (DCIS) 56%; atypical ductal hyperplasia 36% and other benign cases 33%. 81% obtained second opinions in the absence of policies. Participants believed they improve diagnostic accuracy (96%) and protect from malpractice suits (83%), and were easy to obtain, did not take too much time and did not make them look less adequate. The most common (60%) approach to resolving differences between the first and second opinion is to ask for a third opinion, followed by reaching a consensus. CONCLUSIONS: Laboratory-based second opinion policies vary for breast pathology but are most common for invasive cancer and DCIS cases. Pathologists have favourable attitudes towards second opinions, adhere to policies and obtain them even when policies are absent. Those without a formal policy may benefit from supportive clinical practices and systems that help obtain second opinions.

Geltzeiler, C. B., Rotramel, A., Wilson, C., Deng, L., Whiteford, M. H., & Frankhouse, J. (2014). Prospective study of colorectal enhanced recovery after surgery in a community hospital. *JAMA Surgery,*

Importance: Enhanced recovery after surgery (ERAS) colorectal programs have shown to be successful at reducing length of stay in many international and academic centers; however, their efficacy in a community hospital setting remains unclear. Objective: To determine if favorable results could be reproduced in a community hospital setting using our ERAS program, which was developed using core ERAS guidelines with the goal of accelerated recovery while also addressing other important outcomes affecting patient experience and safety. Design, Setting, and Participants: Prospective study of ERAS program, a multidisciplinary effort involving anesthesia, preadmission staff, nursing, and surgery staff at a community hospital. The program was initiated in 2010 and was in full practice by 2011. We assessed practice patterns and patient outcomes for all elective colon and rectal resection cases performed in 2009 (prior to ERAS implementation), 2011, and 2012. Main Outcomes and Measures: Laparoscopic approach, narcotic use, length of

stay, 30-day readmission, ileus (defined as reinsertion of nasogastric tube), and intra-abdominal infection and association between colorectal cancer (CRC) diagnosis and these outcomes. Results: From 2009 to 2012, the use of laparoscopy increased from 57.4% to 88.8% (P .05). Length of stay reductions resulted in an estimated cost savings of $3202 per patient (2011) and $4803 per patient (2012). Conclusions and Relevance: Implementation of this patient care-directed enhanced recovery program is feasible in a community hospital setting, and it is associated with decreased LOS without increased readmission or morbidity, as well as significant decreases in narcotic use and cost. Improved outcomes are independent of the laparoscopic approach and CRC diagnosis.

Giardiello, F. M., Allen, J. I., Axilbund, J. E., Boland, C. R., Burke, C. A., Burt, R. W., et al. (2014). Guidelines on genetic evaluation and management of lynch syndrome: A consensus statement by the US multi-society task force on colorectal cancer. *Gastroenterology, 147*(2), 502-526. The Multi-Society Task Force, in collaboration with invited experts, developed guidelines to assist health care providers with the appropriate provision of genetic testing and management of patients at risk for and affected with Lynch syndrome as follows: Figure 1 provides a colorectal cancer risk assessment tool to screen individuals in the office or endoscopy setting; Figure 2 illustrates a strategy for universal screening for Lynch syndrome by tumor testing of patients diagnosed with colorectal cancer; Figures 3-6 provide algorithms for genetic evaluation of affected and at-risk family members of pedigrees with Lynch syndrome; Table 10 provides guidelines for screening at-risk and affected persons with Lynch syndrome; and Table 12 lists the guidelines for the management of patients with Lynch syndrome. A detailed explanation of Lynch syndrome and the methodology utilized to derive these guidelines, as well as an explanation of, and supporting literature for, these guidelines are provided.

Gold, M. C., McLaren, J. E., Reistetter, J. A., Smyk-Pearson, S., Ladell, K., Swarbrick, G. M., et al. (2014). MR1-restricted MAIT cells display ligand discrimination and pathogen selectivity through distinct T cell receptor usage. *The Journal of Experimental Medicine, 211*(8), 1601-1610. Mucosal-associated invariant T (MAIT) cells express a semi-invariant T cell receptor (TCR) that detects microbial metabolites presented by the nonpolymorphic major histocompatibility complex

(MHC)-like molecule MR1. The highly conserved nature of MR1 in conjunction with biased MAIT TCRalpha chain usage is widely thought to indicate limited ligand presentation and discrimination within a pattern-like recognition system. Here, we evaluated the TCR repertoire of MAIT cells responsive to three classes of microbes. Substantial diversity and heterogeneity were apparent across the functional MAIT cell repertoire as a whole, especially for TCRbeta chain sequences. Moreover, different pathogen-specific responses were characterized by distinct TCR usage, both between and within individuals, suggesting that MAIT cell adaptation was a direct consequence of exposure to various exogenous MR1-restricted epitopes. In line with this interpretation, MAIT cell clones with distinct TCRs responded differentially to a riboflavin metabolite. These results suggest that MAIT cells can discriminate between pathogen-derived ligands in a clonotype-dependent manner, providing a basis for adaptive memory via recruitment of specific repertoires shaped by microbial exposure.

Gong, Q., Stump, M. R., Deng, V., Zhang, L., & Zhou, Z. (2014). Identification of Kv11.1 isoform switch as a novel pathogenic mechanism of long QT syndrome. *Circulation.Cardiovascular Genetics,*

BACKGROUND: -The KCNH2 gene encodes the Kv11.1 potassium channel that conducts the rapidly activating delayed rectifier current in the heart. The relative expression of the full-length Kv11.1a isoform and the C-terminally truncated Kv11.1a-USO isoform play an important role in regulation of channel function. The formation of C-terminal isoforms is determined by competition between the splicing and alternative polyadenylation of KCNH2 intron 9. It is not known whether changes in the relative expression of Kv11.1a and Kv11.1a-USO can cause long QT syndrome. METHODS AND RESULTS: -We identified a novel KCNH2 splice site mutation in a large family. The mutation, IVS9-2delA, is a deletion of the A in the AG dinucleotide of the 3' acceptor site of intron 9. We designed an intron-containing full-length KCNH2 gene construct to study the effects of the mutation on the relative expression of Kv11.1a and Kv11.1a-USO at the mRNA, protein and functional levels. We found that this mutation disrupted normal splicing and resulted in exclusive polyadenylation of intron 9, leading to a switch from the functional Kv11.1a to the non-functional Kv11.1a-USO isoform in HEK293 cells and HL-1 cardiomyocytes. We also showed that IVS9-2delA caused isoform switch in the mutant allele of mRNA isolated from patient

lymphocytes. CONCLUSIONS: -Our findings indicate that the IVS9-2delA mutation causes a switch in the expression of the functional Kv11.1a isoform to the non-functional Kv11.1a-USO isoform. Kv11.1 isoform switch represents a novel mechanism in the pathogenesis of long QT syndrome.

Gonzales, D., Hajek, P., Pliamm, L., Nackaerts, K., Tseng, L. -., McRae, T. D., et al. (2014). Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: A randomized, placebo-controlled trial. *Clinical Pharmacology and Therapeutics,*
The efficacy and safety of retreatment with varenicline in smokers attempting to quit were evaluated in this randomized, double-blind, placebo-controlled, multicenter trial (Australia, Belgium, Canada, the Czech Republic, France, Germany, the United Kingdom, and the United States). Participants were generally healthy adult smokers (≥10 cigarettes/day) with ≥1 prior quit attempt (≥2 weeks) using varenicline and no quit attempts in ≤3 months; they were randomly assigned (1:1) to 12 weeks' varenicline (n = 251) or placebo (n = 247) treatment, with individual counseling, plus 40 weeks' nontreatment follow-up. The primary efficacy end point was the carbon monoxide-confirmed (≤10 ppm) continuous abstinence rate for weeks 9-12, which was 45.0% (varenicline; n = 249) vs. 11.8% (placebo; n = 245; odds ratio: 7.08; 95% confidence interval: 4.34, 11.55; P < 0.0001). Common varenicline group adverse events were nausea, abnormal dreams, and headache, with no reported suicidal behavior. Varenicline is efficacious and well tolerated in smokers who have previously taken it. Abstinence rates are comparable with rates reported for varenicline-naive smokers.Clinical Pharmacology and Therapeutics (2014); advance online publication 09 July 2014. doi:10.1038/clpt.2014.124.

Grygoryev, D., Dan, C., Gauny, S., Eckelmann, B., Ohlrich, A. P., Connolly, M., et al. (2014). Autosomal mutants of proton-exposed kidney cells display frequent loss of heterozygosity on nonselected chromosomes. *Radiation Research, 181*(5), 452-463.
High-energy protons found in the space environment can induce mutations and cancer, which are inextricably linked. We hypothesized that some mutants isolated from proton-exposed kidneys arose through a genome-wide incident that causes loss of heterozygosity (LOH)-generating mutations on multiple chromosomes (termed here genomic LOH). To test this hypothesis, we

examined 11 pairs of nonselected chromosomes for LOH events in mutant cells isolated from the kidneys of mice exposed to 4 or 5 Gy of 1 GeV protons. The mutant kidney cells were selected for loss of expression of the chromosome 8-encoded Aprt gene. Genomic LOH events were also assessed in Aprt mutants isolated from isogenic cultured kidney epithelial cells exposed to 5 Gy of protons in vitro. Control groups were spontaneous Aprt mutants and clones isolated without selection from the proton-exposed kidneys or cultures. The in vivo results showed significant increases in genomic LOH events in the Aprt mutants from proton-exposed kidneys when compared with spontaneous Aprt mutants and when compared with nonmutant (i.e., nonselected) clones from the proton-exposed kidneys. A bias for LOH events affecting chromosome 14 was observed in the proton-induced Aprt mutants, though LOH for this chromosome did not confer increased radiation resistance. Genomic LOH events were observed in Aprt mutants isolated from proton-exposed cultured kidney cells; however the incidence was fivefold lower than in Aprt mutants isolated from exposed intact kidneys, suggesting a more permissive environment in the intact organ and/or the evolution of kidney clones prior to their isolation from the tissue. We conclude that proton exposure creates a subset of viable cells with LOH events on multiple chromosomes, that these cells form and persist in vivo, and that they can be isolated from an intact tissue by selection for a mutation on a single chromosome.

Haendel, M. A., Balhoff, J. P., Bastian, F. B., Blackburn, D. C., Blake, J. A., Bradford, Y., et al. (2014). Unification of multi-species vertebrate anatomy ontologies for comparative biology in uberon. *Journal of Biomedical Semantics, 5*, 21-1480-5-21. eCollection 2014.

BACKGROUND: Elucidating disease and developmental dysfunction requires understanding variation in phenotype. Single-species model organism anatomy ontologies (ssAOs) have been established to represent this variation. Multi-species anatomy ontologies (msAOs; vertebrate skeletal, vertebrate homologous, teleost, amphibian AOs) have been developed to represent 'natural' phenotypic variation across species. Our aim has been to integrate ssAOs and msAOs for various purposes, including establishing links between phenotypic variation and candidate genes. RESULTS: Previously, msAOs contained a mixture of unique and overlapping content. This hampered integration and coordination due to the need to maintain cross-references or inter-ontology equivalence axioms to the ssAOs, or to perform large-scale obsolescence and modular

import. Here we present the unification of anatomy ontologies into Uberon, a single ontology resource that enables interoperability among disparate data and research groups. As a consequence, independent development of TAO, VSAO, AAO, and vHOG has been discontinued. CONCLUSIONS: The newly broadened Uberon ontology is a unified cross-taxon resource for metazoans (animals) that has been substantially expanded to include a broad diversity of vertebrate anatomical structures, permitting reasoning across anatomical variation in extinct and extant taxa. Uberon is a core resource that supports single- and cross-species queries for candidate genes using annotations for phenotypes from the systematics, biodiversity, medical, and model organism communities, while also providing entities for logical definitions in the Cell and Gene Ontologies. THE ONTOLOGY RELEASE FILES ASSOCIATED WITH THE ONTOLOGY MERGE DESCRIBED IN THIS MANUSCRIPT ARE AVAILABLE AT: http://purl.obolibrary.org/obo/uberon/releases/2013-02-21/ CURRENT ONTOLOGY RELEASE FILES ARE AVAILABLE ALWAYS AVAILABLE AT: http://purl.obolibrary.org/obo/uberon/releases/

Hagler, S., Jimison, H. B., & Pavel, M. (2014). Assessing executive function using a computer game: Computational modeling of cognitive processes. *IEEE Journal of Biomedical and Health Informatics, 18*(4), 1442-1452.

Early and reliable detection of cognitive decline is one of the most important challenges of current healthcare. In this project, we developed an approach whereby a frequently played computer game can be used to assess a variety of cognitive processes and estimate the results of the pen-and-paper trail making test (TMT) - known to measure executive function, as well as visual pattern recognition, speed of processing, working memory, and set-switching ability. We developed a computational model of the TMT based on a decomposition of the test into several independent processes, each characterized by a set of parameters that can be estimated from play of a computer game designed to resemble the TMT. An empirical evaluation of the model suggests that it is possible to use the game data to estimate the parameters of the underlying cognitive processes and using the values of the parameters to estimate the TMT performance. Cognitive measures and trends in these measures can be used to identify individuals for further assessment, to provide a mechanism for improving the early detection of neurological problems, and to provide feedback and monitoring for cognitive interventions in the home.

Hamadani, M., Hari, P. N., Zhang, Y., Carreras, J., Akpek, G., Aljurf, M. D., et al. (2014). Early failure of frontline rituximab-containing chemoimmunotherapy in diffuse large B-cell lymphoma does not predict futility of autologous hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,*

The poor prognosis of diffuse large B-cell lymphoma (DLBCL) patients relapsing within 1-year of initial diagnosis after first-line rituximab-based chemoimmunotherapy has created controversy about the role of autologous transplantation (auto-HCT) in this setting. We compared auto-HCT outcomes of chemosensitive DLBCL patients between 2000 and 2011 in two cohorts based on time to relapse from diagnosis. The early rituximab failure (ERF) cohort consisted of patients with primary refractory disease or those with first relapse within 1-year of initial diagnosis. The ERF cohort was compared with those relapsing >1-year after initial diagnosis (Late Rituximab Failure [LRF] cohort). ERF and LRF cohorts included 300 and 216 patients, respectively. Non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS) and overall survival (OS) of ERF vs. LRF cohorts at 3-years were 9% (95%CI 6-13) vs. 9% (95%CI 5-13), 47% (95%CI 41-52) vs. 39% (95%CI 33-46), 44% (95%CI 38-50) vs. 52% (95%CI 45-59) and 50% (95 CI 44-56) vs. 67% (95%CI 60-74), respectively. On multivariate analysis, ERF was not associated with higher NRM (relative risk (RR) 1.31, p=0.34). ERF cohort had a higher risk of treatment failure (progression/relapse or death) (RR 2.08, p<0.001) and overall mortality (RR 3.75, p<0.001) within the first 9 months post auto-HCT. Beyond this period, PFS and OS were not significantly different between ERF and LRF cohorts. Auto-HCT provides durable disease control to a sizeable subset of DLBCL despite ERF (3-year PFS 44%), and remains the standard-of-care in chemosensitive DLBCL regardless of the timing of disease relapse.

Hambly, C., & Fombonne, E. (2014). Factors influencing bilingual expressive vocabulary size in children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 8*(9), 1079-1089.

This study explored bilingual exposure, language, social impairment and cognitive factors that could influence second language (L2) expressive vocabulary size as measured on the MacArthur-Bates Communicative Development Inventories (various languages) in 33 children (mean age = 60 months) diagnosed with ASD. In the 23 children with L2 vocabularies, recent language

exposure estimates accounted for 69% of the variation in L2 vocabulary size, and the VABS-II expressive scale score explained an additional 13% of the difference. The complete sample was then subgrouped into three levels of L2 vocabulary size to compare children with no L2 vocabularies (NON-B, n = 10), low L2 word counts (LOW-B, n = 11) and high L2 counts (HIGH-B, n = 12), as determined by a median split procedure. The HIGH-B group had significantly larger L1 vocabularies than both the LOW-B (p =.045) and the NON-B (p =.003) groups, and higher VABS-II expressive scale scores than both the LOW-B (p =.008) and the NON-B (p =.012) groups. Social impairment did not significantly differ across groups and cognitive impairment did not preclude the development of L2 vocabularies. Expressive bilingualism in this population appears related to high levels of recent direct L2 exposure in combination with stronger dominant language abilities. © 2014 Elsevier Ltd.

Hampton, D. A., Wiles, C., Fabricant, L. J., Kiraly, L., Differding, J., Underwood, S., et al. (2014). Cryopreserved red blood cells are superior to standard liquid red blood cells. *The Journal of Trauma and Acute Care Surgery, 77*(1), 20-27.

BACKGROUND: Liquid preserved packed red blood cell (LPRBC) transfusions are used to treat anemia and increase end-organ perfusion. Throughout their storage duration, LPRBCs undergo biochemical and structural changes collectively known as the storage lesion. These changes adversely affect perfusion and oxygen off-loading. Cryopreserved RBCs (CPRBC) can be stored for up to 10 years and potentially minimize the associated storage lesion. We hypothesized that CPRBCs maintain a superior biochemical profile compared with LPRBCs. METHODS: This was a prospective, randomized, double-blinded study. Adult trauma patients with an Injury Severity Score (ISS) greater than 4 and an anticipated 1-U to 2-U transfusion of PRBCs were eligible. Enrolled patients were randomized to receive either CPRBCs or LPRBCs. Serum proteins (haptoglobin, serum amyloid P, and C-reactive protein), proinflammatory and anti-inflammatory cytokines, d-dimer, nitric oxide, and 2,3-DPG concentrations were analyzed. Mann-Whitney U-test and Wilcoxon rank sum test were used to assess significance ($p < 0.05$). RESULTS: Fifty-seven patients were enrolled (CPRBC, n = 22; LPRBC, n = 35). The LPRBC group's final interleukin 8, tumor necrosis factor alpha, and d-dimer concentrations were elevated compared with their pretransfusion values ($p < 0.05$). After the second transfused units, 2,3-DPG was

higher in the patients receiving CPRBCs ($p < 0.05$); this difference persisted throughout the study. Finally, serum protein concentrations were decreased in the transfused CPRBC units compared with LPRBC ($p < 0.01$). CONCLUSION: CPRBC transfusions have a superior biochemical profile: an absent inflammatory response, attenuated fibrinolytic state, and increased 2,3-DPG. A blood banking system using both storage techniques will offer the highest-quality products to critically injured patients virtually independent of periodic changes in donor availability and transfusion needs. LEVEL OF EVIDENCE: Therapeutic study, level II.

Hamrahian, A. H., Yuen, K. C., Hoffman, A. R., & For The Aace Neuroendocrine And Pituitary Scientific,Committee. (2014). AACE/ACE disease state clinical review: Medical management of cushing disease. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 20*(7), 746-757.

OBJECTIVE: To review available medical therapies for patients with Cushing disease and to provide a roadmap for their use in clinical practice. METHODS: PubMed searches were performed to identify all of the available published data on medical management of Cushing disease. RESULTS: Medical therapy is usually not the first-line treatment for patients with Cushing disease but may be used to improve clinical manifestations of Cushing disease in patients who are not suitable candidates for surgery, following unsuccessful surgery or recurrence, or as a "bridge therapy" in those who have undergone radiotherapy. Medical therapy may also be used in preoperative preparation of patients with severe disease. Current available medical options for patients with Cushing disease include centrally acting agents, steroidogenesis inhibitors, and a glucocorticoid receptor antagonists. At present, there are no head-to-head studies comparing the efficacy, tolerability, and safety of different U.S. Food and Drug Administration (FDA)- and non-FDA-approved drugs in patients with Cushing disease. With the initiation of new studies and the completion of ongoing clinical trials, the number of FDA-approved drugs for medical treatment of Cushing disease is expected to increase. CONCLUSION: Medical therapy has an important adjunctive role in the management of patients with Cushing disease. The decision to initiate medical treatment depends on many factors, including patient characteristics and preference. Long-term studies are needed to better define the clinical efficacy, safety, and tolerability of medical treatment of Cushing disease, including the role of combination therapies.

Han, J., He, G. W., & Chen, Z. W. (2014). Protective effect and mechanism of total flavones from rhododendron simsii planch on endothelium-dependent dilatation and hyperpolarization in cerebral ischemia-reperfusion and correlation to hydrogen sulphide release in rats. *Evidence-Based Complementary and Alternative Medicine : ECAM, 2014*, 904019.

We for the first time investigated the effect and mechanism of the total flavones of Rhododendron simsii Planch (TFR), a widely-used Chinese herb for a thousand years, on vasodilatation and hyperpolarization in middle cerebral artery (MCA) of rats subject to global cerebral ischemia-reperfusion (CIR). TFR (11~2700 mg/L) evoked dose-dependent vasodilation and hyperpolarization in MCA of both sham and CIR that were partially inhibited by 30 muM N-nitro-L-arginine-methyl-ester and 10 muM indomethacin and further attenuated by endogenous H2S synthese-CSE inhibitor PPG (100 muM) or Ca(2+)-activated potassium channel (Kca) inhibitor TEA (1 mM). In whole-cell patch clamp recording, TFR remarkably enhanced the outward current that was inhibited by TEA. CIR increased CSE mRNA expression and the contents of H2S that were further increased by TFR. We conclude that, in MCA of CIR rats, TFR induces non-NO and non-PGI2-mediated effects of vasodilatation and hyperpolarization involving Kca and increases CSE mRNA expression level in endothelial cells and H2S content in the cerebrum. These findings suggest that the response induced by TFR is potentially related to endothelium-derived hyperpolarizing factor mediated by the endogenous H2S and promote the use of TFR in protection of brain from ischemia-reperfusion injury.

Hauck, M. J., & Steele, E. A. (2014). Dermis fat graft implantation after unilateral enucleation for retinoblastoma in pediatric patients. *Ophthalmic Plastic and Reconstructive Surgery,*

PURPOSE:: To evaluate the efficacy of dermis fat graft (DFG) as a primary implant technique in pediatric patients requiring unilateral enucleation due to retinoblastoma. METHODS:: A retrospective chart review of 14 consecutive pediatric patients who underwent dermis fat graft implantation after unilateral enucleation for retinoblastoma by 1 surgeon (E.A.S.) was performed to evaluate graft efficacy with regard to orbital volume growth and any associated morbidity. Patients who received chemotherapy or external beam radiation were excluded. Demographic information was recorded. Serial MRIs were used to measure orbital volumes to compare the surgical and contralateral orbits over time. The main outcome measure was the difference in

bony orbital volume between enucleated and contralateral, uninvolved orbits. Mann-Whitney U test was used to compare orbital volume measurements between surgical and nonsurgical orbits. Correlation testing was performed to determine the effect of age, sex, and follow-up time on the orbital volume changes. RESULTS:: There was no statistical difference between the MRI volume measured for surgical and nonsurgical orbits over time. This was the case at all measured time points and for all ages and genders. All patients were under the age of 4 years at the time of surgery. The median difference in orbital volumes between surgical and nonsurgical orbits was -0.095 cm (range -1.26 to 1.01 cm; quartiles -0.32 to 0.07 cm; mean +/- SD, -0.144 +/- 0.0522 cm; 95% confidence interval, -0.247 to -0.0419 cm). The median follow-up time from surgery date to the most recent clinical examination was 38.5 months (range, 13 to 70 months; quartiles, 28.75 to 45.5 months; mean +/- standard deviation [SD], 38.43 +/- 17.21 months; 95% confidence interval, 29.41 to 47.45 months). CONCLUSIONS:: In pediatric patients below 4 years of age with unilateral retinoblastoma treated with enucleation and primary dermis fat graft implantation, there was no statistically significant difference in bony orbital volume between the surgical and nonsurgical orbits during the follow-up period.

Hayes, M., Muhota, J., Nguyen, L., Nedrow, A., Calabrese, C., & Shinto, L. (2014). A framework for credentialing naturopathic physicians in academic health centers: Oregon health and science university. *Journal of Alternative and Complementary Medicine, 20*(3), 217-218.

He, W., Li, Y., Chen, X., Lu, L., Tang, B., Wang, Z., et al. (2014). miR-494 acts as an anti-oncogene in gastric carcinoma by targeting c-myc. *Journal of Gastroenterology and Hepatology (Australia), 29*(7), 1427-1434.

Background: We recently showed that miR-494 was downregulated in gastric carcinoma (GC). The objectives of this study were to determine the role of miR-494 in GC malignancy and to identify its target genes. Methods: Real-time polymerase chain reaction was employed to quantify the expression level of miR-494 and c-myc in gastric cancer tissues. Bioinformatics was used to predict the downstream target genes of miR-494, which were confirmed by luciferase and RNA immunoprecipitation assays. Cell functional analyses and a xenograft mouse model were used to evaluate the role of miR-494 in malignancy. Results: miR-494 was downregulated in human GC

tissues and in GC cells and was negatively correlated with c-myc expression. High level of c-myc or low level of miR-494 correlated with poor prognosis. The miR-494-binding site in the c-myc 3′ untranslated region was predicted using TargetScan and was confirmed by the luciferase assay. Additionally, c-myc and miR-494 were enriched in coimmunoprecipitates with tagged Argonaute2 proteins in cells overexpressing miR-494. Furthermore, a miR-494 mimic significantly downregulated endogenous c-myc expression, which may contribute to the delayed G1/S transition, decreased synthesis phase bromodeoxyuridine incorporation, and impaired cell growth and colony formation; on the other hand, treatment with a miR-494 inhibitor displayed the opposite effects. Reduced tumor burden and decreased cell proliferation were observed following the delivery of miR-494 into xenograft mice. Conclusion: miR-494 is downregulated in human GC and acts as an anti-oncogene by targeting c-myc. miR-494 plays a role in the pathogenesis of gastric cancer in a recessive fashion.

Hegarty, D. M., Hermes, S. M., Largent-Milnes, T. M., & Aicher, S. A. (2014). Capsaicin-responsive corneal afferents do not contain TRPV1 at their central terminals in trigeminal nucleus caudalis in rats. *Journal of Chemical Neuroanatomy, 61-62C*, 1-12.

We examined the substrates for ocular nociception in adult male Sprague-Dawley rats. Capsaicin application to the ocular surface in awake rats evoked nocifensive responses and suppressed spontaneous grooming responses. Thus, peripheral capsaicin was able to activate the central pathways encoding ocular nociception. Our capsaicin stimulus evoked c-Fos expression in a select population of neurons within rostral trigeminal nucleus caudalis in anesthetized rats. These activated neurons also received direct contacts from corneal afferent fibers traced with cholera toxin B from the corneal surface. However, the central terminals of the corneal afferents that contacted capsaicin-activated trigeminal neurons did not contain TRPV1. To determine if TRPV1 expression had been altered by capsaicin stimulation, we examined TRPV1 content of corneal afferents in animals that did not receive capsaicin stimulation. These studies confirmed that while TRPV1 was present in 30% of CTb-labeled corneal afferent neurons within the trigeminal ganglion, TRPV1 was only detected in 2% of the central terminals of these corneal afferents within the trigeminal nucleus caudalis. Other TRP channels were also present in low proportions

of central corneal afferent terminals in unstimulated animals (TRPM8, 2%; TRPA1, 10%). These findings indicate that a pathway from the cornea to rostral trigeminal nucleus caudalis is involved in corneal nociceptive transmission, but that central TRP channel expression is unrelated to the type of stimulus transduced by the peripheral nociceptive endings.

Helms, C. M., Park, B., & Grant, K. A. (2014). Erratum to: Adrenal steroid hormones and ethanol self-administration in male rhesus macaques. *Psychopharmacology,*

Hersh, W. R., Gorman, P. N., Biagioli, F. E., Mohan, V., Gold, J. A., & Mejicano, G. C. (2014). Beyond information retrieval and electronic health record use: Competencies in clinical informatics for medical education. *Advances in Medical Education and Practice, 5*, 205-212.

Physicians in the 21st century will increasingly interact in diverse ways with information systems, requiring competence in many aspects of clinical informatics. In recent years, many medical school curricula have added content in information retrieval (search) and basic use of the electronic health record. However, this omits the growing number of other ways that physicians are interacting with information that includes activities such as clinical decision support, quality measurement and improvement, personal health records, telemedicine, and personalized medicine. We describe a process whereby six faculty members representing different perspectives came together to define competencies in clinical informatics for a curriculum transformation process occurring at Oregon Health & Science University. From the broad competencies, we also developed specific learning objectives and milestones, an implementation schedule, and mapping to general competency domains. We present our work to encourage debate and refinement as well as facilitate evaluation in this area.

Hill, A. P., Zuckerman, K. E., Hagen, A. D., Kriz, D. J., Duvall, S. W., Van Santen, J., et al. (2014). Aggressive behavior problems in children with autism spectrum disorders: Prevalence and correlates in a large clinical sample. *Research in Autism Spectrum Disorders, 8*(9), 1121-1133.

Aggressive behavior problems (ABP) are frequent yet poorly understood in children with autism spectrum disorders (ASD) and are likely to co-vary significantly with comorbid problems. We examined the prevalence and sociodemographic correlates of ABP in a clinical sample of children with ASD (N = 400; 2-16.9 years). We also investigated whether children with ABP experience

more intensive medical interventions, greater impairments in behavioral functioning, and more severe comorbid problems than children with ASD who do not have ABP. One in four children with ASD had Child Behavior Checklist scores on the Aggressive Behavior scale in the clinical range (T-scores ≥ 70). Sociodemographic factors (age, gender, parent education, race, ethnicity) were unrelated to ABP status. The presence of ABP was significantly associated with increased use of psychotropic drugs and melatonin, lower cognitive functioning, lower ASD severity, and greater comorbid sleep, internalizing, and attention problems. In multivariate models, sleep, internalizing, and attention problems were most strongly associated with ABP. These comorbid problems may hold promise as targets for treatment to decrease aggressive behavior and proactively identify high-risk profiles for prevention. © 2014 Elsevier Ltd.

Hitzemann, R., Bottomly, D., Iancu, O., Buck, K., Wilmot, B., Mooney, M., et al. (2014). The genetics of gene expression in complex mouse crosses as a tool to study the molecular underpinnings of behavior traits. *Mammalian Genome, 25*(1-2), 12-22.

Complex Mus musculus crosses provide increased resolution to examine the relationships between gene expression and behavior. While the advantages are clear, there are numerous analytical and technological concerns that arise from the increased genetic complexity that must be considered. Each of these issues is discussed, providing an initial framework for complex cross study design and planning. © 2013 The Author(s).

Holt, H. D., Hinkle, D. M., Falk, N. S., Fraunfelder, F. T., & Fraunfelder, F. W. (2014). Human papilloma virus vaccine associated uveitis. *Current Drug Safety, 9*(1), 65-68.

Purpose: To report a possible association between human papilloma virus (HPV) vaccination and uveitis. Methods: Spontaneous reports from the National Registry of Drug-Induced Ocular Side effects, World Health Organization and Food and Drug Administration were collected on uveitis associated with human papilloma virus vaccination. A MEDLINE search was performed using keywords "uveitis," "iritis," "iridocyclitis," "human papilloma virus," "Cervarix", and "Gardasil." Main Outcome Measures: Data garnered from spontaneous reports included the age, gender, adverse drug reaction (ADR), date of administration, concomitant administration of other vaccinations, time until onset of ADR, other systemic reactions, and dechallenge and rechallenge

data. Results: A total of 24 case reports of uveitis associated with human papilloma virus vaccination were identified, all cases were female, and the median age was 17. Median time from HPV vaccination to reported ADR was 30 days (range 0-476 days). Discussion: According to World Health Organization criteria, the relationship between human papilloma virus vaccination and uveitis is "possible." Causality assessments are based on the time relationship of drug administration, uveitis development and re-challenge data. Conclusions: Clinicians should be aware of a possible bilateral uveitis and papillitis following HPV vaccination. © 2014 Bentham Science Publishers.

Home, P. D., Bolli, G. B., Mathieu, C., Deerochanawong, C., Landgraf, W., Candelas, C., et al. (2014). Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: Insulin glargine versus neutral protamine hagedorn insulin in insulin-naïve people with type 2 diabetes. *Diabetes, Obesity and Metabolism*,

Aims: To examine whether insulin glargine can lead to better control of glycated haemoglobin (HbA1c) than that achieved by neutral protamine Hagedorn (NPH) insulin, using a protocol designed to limit nocturnal hypoglycaemia. Methods: The present study, the Least One Oral Antidiabetic Drug Treatment (LANCELOT) Study, was a 36-week, randomized, open-label, parallel-arm study conducted in Europe, Asia, the Middle East and South America. Participants were randomized (1:1) to begin glargine or NPH, on background of metformin with glimepiride. Weekly insulin titration aimed to achieve median prebreakfast and nocturnal plasma glucose levels ≤5.5mmol/l, while limiting values ≤4.4mmol/l. Results: The efficacy population (n=701) had a mean age of 57 years, a mean body mass index of 29.8kg/m2, a mean duration of diabetes of 9.2years and a mean HbA1c level of 8.2% (66mmol/mol). At treatment end, HbA1c values and the proportion of participants with HbA1c <7.0 % (<53mmol/mol) were not significantly different for glargine [7.1 % (54mmol/mol) and 50.3%] versus NPH [7.2 % (55mmol/mol) and 44.3%]. The rate of symptomatic nocturnal hypoglycaemia, confirmed by plasma glucose ≤3.9 or ≤3.1mmol/l, was 29 and 48% less with glargine than with NPH insulin. Other outcomes were similar between the groups. Conclusion: Insulin glargine was not superior to NPH insulin in improving glycaemic control. The insulin dosing algorithm was not sufficient to equalize nocturnal hypoglycaemia between the two insulins. This study confirms, in a globally

heterogeneous population, the reduction achieved in nocturnal hypoglycaemia while attaining good glycaemic control with insulin glargine compared with NPH, even when titrating basal insulin to prevent nocturnal hypoglycaemia rather than treating according to normal fasting glucose levels. © 2014 The Authors.

Hook, L. M., Grey, F., Grabski, R., Tirabassi, R., Doyle, T., Hancock, M., et al. (2014). Cytomegalovirus miRNAs target secretory pathway genes to facilitate formation of the virion assembly compartment and reduce cytokine secretion. *Cell Host and Microbe, 15*(3), 363-373. Herpesviruses, including human cytomegalovirus (HCMV), encode multiple microRNAs (miRNA) whose targets are just being uncovered. Moreover, miRNA function during the virus life cycle is relatively unknown. We find that HCMV miRs UL112-1, US5-1, and US5-2 target multiple components of the host secretory pathway, including VAMP3, RAB5C, RAB11A, SNAP23, and CDC42. A HCMV miR UL112-1, US5-1, and US5-2 triple mutant displayed aberrant morphogenesis of the virion assembly compartment (VAC), increased secretion of noninfectious particles, and increased IL-6 release from infected cells. Ectopic expression of miRs UL112-1, US5-1, and US5-2 or siRNAs directed against RAB5C, RAB11A, SNAP23, and CDC42 caused the loss of Golgi stacks with reorganization into structures that resemble the VAC and a decrease in cytokine release. These observations indicate that multiple HCMV miRNAs coordinately regulate reorganization of the secretory pathway to control cytokine secretion and facilitate formation of the VAC for efficient infectious virus production. ©2014 Elsevier Inc.

Howard, P. W., Wright, C. C., Howard, T., & Johnson, D. C. (2014). Herpes simplex virus gE/gI extracellular domains promote axonal transport and spread from neurons to epithelial cells. *Journal of Virology,*

Following reactivation from latency, there are two distinct steps in the spread of herpes simplex virus (HSV) from infected neurons to epithelial cells: i) anterograde axonal transport of virus particles from neuron cell bodies to axon tips and ii) exocytosis and spread of extracellular virions across cell junctions into adjacent epithelial cells. HSV heterodimeric glycoprotein gE/gI is important for anterograde axonal transport and gE/gI cytoplasmic domains play important roles in sorting of virus particles into axons. However, the roles of the large (approximately 400

residue) gE/gI extracellular (ET) domains in both axonal transport and neuron-to-epithelial cell spread have not been characterized. Two gE mutants: gE-277 and gE-348 contain small insertions in the gE ET domain, fold normally, form gE/gI heterodimers and are incorporated into virions. Both gE-277 and gE-348 did not function in anterograde axonal transport, there was markedly reduced numbers of viral capsids and glycoproteins, compared with wild type HSV. The defects in axonal transport were manifest in neuronal cell bodies involving missorting of HSV capsids before entry into proximal axons. Although there were diminished numbers of mutant gE-348 capsids and glycoproteins in distal axons, there was efficient spread to adjacent epithelial cells, similar to wild type HSV. By contrast, virus particles produced by HSV gE-277 spread poorly to epithelial cells, despite similar numbers of virus particles as gE-348. These results genetically separate the two steps in HSV spread from neurons to epithelial cells and demonstrate that the gE/gI ET domains functions in both processes. IMPORTANCE: An essential phase of the life cycle of herpes simplex virus (HSV) and other alpha-herpesviruses is the capacity to reactivate from latency then spread from infected neurons to epithelial tissues. This spread involves at least two steps: i) anterograde transport to axon tips, followed by ii) exocytosis and extracellular spread from axons to epithelial cells. HSV gE/gI is a glycoprotein that facilitates this virus spread, although by poorly understood mechanisms. Here, we show that the extracellular (ET) domains of gE/gI promote the sorting of viral structural proteins into proximal axons to begin axonal transport. However, the gE/gI ET domains also participate in the extracellular spread from axon tips across cell junctions to epithelial cells. Understanding the molecular mechanisms involved in gE/gI-mediated sorting of virus particles into axons and extracellular spread to adjacent cells is fundamentally important in terms of identifying novel targets to reduce alpha-herpesvirus disease.

Ilgen, J. S., Bowen, J. L., & Eva, K. W. (2014). In reply to mamede and schmidt. *Academic Medicine : Journal of the Association of American Medical Colleges, 89*(7), 960.

Ishikawa, Y., & Bächinger, H. P. (2014). A substrate preference for the rough endoplasmic reticulum resident protein FKBP22 during collagen biosynthesis. *Journal of Biological Chemistry, 289*(26), 18189-18201.

The biosynthesis of collagens occurs in the rough endoplasmic reticulum and requires a large numbers of molecular chaperones, foldases, and post-translational modification enzymes. Collagens contain a large number of proline residues that are post-translationally modified to 3-hydroxyproline or 4-hydroxyproline, and the rate-limiting step in formation of the triple helix is the cis-trans isomerization of peptidyl-proline bonds. This step is catalyzed by peptidylprolyl cis-trans isomerases. There are seven peptidyl-prolyl cis-trans isomerases in the rER, and so far, two of these enzymes, cyclophilin B and FKBP65, have been shown to be involved in collagen biosynthesis. The absence of either cyclophilin B or FKBP65 leads to a recessive form of osteogenesis imperfecta. The absence of FKBP22 leads to a kyphoscoliotic type of Ehlers-Danlos syndrome (EDS), and this type of EDS is classified as EDS type VI, which can also be caused by a deficiency in lysyl-hydroxylase 1. However, the lack of FKBP22 shows a wider spectrum of clinical phenotypes than the absence of lysyl-hydroxylase 1 and additionally includes myopathy, hearing loss, and aortic rupture. Here we show that FKBP22 catalyzes the folding of type III collagen and interacts with type III collagen, type VI collagen, and type X collagen, but not with type I collagen, type II collagen, or type V collagen. These restrictive interactions might help explain the broader phenotype observed in patients that lack FKBP22.

Jeon, B. T., Heo, R. W., Shin, H. J., Yi, C. O., Lee, Y. H., Joung, H. N., et al. (2014). Attenuation by a vigna nakashimae extract of nonalcoholic fatty liver disease in high-fat diet-fed mice. *Bioscience, Biotechnology, and Biochemistry, 78*(3), 482-489.

A Vigna nakashimae (VN) extract has been shown to have antidiabetic and anti-obesity effects. However, the mechanism underlying the effect of a VN extract on hepatic inflammation and endoplasmic reticulum (ER) stress remains unclear. In the present study, we investigated how a VN extract protects against the development of non-alcoholic fatty liver disease (NAFLD). A VN extract for 12 weeks reduced the body weight, serum metabolic parameters, cytokines, and hepatic steatosis in high-fat diet (HFD)-fed mice. A VN extract decreased HFD-induced hepatic acetyl CoA carboxylase and glucose transporter 4 expressions. In addition to the levels of high-mobility group box 1 and receptor for advanced glycation, the hepatic expression of ATF4 and caspase-3 was also reduced by a VN extract. Thus, these data indicate that a chronic VN extract

prevented NAFLD through multiple mechanisms, including inflammation, ER stress, and apoptosis in the liver.

Jimison, H., & Pavel, M. (2006). Embedded assessment algorithms within home-based cognitive computer game exercises for elders. *Conference Proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference,* , 6101-6104.

With the recent consumer interest in computer-based activities designed to improve cognitive performance, there is a growing need for scientific assessment algorithms to validate the potential contributions of cognitive exercises. In this paper, we present a novel methodology for incorporating dynamic cognitive assessment algorithms within computer games designed to enhance cognitive performance. We describe how this approach works for variety of computer applications and describe cognitive monitoring results for one of the computer game exercises. The real-time cognitive assessments also provide a control signal for adapting the difficulty of the game exercises and providing tailored help for elders of varying abilities.

Joca, L., Zuloaga, D. G., Raber, J., & Siegel, J. A. (2014). Long-term effects of early adolescent methamphetamine exposure on depression-like behavior and the hypothalamic vasopressin system in mice. *Developmental Neuroscience, 36*(2), 108-118.

Methamphetamine (MA) has neurotoxic effects on the adult human brain that can lead to deficits in behavior and cognition. However, relatively little research has examined the behavioral or neurotoxic effects of MA in adolescents. The rising rates of adolescent MA use make it imperative that we understand the long-term effects of MA exposure on the adolescent brain and how these effects may differ from those seen in adults. In this study, the long-term effects of MA exposure during early adolescence on behavior and the vasopressin system in the paraventricular nucleus of the hypothalamus in late adolescent and adult male and female C57BL/6J mice were examined. MA exposure increased depression-like behavior in the Porsolt forced swim test in both late adolescent and adult male and female mice. Late adolescent male mice exposed to MA also showed a decrease in the number of vasopressin-immunoreactive neurons in the paraventricular nucleus compared to sex-matched saline-treated controls. Thus, similar to humans exposed to

MA during adolescence, mice exposed to MA during adolescence show increased depression-like behavior later in life. These changes in behavior may be related to MA-induced alterations in vasopressin and the hypothalamic- pituitary-adrenal axis, especially in males. © 2014 S. Karger AG, Basel.

Johnson, A. L., Blaine, E. T., & Lewis, A. D. (2014). Renal pigmentation due to chronic bismuth administration in a rhesus macaque (macaca mulatta). *Veterinary Pathology,*

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.

Johnson, A. L., Ducore, R. M., Colgin, L. M., & Lewis, A. D. (2014). Hepatic abscesses in five outdoor-housed rhesus macaques (macaca mulatta). *Journal of Medical Primatology,*

Hepatic abscesses are uncommon in non-human primates and usually occur as multifocal microabscesses originating from bacteremia. Necropsy, histopathology, and bacterial cultures were performed on five subadult to adult female rhesus macaques (Macaca mulatta) that died spontaneously. Necropsy findings included cavitating abscesses in the right central liver lobe of all five animals, with intralesional plant material in four animals. This is the first report of cavitating hepatic abscesses with intralesional plant material in non-human primates.

Kang, K. T., Etheridge, S. P., Kantoch, M. J., Tisma-Dupanovic, S., Bradley, D. J., Balaji, S., et al. (2014). Current management of focal atrial tachycardia in children: A multi-center experience. *Circulation.Arrhythmia and Electrophysiology,*

BACKGROUND: -Focal atrial tachycardia (FAT) is an uncommon cause of supraventricular tachycardia in children. Incessant FAT can lead to tachycardia-induced cardiomyopathy. There is limited information regarding the clinical course and management of FAT. This study characterizes current management strategies for FAT in children including the prevalence of spontaneous resolution and the role of catheter ablation. METHODS AND RESULTS: -This is a retrospective chart review of pediatric patients with FAT managed between January 2000 and November 2010 at 10 pediatric centers. There were 249 patients with a median age at diagnosis of 7.2 years (95% confidence interval (CI) 5.8-10.4 years). Cardiomyopathy was observed in 28%. Resolution of FAT occurred in 89% including spontaneous resolution without catheter ablation in 34%. Antiarrhythmic medications were used for initial therapy in 154 patients with control of FAT in 72%. Among first-line medications, beta blockers were the most common (53%) and effective (42%). Catheter ablation was successful in 80% of patients. FAT recurrence was less common with electroanatomic mapping compared to conventional mapping techniques (16% vs. 35%, p=0.02). Patients were followed for a median of 2.1 years (95% CI 1.8-2.6 years). CONCLUSIONS: -FAT is managed successfully in most children. Current approaches are variable. Many patients have control of FAT with medications; however, catheter ablation is used for most patients. Spontaneous resolution is common for young children, emphasizing the role for delayed ablation in this group. Ablation is successful for all ages. Lower recurrence occurs when electroanatomic mapping techniques are employed.

Kanthaswamy, S., Johnson, Z., Trask, J. S., Smith, D. G., Ramakrishnan, R., Bahk, J., et al. (2014). Development and validation of a SNP-based assay for inferring the genetic ancestry of rhesus macaques (macaca mulatta). *American Journal of Primatology,*

Rhesus macaques (Macaca mulatta) are an important primate model species in several areas of biomedical research. The wide geographic distribution of this species has led to significant genetic differentiation among local and regional populations. These regional differences can be important factors in the selection of the most appropriate subjects for particular research studies, as

animals from different populations can respond differently to the same experimental treatment. Consequently, it is valuable to confirm the ancestry of individual rhesus monkeys from geographically distinct populations. Using DNA samples obtained from rhesus macaques from six National Primate Research Centers, we tested a set of 384 potential ancestry informative single nucleotide polymorphisms (SNPs) and identified a final panel of 91 SNPs that can reliably distinguish Indian-origin from Chinese-origin rhesus monkeys. This genetic test can be used to determine the ancestral origin of animals and to detect individuals that are hybrids between these two regional populations. To demonstrate use of the SNP panel, we investigated the ancestry of 480 animals from the Yerkes NPRC (YNPRC) for which the colony records were insufficient to clearly establish ancestry. Three of the YNPRC animals tested were determined to be hybrids. This SNP ancestry tool will be useful to researchers, colony managers, and others who wish to evaluate the ancestral origin of individual rhesus macaques, and therefore will facilitate more effective and efficient use of these animals in biomedical research. Am. J. Primatol. © 2014 Wiley Periodicals, Inc.

Kaplan, M. S., Huguet, N., Caetano, R., Giesbrecht, N., Kerr, W. C., & McFarland, B. H. (2014). Economic contraction, alcohol intoxication and suicide: Analysis of the national violent death reporting system. *Injury Prevention : Journal of the International Society for Child and Adolescent Injury Prevention,*

OBJECTIVES: Although there is a large and growing body of evidence concerning the impact of contracting economies on suicide mortality risk, far less is known about the role alcohol consumption plays in the complex relationship between economic conditions and suicide. The aims were to compare the postmortem alcohol intoxication rates among male and female suicide decedents before (2005-2007), during (2008-2009) and after (2010-2011) the economic contraction in the USA. METHODS: Data from the restricted National Violent Death Reporting System (2005-2011) for male and female suicide decedents aged 20 years and older were analysed by Poisson regression analysis to test whether there was significant change in the fractions of suicide decedents who were acutely intoxicated at the time of death (defined as blood alcohol content >/=0.08 g/dL) prior, during and after the downturn. RESULTS: The fraction of all suicide decedents with alcohol intoxication increased by 7% after the onset of the recession from

22.2% in 2005-2007 to 23.9% in 2008-2011. Compared with the years prior to the recession, male suicide decedents showed a 1.09-fold increased risk of alcohol intoxication within the first 2 years of the recession. Surprisingly, there was evidence of a lag effect among female suicide decedents, who had a 1.14-fold (95% CI 1.02 to 1.27) increased risk of intoxication in 2010-2011 compared with 2005-2007. CONCLUSIONS: These findings suggest that acute alcohol intoxication in suicide interacts with economic conditions, becoming more prevalent during contractions.

Karalunas, S. L., Fair, D., Musser, E. D., Aykes, K., Iyer, S. P., & Nigg, J. T. (2014). Subtyping attention-Deficit/Hyperactivity disorder using temperament dimensions : Toward biologically based nosologic criteria. *JAMA Psychiatry,*

Importance: Psychiatric nosology is limited by behavioral and biological heterogeneity within existing disorder categories. The imprecise nature of current nosologic distinctions limits both mechanistic understanding and clinical prediction. We demonstrate an approach consistent with the National Institute of Mental Health Research Domain Criteria initiative to identify superior, neurobiologically valid subgroups with better predictive capacity than existing psychiatric categories for childhood attention-deficit/hyperactivity disorder (ADHD). Objective: To refine subtyping of childhood ADHD by using biologically based behavioral dimensions (ie, temperament), novel classification algorithms, and multiple external validators. Design, Setting, and Participants: A total of 437 clinically well-characterized, community-recruited children, with and without ADHD, participated in an ongoing longitudinal study. Baseline data were used to classify children into subgroups based on temperament dimensions and examine external validators including physiological and magnetic resonance imaging measures. One-year longitudinal follow-up data are reported for a subgroup of the ADHD sample to address stability and clinical prediction. Main Outcomes and Measures: Parent/guardian ratings of children on a measure of temperament were used as input features in novel community detection analyses to identify subgroups within the sample. Groups were validated using 3 widely accepted external validators: peripheral physiological characteristics (cardiac measures of respiratory sinus arrhythmia and pre-ejection period), central nervous system functioning (via resting-state functional connectivity magnetic resonance imaging), and clinical outcomes (at 1-year

longitudinal follow-up). Results: The community detection algorithm suggested 3 novel types of ADHD, labeled as mild (normative emotion regulation), surgent (extreme levels of positive approach-motivation), and irritable (extreme levels of negative emotionality, anger, and poor soothability). Types were independent of existing clinical demarcations including DSM-5 presentations or symptom severity. These types showed stability over time and were distinguished by unique patterns of cardiac physiological response, resting-state functional brain connectivity, and clinical outcomes 1 year later. Conclusions and Relevance: Results suggest that a biologically informed temperament-based typology, developed with a discovery-based community detection algorithm, provides a superior description of heterogeneity in the ADHD population than does any current clinical nosologic criteria. This demonstration sets the stage for more aggressive attempts at a tractable, biologically based nosology.

Katznelson, L., Loriaux, D. L., Feldman, D., Braunstein, G. D., Schteingart, D. E., & Gross, C. (2014). Global clinical response in cushing's syndrome patients treated with mifepristone. *Clinical Endocrinology, 80*(4), 562-569.

Objective Mifepristone, a glucocorticoid receptor antagonist, improves clinical status in patients with Cushing's syndrome (CS). We examined the pattern, reliability and correlates of global clinical response (GCR) assessments during a 6-month clinical trial of mifepristone in CS. Design Post hoc analysis of secondary end-point data from a 24-week multicentre, open-label trial of mifepristone (300-1200 mg daily) in CS. Intraclass correlation coefficient (ICC) was used to examine rater concordance, and drivers of clinical improvement were determined by multivariate regression analysis. Patients Forty-six adult patients with refractory CS along with diabetes mellitus type 2 or impaired glucose tolerance, and/or a diagnosis of hypertension. Measurements Global clinical assessment made by three independent reviewers using a three-point ordinal scale (+1 = improvement; 0 = no change; -1 = worsening) based on eight broad clinical categories including glucose control, lipids, blood pressure, body composition, clinical appearance, strength, psychiatric/cognitive symptoms and quality of life at Weeks 6, 10, 16, and 24. Results Positive GCR increased progressively over time with 88% of patients having improved at Week 24 ($P < 0{\cdot}001$). The full concordance among reviewers occurred in 76·6% of evaluations resulting in an ICC of 0·652 ($P < 0{\cdot}001$). Changes in body weight ($P < 0{\cdot}0001$), diastolic blood pressure (P <

0·0001), two-hour postoral glucose challenge glucose concentration (P = 0·0003), and Cushingoid appearance (P = 0·022) were strong correlates of GCR. Conclusions Mifepristone treatment for CS results in progressive clinical improvement. Overall agreement among clinical reviewers was substantial and determinants of positive GCR included change in weight, blood pressure, glucose levels and appearance. © 2013 The Authors. Clinical Endocrinology published by John Wiley & Sons Ltd.

Keenan, B. P., Saenger, Y., Kafrouni, M. I., Leubner, A., Lauer, P., Maitra, A., et al. (2014). A listeria vaccine and depletion of T-regulatory cells activate immunity against early stage pancreatic intraepithelial neoplasms and prolong survival of mice. *Gastroenterology, 146*(7), 1784-94.e6. BACKGROUND & AIMS: Premalignant lesions and early stage tumors contain immunosuppressive microenvironments that create barriers for cancer vaccines. Kras(G12D/+);Trp53(R172H/+);Pdx-1-Cre (KPC) mice, which express an activated form of Kras in pancreatic tissues, develop pancreatic intraepithelial neoplasms (PanIN) that progress to pancreatic ductal adenocarcinoma (PDA). We used these mice to study immune suppression in PDA. METHODS: We immunized KPC and Kras(G12D/+);Pdx-1-Cre mice with attenuated intracellular Listeria monocytogenes (which induces CD4(+) and CD8(+) T-cell immunity) engineered to express Kras(G12D) (LM-Kras). The vaccine was given alone or in sequence with an anti-CD25 antibody (PC61) and cyclophosphamide to deplete T-regulatory (Treg) cells. Survival times were measured; pancreatic and spleen tissues were collected and analyzed by histologic, flow cytometry, and immunohistochemical analyses. RESULTS: Interferon gamma-mediated, CD8(+) T-cell responses were observed in KPC and Kras(G12D/+);Pdx-1-Cre mice given LM-Kras, but not in unvaccinated mice. Administration of LM-Kras to KPC mice 4-6 weeks old (with early stage PanINs), depleted of Treg cells, significantly prolonged survival and reduced PanIN progression (median survival, 265 days), compared with unvaccinated mice (median survival, 150 days; P = .002), mice given only LM-Kras (median survival, 150 days; P = .050), and unvaccinated mice depleted of Treg cells (median survival, 170 days; P = .048). In 8- to 12-week-old mice (with late-stage PanINs), LM-Kras, alone or in combination with Treg cell depletion, did not increase survival time or slow PanIN progression. The combination of LM-Kras and Treg cell depletion reduced numbers of Foxp3(+)CD4(+) T cells in pancreatic lymph nodes, increased numbers of CD4(+) T cells that

secrete interleukin 17 and interferon gamma, and caused CD11b(+)Gr1(+) cells in the pancreas to acquire an immunostimulatory phenotype. CONCLUSIONS: Immunization of KPC mice with Listeria monocytogenes engineered to express Kras(G12D), along with depletion of Treg cells, reduces progression of early stage, but not late-stage, PanINs. This approach increases infiltration of the lesion with inflammatory cells. It might be possible to design immunotherapies against premalignant pancreatic lesions to slow or prevent progression to PDA.

Keller, T. E., Collier, P. J., Blakeslee, J. E., Logan, K., McCracken, K., & Morris, C. (2014). Early career mentoring for translational researchers: Mentee perspectives on challenges and issues. *Teaching and Learning in Medicine, 26*(3), 211-216.

Background: The education and training of early career biomedical translational researchers often involves formal mentoring by more experienced colleagues. Purposes: This study investigated the nature of these mentoring relationships from the perspective of mentees. The objective was to understand the challenges and issues encountered by mentees in forming and maintaining productive mentoring relationships. Methods: Three focus groups (n = 14) were conducted with early career researchers who had mentored career development awards. Thematic analysis identified, categorized, and illustrated the challenges and issues reported by mentees. Results: The range of mentee challenges was reflected in five major categories: (a) network-finding appropriate mentors to meet various needs; (b) access-structuring schedules and opportunities to receive mentoring; (c) expectations-negotiating the mechanics of the mentoring relationship and its purpose; (d) alignment-managing mentor-mentee mismatches regarding interests, priorities, and goals; and (e) skills and supports-developing the institutional supports to be successful. Conclusions: Mentoring relationships created for academic training and career development contend with tasks common to many other relationships, namely, recognizing compatibility, finding time, establishing patterns, agreeing to goals, and achieving aims. Identifying challenges faced by mentees can facilitate the development of appropriate trainings and supports to foster mentoring relationships in academic and career settings. © 2014

Kelly, D. F., Chaloner, C., Evans, D., Mathews, A., Cohan, P., Wang, C., et al. (2014). Prevalence of pituitary hormone dysfunction, metabolic syndrome, and impaired quality of life in retired professional football players: A prospective study. *Journal of Neurotrauma, 31*(13), 1161-1171. Hypopituitarism is common after moderate and severe traumatic brain injury (TBI). Herein, we address the association between mild TBI (mTBI) and pituitary and metabolic function in retired football players. Retirees 30-65 years of age, with one or more years of National Football League (NFL) play and poor quality of life (QoL) based on Short Form 36 (SF-36) Mental Component Score (MCS) were prospectively enrolled. Pituitary hormonal and metabolic syndrome (MetS) testing was performed. Using a glucagon stimulation test, growth hormone deficiency (GHD) was defined with a standard cut point of 3 ng/mL and with a more stringent body mass index (BMI)-adjusted cut point. Subjects with and without hormonal deficiency (HD) were compared in terms of QoL, International Index of Erectile Function (IIEF) scores, metabolic parameters, and football career data. Of 74 subjects, 6 were excluded because of significant non-football-related TBIs. Of the remaining 68 subjects (mean age, 47.3±10.2 years; median NFL years, 5; median NFL concussions, 3; mean BMI, 33.8±6.0), 28 (41.2%) were GHD using a peak GH cutoff of <3 ng/mL. However, with a BMI-adjusted definition of GHD, 13 of 68 (19.1%) were GHD. Using this BMI-adjusted definition, overall HD was found in 16 (23.5%) subjects: 10 (14.7%) with isolated GHD; 3 (4.4%) with isolated hypogonadism; and 3 (4.4%) with both GHD and hypogonadism. Subjects with HD had lower mean scores on the IIEF survey (p=0.016) and trended toward lower scores on the SF-36 MCS (p=0.113). MetS was present in 50% of subjects, including 5 of 6 (83%) with hypogonadism, and 29 of 62 (46.8%) without hypogonadism (p=0.087). Age, BMI, median years in NFL, games played, number of concussions, and acknowledged use of performance-enhancing steroids were similar between HD and non-HD groups. In summary, in this cohort of retired NFL players with poor QoL, 23.5% had HD, including 19% with GHD (using a BMI-adjusted definition), 9% with hypogonadism, and 50% had MetS. Although the cause of HD is unclear, these results suggest that GHD and hypogonadism may contribute to poor QoL, erectile dysfunction, and MetS in this population. Further study of pituitary function is warranted in athletes sustaining repetitive mTBI.

Kernstine, K. H., Moon, J., Kraut, M. J., Pisters, K. M., Sonett, J. R., Rusch, V. W., et al. (2014). Trimodality therapy for superior sulcus non-small cell lung cancer: Southwest oncology group-intergroup trial S0220. *The Annals of Thoracic Surgery,*

BACKGROUND: Although preoperative chemotherapy (cisplatin-etoposide) and radiotherapy, followed by surgical resection, is considered a standard of care for superior sulcus cancers, treatment is rigorous and relapse limits long-term survival. The Southwest Oncology Group-Intergroup Trial S0220 was designed to incorporate an active systemic agent, docetaxel, as consolidation therapy. METHODS: Patients with histologically proven and radiologically defined T3 to 4, N0 to 1, M0 superior sulcus non-small cell lung cancer underwent induction therapy with cisplatin-etoposide, concurrently with thoracic radiotherapy at 45 Gy. Nonprogressing patients underwent surgical resection within 7 weeks. Consolidation consisted of docetaxel every 3 weeks for 3 doses. The accrual goal was 45 eligible patients. The primary objective was feasibility. RESULTS: Of 46 patients registered, 44 were eligible and assessable; 38 (86%) completed induction, 29 (66%) underwent surgical resection, and 20 (45% of eligible, 69% surgical, and 91% of those initiating consolidation therapy) completed consolidation docetaxel; 28 of 29 (97%) underwent a complete (R0) resection; 2 (7%) died of adult respiratory distress syndrome. In resected patients, 21 of 29 (72%) had a pathologic complete or nearly complete response. The known site of first recurrence was local in 2, local-systemic in 1, and systemic in 10, with 7 in the brain only. The 3-year progression-free survival was 56%, and 3-year overall survival was 61%. CONCLUSIONS: Although trimodality therapy provides excellent R0 and local control, only 66% of patients underwent surgical resection and only 45% completed the treatment regimen. Even in this subset, distant recurrence continues to be a major problem, particularly brain-only relapse. Future strategies to improve treatment outcomes in this patient population must increase the effectiveness of systemic therapy and reduce the incidence of brain-only metastases.

Kimani, S., Sinei, K., Bukachi, F., Tshala-Katumbay, D., & Maitai, C. (2014). Memory deficits associated with sublethal cyanide poisoning relative to cyanate toxicity in rodents. *Metabolic Brain Disease, 29*(1), 105-112.

Food (cassava) linamarin is metabolized into neurotoxicants cyanide and cyanate, metabolites of which we sought to elucidate the differential toxicity effects on memory. Young 6-8 weeks old

male rats were treated intraperitoneally with either 2.5 mg/kg body weight (bw) cyanide (NaCN), or 50 mg/kg bw cyanate (NaOCN), or 1 µl/g bw saline, daily for 6 weeks. Short-term and long-term memories were assessed using a radial arm maze (RAM) testing paradigm. Toxic exposures had an influence on short-term working memory with fewer correct arm entries ($F2, 19=4.57$ $p<0.05$), higher working memory errors (WME) ($F2, 19=5.09$, $p<0.05$) and longer RAM navigation time ($F 2, 19=3.91$, $p<0.05$) for NaOCN relative to NaCN and saline treatments. The long-term working memory was significantly impaired by cyanide with fewer correct arm entries ($F2, 19=7.45$, $p<0.01$) and increased working memory errors ($F2, 19=9.35$ $p<0.05$) in NaCN relative to NaOCN or vehicle treated animals. Reference memory was not affected by either cyanide or cyanate. Our study findings provide an experimental evidence for the biological plausibility that cassava cyanogens may induce cognition deficits. Differential patterns of memory deficits may reflect the differences in toxicity mechanisms of NaOCN relative to NaCN. Cognition deficits associated with cassava cyanogenesis may reflect a dual toxicity effect of cyanide and cyanate.

Kircher, M., Witten, D. M., Jain, P., O'roak, B. J., Cooper, G. M., & Shendure, J. (2014). A general framework for estimating the relative pathogenicity of human genetic variants. *Nature Genetics, 46*(3), 310-315.

Current methods for annotating and interpreting human genetic variation tend to exploit a single information type (for example, conservation) and/or are restricted in scope (for example, to missense changes). Here we describe Combined Annotation-Dependent Depletion (CADD), a method for objectively integrating many diverse annotations into a single measure (C score) for each variant. We implement CADD as a support vector machine trained to differentiate 14.7 million high-frequency human-derived alleles from 14.7 million simulated variants. We precompute C scores for all 8.6 billion possible human single-nucleotide variants and enable scoring of short insertions-deletions. C scores correlate with allelic diversity, annotations of functionality, pathogenicity, disease severity, experimentally measured regulatory effects and complex trait associations, and they highly rank known pathogenic variants within individual genomes. The ability of CADD to prioritize functional, deleterious and pathogenic variants across

many functional categories, effect sizes and genetic architectures is unmatched by any current single-annotation method. © 2014 Nature America, Inc. © 2014 Nature America, Inc.

Kopelovich, J. C., Reiss, L. A., Oleson, J. J., Lundt, E. S., Gantz, B. J., & Hansen, M. R. (2014). Risk factors for loss of ipsilateral residual hearing after hybrid cochlear implantation. *Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology,*

OBJECTIVE: Residual low-frequency acoustic hearing benefits cochlear implantees in difficult listening situations such as understanding speech in noise and music appreciation. Most subjects retain functional residual hearing in the operated ear. A small number of patients, however, will lose significant ipsilateral residual hearing after short-electrode cochlear implantation. The objectives of this retrospective series are to determine whether predisposition to hearing loss after implantation exists in a subset of patients and to assess the functional impact of this hearing loss on clinical measures of combined electric and acoustic hearing. STUDY DESIGN: Retrospective case series. SETTING: Multicenter clinical trial; tertiary care facility. PATIENTS: Hearing preservation cochlear implant recipients. MAIN OUTCOME MEASURE: Frequency-averaged ipsilateral hearing loss at 1 year after activation. RESULTS: Eighty-five patients from the Hybrid S8 FDA trial had serial postoperative audiometric measurements. Twenty-two of these patients, implanted at the home institution, provided additional medical data. Univariate analysis (Pearson's, Spearman's, Student's t test) showed that the severity of hearing loss at 1 year after activation was significantly correlated with age, male gender, and noise-induced hearing loss as the etiology of hearing impairment. A multivariate regression model corroborated these variables. No other medical factors were predictive. Clinical measures of speech perception (Consonant-Nucleus-Consonant and Hearing in Noise Test) worsened with hearing loss in ipsilateral but not bilateral listening conditions. CONCLUSION: Age, male gender, and a history of noise-induced hearing loss correlate with the severity of hearing loss at 1 year after activation. Even the most severely affected patients benefit from bilateral electric and acoustic inputs.

Krishnamoorthy, B., Bay, B. K., & Hart, R. A. (2014). Bone mineral density and donor age are not predictive of femoral ring allograft bone mechanical strength. *Journal of Orthopaedic Research,*

While metal or plastic interbody spinal fusion devices are manufactured to appropriate mechanical standards, mechanical properties of commercially prepared structural allograft bone remain relatively unassessed. Robust models predicting compressive load to failure of structural allograft bone based on easily measured variables would be useful. Three hundred twenty seven femoral rings from 34 cadaver femora were tested to failure in axial compression. Predictive variables included age, gender, bone mineral density (BMD), position along femoral shaft, maximum/minimum wall thickness, outer/inner diameter, and area. We used support vector regression and 10-fold cross-validation to develop robust nonlinear predictive models for load to failure. Model performance was measured by the root-mean-squared-deviation (RMSD) and correlation coefficients (r). A polynomial model using all variables had RMSD=7.92, r=0.84, indicating excellent performance. A model using all variables except BMD was essentially unchanged (RMSD=8.12, r=0.83). Eliminating both age and BMD produced a model with RMSD=8.41, r=0.82, again essentially unchanged. Compressive strength of structural allograft bone can be estimated using easily measured geometric parameters, without including BMD or age. As DEXA is costly and cumbersome, and setting upper age-limits for potential donors reduces the supply, our results may prove helpful to increase the quality and availability of structural allograft.

Kuchena, A., Merkel, M. J., & Hutchens, M. P. (2014). Postcardiac arrest temperature management: Infectious risks. *Current Opinion in Critical Care,*

PURPOSE OF REVIEW: Therapeutic hypothermia following out-of-hospital cardiac arrest improves neurological recovery. Coupled with neurological benefit, multiple complications including infection have been associated with therapeutic hypothermia following out-of-hospital cardiac arrest. In this review, we will discuss therapeutic hypothermia, and more broadly, temperature management, as a risk for ICU infection. RECENT FINDINGS: The application of therapeutic hypothermia following out-of-hospital cardiac arrest has been associated with infectious complications. Studies of hypothermic animal models have provided useful insights into mechanisms by which therapeutic hypothermia confers neuroprotection. Ironically, the same mechanisms through which therapeutic hypothermia provides neuroprotection have been implicated in the risk of infection associated with therapeutic hypothermia. Studies have

demonstrated types of infections, pathogens, and the impact of infections on mortality and neurological recovery. SUMMARY: Studies demonstrate increased rate of pneumonia and bacteremia but decreased rate of other infections, suggesting redistribution but no overall increased risk of infection per se. The diagnosis of infection during therapeutic hypothermia does not impact mortality or neurological recovery.

Landry, G. J. (2004). *Chronic limb-threatening ischemia* Elsevier Inc.

Lee, C. H., Lu, W., Michel, J. C., Goehring, A., Du, J., Song, X., et al. (2014). NMDA receptor structures reveal subunit arrangement and pore architecture. *Nature, 511*(7508), 191-197. N-methyl-d-aspartate (NMDA) receptors are Hebbian-like coincidence detectors, requiring binding of glycine and glutamate in combination with the relief of voltage-dependent magnesium block to open an ion conductive pore across the membrane bilayer. Despite the importance of the NMDA receptor in the development and function of the brain, a molecular structure of an intact receptor has remained elusive. Here we present X-ray crystal structures of the Xenopus laevis GluN1-GluN2B NMDA receptor with the allosteric inhibitor, Ro25-6981, partial agonists and the ion channel blocker, MK-801. Receptor subunits are arranged in a 1-2-1-2 fashion, demonstrating extensive interactions between the amino-terminal and ligand-binding domains. The transmembrane domains harbour a closed-blocked ion channel, a pyramidal central vestibule lined by residues implicated in binding ion channel blockers and magnesium, and a approximately twofold symmetric arrangement of ion channel pore loops. These structures provide new insights into the architecture, allosteric coupling and ion channel function of NMDA receptors.

Lee, C. S., Hiatt, S. O., Denfeld, Q. E., Mudd, J. O., Chien, C., & Gelow, J. M. (2014). Symptom-hemodynamic mismatch and heart failure event risk. *The Journal of Cardiovascular Nursing,* BACKGROUND:: Heart failure (HF) is a heterogeneous condition of both symptoms and hemodynamics. OBJECTIVE:: The goals of this study were to identify distinct profiles among integrated data on physical and psychological symptoms and hemodynamics and quantify differences in 180-day event risk among observed profiles. METHODS:: A secondary analysis of data collected during 2 prospective cohort studies by a single group of investigators was performed. Latent class mixture modeling was used to identify distinct symptom-hemodynamic

profiles. Cox proportional hazards modeling was used to quantify difference in event risk (HF emergency visit, hospitalization, or death) among profiles. RESULTS:: The mean age (n = 291) was 57 +/- 13 years, 38% were female, and 61% had class III/IV HF. Three distinct symptom-hemodynamic profiles were identified: 17.9% of patients had concordant symptoms and hemodynamics (ie, moderate physical and psychological symptoms matched the comparatively good hemodynamic profile), 17.9% had severe symptoms and average hemodynamics, and 64.2% had poor hemodynamics and mild symptoms. Compared with those in the concordant profile, both profiles of symptom-hemodynamic mismatch were associated with a markedly increased event risk (severe symptoms hazards ratio, 3.38; P = .033; poor hemodynamics hazards ratio, 3.48; P = .016). CONCLUSIONS:: A minority of adults with HF have concordant symptoms and hemodynamics. Either profile of symptom-hemodynamic mismatch in HF is associated with a greater risk of healthcare utilization for HF or death.

Lee, C. S., Mudd, J. O., Hiatt, S. O., Gelow, J. M., Chien, C., & Riegel, B. (2014). Trajectories of heart failure self-care management and changes in quality of life. *European Journal of Cardiovascular Nursing : Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology,*

INTRODUCTION: Heart failure patients vary considerably in their self-care management behaviors (i.e. recognizing and responding to symptoms). The goal of this study was to identify unique patterns of change in heart failure self-care management and quantify associations between self-care management and quality of life (HRQOL) over time. METHODS: A prospective cohort study among adults with symptomatic heart failure was designed to measure changes in self-care management (Self-care of Heart Failure Index) and HRQOL (Kansas City Cardiomyopathy Questionnaire) over six months. Growth mixture modeling was used to identify unique trajectories of change in self-care management. RESULTS: The mean age (n=146) was 57 years, 70% were male, and 41% had class II heart failure. Two trajectories of self-care management were identified (entropy = 0.88). The larger trajectory (73.3%) was characterized by a significant decline in self-care management over time and no change in HRQOL. The smaller trajectory (26.7%) was characterized by marked improvements in self-care management and HRQOL. Changes in heart failure self-care management occurred in the absence of change in

routine self-care maintenance behaviors, functional classification, and physical and psychological symptoms. Patients with greater physical symptoms at enrollment (odds ratio (OR) =1.04, p=0.037), larger left ventricles (OR=1.50, p=0.044), and ischemic heart failure (OR=3.84, p=0.014) were more likely to have the declining trajectory of self-care management. Higher levels of depression at enrollment were associated with reduced odds of having a decline in self-care management over time (OR=0.85, p<0.001). CONCLUSIONS: There are unique and clinically-relevant trajectories of change in heart failure self-care management that are associated with differences in HRQOL.

Lee, K. K., Gorman, A. K., & Swanson, N. A. (2005). *Scar revision* Elsevier Inc.

Lee, S. W., Parker, D. L., Geszvain, K., & Tebo, B. M. (2014). Effects of exogenous pyoverdines on fe availability and their impacts on mn(II) oxidation by pseudomonas putida GB-1. *Frontiers in Microbiology, 5*, 301.

Pseudomonas putida GB-1 is a Mn(II)-oxidizing bacterium that produces pyoverdine-type siderophores (PVDs), which facilitate the uptake of Fe(III) but also influence MnO2 formation. Recently, a non-ribosomal peptide synthetase mutant that does not synthesize PVD was described. Here we identified a gene encoding the PVDGB-1 (PVD produced by strain GB-1) uptake receptor (PputGB1_4082) of strain GB-1 and confirmed its function by in-frame mutagenesis. Growth and other physiological responses of these two mutants and of wild type were compared during cultivation in the presence of three chemically distinct sets of PVDs (siderotypes n degrees 1, n degrees 2, and n degrees 4) derived from various pseudomonads. Under iron-limiting conditions, Fe(III) complexes of various siderotype n degrees 1 PVDs (including PVDGB-1) allowed growth of wild type and the synthetase mutant, but not the receptor mutant, confirming that iron uptake with any tested siderotype n degrees 1 PVD depended on PputGB1_4082. Fe(III) complexes of a siderotype n degrees 2 PVD were not utilized by any strain and strongly induced PVD synthesis. In contrast, Fe(III) complexes of siderotype n degrees 4 PVDs promoted the growth of all three strains and did not induce PVD synthesis by the wild type, implying these complexes were utilized for iron uptake independent of PputGB1_4082. These differing properties of the three PVD types provided a way to differentiate between effects on

MnO2 formation that resulted from iron limitation and others that required participation of the PVDGB-1 receptor. Specifically, MnO2 production was inhibited by siderotype n degrees 1 but not n degrees 4 PVDs indicating PVD synthesis or PputGB1_4082 involvement rather than iron-limitation caused the inhibition. In contrast, iron limitation was sufficient to explain the inhibition of Mn(II) oxidation by siderotype n degrees 2 PVDs. Collectively, our results provide insight into how competition for iron via siderophores influences growth, iron nutrition and MnO2 formation in more complex environmental systems.

Lee, T. H., Hampton, D. A., Diggs, B. S., McCully, S. P., Kutcher, M., Redick, B. J., et al. (2014). Traumatic brain injury is not associated with coagulopathy out of proportion to injury in other body regions. *The Journal of Trauma and Acute Care Surgery, 77*(1), 67-72.
BACKGROUND: Coagulopathy following trauma is associated with poor outcomes. Traumatic brain injury has been associated with coagulopathy out of proportion to other body regions. We hypothesized that injury severity and shock determine coagulopathy independent of body region injured. METHODS: We performed a prospective, multicenter observational study at three Level 1 trauma centers. Conventional coagulation tests (CCTs) and rapid thrombelastography (r-TEG) were used. Admission vital signs, base deficit (BD), CCTs, and r-TEG data were collected. The Abbreviated Injury Scale (AIS) score and Injury Severity Score (ISS) were obtained. Severe injury was defined as AIS score greater than or equal to 3 for each body region. Patients were grouped according to their dominant AIS region of injury. Dominant region of injury was defined as the single region with the highest AIS score. Patients with two or more regions with the same greatest AIS score and patients without a region with an AIS score greater than or equal to 3 were excluded. Coagulation parameters were compared between the dominant AIS region. Significant hypoperfusion was defined as BD greater than or equal to 6. RESULTS: Of the 795 patients enrolled, 462 met criteria for grouping by dominant AIS region. Patients were predominantly white (59%), were male (75%), experienced blunt trauma (71%), and had a median ISS of 25 (interquartile range, 14-29). Patients with BD greater than or equal to 6 (n = 110) were hypocoagulable by CCT and r-TEG compared with patients with BD less than 6 (n = 223). Patients grouped by dominant AIS region showed no significant differences for any r-TEG or CCT parameter. Patients with BD greater than or equal to 6 demonstrated no difference in any r-

TEG or CCT parameter between dominant AIS regions. CONCLUSION: Coagulopathy results from a combination of tissue injury and shock independent of the dominant region of injury. With the use of AIS as a measure of injury severity, traumatic brain injury was not independently associated with more profound coagulopathy. LEVEL OF EVIDENCE: Epidemiologic study, level III.

Li, H., Margolick, J. B., Bream, J. H., Nilles, T. L., Langan, S., Bui, H. T., et al. (2014). Heterogeneity of CD4+ and CD8+ T-cell responses to cytomegalovirus in HIV-infected and HIV-uninfected men who have sex with men. *Journal of Infectious Diseases, 210*(3), 400-404.
Studies of T-cell immunity to human cytomegalovirus (CMV) primarily reflect anti-CMV pp65 or immediate early antigen 1 (IE-1) activity. We assessed responses of T cells from human immunodeficiency virus (HIV)-negative and HIV-infected men to peptide pools spanning 19 CMV open reading frames selected because they previously correlated with total CMV-specific T-cell responses in healthy donors. Cells producing cytokines in response to pp65 or IE-1 together composed <12% and <40% of the total CD4+ and CD8+ T-cell responses to CMV, respectively. These proportions were generally similar regardless of HIV serostatus. Thus, analyses of total CMV-specific T-cell responses should extend beyond pp65 and IE-1 regardless of HIV serostatus.

Liebling, M. R. (2014). Headache in systemic lupus erythematosus: Results from a prospective, international inception cohort study. *Arthritis & Rheumatology (Hoboken, N.J.),*

Liem, T. K., & DeLoughery, T. G. (2014). Randomised controlled trial: Extended-duration dabigatran is non-inferior to warfarin and more effective than placebo for symptomatic VTE. *Evidence-Based Medicine, 19*(1), 29.

Link, H. W. (2014). Pediatric asthma in a nutshell. *Pediatrics in Review / American Academy of Pediatrics, 35*(7), 287-298.

Liu, X., Grandy, D. K., & Janowsky, A. (2014). Ractopamine, a livestock feed additive, is a full agonist at trace amine-associated receptor 1. *Journal of Pharmacology and Experimental Therapeutics,*

350(1), 124-129.

Ractopamine (RAC) is fed to an estimated 80% of all beef, swine, and turkey raised in the United States. It promotes muscle mass development, limits fat deposition, and reduces feed consumption. However, it has several undesirable behavioral side effects in livestock, especially pigs, including restlessness, agitation, excessive oral-facial movements, and aggressive behavior. Numerous in vitro and in vivo studies suggest RAC's physiological actions begin with its stimulation of ß1- and ß2-adrenergic receptor-mediated signaling in skeletal muscle and adipose tissue; however, the molecular pharmacology of RAC's psychoactive effects is poorly understood. Using human cystic fibrosis transmembrane conductance regulator (hCFTR) chloride channels as a sensor for intracellular cAMP, we found that RAC and p-tyramine (TYR) produced concentrationdependent increases in chloride conductance in oocytes coexpressing hCFTR and mouse trace amine-associated receptor 1 (mTAAR1), which was completely reversed by the trace amine-associated receptor 1 (TAAR1)-selective antagonist EPPTB [N-(3-ethoxyphenyl)-4-pyrrolidin-1-yl-3- trifluoromethylbenzamide]. Oocytes coexpressing hCFTR and the human ß2-adrenergic receptor showed no response to RAC or TYR. These studies demonstrate that, contrary to expectations, RAC is not an agonist of the human ß2-adrenergic receptor but rather a full agonist for mTAAR1. Since TAAR1-mediated signaling can influence cardiovascular tone and behavior in several animal models, our finding that RAC is a full mTAAR1 agonist supports the idea that this novel mechanism of action influences the physiology and behavior of pigs and other species. These findings should stimulate future studies to characterize the pharmacological, physiological, and behavioral actions of RAC in humans and other species exposed to this drug.

Lo, J. O., Kerns, E., Rueda, J., & Marshall, N. E. (2014). Minimal change disease in pregnancy. *Journal of Maternal-Fetal and Neonatal Medicine, 27*(12), 1282-1284.

Background: New onset minimal change disease (MCD) is rare in pregnancy with the potential for serious complications including acute kidney injury (AKI). Case: A case of MCD was diagnosed at 19 weeks gestation by renal biopsy. Within one month of starting steroids, the patient experienced normalization of renal function and resolution of nephrotic syndrome, although hemodialysis was needed as a temporizing measure. Conclusion: The differential diagnosis for new onset proteinuria in pregnancy should include MCD. In selected cases, renal biopsy can be

used to confirm diagnosis, and when indicated, hemodialysis should be instituted while awaiting a response to steroid therapy.

Lo, J. O., Reddy, A. P., Wilmarth, P. A., Roberts, V. H. J., Kinhnarath, A., Snyder, J., et al. (2014). Proteomic analysis of cervical vaginal fluid proteins among women in recurrent preterm labor. *Journal of Maternal-Fetal and Neonatal Medicine, 27*(12), 1183-1188.

Objective: Proteomic analysis of four cervical-vaginal fluid (CVF) proteins to identify biomarkers of recurrent preterm birth (rPTB) in at-risk women prior to onset of preterm labor. Methods: Nested case control study from 2007 to 2011 of women with prior spontaneous preterm birth(s) (PTB) who underwent serial CVF sampling. Mass spectrometry analysis was used and ELISA analysis was performed to validate candidates. Results: 108 patients were enrolled and 10 cases and 20 gestational age matched controls were analyzed after exclusions. Of 748 CVF proteins identified, 72 had statistically significant ($p<0.05$) expression differences and 38 were highly differentially expressed ($p<0.01$). Four candidate proteins were abundant and involved in immune/inflammatory response, but ELISA analysis did not confirm altered expression patterns. Conclusion: The lack of confirmation of potential biomarkers identified by mass spectrometry and ELISA demonstrates the challenges of validating PTB biomarkers and suggests that a panel of biomarkers would improve the predictive value of CVF testing.

Long, C. R., Ackerman, D. L., Hammerschlag, R., Delagran, L., Peterson, D. H., Berlin, M., et al. (2014). Faculty development initiatives to advance research literacy and evidence-based practice at CAM academic institutions. *Journal of Alternative and Complementary Medicine, 20*(7), 563-570.

Objectives: To present the varied approaches of 9 complementary and alternative medicine (CAM) institutions (all grantees of the National Center for Complementary and Alternative Medicine) used to develop faculty expertise in research literacy and evidence-based practice (EBP) in order to integrate these concepts into CAM curricula. Design: A survey to elicit information on the faculty development initiatives was administered via e-mail to the 9 program

directors. All 9 completed the survey, and 8 grantees provided narrative summaries of faculty training outcomes. Results: The grantees found the following strategies for implementing their programs most useful: assess needs, develop and adopt research literacy and EBP competencies, target early adopters and change leaders, employ best practices in teaching and education, provide meaningful incentives, capitalize on resources provided by grant partners, provide external training opportunities, and garner support from institutional leadership. Instructional approaches varied considerably across grantees. The most common were workshops, online resources, in-person short courses, and in-depth seminar series developed by the grantees. Many also sent faculty to intensive multiday extramural training programs. Program evaluation included measuring participation rates and satisfaction and the integration of research literacy and EBP learning objectives throughout the academic curricula. Most grantees measured longitudinal changes in beliefs, attitudes, opinions, and competencies with repeated faculty surveys. Conclusions: A common need across all 9 CAM grantee institutions was foundational training for faculty in research literacy and EBP. Therefore, each grantee institution developed and implemented a faculty development program. In developing the framework for their programs, grantees used strategies that were viewed critical for success, including making them multifaceted and unique to their specific institutional needs. These strategies, in conjunction with the grantees' instructional approaches, can be of practical use in other CAM and non-CAM academic environments considering the introduction of research literacy and EBP competencies into their curricula.

Lopez, C. S., Sloan, R., Cylinder, I., Kozak, S. L., Kabat, D., & Barklis, E. (2014). RRE-dependent HIV-1 env RNA effects on gag protein expression, assembly and release. *Virology, 462-463C*, 126-134.

The HIV-1 Gag proteins are translated from the full-length HIV-1 viral RNA (vRNA), whereas the envelope (Env) protein is translated from incompletely spliced Env mRNAs. Nuclear export of vRNAs and Env mRNAs is mediated by the Rev accessory protein which binds to the rev-responsive element (RRE) present on these RNAs. Evidence has shown there is a direct or indirect interaction between the Gag protein, and the cytoplasmic tail (CT) of the Env protein. Our current work shows that env gene expression impacts HIV-1 Gag expression and function in

two ways. At the protein level, full-length Env expression altered Gag protein expression, while Env CT-deletion proteins did not. At the RNA level, RRE-containing Env mRNA expression reduced Gag expression, processing, and virus particle release from cells. Our results support models in which Gag is influenced by the Env CT, and Env mRNAs compete with vRNAs for nuclear export.

Lou, S. M., Larkin, K. L., Winthrop, K., Rosenbaum, J. T., & members of Uveitis Specialists Study Group. (2014). Lack of consensus in the diagnosis and treatment for ocular tuberculosis among uveitis specialists. *Ocular Immunology and Inflammation,* , 1-7.

Abstract Purpose: To assess the approach of specialists to ocular tuberculosis (TB). Methods: The American Uveitis Society (AUS) Listserv was surveyed using two clinical cases and general questions. Results: Of 196 members, 87 responded (44.4%), of whom 64 were affiliated with practices in North America, while 23 were outside of North America. The survey provided normative data on how physicians evaluate patients with uveitis as well as opinions about ocular TB. Responses varied widely on such issues as (1) the pretest probability that a patient with granulomatous panuveitis had TB uveitis (range 1-75%) or that a patient with a risk factor for TB had ocular TB (range 0-90%); (2) the optimal duration of anti-TB therapy; and (3) whether therapy should be discontinued after 2 months in nonresponders. Conclusions: Consensus is lacking among uveitis specialists for the diagnosis or management of ocular TB.

Lu, Y., Wajapeyee, N., Turker, M. S., & Glazer, P. M. (2014). Silencing of the DNA mismatch repair gene MLH1 induced by hypoxic stress in a pathway dependent on the histone demethylase LSD1. *Cell Reports, 8*(2), 501-513.

Silencing of MLH1 is frequently seen in sporadic colorectal cancers. We show here that hypoxia causes decreased histone H3 lysine 4 (H3K4) methylation at the MLH1 promoter via the action of the H3K4 demethylases LSD1 and PLU-1 and promotes durable long-term silencing in a pathway that requires LSD1. Knockdown of LSD1 or its corepressor, CoREST, also prevents the resilencing (and associated cytosine DNA methylation) of the endogenous MLH1 promoter in RKO colon cancer cells following transient reactivation by treatment with the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (5-aza-dC). The results demonstrate that hypoxia is a driving force for silencing of MLH1 and that the LSD1/CoREST complex is necessary for this process. The

results reveal a mechanism by which hypoxia promotes cancer cell evolution to drive malignant progression through epigenetic modulation. Our findings suggest that LSD1/CoREST acts as a colon cancer oncogene by epigenetically silencing MLH1 and also identify the LSD1/CoREST complex as a potential target for therapy.

Luteijn, R. D., Hoelen, H., Kruse, E., van Leeuwen, W. F., Grootens, J., Horst, D., et al. (2014). Cowpox virus protein CPXV012 eludes CTLs by blocking ATP binding to TAP. *Journal of Immunology (Baltimore, Md.: 1950), 193*(4), 1578-1589.
CD8(+) CTLs detect virus-infected cells through recognition of virus-derived peptides presented at the cell surface by MHC class I molecules. The cowpox virus protein CPXV012 deprives the endoplasmic reticulum (ER) lumen of peptides for loading onto newly synthesized MHC class I molecules by inhibiting the transporter associated with Ag processing (TAP). This evasion strategy allows the virus to avoid detection by the immune system. In this article, we show that CPXV012, a 9-kDa type II transmembrane protein, prevents peptide transport by inhibiting ATP binding to TAP. We identified a segment within the ER-luminal domain of CPXV012 that imposes the block in peptide transport by TAP. Biophysical studies show that this domain has a strong affinity for phospholipids that are also abundant in the ER membrane. We discuss these findings in an evolutionary context and show that a frameshift deletion in the CPXV012 gene in an ancestral cowpox virus created the current form of CPXV012 that is capable of inhibiting TAP. In conclusion, our findings indicate that the ER-luminal domain of CPXV012 inserts into the ER membrane, where it interacts with TAP. CPXV012 presumably induces a conformational arrest that precludes ATP binding to TAP and, thus, activity of TAP, thereby preventing the presentation of viral peptides to CTLs.

Ma, H., Morey, R., O'Neil, R. C., He, Y., Daughtry, B., Schultz, M. D., et al. (2014). Abnormalities in human pluripotent cells due to reprogramming mechanisms. *Nature, 511*(7508), 177-183.
Human pluripotent stem cells hold potential for regenerative medicine, but available cell types have significant limitations. Although embryonic stem cells (ES cells) from in vitro fertilized embryos (IVF ES cells) represent the 'gold standard', they are allogeneic to patients. Autologous induced pluripotent stem cells (iPS cells) are prone to epigenetic and transcriptional aberrations.

To determine whether such abnormalities are intrinsic to somatic cell reprogramming or secondary to the reprogramming method, genetically matched sets of human IVF ES cells, iPS cells and nuclear transfer ES cells (NT ES cells) derived by somatic cell nuclear transfer (SCNT) were subjected to genome-wide analyses. Both NT ES cells and iPS cells derived from the same somatic cells contained comparable numbers of de novo copy number variations. In contrast, DNA methylation and transcriptome profiles of NT ES cells corresponded closely to those of IVF ES cells, whereas iPS cells differed and retained residual DNA methylation patterns typical of parental somatic cells. Thus, human somatic cells can be faithfully reprogrammed to pluripotency by SCNT and are therefore ideal for cell replacement therapies.

Macy, M., Marks, K., & Towle, A. (2014). Missed, misused, or mismanaged: Improving early detection systems to optimize child outcomes. *Topics in Early Childhood Special Education, 34*(2), 94-105. Early detection efforts have been shown to vary greatly in practice, and there is a general lack of systematic accountability built into monitoring early detection effort impact. This article reviews current early detection practices and the drawbacks of these practices, with particular attention given to prevalent issues of mismeasurement, misuse, and mismanagement across the Child Find system under Individuals With Disabilities Education Act (IDEA). The benefits of a nationally recognized research and/or consensus-driven "baseline definition" for which children should be deemed Early Intervention (EI) or Early Childhood Special Education (ECSE) eligible are discussed. Recommendations are provided to better identify and serve young children with developmental-behavioral problems (as well as their families), and to cultivate more cohesive standards for professional practice in referring children for appropriate medical, social, and educational services.

Maggiore, R. J., Dale, W., Gross, C. P., Feng, T., Tew, W. P., Mohile, S. G., et al. (2014). Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: Effect on chemotherapy-related toxicity and hospitalization during treatment. *Journal of the American Geriatrics Society,*

OBJECTIVES: To evaluate the prevalence of polypharmacy and potentially inappropriate medication (PIM) use and the association between these and chemotherapy-related adverse

events in older adults with cancer undergoing chemotherapy. DESIGN: Secondary analysis of prospectively collected data. SETTING: Outpatient oncology clinics in seven academic medical centers. PARTICIPANTS: Adults aged 65 and older with cancer undergoing chemotherapy. MEASUREMENTS: Measures included number of daily medications (polypharmacy); PIM use based on three indices (Beers, Zhan, and Drugs to Avoid in the Elderly criteria), and use of six "high risk" medication classes for adverse drug events (anticoagulants, antiplatelet agents, opioids, insulin, oral hypoglycemics, antiarrhythmics). Using multivariate logistic regression, the relations were evaluated between these criteria and Grade 3 to 5 chemotherapy-related toxicity and between these criteria and hospitalization during chemotherapy. RESULTS: Participants (N = 500; mean age 73, 61% Stage IV disease) took a mean of 5 +/- 4 daily medications (range 0-23). PIM use was common (up to 29% according to Beers criteria). No association was found between number of daily medications (reference 0-3 medications) and toxicity (4-9 medications, odds ratio (OR) = 1.34, 95% confidence interval (CI)=0.92-1.97; >/=10 medications, OR=0.82, 95% CI=0.45-1.49) or hospitalization (>/=4 medications, OR=1.34, 95% CI=0.82-2.18, P = .24). There was also no association between PIM use and toxicity (P = .93) or hospitalization (P = .98). No medication class was associated with either outcome. CONCLUSIONS: Polypharmacy and PIM use were common but were not associated with chemotherapy-related toxicity or hospitalization in older adults with cancer.

Mann, J. A. (2014). Update on pediatric dermatologic surgery from tots to teens. *Current Opinion in Pediatrics, 26*(4), 452-459.

PURPOSE OF REVIEW: Children and their parents typically present to pediatricians to discuss treatment options for melanocytic nevi, nevus sebaceus, port-wine stains, and hemangiomas. Each of these conditions may be medically managed, but in some situations surgical intervention may be preferable. RECENT FINDINGS: Although recent studies have improved our understanding of melanoma risk among patients with congenital nevi, prospective trials are needed to more accurately assess whether surgical excision mitigates this risk. The risk of basal cell carcinoma within nevus sebaceus appears to be low, but more conclusive data requires further studies with modern immunohistochemical analysis. Pulsed dye laser is effective for treating port-wine stains, although the optimal timing is controversial. While oral and topical beta

blockers have revolutionized the treatment of proliferating infantile hemangiomas, laser and/or surgical excision are useful in selected situations. SUMMARY: Excisional and/or laser surgery are indicated for certain common dermatologic conditions in children, although the optimal timing of these interventions is often subjective. Pediatricians should be familiar with why and when to refer patients for surgery of these common dermatological conditions.

Mansoor, D., & Ganzini, L. (2014). Musical hallucinations successfully treated with antipsychotic medications: Three case reports. *Psychosomatics, 55*(2), 191-193.

Maroules, C. D., Ghoshhajra, B. B., Malguria, N., Landay, M., Hummel, J., Ferencik, M., et al. (2014). Noncardiac incidental findings on cardiac CT: A step-by-step approach. *Current Cardiovascular Imaging Reports, 7*(8), 1-10.

Noncardiac incidental findings on cardiac CT are remarkably common and some of these may have a significant impact on patient management. Herein, we present a straightforward and cost-effective step-by-step approach for identifying and reporting noncardiac incidental findings. In Step 1, we discuss the 'ABCDEFG' search pattern for systematically reviewing noncardiac organ systems. The most prevalent and clinically significant incidental findings are highlighted with strategies for increasing their conspicuity. In Step 2, the importance of reviewing clinical history and prior imaging studies is discussed. In Step 3, we provide a classification scheme and follow-up recommendations for incidental findings based on their potential clinical significance.

Marshall, L. M., Holton, K. F., Parsons, J. K., Lapidus, J. A., Ramsey, K., & Barrett-Connor, E. (2014). Lifestyle and health factors associated with progressing and remitting trajectories of untreated lower urinary tract symptoms among elderly men. *Prostate Cancer and Prostatic Diseases,*

Background:Knowledge of factors associated with the course of lower urinary tract symptoms (LUTS) before treatment is needed to inform preventive interventions. In a prospective study of elderly men untreated for LUTS, we identified factors associated with symptom progression and remission.Methods:In community-dwelling US men aged 65 years, the American Urological Association Symptom Index (AUA-SI) was repeated four times, once at baseline (2000-2002) and then every 2 years thereafter. Analyses included 1740 men with all four AUA-SI assessments,

who remained free from diagnosed prostate cancer, and who reported no treatment for LUTS or BPH during follow-up that averaged 6.9 (+/-0.4) years. LUTS change was determined with group-based trajectory modelingof the repeated AUA-SI measures. Multivariable logistic regression was then used to determine the baseline factors associated with progressing compared with stable trajectories, and with remitting compared with progressing trajectories. Lifestyle, body mass index (BMI) (kg/m2), mobility, mental health (Short-Form 12), medical history and prescription medications were considered for selection. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for variables in each model.Results:We identified 10 AUA-SI trajectories: 4 stable (1277 men, 73%), three progressing (345 men, 20%), two remitting (98 men, 6%) and one mixed (20 men, 1%). Men in progressing compared with stable trajectories were more likely to have mobility limitations (OR=2.0, 95% CI: 1.0-3.8), poor mental health (OR=1.9, 95% CI: 1.1-3.4), BMI25.0 kg m-2 (OR=1.7, 95% CI: 1.0-2.8), hypertension (OR=1.5, 95% CI: 1.0-2.4) and back pain (OR=1.5, 95% CI: 1.0-2.4). Men in remitting compared with progressing trajectories more often used central nervous system medications (OR=2.3, 95% CI: 1.1-4.9) and less often had a history of problem drinking (OR=0.4, 95% CI: 0.2-0.9).Conclusions:Several non-urological lifestyle and health factors were independently associated with risk of LUTS progression in older men.Prostate Cancer and Prostatic Disease advance online publication, 8 July 2014; doi:10.1038/pcan.2014.22.

Martin, B. I., Franklin, G. M., Deyo, R. A., Wickizer, T. M., Lurie, J. D., & Mirza, S. K. (2014). How do coverage policies influence practice patterns, safety, and cost of initial lumbar fusion surgery? A population-based comparison of workers' compensation systems. *Spine Journal, 14*(7), 1237-1246.

Background context In response to increasing use of lumbar fusion for improving back pain, despite unclear efficacy, particularly among injured workers, some insurers have developed limited coverage policies. Washington State's workers' compensation (WC) program requires imaging confirmation of instability and limits initial fusions to a single level. In contrast, California requires coverage if a second opinion supports surgery, allows initial multilevel fusion, and provides additional reimbursement for surgical implants. There are no studies that compare population-level effects of these policy differences on utilization, costs, and safety of lumbar

fusion. Purpose The purpose of this study was to compare population-level data on the use of complex fusion techniques, adverse outcomes within 3 months, and costs for two states with contrasting coverage policies. Study design and setting The study design was an analysis of WC patients in California and Washington using the Agency for Healthcare Research and Quality's State Inpatient Databases, 2008-2009. Patient sample All patients undergoing an inpatient lumbar fusion for degenerative disease (n=4,628) were included the patient sample. Outcome measure(s) Outcome measures included repeat lumbar spine surgery, all-cause readmission, life-threatening complications, wound problems, device complications, and costs. Methods Log-binomial regressions compared 3-month complications and costs between states, adjusting for patient characteristics. Results Overall rate of lumbar fusion operations through WC programs was 47% higher in California than in Washington. California WC patients were more likely than those in Washington to undergo fusion for controversial indications, such as nonspecific back pain (28% versus 21%) and disc herniation (37% versus 21%), as opposed to spinal stenosis (6% versus 15%), and spondylolisthesis (25% versus 41%). A higher percentage of patients in California received circumferential procedures (26% versus 5%), fusion of three or more levels (10% versus 5%), and bone morphogenetic protein (50% versus 31%). California had higher adjusted risk for reoperation (relative risk [RR] 2.28; 95% confidence interval [CI], 2.27-2.29), wound problems (RR 2.64; 95% CI, 2.62-2.65), device complications (RR 2.49; 95% CI, 2.38-2.61), and life-threatening complications (RR 1.31; 95% CI, 1.31-1.31). Hospital costs for the index procedure were greater in California ($49,430) than in Washington ($40,114). Conclusions Broader lumbar fusion coverage policy was associated with greater use of lumbar fusion, use of more invasive operations, more reoperations, higher rates of complications, and greater inpatient costs.

Mavroidis, P., Giantsoudis, D., Awan, M. J., Nijkamp, J., Rasch, C. R., Duppen, J. C., et al. (2014). Consequences of anorectal cancer atlas implementation in the cooperative group setting: Radiobiologic analysis of a prospective randomized in silico target delineation study. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology,* PURPOSE: The aim of this study is to ascertain the subsequent radiobiological impact of using a consensus guideline target volume delineation atlas. MATERIALS AND METHODS: Using a

representative case and target volume delineation instructions derived from a proposed IMRT rectal cancer clinical trial, gross tumor volume (GTV) and clinical/planning target volumes (CTV/PTV) were contoured by 13 physician observers (Phase 1). The observers were then randomly assigned to follow (atlas) or not-follow (control) a consensus guideline/atlas for anorectal cancers, and instructed to re-contour the same case (Phase 2). RESULTS: The atlas group was found to have increased tumor control probability (TCP) after the atlas intervention for both the CTV ($p<0.0001$) and PTV1 ($p=0.0011$) with decreasing normal tissue complication probability (NTCP) for small intestine, while the control group did not. Additionally, the atlas group had reduced variance in TCP for all target volumes and reduced variance in NTCP for the bowel. In Phase 2, the atlas group had increased TCP relative to the control for CTV ($p=0.03$). CONCLUSIONS: Visual atlas and consensus treatment guideline usage in the development of rectal cancer IMRT treatment plans reduced the inter-observer radiobiological variation, with clinically relevant TCP alteration for CTV and PTV volumes.

Maziarz, R. T., Farnia, S., Martin, P., & Komanduri, K. V. (2014). Optimal benefits for hematopoietic stem cell transplantation: A consensus opinion. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,*

Variability in transplant benefits may directly impact outcomes of individuals undergoing autologous or allogeneic hematopoietic stem cell transplantation procedures. The Financial Working Group of the National Marrow Donor Program- sponsored System Capacity Initiative addressed the issue of variable benefits and reviewed multiple transplant benefit packages from both public and private payer organizations. On completion of the review, a consensus was obtained on defining a recipient benefit package that would avoid major coverage gaps that could negatively influence patient outcomes. The recommendation was to encourage adoption of these benefits at a national level by payers, benefit brokers/consultants and sales teams.

McDonagh, M. S., Matthews, A., Phillipi, C., Romm, J., Peterson, K., Thakurta, S., et al. (2014). Depression drug treatment outcomes in pregnancy and the postpartum period: A systematic review and meta-analysis. *Obstetrics and Gynecology,*

OBJECTIVE:: To evaluate the comparative benefits and harms in both mother and child of

antidepressant treatment for depression in pregnant or postpartum women. DATA SOURCES:: MEDLINE, the Cochrane Library, CINAHL, Scopus, ClinicalTrials.gov (inception to July 2013), manufacturers, and reference lists. METHODS OF STUDY SELECTION:: Two reviewers independently selected studies of pregnant women with depression comparing antidepressants with each other, placebo or no treatment, or nondrug treatments. Studies making comparisons among women taking antidepressants for any reason and those not taking antidepressants (depression status unknown) were used to fill gaps in the evidence. TABULATION, INTEGRATION, AND RESULTS:: Dual study data extraction and quality assessment were used. Six randomized controlled trials and 15 observational studies provided evidence. Low-strength evidence suggested neonates of pregnant women with depression taking selective serotonin reuptake inhibitors had higher risk of respiratory distress than did neonates of untreated women (13.9% compared with 7.8%; P<.001) but no difference in risk of neonatal convulsions (0.14% compared with 0.11%; P=.64) or preterm birth (17% compared with 10%; P=.07). Indirect evidence from studies of pregnant women receiving antidepressants for mixed or unreported reasons compared with pregnant women not taking antidepressants (depression status unknown) suggested future research should focus on congenital anomalies and autism spectrum and attention deficit disorders in the child. In postpartum depression, low-strength evidence suggested symptom response was not improved when sertraline was added to psychotherapy or when cognitive-behavioral therapy was added to paroxetine. Evidence was insufficient for other outcomes, including depression symptoms, functional capacity, breastfeeding, and infant and child development. A serious limitation is the lack of study populations of exclusively depressed pregnant and postpartum women. CONCLUSION:: Evidence about the comparative benefits and harms of pharmacologic treatment of depression in pregnant and postpartum women was largely inadequate to allow informed decisions about treatment. Considering the prevalence of depression, filling this gap is essential.

McGraw, H. F., Culbertson, M. D., & Nechiporuk, A. V. (2014). Kremen1 restricts dkk activity during posterior lateral line development in zebrafish. *Development (Cambridge, England),*

Canonical Wnt signaling plays crucial roles during development and disease. How Wnt signaling is modulated in different in vivo contexts is currently not well understood. Here, we investigate the

modulation of Wnt signaling in the posterior lateral line primordium (pLLP), a cohort of approximately 100 cells that collectively migrate along the trunk of the zebrafish embryo. The pLLP comprises proliferative progenitor cells and organized epithelial cells that will form the mechanosensory organs of the posterior lateral line. Wnt signaling is active in the leading progenitor zone of the pLLP and restricted from the trailing zone through expression of the secreted Wnt inhibitors dkk1b and dkk2. We have identified a zebrafish strain, krm1nl10, which carries a mutation in the kremen1 gene, a non-obligate co-receptor for the Dkk family of proteins. Previous studies have shown that Kremen1 inhibits Wnt signaling by facilitating internalization of the Kremen1-Dkk-Lrp5/6 complex. Surprisingly, we found that disruption of Kremen1 in the pLLP exhibited molecular and cellular phenotypes associated with a decrease rather than overactivation of Wnt signaling. Transplantation of wild-type cells into the mutant primordia failed to rescue the krm1nl10 phenotype, thus revealing that the effects of Kremen1 loss are non-cell-autonomous. Finally, ectopic expression of Dkk1b-mTangerine protein revealed larger spread of the fusion protein in the mutant primordia compared with the wild type. Based on our data, we propose a novel mechanism in which Kremen1 modulates Wnt activity by restricting the range of secreted Dkk proteins during collective cell migration in the pLLP.

Melhorn, S. J., Tyagi, V., Smeraglio, A., Roth, C. L., & Schur, E. A. (2014). Initial evidence that GLP-1 receptor blockade fails to suppress postprandial satiety or promote food intake in humans. *Appetite,*

Glucagon-like peptide 1 (GLP-1) has incretin effects that are well-documented, but the independent role of GLP-1 action in human satiety perception is debated. We hypothesized that blockade of GLP-1 receptors would suppress postprandial satiety and increase voluntary food intake. After an overnight fast, eight normal weight participants (seven men, BMI 19-24.7 kg/m2, age 19-29 year) were enrolled in a double-blind, placebo-controlled, randomized crossover study of the GLP-1 antagonist Exendin-[9-39] (Ex-9) to determine if the satiating effects of a meal are dependent on GLP-1 signaling in humans. Following a fasting blood draw, iv infusion of Ex-9 (600-750 pmol/kg/min) or saline began. Thirty minutes later, subjects consumed a standardized breakfast followed 90 min later (at the predicted time of maximal endogenous circulating GLP-1) by an ad libitum buffet meal to objectively measure satiety. Infusions ended

once the buffet meal was complete. Visual analog scale ratings of hunger and fullness and serial assessments of plasma glucose, insulin, and GLP-1 concentrations were done throughout the experiment. Contrary to the hypothesis, during Ex-9 infusion subjects reported a greater decrease in hunger due to consumption of the breakfast (Ex-9 -62 +/- 5; placebo -41 +/- 9; P = 0.01) than during placebo. There were no differences in ad libitum caloric intake between Ex-9 and placebo. Ex-9 increased glucose, insulin, and endogenous GLP-1, which may have counteracted any effects of Ex-9 infusion to block satiety signaling. Blockade of GLP-1 receptors failed to suppress subjective satiety following a standardized meal or increase voluntary food intake in healthy, normal-weight subjects.

Mendelsohn, J., Gray, J. W., Howley, P. M., Israel, M. A., & Thompson, C. B. (2015). *The molecular basis of cancer: Fourth edition* Elsevier Inc.

The Molecular Basis of Cancer arms you with the latest knowledge and cutting-edge advances in the battle against cancer. This thoroughly revised, comprehensive oncology reference explores the scientific basis for our current understanding of malignant transformation and the pathogenesis and treatment of this disease. A team of leading experts thoroughly explains the molecular biologic principles that underlie the diagnostic tests and therapeutic interventions now being used in clinical trials and practice. Detailed descriptions of topics from molecular abnormalities in common cancers to new approaches for cancer therapy equip you to understand and apply the complexities of ongoing research in everyday clinical application. © 2015 Elsevier Inc. All rights reserved.

Mendelsohn, J., Gray, J. W., Howley, P. M., Israel, M. A., & Thompson, C. B. (2015). Preface. *The Molecular Basis of Cancer: Fourth Edition,*

Merkens, M. J., Sinden, N. L., Brown, C. D., Merkens, L. S., Roullet, J. B., Nguyen, T., et al. (2014). Feeding impairments associated with plasma sterols in smith-lemli-opitz syndrome. *The Journal of Pediatrics,*

OBJECTIVE: To quantitatively evaluate feeding impairment in children with Smith-Lemli-Opitz syndrome (SLOS) and to correlate feeding impairment with clinical and biochemical indices of disease severity. STUDY DESIGN: The study subjects were 26 children with SLOS ranging in age

from 0.4 to 19 years. Clinical severity was measured using an existing scoring system. We created a tool to quantitatively evaluate feeding. Plasma sterol concentrations were measured, and statistical associations (correlations) with feeding scores were calculated. RESULTS: Oral hyposensitivity or hypersensitivity, adverse behaviors, and risk for dysphagia were seen in approximately 65% of the children with SLOS. Thirteen of the 26 children experienced failure to thrive, and 10 children required gastrostomy. Plasma concentration of 7-dehydrocholesterol, as a measure of severity, was correlated with total feeding score and oral function subcategory score (P 0.24 mmol/L or cholesterol concentration <1.95 mmol/L was predictive of gastrostomy tube use. Feeding impairments may improve with age. CONCLUSION: Feeding impairment is common and complex in patients with SLOS. Our findings confirm that oral sensitivities, adverse feeding behaviors, and risk of oral phase dysphagia are amenable to quantitative evaluation and analysis. Feeding difficulties in children with SLOS are correlated with plasma sterol concentrations, suggesting a link between the biochemical severity of SLOS and feeding function. These findings expand the behavioral phenotype of SLOS and begin to provide insight into the biological causes of feeding difficulties.

Merlin, L. R., Horak, H. A., Milligan, T. A., Kraakevik, J. A., & Ali, I. I. (2014). A competency-based longitudinal core curriculum in medical neuroscience. *Neurology, 83*(5), 456-462.

Current medical educational theory encourages the development of competency-based curricula. The Accreditation Council for Graduate Medical Education's 6 core competencies for resident education (medical knowledge, patient care, professionalism, interpersonal and communication skills, practice-based learning, and systems-based practice) have been embraced by medical schools as the building blocks necessary for becoming a competent licensed physician. Many medical schools are therefore changing their educational approach to an integrated model in which students demonstrate incremental acquisition and mastery of all competencies as they progress through medical school. Challenges to medical schools include integration of preclinical and clinical studies as well as development of learning objectives and assessment measures for each competency. The Undergraduate Education Subcommittee (UES) of the American Academy of Neurology (AAN) assembled a group of neuroscience educators to outline a longitudinal competency-based curriculum in medical neuroscience encompassing both preclinical and clinical

coursework. In development of this curriculum, the committee reviewed United States Medical Licensing Examination content outlines, Liaison Committee on Medical Education requirements, prior AAN-mandated core curricula for basic neuroscience and clinical neurology, and survey responses from educators in US medical schools. The newly recommended curriculum provides an outline of learning objectives for each of the 6 competencies, listing each learning objective in active terms. Documentation of experiences is emphasized, and assessment measures are suggested to demonstrate adequate achievement in each competency. These guidelines, widely vetted and approved by the UES membership, aspire to be both useful as a stand-alone curriculum and also provide a framework for neuroscience educators who wish to develop a more detailed focus in certain areas of study.

Michaud, H. A., SenGupta, D., de Mulder, M., Deeks, S. G., Martin, J. N., Kobie, J. J., et al. (2014). Cutting edge: An antibody recognizing ancestral endogenous virus glycoproteins mediates antibody-dependent cellular cytotoxicity on HIV-1-infected cells. *Journal of Immunology (Baltimore, Md.: 1950), 193*(4), 1544-1548.

The failure of antiviral vaccines is often associated with rapid viral escape from specific immune responses. In the past, conserved epitope or algorithmic epitope selections, such as mosaic vaccines, have been designed to diversify immunity and to circumvent potential viral escape. An alternative approach is to identify conserved stable non-HIV-1 self-epitopes present exclusively in HIV-1-infected cells. We showed previously that human endogenous retroviral (HERV) mRNA transcripts and protein are found in cells of HIV-1-infected patients and that HERV-K (HML-2)-specific T cells can eliminate HIV-1-infected cells in vitro. In this article, we demonstrate that a human anti-HERV-K (HML-2) transmembrane protein Ab binds specifically to HIV-1-infected cells and eliminates them through an Ab-dependent cellular cytotoxicity mechanism in vitro. Thus, Abs directed against epitopes other than HIV-1 proteins may have a role in eliminating HIV-1-infected cells and could be targeted in novel vaccine approaches or immunotherapeutic modalities.

Midgett, M., & Rugonyi, S. (2014). Congenital heart malformations induced by hemodynamic altering surgical interventions. *Frontiers in Physiology, 5 JUL*

Embryonic heart formation results from a dynamic interplay between genetic and environmental

factors. Blood flow during early embryonic stages plays a critical role in heart development, as interactions between flow and cardiac tissues generate biomechanical forces that modulate cardiac growth and remodeling. Normal hemodynamic conditions are essential for proper cardiac development, while altered blood flow induced by surgical manipulations in animal models result in heart defects similar to those seen in humans with congenital heart disease. This review compares the altered hemodynamics, changes in tissue properties, and cardiac defects reported after common surgical interventions that alter hemodynamics in the early chick embryo, and shows that interventions produce a wide spectrum of cardiac defects. Vitelline vein ligation and left atrial ligation decrease blood pressure and flow; and outflow tract banding increases blood pressure and flow velocities. These three surgical interventions result in many of the same cardiac defects, which indicate that the altered hemodynamics interfere with common looping, septation and valve formation processes that occur after intervention and that shape the fourchambered heart. While many similar defects develop after the interventions, the varying degrees of hemodynamic load alteration among the three interventions also result in varying incidence and severity of cardiac defects, indicating that the hemodynamic modulation of cardiac developmental processes is strongly dependent on hemodynamic load. © 2014 Midgett and Rugonyi.

Miller, K. R., McClave, S. A., Kiraly, L. N., Martindale, R. G., & Benns, M. V. (2014). A tutorial on enteral access in adult patients in the hospitalized setting. *Journal of Parenteral and Enteral Nutrition, 38*(3), 282-295.

Enteral access is a cornerstone in the provision of nutrition support. Early and adequate enteral support has consistently demonstrated improved patient outcomes throughout a wide range of illness. In patients unable to tolerate oral intake, multiple options of delivery are available to the clinician. Access requires a multidisciplinary effort that involves nurses, dietitians, and physicians to be successful. These techniques and procedures are not without morbidity and even mortality. A comprehensive understanding of the appropriate management of these tubes and their inherent complications should be garnered by all those involved with nutrition support teams. This tutorial reviews available options for enteral access in addition to commonly encountered

complications and their management. © 2014 American Society for Parenteral and Enteral Nutrition.

Miousse, I. R., Shao, L., Chang, J., Feng, W., Wang, Y., Allen, A. R., et al. (2014). Exposure to low-dose 56Fe-ion radiation induces long-term epigenetic alterations in mouse bone marrow hematopoietic progenitor and stem cells. *Radiation Research, 182*(1), 92-101.

There is an increasing need to better understand the long-term health effects of high-linear energy transfer (LET) radiation due to exposure during space missions, as well as its increasing use in clinical treatments. Previous studies have indicated that exposure to 56Fe heavy ions increases the incidence of acute myeloid leukemia (AML) in mice but the underlying molecular mechanisms remain elusive. Epigenetic alterations play a role in radiation-induced genomic instability and the initiation and progression of AML. In this study, we assessed the effects of low-dose 56Fe-ion irradiation on epigenetic alterations in bone marrow mononuclear cells (BM-MNCs) and hematopoietic progenitor and stem cells (HPSCs). Exposure to 56Fe ions (600 MeV, 0.1, 0.2 and 0.4 Gy) resulted in significant epigenetic alterations involving methylation of DNA, the DNA methylation machinery and expression of repetitive elements. Four weeks after irradiation, these changes were primarily confined to HPSCs and were exhibited as dose-dependent hypermethylation of LINE1 and SINE B1 repetitive elements [4.2-fold increase in LINE1 ($P < 0.001$) and 7.6-fold increase in SINE B1 ($P < 0.01$) after exposure to 0.4 Gy; $n = 5$]. Epigenetic alterations were persistent and detectable for at least 22 weeks after exposure, when significant loss of global DNA hypomethylation (1.9-fold, $P < 0.05$), decreased expression of Dnmt1 (1.9-fold, $P < 0.01$), and increased expression of LINE1 and SINE B1 repetitive elements (2.8-fold, $P < 0.001$ for LINE1 and 1.9-fold, $P < 0.05$ for SINE B1; $n = 5$) were observed after exposure to 0.4 Gy. In contrast, exposure to 56Fe ions did not result in accumulation of increased production of reactive oxygen species (ROS) and DNA damage, exhibited as DNA strand breaks. Furthermore, no significant alterations in cellular senescence and apoptosis were detected in HPSCs after exposure to 56Fe-ion radiation. These findings suggest that epigenetic reprogramming is possibly involved in the development of radiation-induced genomic instability and thus, may have a causative role in the development of AML. © 2014 by Radiation Research Society.

Murphy, S. J., Lusardi, T. A., Phillips, J. I., & Saugstad, J. A. (2014). Sex differences in microRNA expression during developmentin rat cortex. *Neurochemistry International,*

There are important sex differences in the risk and outcome of conditions and diseases between males and females. For example, stroke occurs with greater frequency in men than in women across diverse ethnic backgrounds and nationalities. Work from our lab and others have revealed a sex-specific sensitivity to cerebral ischemia whereby males exhibit a larger extent of brain damage following an ischemic event compared to females. Studies suggest that the difference in male and female susceptibility to ischemia may be triggered by innate variations in gene regulation and protein expression between the sexes that are independent of post-natal exposure to sex hormones. We have shown that there are differences in microRNA (miRNA) expression in adult male and female brain following focal cerebral ischemia in mouse cortex. Herein we examine a role for differential expression of miRNAs during development in male and female rat cortex as potential effectors of the phenotype that leads to sex differences to ischemia. Expression studies in male and female cortices isolated from postnatal day 0 (P0), postnatal day 7 (P7), and adult rats using TaqMan Low Density miRNA arrays and NanoString nCounter analysis revealed differential miRNA levels between males and females at each developmental stage. We focused on the miR-200 family of miRNAs that showed higher levels in females at P0, but higher levels in males at P7 that persisted into adulthood, and validated the expression of miR-200a, miR-200b, and miR-429 by individual qRT-PCR as these are clustered on chromosome 5 and may be transcriptionally co-regulated. Prediction analysis of the miR-200 miRNAs revealed that genes within the Gonadotropin releasing hormone receptor pathway are the most heavily targeted. These studies support that developmental changes in miRNA expression may influence phenotypes in adult brain that underlie sexually dimorphic responses to disease, including ischemia.

Nakajima, T., Shearer, T. R., & Azuma, M. (2014). Loss of calpastatin leads to activation of calpain in human lens epithelial cells. *Investigative Ophthalmology & Visual Science,*

Purpose: Activation of calpains (calpain 2 and Lp82) in rodent lenses readily causes proteolysis and cataract formation. In contrast, primate lenses are quite resistant to activation of calpains. The hypothesis is that high levels of human endogenous calpain inhibitor, calpastatin (CS),

prevent calpain activation in human lenses. The purpose of present study was to directly test if CS is a major inhibitory factor in a human lens epithelial cell line, HLE B-3. Methods: siRNAs were used to knock down expression of CS in HLE B-3. The cells were then cultured with the calcium ionophore ionomycin, with or without a calpain inhibitor SNJ-1945.Transcripts for calpain 2 and CS were measured by qPCR. Calpain 2 activity was detected by immunoblotting for the calpain-specific, alpha-spectrin breakdown product and for activation-associated, fragments of calpain 2. Results: Expression of CS in HLE B-3 was remarkably higher than in alpha-TN-4 (mouse comparator cell line). Proteolysis of alpha-spectrin was observed in the soluble proteins from alpha-TN-4 incubated with Ca2+, but not in the human HLE B-3. When CS-reduced HLE B-3 cells (transfected with CS siRNA) were cultured with ionomycin, calpain 2 was activated, specific proteolysis of alpha-spectrin occurred, and cell death ensued. SNJ-1945 inhibited these changes. Conclusions: Our data demonstrate that the high levels of endogenous CS do indeed inhibit calpain activity in normal human lens epithelial cells. We speculate that age-related oxidation might cause loss of CS activity in human lens epithelial cells, allowing activation of long-dormant calpain 2, proteolysis of critical cytoskeletal proteins, and cataract formation.

Nardos, R., Gregory, W. T., Krisky, C., Newell, A., Nardos, B., Schlaggar, B., et al. (2014). Examining mechanisms of brain control of bladder function with resting state functional connectivity MRI. *Neurourology and Urodynamics, 33*(5), 493-501.

Aims This aim of this study is to identify the brain mechanisms involved in bladder control. Methods We used fMRI to identify brain regions that are activated during bladder filling. We then used resting state connectivity fMRI (rs-fcMRI) to assess functional connectivity of regions identified by fMRI with the rest of the brain as the bladder is filled to capacity. Results Female participants (n = 20) were between ages 40 and 64 with no significant history of symptomatic urinary incontinence. Main effect of time (MET) fMRI analysis resulted in 20 regions of interest (ROIs) that have significant change in BOLD signal ($z = 3.25$, $P < 0.05$) over the course of subtle bladder filling and emptying regardless of full versus empty bladder state. Bladder-state by time (BST) fMRI analysis resulted in three ROIs that have significant change in BOLD signal ($z = 3.25$, $P < 0.05$) over the course of bladder runs comparing full versus empty bladder state. Rs-fcMRI fixed effects analysis identified significant changes in connectivity between full and empty bladder

states in seven brain regions (z = 4.0) using the three BST ROIs and sixteen brain regions (z = 7) using the twenty MET ROIs. Regions identified include medial frontal gyrus, posterior cingulate (PCC), inferiolateral temporal and post-central gyrus, amygdale, the caudate, inferior parietal lobe as well as anterior and middle cingulate gyrus. Conclusions There is significant and vast changes in the brain's functional connectivity when bladder is filled suggesting that the central process responsible for the increased control during the full bladder state appears to largely rely on the how distributed brain systems are functionally integrated. Neurourol. Urodynam. 33:493-501, 2014. © 2013 Wiley Periodicals, Inc. © 2013 Wiley Periodicals, Inc.

Nardos, R., Thurmond, A., Holland, A., & Gregory, W. T. (2014). Pelvic floor levator hiatus measurements: MRI versus ultrasound. *Female Pelvic Medicine & Reconstructive Surgery, 20*(4), 216-221.

OBJECTIVE: The objective of this study is to compare levator hiatus measurements between pelvic magnetic resonance imaging (MRI) and pelvic ultrasound (US) imaging modalities. METHODS: We performed pelvic MRI and 3-dimensional US in 37 asymptomatic nulliparous women. For the MRI protocols, we performed axial and sagittal sequences at rest. We then obtained sagittal sequences during Kegel squeeze and Valsalva maneuvers. Blinded to the findings of the MRI, we obtained 3-dimensional pelvic US images using a perineal approach at rest, Kegel and Valsalva maneuvers. Finally, we measured the levator hiatus in both sagittal and axial planes. RESULTS: For the resting sagittal measurements, the mean levator hiatus measurement using MRI (5.0 cm; SD, 0.8) is significantly greater than that using US (4.4 cm; SD, 0.6; $P < 0.05$). Although the absolute mean levator measurements between the 2 modalities are significantly different, this difference is not influenced by the magnitude of the measurements as noted in Bland-Altman plots of the limits of agreement. CONCLUSIONS: We found that the MRI measurements obtained from the sagittal images were consistently greater than the corresponding US images. In contrast, there was not the same consistency of difference between MRI and US for the axial images. This suggests possible variation in acquisition planes for axial images or interpretation of landmarks for the sagittal images.

Neely, K. W., & Spitzer, W. J. (1997). A model for a statewide critical incident stress (CIS) debriefing program for emergency services personnel. *Prehospital and Disaster Medicine, 12*(2), 43-48.

Purpose: Emergency services personnel are highly vulnerable to acute and cumulative critical incident stress (CIS) that can manifest as anger, guilt, depression, and impaired decision-making, and, in certain instances, job loss. Interventions designed to identify such distress and restore psychological functioning becomes imperative. Methods: A statewide debriefing team was formed in 1988 through a collaborative effort between an academic department of emergency medicine and a social work department of a teaching hospital, and a metropolitan area fire department and ambulance service. Using an existing CIS debriefing model, 84 pre-screened, mental health professionals and emergency services personnel were provided with 16 hours of training and were grouped into regional teams. Debriefing requests are received through a central number answered by a communicator in a 24-hour communications center located within the emergency department. Debriefings are conducted 48-72 hours after the event for specific types of incidents. Follow-up telephone calls are made by the debriefing team leader two to three weeks following a debriefing. The teams rely on donations to pay for travel and meals. Results: One hundred sixty-eight debriefings were conducted during the first four years. Rural agencies accounted for 116 (69%) requests. During this period, 1,514 individuals were debriefed: 744 (49%) firefighters, 460 (30%) EMTs, and 310 (21%) police officers, dispatchers, and other responders. Deaths of children, extraordinary events, and incidents involving victims known to the responders (35%, 14%, and 14% respectively) were the most common reasons for requesting debriefings. Feedback was received from 48 (28%) of the agencies that requested the debriefing. All of those who responded felt that the debriefing had a beneficial effect on its personnel. Specific individuals identified by agency representatives as having the greatest difficulty were observed to be returned to their pre-incident state. Conclusion: CIS debriefings are judged as beneficial. A statewide response team is an effective way to provide these services at no cost to agencies. Copyright © World Association for Disaster and Emergency Medicine 1997.

Nikolas, M. A., & Nigg, J. T. (2014). Moderators of neuropsychological mechanism in attention-deficit hyperactivity disorder. *Journal of Abnormal Child Psychology,*

Neuropsychological measures have been proposed as both a way to tap mechanisms and as

endophenotypes for child ADHD. However, substantial evidence supporting heterogeneity in neuropsychological performance among youth with ADHD as well as apparent effect differences by sex, age, and comorbidity have slowed progress. To address this, it is important to understand sibling effects in relation to these moderators. 461 youth ages 6-17 years (54.8 % male, including 251 youth with ADHD, 107 of their unaffected biological siblings, and 103 non-ADHD controls) completed diagnostic interviews and a theoretically informed battery of neuropsychological functioning. A structural equation model was used to consolidate neuropsychological domains. Group differences between unaffected siblings of youth with ADHD and controls across each domain were first examined as the primary endophenotype test for ADHD. Moderation of these effects was evaluated via investigation of interactions between diagnostic group and both proband and individual level characteristics, including sex, age, and comorbidity status. Unaffected siblings performed worse than control youth in the domains of inhibition, response time variability, and temporal information processing. Individual age moderated these effects, such that differences between controls and unaffected siblings were pronounced among younger children (ages 6-10 years) but absent among older youth (ages 11-17 years). Evidence for moderation of effects by proband sex and comorbidity status produced more variable and smaller effects. Results support the utility of inhibition, response time variability, and temporal processing as useful endophenotypes for ADHD in future genetic associations studies of the disorder, but suggest this value will vary by age among unaffected family members.

Nishiyama, C., Brown, S. P., May, S. J., Iwami, T., Koster, R. W., Beesems, S. G., et al. (2014). Apples to apples or apples to oranges? international variation in reporting of process and outcome of care for out-of-hospital cardiac arrest. *Resuscitation,*

OBJECTIVES: Survival after out-of-hospital cardiac arrest (OHCA) varies between communities, due in part to variation in the methods of measurement. The Utstein template was disseminated to standardize comparisons of risk factors, quality of care, and outcomes in patients with OHCA. We sought to assess whether OHCA registries are able to collate common data using the Utstein template. A subsequent study will assess whether the Utstein factors explain differences in survival between emergency medical services (EMS) systems. STUDY DESIGN: Retrospective

study. SETTING: This retrospective analysis of prospective cohorts included adults treated for OHCA, regardless of the etiology of arrest. Data describing the baseline characteristics of patients, and the process and outcome of their care were grouped by EMS system, de-identified, and then collated. Included were core Utstein variables and timed event data from each participating registry. This study was classified as exempt from human subjects' research by a research ethics committee. MEASUREMENTS AND MAIN RESULTS: Twelve registries with 265 first-responding EMS agencies in 14 countries contributed data describing 125,840 cases of OHCA. Variation in inclusion criteria, definition, coding, and process of care variables were observed. Contributing registries collected 61.9% of recommended core variables and 42.9% of timed event variables. Among core variables, the proportion of missingness was mean 1.9+/-2.2%. The proportion of unknown was mean 4.8+/-6.4%. Among time variables, missingness was mean 9.0+/-6.3%. CONCLUSIONS: International differences in measurement of care after OHCA persist. Greater consistency would facilitate improved resuscitation care and comparison within and between communities.

Olsen, R. H. J., Marzulla, T., & Raber, J. (2014). Impairment in extinction of contextual and cued fear following post-training whole-body irradiation. *Frontiers in Behavioral Neuroscience, 8*(JULY) Because of the use of radiation in cancer therapy, the risk of nuclear contamination from power plants, military conflicts, and terrorism, there is a compelling scientific and public health interest in the effects of environmental radiation exposure on brain function, in particular hippocampal function and learning and memory. Previous studies have emphasized changes in learning and memory following radiation exposure. These approaches have ignored the question of how radiation exposure might impact recently acquired memories, which might be acquired under traumatic circumstances (cancer treatment, nuclear disaster, etc.). To address the question of how radiation exposure might affect the processing and recall of recently acquired memories, we employed a fear conditioning paradigm wherein animals were trained, and subsequently irradiated (whole-body X-ray irradiation) 24 h later. Animals were given 2 weeks to recover, and were tested for retention and extinction of hippocampus-dependent contextual fear conditioning or hippocampus-independent cued fear conditioning. Exposure to irradiation following training was associated with reduced daily increases in body weights over the 22-days of the study and

resulted in greater freezing levels and aberrant extinction 2 weeks later. This was also observed when the intensity of the training protocol was increased. Cued freezing levels and measures of anxiety 2 weeks after training were also higher in irradiated than sham-irradiated mice. In contrast to contextual freezing levels, cued freezing levels were even higher in irradiated mice receiving 5 shocks during training than sham-irradiated mice receiving 10 shocks during training. In addition, the effects of radiation on extinction of contextual fear were more profound than those on the extinction of cued fear. Thus, whole-body irradiation elevates contextual and cued fear memory recall.

Orwoll, E. S., Vanderschueren, D., & Boonen, S. (2013). *Osteoporosis in men. epidemiology, pathophysiology, and clinical characterization* Elsevier Inc.

Although osteoporosis has long been considered a disease of women, the earliest reports of the epidemiology of fractures associated with osteoporosis clearly showed that the classical age-related increase in fractures seen in women was also evident in men. It has been recognized that the problem of osteoporosis in men represents an important public health issue [1] as well as a huge personal burden for those men affected [2]. It also presents a unique array of scientific challenges and opportunities [3-8]. Here we examine the issue of osteoporosis in men, and compare its pathophysiology and clinical presentation to parallel processes in women.

Parkinson Study Group QE3 Investigators, Beal, M. F., Oakes, D., Shoulson, I., Henchcliffe, C., Galpern, W. R., et al. (2014). A randomized clinical trial of high-dosage coenzyme Q10 in early parkinson disease: No evidence of benefit. *JAMA Neurology, 71*(5), 543-552.

IMPORTANCE: Coenzyme Q10 (CoQ10), an antioxidant that supports mitochondrial function, has been shown in preclinical Parkinson disease (PD) models to reduce the loss of dopamine neurons, and was safe and well tolerated in early-phase human studies. A previous phase II study suggested possible clinical benefit. OBJECTIVE: To examine whether CoQ10 could slow disease progression in early PD. DESIGN, SETTING, AND PARTICIPANTS: A phase III randomized, placebo-controlled, double-blind clinical trial at 67 North American sites consisting of participants 30 years of age or older who received a diagnosis of PD within 5 years and who had the following

inclusion criteria: the presence of a rest tremor, bradykinesia, and rigidity; a modified Hoehn and Yahr stage of 2.5 or less; and no anticipated need for dopaminergic therapy within 3 months. Exclusion criteria included the use of any PD medication within 60 days, the use of any symptomatic PD medication for more than 90 days, atypical or drug-induced parkinsonism, a Unified Parkinson's Disease Rating Scale (UPDRS) rest tremor score of 3 or greater for any limb, a Mini-Mental State Examination score of 25 or less, a history of stroke, the use of certain supplements, and substantial recent exposure to CoQ10. Of 696 participants screened, 78 were found to be ineligible, and 18 declined participation. INTERVENTIONS: The remaining 600 participants were randomly assigned to receive placebo, 1200 mg/d of CoQ10, or 2400 mg/d of CoQ10; all participants received 1200 IU/d of vitamin E. MAIN OUTCOMES AND MEASURES: Participants were observed for 16 months or until a disability requiring dopaminergic treatment. The prospectively defined primary outcome measure was the change in total UPDRS score (Parts I-III) from baseline to final visit. The study was powered to detect a 3-point difference between an active treatment and placebo. RESULTS: The baseline characteristics of the participants were well balanced, the mean age was 62.5 years, 66% of participants were male, and the mean baseline total UPDRS score was 22.7. A total of 267 participants required treatment (94 received placebo, 87 received 1200 mg/d of CoQ10, and 86 received 2400 mg/d of CoQ10), and 65 participants (29 who received placebo, 19 who received 1200 mg/d of CoQ10, and 17 who received 2400 mg/d of CoQ10) withdrew prematurely. Treatments were well tolerated with no safety concerns. The study was terminated after a prespecified futility criterion was reached. At study termination, both active treatment groups showed slight adverse trends relative to placebo. Adjusted mean changes (worsening) in total UPDRS scores from baseline to final visit were 6.9 points (placebo), 7.5 points (1200 mg/d of CoQ10; P = .49 relative to placebo), and 8.0 points (2400 mg/d of CoQ10; P = .21 relative to placebo). CONCLUSIONS AND RELEVANCE: Coenzyme Q10 was safe and well tolerated in this population, but showed no evidence of clinical benefit. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00740714.

Patel, M. S., Zatarain, J., De La Cruz, S., Sally, M. B., Ewing, T., Crutchfield, M., et al. (2014). The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: A prospective study from the UNOS region 5 donor management goals workgroup.

JAMA Surgery,

Importance: The shortage of organs available for transplant has led to the use of expanded criteria donors (ECDs) to extend the donor pool. These donors are older and have more comorbidities and efforts to optimize the quality of their organs are needed. Objective: To determine the impact of meeting a standardized set of critical care end points, or donor management goals (DMGs), on the number of organs transplanted per donor in ECDs. Design, Setting, and Participants: Prospective interventional study from February 2010 to July 2013 of all ECDs managed by the 8 organ procurement organizations in the southwestern United States (United Network for Organ Sharing Region 5). Interventions: Implementation of 9 DMGs as a checklist to guide the management of every ECD. The DMGs represented normal cardiovascular, pulmonary, renal, and endocrine end points. Meeting the DMG bundle was defined a priori as achieving any 7 of the 9 end points and was recorded at the time of referral to the organ procurement organization, at the time of authorization for donation, 12 to 18 hours later, and prior to organ recovery. Main Outcomes and Measures: The primary outcome measure was 3 or more organs transplanted per donor and binary logistic regression was used to identify independent predictors with $P < .05$. Results: There were 671 ECDs with a mean (SD) number of 2.1 (1.3) organs transplanted per donor. Ten percent of the ECDs had met the DMG bundle at referral, 15% at the time of authorization, 33% at 12 to 18 hours, and 45% prior to recovery. Forty-three percent had 3 or more organs transplanted per donor. Independent predictors of 3 or more organs transplanted per donor were older age (odds ratio [OR] = 0.95 per year [95% CI, 0.93-0.97]), increased creatinine level (OR = 0.73 per mg/dL [95% CI, 0.63-0.85]), DMGs met prior to organ recovery (OR = 1.90 [95% CI, 1.35-2.68]), and a change in the number of DMGs achieved from referral to organ recovery (OR = 1.11 per additional DMG [95% CI, 1.00-1.23]). Conclusions and Relevance: Meeting DMGs prior to organ recovery with ECDs is associated with achieving 3 or more organs transplanted per donor. An increase in the number of critical care end points achieved throughout the care of a potential donor by both donor hospital and organ procurement organization is also associated with an increase in organ yield.

Patel, S., Lalwani, K., Koh, J., Wu, L., & Fu, R. (2014). Temporal variation of the leak pressure of uncuffed endotracheal tubes following pediatric intubation: An observational study. *Journal of*

Anesthesia, 28(3), 368-373.

Purpose: Uncuffed endotracheal tubes are still preferred over cuffed tubes in certain situations in pediatric anesthesia. Inaccurately sized uncuffed endotracheal tubes may lead to inadequate ventilation or tracheal mucosal damage during anesthesia. Endotracheal tube size in children is usually assessed by measuring the audible leak pressure; if the fit of the tube and the leak pressure decrease significantly with time, reintubation during surgery as a result of inability to ventilate effectively may be challenging, and could lead to patient morbidity. There is no evidence to indicate whether leak pressure increases or decreases with time following endotracheal intubation with uncuffed tubes in children. Methods: We measured leak pressure for 30 min following tracheal intubation in 46 ASA I children age 0-7 years after excluding factors known to modify leak pressure. Results: The largest mean change in leak pressure occurred between time points 0 and 15 min, an increase of 3.5 cmH2O. Endotracheal tube size and type of procedure were associated with the leak pressure. In the final linear mixed model, there were no statistically significant variations in leak pressure over time (P = 0.129) in this group of children. Conclusions: We did not identify a consistent change in leak pressure within 30 min following tracheal intubation with uncuffed endotracheal tubes in this group of children. © 2013 Japanese Society of Anesthesiologists.

Peavy, K. M., Guydish, J., Manuel, J. K., Campbell, B. K., Lisha, N., Le, T., et al. (2014). Treatment adherence and competency ratings among therapists, supervisors, study-related raters and external raters in a clinical trial of a 12-step facilitation for stimulant users. *Journal of Substance Abuse Treatment, 47*(3), 222-228.

This study investigated the correspondence among four groups of raters on adherence to STAGE-12, a manualized 12-step facilitation (TSF) group and individual treatment targeting stimulant abuse. The four rater groups included the study therapists, supervisors, study-related ("TSF expert") raters, and non-project related ("external") raters. Results indicated that external raters rated most critically mean adherence - the mean of all the adherence items - and global performance. External raters also demonstrated the highest degree of reliability with the designated expert. Therapists rated their own adherence lower, on average, than did supervisors and TSF expert raters, but therapist ratings also had the poorest reliability. Findings highlight the

challenges in developing practical, but effective methods of fidelity monitoring for evidence based practice in clinical settings. Recommendations based on study findings are provided.

Perkins, J., Pavel, M., Jimison, H. B., & Scott, S. (2008). Gesture recognition for interactive exercise programs. *Conference Proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference,* , 1915-1917.

This paper describes a gesture recognition system which can recognize seated exercises that will be incorporated into an in-home automated interactive exercise program. Hidden Markov Models (HMMs) are used as a motion classifier, with motion features extracted from the grayscale images and the location of the subject's head estimated at initialization. An overall recognition rate of 94.1% is achieved.

Peskind, E. R., Li, G., Shofer, J. B., Millard, S. P., Leverenz, J. B., Yu, C. E., et al. (2014). Influence of lifestyle modifications on age-related free radical injury to brain. *JAMA Neurology,*

Importance: The Healthy Brain Initiative 2013-2018 seeks to optimize brain health as we age. Free radical injury is an important effector of molecular and cellular stress in the aging brain that derives from multiple sources. Objective: To identify potentially modifiable risk factors associated with increased markers of brain oxidative stress. Design, Setting, and Participants: This cross-sectional, academic multicenter study consisted of 320 research volunteers (172 women) aged 21 to 100 years who were medically healthy and cognitively normal. Main Outcomes and Measures: Free radical injury to the brain was assessed using cerebrospinal fluid (CSF) F2-isoprostane (F2-IsoP) concentrations correlated with age, sex, race, cigarette smoking, body mass index, inheritance of the epsilon4 allele of the apolipoprotein E gene (APOE), and CSF biomarkers of Alzheimer disease. Results: The concentration of CSF F2-IsoP increased with age by approximately 3 pg/mL (approximately 10%) from age 45 to 71 years in medically healthy, cognitively normal adults (P .05). The association between CSF F2-IsoP concentrations and race was not significant after controlling for the effect of current smoking status (P = .45). Conclusions and Relevance: Our results are consistent with an age-related increase in free radical injury in the human brain and uniquely suggest that this form of injury may be greater in women

than in men. Our results also highlighted 2 lifestyle modifications (ie, body mass index and smoking) that would have an even greater effect on suppressing free radical injury to the brain than would suppressing the processes of aging. These results inform efforts to achieve success in the Healthy Brain Initiative 2013-2018.

Petraglia, A. L., Plog, B. A., Dayawansa, S., Chen, M., Dashnaw, M. L., Czerniecka, K., et al. (2014). The spectrum of neurobehavioral sequelae after repetitive mild traumatic brain injury: A novel mouse model of chronic traumatic encephalopathy. *Journal of Neurotrauma, 31*(13), 1211-1224. There has been an increased focus on the neurological sequelae of repetitive mild traumatic brain injury (TBI), particularly neurodegenerative syndromes, such as chronic traumatic encephalopathy (CTE); however, no animal model exists that captures the behavioral spectrum of this phenomenon. We sought to develop an animal model of CTE. Our novel model is a modification and fusion of two of the most popular models of TBI and allows for controlled closed-head impacts to unanesthetized mice. Two-hundred and eighty 12-week-old mice were divided into control, single mild TBI (mTBI), and repetitive mTBI groups. Repetitive mTBI mice received six concussive impacts daily for 7 days. Behavior was assessed at various time points. Neurological Severity Score (NSS) was computed and vestibulomotor function tested with the wire grip test (WGT). Cognitive function was assessed with the Morris water maze (MWM), anxiety/risk-taking behavior with the elevated plus maze, and depression-like behavior with the forced swim/tail suspension tests. Sleep electroencephalogram/ electromyography studies were performed at 1 month. NSS was elevated, compared to controls, in both TBI groups and improved over time. Repetitive mTBI mice demonstrated transient vestibulomotor deficits on WGT. Repetitive mTBI mice also demonstrated deficits in MWM testing. Both mTBI groups demonstrated increased anxiety at 2 weeks, but repetitive mTBI mice developed increased risk-taking behaviors at 1 month that persist at 6 months. Repetitive mTBI mice exhibit depression-like behavior at 1 month. Both groups demonstrate sleep disturbances. We describe the neurological sequelae of repetitive mTBI in a novel mouse model, which resemble several of the neuropsychiatric behaviors observed clinically in patients sustaining repetitive mild head injury.

Pfeiffer, C. D., & Beldavs, Z. G. (2014). Much to do about carbapenem-resistant enterobacteriaceae: Why supplementing surveillance may be the key to stopping spread. *Infection Control and Hospital Epidemiology : The Official Journal of the Society of Hospital Epidemiologists of America, 35*(8), 984-985.

Pfeiffer, C. D., Cunningham, M. C., Poissant, T., Furuno, J. P., Townes, J. M., Leitz, A., et al. (2014). Establishment of a statewide network for carbapenem-resistant enterobacteriaceae prevention in a low-incidence region. *Infection Control and Hospital Epidemiology, 35*(4), 356-361. Objective. To establish a statewide network to detect, control, and prevent the spread of carbapenem-resistant Enterobacteriaceae (CRE) in a region with a low incidence of CRE infection. Design. Implementation of the Drug Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP-CRE) Network. setting and participants. Oregon infection prevention and microbiology laboratory personnel, including 48 microbiology laboratories, 62 acute care facilities, and 140 long-term care facilities. Methods. The DROP-CRE working group, comprising representatives from academic institutions and public health, convened an interdisciplinary advisory committee to assist with planning and implementation of CRE epidemiology and control efforts. The working group established a statewide CRE definition and surveillance plan; increased the state laboratory capacity to perform the modified Hodge test and polymerase chain reaction for carbapenemases in real time; and administered surveys that assessed the needs and capabilities of Oregon infection prevention and laboratory personnel. Results of these inquiries informed CRE education and the response plan. Results. Of 60 CRE reported from November 2010 through April 2013, only 3 were identified as carbapenemase producers; the cases were not linked, and no secondary transmission was found. Microbiology laboratories, acute care facilities, and long-term care facilities reported lacking carbapenemase testing capability, reliable interfacility communication, and CRE awareness, respectively. Survey findings informed the creation of the Oregon CRE Toolkit, a state-specific CRE guide booklet. Conclusions. A regional epidemiology surveillance and response network has been implemented in Oregon in advance of widespread CRE transmission. Prospective surveillance will determine whether this collaborative approach will be successful at forestalling the emergence of this important healthcare-associated pathogen. © 2014 by The Society for Healthcare Epidemiology of America. All rights reserved.

Picker, L. J. (2014). Are effector memory T cells the key to an effective HIV/AIDS vaccine? *EMBO Reports, 15*(8), 820-821.

Polonsky, W. H., Thompson, S., Wei, W., Riddle, M. C., Chaudhari, S., Jackson, J., et al. (2014). Greater fear of hypoglycaemia with premixed insulin than with basal-bolus insulin glargine and glulisine: Patient-reported outcomes from a 60-week randomised study. *Diabetes, Obesity and Metabolism,*

Aim: To assess the effect of initiating insulin treatment on quality of life of patients with type 2 diabetes (T2DM) in the 60-week All-to-Target trial (NCT00384085). Methods: Patient-reported outcomes from a phase IV, multicentre, randomised, open-label, parallel-group study were analysed. Participants were randomised to: insulin glargine with up to one insulin glulisine injection (G+1); insulin glargine with stepwise addition of up to three insulin glulisine injections (G+3); or twice-daily premixed 70/30 insulin protamine-aspart/aspart (PM-2). Patient-reported outcome questionnaires were administered at weeks 0, 6, 12, 24, 36, 48 and 60. Results: There were no between-group differences in the Psychosocial Adjustment to Illness State-Self Report (PAIS-SR) or in the EuroQoL Group Five-Dimension Self-Report Index Questionnaire (EQ-5D) from baseline to week 60; however, PAIS-SR scores improved significantly over this period in the G+3 group (p=0.0016) and EQ-5D scores worsened significantly in the PM-2 group (p=0.02). Hypoglycemia Fear Survey Behaviour and Worry subscales worsened significantly for all groups, with greater deterioration being observed in the PM-2 group than in the G+1 group (Behaviour, p=0.0050; Worry, p=0.0017) and G+3 groups (Behaviour, p=0.0105; Worry, p=0.0016). Total scores on the Diabetes Quality of Life (DQoL) questionnaire improved more in the G+3 group than in the PM-2 group over the study period (p=0.0284), with all groups showing a significant improvement in DQoL score over time. Conclusion: Insulin glargine-based regimens showed advantages over premixed insulin in a number of patient-reported outcome measures. The potential impact on fear of hypoglycaemia may be of particular relevance when addressing the major barriers to early insulin treatment. © 2014 John Wiley & Sons Ltd.

Punthakee, Z., Miller, M. E., Simmons, D. L., Riddle, M. C., Ismail-Beigi, F., Brillon, D. J., et al. (2014). Durable change in glycaemic control following intensive management of type 2 diabetes

in the ACCORD clinical trial. *Diabetologia,*

Aims/hypothesis We aimed to determine the persistence of glycaemic control 1 year after a limited period of intensive glycaemic management of type 2 diabetes. Methods 4119 ACCORD Trial participants randomised to target HbA1c <6.0% (42 mmol/mol) for 4.0 ± 1.2 years were systematically transitioned to target HbA1c 7.0-7.9% (53-63 mmol/mol) and followed for an additional 1.1 ± 0.2 years. Characteristics of participants with HbA1c <6.5% (48 mmol/mol) or ≥6.5% at transition were compared. Changes in BMI and glucose-lowering medications were compared between those ending with HbA1c <6.5% vs ≥6.5%. Poisson models were used to assess the independent effect of attaining HbA1c <6.5% before transition on ending with HbA1c <6.5%. Results Participants with pre-transition HbA1c <6.5% were older with shorter duration diabetes and took less insulin but more non-insulin glucose-lowering agents than those with higher HbA1c. A total of 823 participants achieved a final HbA1c <6.5%, and had greater post-transition reductions in BMI, insulin dose and secretagogue and acarbose use than those with higher HbA1c (p < 0.0001). HbA1c <6.5% at transition predicted final HbA1c <6.5% (crude RR 4.9 [95% CI 4.0, 5.9]; RR 3.9 [95% CI 3.2, 4.8] adjusted for demographics, co-interventions, pre-intervention HbA1c, BMI and glucose-lowering medication, and post-transition change in both BMI and glucose-lowering medication). Progressively lower pre-transition HbA1c levels were associated with a greater likelihood of maintaining a final HbA1c of <6.5%. Follow-up duration was not associated with post-transition rise in HbA1c. Conclusions/interpretation Time-limited intensive glycaemic management using a combination of agents that achieves HbA1c levels below 6.5% in established diabetes is associated with glycaemic control more than 1 year after therapy is relaxed. © 2014 Springer-Verlag Berlin Heidelberg.

Qaseem, A., Humphrey, L. L., Harris, R., Starkey, M., & Denberg, T. D. (2014). Screening pelvic examination in adult women: A clinical practice guideline from the american college of physicians. *Annals of Internal Medicine, 161*(1), 67-72.

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the utility of screening pelvic examination for the detection of pathology in asymptomatic, nonpregnant, adult women. Methods: This guideline is based on a systematic review of the published literature in the English language from 1946

through January 2014 identified using MEDLINE and hand-searching. Evaluated outcomes include morbidity; mortality; and harms, including overdiagnosis, overtreatment, diagnostic procedure-related harms, fear, anxiety, embarrassment, pain, and discomfort. The target audience for this guideline includes all clinicians, and the target patient population includes asymptomatic, nonpregnant, adult women. This guideline grades the evidence and recommendations using the ACP's clinical practice guidelines grading system. Recommendation: ACP recommends against performing screening pelvic examination in asymptomatic, nonpregnant, adult women (strong recommendation, moderate-quality evidence).

Ramamoorthy, S., Zha, D., Chen, F., Jacques, S. L., Wang, R., Choudhury, N., et al. (2014). Filtering of acoustic signals within the hearing organ. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(27), 9051-9058.

The detection of sound by the mammalian hearing organ involves a complex mechanical interplay among different cell types. The inner hair cells, which are the primary sensory receptors, are stimulated by the structural vibrations of the entire organ of Corti. The outer hair cells are thought to modulate these sound-evoked vibrations to enhance hearing sensitivity and frequency resolution, but it remains unclear whether other structures also contribute to frequency tuning. In the current study, sound-evoked vibrations were measured at the stereociliary side of inner and outer hair cells and their surrounding supporting cells, using optical coherence tomography interferometry in living anesthetized guinea pigs. Our measurements demonstrate the presence of multiple vibration modes as well as significant differences in frequency tuning and response phase among different cell types. In particular, the frequency tuning at the inner hair cells differs from other cell types, causing the locus of maximum inner hair cell activation to be shifted toward the apex of the cochlea compared with the outer hair cells. These observations show that additional processing and filtering of acoustic signals occur within the organ of Corti before inner hair cell excitation, representing a departure from established theories.

Rapoport, B. I., Baird, L. C., & Cohen, A. R. (2014). Third-ventricular neurocysticercosis: Hydraulic maneuvers facilitating endoscopic resection. *Child's Nervous System, 30*(3), 541-546.

Background: Neurocysticercosis, an infection of the central nervous system with the larval cysts

of the pork tapeworm, Taenia solium, is the most common parasitic disease of the central nervous system. The disease is a major global cause of acquired epilepsy and may also manifest as intracranial hypertension due to mass effect from large cysts or to cerebrospinal fluid flow obstruction by intraventricular cysts or inflammation of the subarachnoid space. While the condition is endemic in several regions of the world and has been appreciated as a public health problem in such regions for several decades, its emergence in the USA in areas far from the Mexican border is a more recent phenomenon. Methods: We present a case of surgically corrected acute hydrocephalus in a recent Haitian emigrant child due to a third ventricular neurocysticercal cyst complex. Results: We describe the endoscope-assisted en bloc removal of the complex, together with hydraulic maneuvers facilitating the removal of the intact cyst. Conclusions: Simple hydraulic maneuvers can facilitate the endoscopic en bloc removal of third ventricular neurocysticercal cysts. © 2013 Springer-Verlag.

Rappaport, L. D., Burns, B., Brown, S., Sheridan, D. C., Hansen, M., & Warden, C. R. (2014). Advocacy for emergency medical services for children: Education, practice, and policy implications. *Clinical Pediatric Emergency Medicine, 15*(1), 104-113.
Advocacy for maintaining and expanding Emergency Medical Services for Children is needed on many fronts. Pediatric emergency medicine (PEM) physicians are uniquely qualified to serve this role due to their expertise in the acute care of sick or injured pediatric patients. Given this, in addition to maintaining the highest standards in the emergency departments in which they work, PEM physicians also have responsibilities in the education, training, and practice of emergency medical services providers in their region. These providers are also well positioned to advocate for Emergency Medical Services for Children on a policy level at local, regional, and state governments and in organizations that deal with the care of children in both the prehospital and hospital arenas. Greater engagement by PEM physicians in such activities is required to optimize pediatric care across the spectrum of emergency services. © 2014.

Raslan, A. M., & Burchiel, K. J. (2013). *Neurosurgical approaches to pain management* Elsevier Inc.

Raslan, A. M., & Burchiel, K. J. (2014). Letters to the editor: Value-based neurosurgery and microvascular decompression. *Journal of Neurosurgery, 121*(2), 495-497.

Read, R. W., Levy-Clarke, G., Jabs, D. A., Rosenbaum, J. T., Vitale, A., & Van Gelder, R. N. (2014). Author reply. *Ophthalmology,*

Ren, T., Zheng, J., He, W., & Nuttall, A. L. (2013). Measurement of amplitude and delay of stimulus frequency otoacoustic emissions. *Journal of Otology, 8*(1), 57-62.
Although stimulus frequency otoacoustic emissions (SFOAEs) have been used as a non-invasive measure of cochlear mechanics, clinical and experimental application of SFOAEs has been limited by difficulties in accurately deriving quantitative information from sound pressure measured in the ear canal. In this study, a novel signal processing method for multicomponent analysis (MCA) was used to measure the amplitude and delay of the SFOAE. This report shows the delay-frequency distribution of the SFOAE measured from the human ear. A low level acoustical suppressor near the probe tone significantly suppressed the SFOAE, strongly indicating that the SFOAE was generated at characteristic frequency locations. Information derived from this method may reveal more details of cochlear mechanics in the human ear.

Roayaie, K., & Roayaie, S. (2014). Liver transplant for hepatocellular cancer: Very small tumors, very large tumors, and waiting time. *Clinics in Liver Disease, 18*(3), 603-612.
The role of liver transplant for treatment of early hepatocellular cancer (HCC) is no longer contested. However, its benefit relative to other therapies for patients with very early (<2 cm) HCC is still a matter of debate. Twenty years after the establishment of the Milan criteria, we are beginning to realize that the number and size of tumors may not be the best metric by which to prognosticate outcomes and allocate organs. A better assessment of tumor aggressiveness is clearly needed.

Rodriguez-Barranco, M., Lacasana, M., Gil, F., Lorca, A., Alguacil, J., Rohlman, D. S., et al. (2014). Cadmium exposure and neuropsychological development in school children in southwestern spain. *Environmental Research, 134C*, 66-73.
This study assessed the association between cadmium exposure and neuropsychological development in children from a region with high industrial and mining activities in southwestern Spain. We conducted a cross-sectional study with 261 children aged 6-9 years between January and March 2012. Cadmium exposure was measured in urine and hair of children, and

neuropsychological development was assessed with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and with three computerized tests from the Behavioral Assessment and Research System (BARS): Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT). Multivariate linear regression models, adjusted for potential confounders, were used to estimate the association between neuropsychological development and cadmium exposure measured in urine and hair samples. Geometric means of urine and hair cadmium levels were 0.75mug/g creatinine and 0.01mug/g, respectively. We observed that doubling of levels of cadmium in urine was associated with a reduction of two points (95% CI: -3.8 to -0.4) in the Full-Scale intelligence quotient (IQ) in boys. By domains, association was statistically significant for Verbal Comprehension (beta=-2.0; p=0.04) and close to the significance level for Perceptual Reasoning (beta=-1.8; p=0.06). Among girls, only Verbal Comprehension showed suggestive associations with cadmium exposure (beta=-1.7; p=0.06). Cadmium exposure is associated with cognitive delays in boys in our region. Our results provide additional evidence of the neurotoxic effect of low-level postnatal cadmium exposure among children, and support the hypothesis of differences between sexes in the neurotoxic effect of metals on children.

Rose, K., Jong, M., Yusof, F., Tayyari, F., Tan, O., Huang, D., et al. (2014). Grader learning effect and reproducibility of doppler spectral-domain optical coherence tomography derived retinal blood flow measurements. *Acta Ophthalmologica,*

Purpose: To investigate grader learning effect and to quantify intergrader reproducibility of Doppler Spectral-Domain Optical Coherence Tomography (SD-OCT) derived retinal blood flow measurements. Methods: Fifteen healthy young subjects (mean age 28.44; SD 3 years) underwent Doppler SD-OCT scans of one eye using the circumpapillary double circular scan protocol of the Optovue RTVue by one of two experienced operators. One trained (i.e. having undergone certification) and one novice (i.e. preliminary training comprising five standard practice data sets) individual then graded a standardized set of scans, consisting of 15 data sets (session 1) using custom Doppler Optical Coherence Tomography of Retinal Circulation (doctorc) software. One week later (session 2), the novice grader underwent further training by grading an additional 15 practice data sets and then both graders subsequently regraded the original 15 data

sets. Results: Measurements achieved by a novice grader during session 1 showed a trend to be higher in terms of total retinal venous blood flow (TRBF) and also to be significantly ($p = 0.03$) higher for venous area, compared with a trained grader. Session 2 results were not significantly different for either grader. The mean TRBF for session 2 for the trained and novice grader was 45.29 ± 9.28 μl/min and 44.39 ± 7.36 μl/min, respectively. The coefficient of repeatability (COR) of session 2 TRBF values between the trained and novice grader was 8.09 μl/min. Conclusions: There is a grader learning effect which impacts the venous area measurements. Reproducible and repeatable retinal blood flow measurements were achieved among trained graders using doctorc software. © 2014 Acta Ophthalmologica Scandinavica Foundation.

Rosenbaum, B. P., Kelly, M. L., Kshettry, V. R., & Weil, R. J. (2014). Neurologic disorders, in-hospital deaths, and years of potential life lost in the USA, 1988-2011. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia,*

Premature mortality is a public health concern that can be quantified as years of potential life lost (YPLL). Studying premature mortality can help guide hospital initiatives and resource allocation. We investigated the categories of neurologic and neurosurgical conditions associated with in-hospital deaths that account for the highest YPLL and their trends over time. Using the Nationwide Inpatient Sample (NIS), we calculated YPLL for patients hospitalized in the USA from 1988 to 2011. Hospitalizations were categorized by related neurologic principal diagnoses. An estimated 2,355,673 in-hospital deaths accounted for an estimated 25,598,566 YPLL. The traumatic brain injury (TBI) category accounted for the highest annual mean YPLL at 361,748 (33.9% of total neurologic YPLL). Intracerebral hemorrhage, cerebral ischemia, subarachnoid hemorrhage, and anoxic brain damage completed the group of five diagnoses with the highest YPLL. TBI accounted for 12.1% of all inflation adjusted neurologic hospital charges and 22.4% of inflation adjusted charges among neurologic deaths. The in-hospital mortality rate has been stable or decreasing for all of these diagnoses except TBI, which rose from 5.1% in 1988 to 7.8% in 2011. Using YPLL, we provide a framework to compare the burden of premature in-hospital mortality on patients with neurologic disorders, which may prove useful for informing decisions related to allocation of health resources or research funding. Considering premature mortality

alone, increased efforts should be focused on TBI, particularly in and related to the hospital setting.

Rosenbaum, B. P., & Weil, R. J. (2014). Aneurysmal subarachnoid hemorrhage: Relationship to solar activity in the united states, 1988-2010. *Astrobiology, 14*(7), 568-576.

Aneurysmal subarachnoid hemorrhage (SAH) is a common condition treated by neurosurgeons. The inherent variability in the incidence and presentation of ruptured cerebral aneurysms has been investigated in association with seasonality, circadian rhythm, lunar cycle, and climate factors. We aimed to identify an association between solar activity (solar flux and sunspots) and the incidence of aneurysmal SAH, all of which appear to behave in periodic fashions over long time periods. The Nationwide Inpatient Sample (NIS) provided longitudinal, retrospective data on patients hospitalized with SAH in the United States, from 1988 to 2010, who underwent aneurysmal clipping or coiling. Solar activity and SAH incidence data were modeled with the cosinor methodology and a 10-year periodic cycle length. The NIS database contained 32,281 matching hospitalizations from 1988 to 2010. The acrophase (time point in the cycle of highest amplitude) for solar flux and for sunspots were coincident. The acrophase for aneurysmal SAH incidence was out of phase with solar activity determined by non-overlapping 95% confidence intervals (CIs). Aneurysmal SAH incidence peaks appear to be delayed behind solar activity peaks by 64 months (95% CI; 56-73 months) when using a modeled 10-year periodic cycle. Solar activity (solar flux and sunspots) appears to be associated with the incidence of aneurysmal SAH. As solar activity reaches a relative maximum, the incidence of aneurysmal SAH reaches a relative minimum. These observations may help identify future trends in aneurysmal SAH on a population basis.

Rosenbaum, R. B. (2014). *Connective tissue diseases, vasculitis, and the nervous system* Elsevier Inc.

The inflammatory systemic autoimmune diseases can affect the peripheral and central nervous systems in diverse ways. In this chapter, the neurologic presentation of connective tissue disorders and vasculitis is discussed. In addition, the differential diagnosis of central and peripheral nervous system syndromes in relation to these disorders as well as their treatments are presented so that clinicians can make rapid therapeutic and treatment decisions when

confronted with these problems. The bibliography is largely confined to papers published in the last 20 years, but references to the earlier literature can be found in this chapter as it appeared in the previous edition of this book.

Rose-Nussbaumer, J., Goldstein, D. A., Thorne, J. E., Arantes, T. E., Acharya, N. R., Shakoor, A., et al. (2014). Uveitis in human immunodeficiency virus-infected persons with CD4+ T-lymphocyte count over 200 cells/mL. *Clinical and Experimental Ophthalmology, 42*(2), 118-125.

Background: Introduction of highly active antiretroviral therapy has altered the course of disease for persons infected with human immunodeficiency virus by elevating CD4+ T-lymphocyte levels. Changes in the spectrum of systemic diseases encountered in human immunodeficiency virus-positive individuals are reported in the general medical literature. Design: Retrospective case series. Participants: Sixty-one individuals infected with human immunodeficiency virus, who presented with uveitis when the peripheral CD4+ T-lymphocyte count was over 200cells/μL. Methods: Standardized data collection at seven tertiary-referral inflammatory eye disease clinics. Main Outcome Measures: Standardization of Uveitis Nomenclature anatomic classification and descriptors, cause of uveitis, and visual acuity Results: Peripheral CD4+ T cell counts varied between 207 and 1777 (median=421) cells/μL at the time of diagnosis of uveitis. Uveitis was classified anatomically as anterior (47.5%), intermediate (6.6%), anterior/intermediate (16.4%), posterior (14.8%) and pan (14.8%). Specific causes of uveitis included infections (34.4%), with syphilis responsible for 16.4% of all cases, and defined immunological disorders (27.0%); no cause for the inflammation was identified in 34.4% of persons. Visual acuity was better than 6/15 in 66.7% and 6/60 or worse in 11.8% of 93 eyes at presentation, and better than 6/15 in 82.4% and 6/60 or worse in 8.8% of 34 eyes at 1 year of follow-up. Conclusions: Both infectious and non-infectious forms of uveitis occur in individuals who are infected with human immunodeficiency virus and have preserved or restored peripheral CD4+ T cell levels. Individuals who are human immunodeficiency virus-positive and present with uveitis should be evaluated in the same way all patients with uveitis are assessed.

Ross, C. T., Weise, J. A., Bonnar, S., Nolin, D., Satkoski Trask, J., Smith, D. G., et al. (2014). An empirical comparison of short tandem repeats (STRs) and single nucleotide polymorphisms (SNPs) for relatedness estimation in chinese rhesus macaques (macaca mulatta). *American Journal of Primatology, 76*(4), 313-324.

We compare the effectiveness of short tandem repeat (STR) and single nucleotide polymorphism (SNP) genotypes for estimating pairwise relatedness, using molecular data and pedigree records from a captive Chinese rhesus macaque population at the California National Primate Research Center. We find that a panel of 81 SNPs is as effective at estimating first-order kin relationships as a panel of 14 highly polymorphic STRs. We note, however, that the selected STRs provide more precise predictions of relatedness than the selected SNPs, and may be preferred in contexts that require the discrimination of kin related more distantly than first-order relatives. Additionally, we compare the performance of three commonly used relatedness estimation algorithms, and find that the Wang [2002] algorithm outperforms other algorithms when analyzing STR data, while the Queller & Goodnight [1989] algorithm outperforms other algorithms when analyzing SNP data. Future research is needed to address the number of SNPs required to reach the discriminatory power of a standard STR panel in relatedness estimation for primate colony management. © 2013 Wiley Periodicals, Inc.

Roth-Carter, Q. R., Jacoby, D. B., & Nie, Z. (2014). Interactions of eosinophils with nerves. *Methods in Molecular Biology (Clifton, N.J.), 1178*, 215-229.

Coculture of eosinophils and nerves is a powerful tool in determining the interactions between the two cell types. We have developed methods for culture of parasympathetic ganglia and dorsal root ganglia from humans, and we have further refined the technique to coculture with eosinophils. Here we describe methods for coculturing primary parasympathetic ganglia or dorsal root ganglia with eosinophils.

Roulette, C. J., Mann, H., Kemp, B. M., Remiker, M., Roulette, J. W., Hewlett, B. S., et al. (2014). Tobacco use vs. helminths in congo basin hunter-gatherers: Self-medication in humans? *Evolution and Human Behavior,*

We tested a novel hypothesis that recreational use of neurotoxic plants helps defend against

parasites. Specifically, we investigated the relationship between smoking and helminthiasis among the Aka, a remote population of Central African foragers who are avid tobacco smokers, suffer high rates of helminthiasis, and have little-to-no access to commercial anthelmintics. Two hundred and six healthy Aka men provided saliva and stool samples. Saliva samples were assayed for cotinine, a nicotine metabolite; a subsample was genotyped for the CYP2A6 enzyme, which metabolizes nicotine. Stool samples were assayed for intestinal helminth eggs as an index of worm burden. After 1 year, a subsample of participants was located and provided additional saliva and stool samples. We found (1) an exceptionally high prevalence of tobacco use, (2) a significant negative correlation between cotinine (a nicotine metabolite) and worm burden, (3) that treating helminths with albendazole, a commercial anthelmintic, reduced cotinine concentration two weeks later, compared to placebo controls, (4) among treated participants, higher cotinine concentrations in year 1 predicted less reinfection by year 2, and (5) younger and older participants with slow nicotine-metabolizing CYP2A6 alleles had lower worm burdens compared to those with extensive metabolizing alleles. These results provide the first evidence of a link between helminthiasis and smoking. They also suggest that, in populations where intestinal helminths are endemic, tobacco use might protect against helminth infection and reduce worm burden among infected individuals, and that individuals modulate nicotine exposure in response to infection. The results thus support the hypothesis that substance use helps defend against parasites.

Sakoulas, G., Moise, P. A., Casapao, A. M., Nonejuie, P., Olson, J., Okumura, C. Y., et al. (2014). Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. *Clinical Therapeutics,*

PURPOSE: Guidelines recommend daptomycin combination therapy as an option for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia after vancomycin failure. Recent data suggest that combining daptomycin with a beta-lactam may have unique benefits; however, there are very limited clinical data regarding the use of ceftaroline with daptomycin. METHODS: All 26 cases from the 10 medical centers in which ceftaroline plus daptomycin was used for treatment of documented refractory staphylococcal bacteremia from March 2011 to November 2012 were included. In vitro (synergy studies, binding assays, cathelicidin LL-37 killing assays),

and in vivo (virulence assays using a murine subcutaneous infection model) studies examining the effects of ceftaroline with daptomycin were also performed. FINDINGS: Daptomycin plus ceftaroline was used in 26 cases of staphylococcal bacteremia (20 MRSA, 2 vancomycin-intermediate S aureus, 2 methicillin-susceptible S aureus [MSSA], 2 methicillin-resistant S epidermidis). Bacteremia persisted for a median of 10 days (range, 3-23 days) on previous antimicrobial therapy. After daptomycin plus ceftaroline was started, the median time to bacteremia clearance was 2 days (range, 1-6 days). In vitro studies showed ceftaroline synergy against MRSA and enhanced MRSA killing by cathelicidin LL-37 and neutrophils. Ceftaroline also induced daptomycin binding in MSSA and MRSA to a comparable degree as nafcillin. MRSA grown in subinhibitory concentrations of ceftaroline showed attenuated virulence in a murine subcutaneous infection model. IMPLICATIONS: Ceftaroline plus daptomycin may be an option to hasten clearance of refractory staphylococcal bacteremia. Ceftaroline offers dual benefit via synergy with both daptomycin and sensitization to innate host defense peptide cathelicidin LL37, which could attenuate virulence of the pathogen.

Salgado, V. E., Albuquerque, P. P., Cavalcante, L. M., Pfeifer, C. S., Moraes, R. R., & Schneider, L. F. (2014). Influence of photoinitiator system and nanofiller size on the optical properties and cure efficiency of model composites. *Dental Materials : Official Publication of the Academy of Dental Materials,*

OBJECTIVE: To establish the relationship between photoinitiator system and nanofiller size on the optical properties and cure efficiency of model composites. METHODS: Model composites based on BisGMA/TEGDMA (60:40mol%) were loaded with 40wt% of 7nm or 16nm-sized filler particles. One of the following photoinitiator systems was added: camphorquinone (CQ) associated with an amine (EDMAB), monoacylphosphine oxide (TPO), or bysacylphosphine oxide (BAPO). The optical properties of disk-shaped specimens were measured 24h after curing and repeated after storage in water for 90 days and coffee for 15 days. A large spectrum LED unit (Bluephase G2, Ivoclar Vivadent) was used for photoactivation. CIE L*a*b* parameters, color difference (DeltaE), and translucency parameter (TP) were calculated. Knoop hardness readings were taken at top and bottom composite surfaces. Cure efficiency was determined by bottom/top hardness ratio. Data were statistically analyzed at alpha=0.05 significance level. RESULTS: Composites formulated

with 16nm particles had higher CIE L* than those with 7nm particles in all storage conditions. BAPO-based composites generally had lower CIE a* than the other composites. The group TPO+16nm before storage and all groups with 16nm-sized particles after storage had lower CIE b* (i.e. lower degree of yellowing) than the other groups. TPO-based materials had higher color stability. The cure efficiency was not significantly affected by photoinitiator system or particle size. CQ+7nm had the lowest and BAPO+16nm the highest hardness values. SIGNIFICANCE: Combination of photoinitiator system and filler particle size might affect the optical properties of composites, with low influence on cure efficiency.

Sampath, H. (2014). Oxidative DNA damage in disease-insights gained from base excision repair glycosylase-deficient mouse models. *Environmental and Molecular Mutagenesis,*

Cellular components, including nucleic acids, are subject to oxidative damage. If left unrepaired, this damage can lead to multiple adverse cellular outcomes, including increased mutagenesis and cell death. The major pathway for repair of oxidative base lesions is the base excision repair pathway, catalyzed by DNA glycosylases with overlapping but distinct substrate specificities. To understand the role of these glycosylases in the initiation and progression of disease, several transgenic mouse models have been generated to carry a targeted deletion or overexpression of one or more glycosylases. This review summarizes some of the major findings from transgenic animal models of altered DNA glycosylase expression, especially as they relate to pathologies ranging from metabolic disease and cancer to inflammation and neuronal health. Environ. Mol. Mutagen., 2014. (c) 2014 Wiley Periodicals, Inc.

Sampson, V. B., David, J. M., Puig, I., Patil, P. U., de Herreros, A. G., Thomas, G. V., et al. (2014). Wilms' tumor protein induces an epithelial-mesenchymal hybrid differentiation state in clear cell renal cell carcinoma. *PloS One, 9*(7), e102041.

The Wilms' tumor transcription factor (WT1) was originally classified as a tumor suppressor, but it is now known to also be associated with cancer progression and poor prognosis in several malignancies. WT1 plays an essential role in orchestrating a developmental process known as mesenchymal-to-epithelial transition (MET) during kidney development, but also induces the reverse process, epithelial-to-mesenchymal transition (EMT) during heart development. WT1 is

not expressed in the adult kidney, but shows elevated expression in clear cell renal cell carcinoma (ccRCC). However, the role of WT1 in this disease has not been characterized. In this study, we demonstrate that WT1 is upregulated in ccRCC cells that are deficient in the expression of the von Hippel-Lindau tumor suppressor protein (VHL). We found that WT1 transcriptionally activated Snail, a master transcriptional repressor that is known to induce EMT. Although Snail represses E-cadherin and induces mesenchymal characteristics, we found partial maintenance of E-cadherin and associated epithelial characteristics in kidney cells and ccRCC cells that express WT1, since WT1 upregulates E-cadherin expression and competes with Snail repression. These findings support a novel paradigm in which WT1 induces an epithelial-mesenchymal hybrid transition (EMHT), characterized by Snail up-regulation with E-cadherin maintenance, a tumor cell differentiation state in which cancer cells keep both EMT and MET characteristics which may promote tumor cell plasticity and tumor progression.

Samuels, M. H., Kolobova, I., Smeraglio, A., Peters, D., Janowsky, J. S., & Schuff, K. G. (2014). The effects of levothyroxine replacement or suppressive therapy on health status, mood, and cognition. *The Journal of Clinical Endocrinology and Metabolism, 99*(3), 843-851.
CONTEXT: TSH-suppressive doses of levothyroxine (L-T4) have adverse effects on bone and cardiac function, but it is unclear whether central nervous system function is also affected. OBJECTIVE: The aim of the study was to determine whether women receiving TSH-suppressive L-T4 doses have decrements in health status, mood, or cognitive function. DESIGN AND SETTING: A cross-sectional comparison was made among three groups of women in an academic medical center research clinic. PATIENTS: Twenty-four women receiving chronic TSH-suppressive L-T4 doses, 35 women receiving chronic replacement L-T4 doses, and 20 untreated control women participated in the study. INTERVENTIONS: Subjects underwent testing at a single outpatient visit. MAIN OUTCOME MEASURES: We measured health status (SF-36), mood (Profile of Mood States, Symptom Checklist 90-R, Affective Lability Scale), and cognitive function (declarative memory [Paragraph Recall], working memory [N-back, Subject Ordered Pointing], motor learning [Pursuit Rotor, Motor Sequence Learning Test], and executive function [Letter Cancellation Test, Trail Making Test, Iowa Gambling Test]). RESULTS: Women receiving TSH-suppressive or replacement L-T4 doses had decrements in health status and mood compared to healthy controls.

These decrements were more pronounced in women receiving replacement, rather than suppressive, L-T4 doses. Memory and executive function were not affected in either treated group, compared to healthy controls. CONCLUSIONS: Women receiving TSH-suppressive doses of L-T4 do not have central nervous system dysfunction due to exogenous subclinical thyrotoxicosis, but TSH-suppressed and L-T4-replaced women have slight decrements in health status and mood that may be related to self-knowledge of the presence of a thyroid condition or other uncharacterized factors. These mood alterations do not impair cognitive function.

Scalettar, B. A., Shaver, D., Kaech, S., & Lochner, J. E. (2014). Super-resolution imaging of neuronal dense-core vesicles. *Journal of Visualized Experiments : JoVE, (89). doi*(89), 10.3791/51394. Detection of fluorescence provides the foundation for many widely utilized and rapidly advancing microscopy techniques employed in modern biological and medical applications. Strengths of fluorescence include its sensitivity, specificity, and compatibility with live imaging. Unfortunately, conventional forms of fluorescence microscopy suffer from one major weakness, diffraction-limited resolution in the imaging plane, which hampers studies of structures with dimensions smaller than ~250 nm. Recently, this limitation has been overcome with the introduction of super-resolution fluorescence microscopy techniques, such as photoactivated localization microscopy (PALM). Unlike its conventional counterparts, PALM can produce images with a lateral resolution of tens of nanometers. It is thus now possible to use fluorescence, with its myriad strengths, to elucidate a spectrum of previously inaccessible attributes of cellular structure and organization. Unfortunately, PALM is not trivial to implement, and successful strategies often must be tailored to the type of system under study. In this article, we show how to implement single-color PALM studies of vesicular structures in fixed, cultured neurons. PALM is ideally suited to the study of vesicles, which have dimensions that typically range from ~50-250 nm. Key steps in our approach include labeling neurons with photoconvertible (green to red) chimeras of vesicle cargo, collecting sparsely sampled raw images with a super-resolution microscopy system, and processing the raw images to produce a high-resolution PALM image. We also demonstrate the efficacy of our approach by presenting exceptionally well-resolved images of dense-core vesicles (DCVs) in cultured hippocampal neurons, which refute the hypothesis that extrasynaptic trafficking of DCVs is mediated largely by DCV clusters.

Schmid, M., Steinlein, C., Tian, Q., Hanlon Newell, A. E., Gessler, M., Olson, S. B., et al. (2014). Mosaic variegated aneuploidy in mouse BubR1 deficient embryos and pregnancy loss in human. *Chromosome Research,*

Chromosome aberrations (aneuploidies mostly) are the cause of the majority of spontaneous abortions in humans. However, little is known about defects in the underlying molecular mechanisms resulting in chromosome aberrations and following failure of preimplantation embryo development, initiation of implantation and postimplantation pregnancy loss. We suggest that defects of the spindle assembly checkpoint (SAC) are responsible for aneuploidy and the following abortions. To develop our hypothesis, we modeled this process in the mouse after inactivation of protein BubR1, one of the key players of SAC. We found that soon after implantation, more than 50 % of cells of BubR1-/- embryos were aneuploid and had an increased level of premature sister chromatid separation (PSCS). Aneuploid cells do not have a predominant gain or loss of some specific chromosomes, but they have mosaic variegated aneuploidy (MVA), which is characterised by random mixture of different chromosomes. MVA leads to growth retardation, stochastic massive apoptosis, disruption of bilateral symmetry, and embryo death between embryonic days 7.5 to 13.5. Analysis published human data revealed that human recurrent pregnancy loss (RPL) embryos and rare infant patients carrying BubR1 mutations that have been described so far have the PSCS and MVA as in BubR1 deficient/insufficient mice. Based on this data, we predict that deficiency/insufficiency of BubR1 and other components of the SAC in human are responsible for a significant fraction of both early and late RPLs.

Seminotti, B., Ribeiro, R. T., Amaral, A. U., da Rosa, M. S., Pereira, C. C., Leipnitz, G., et al. (2014). Acute lysine overload provokes protein oxidative damage and reduction of antioxidant defenses in the brain of infant glutaryl-CoA dehydrogenase deficient mice: A role for oxidative stress in GA I neuropathology. *Journal of the Neurological Sciences,*

We evaluated the antioxidant defense system and protein oxidative damage in the brain and liver of 15-day-old GCDH deficient knockout (Gcdh-/-) mice following an acute intraperitoneal administration of Lys (8mumol/g). We determined reduced glutathione (GSH) concentrations, sulfhydryl content, carbonyl formation and the activities of the antioxidant enzymes glutathione

peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR) in the brain and liver of these animals. 2',7'-dihydrodichlorofluorescein (DCFH) oxidation was also measured as an index of free radical formation. The only parameters altered in Gcdh-/- compared to wild type (Gcdh+/+) mice were a reduction of liver GSH concentrations and of brain sulfhydryl content. Acute Lys injection provoked a decrease of GSH concentration in the brain and sulfhydryl content in the liver, and an increase in carbonyl formation in the brain and liver of Gcdh-/- mice. Lys administration also induced a decrease of all antioxidant enzyme activities in the brain, as well as an increase of the activities of SOD and CAT in the liver of Gcdh-/- mice. Finally, Lys elicited a marked increase of DCFH oxidation in the brain and liver. It is concluded that Lys overload compromises the brain antioxidant defenses and induces protein oxidation probably secondary to reactive species generation in infant Gcdh+/+ mice.

Sen, H. N., Vitale, S., Gangaputra, S. S., Nussenblatt, R. B., Liesegang, T. L., Levy-Clarke, G. A., et al. (2014). Periocular corticosteroid injections in uveitis: Effects and complications. *Ophthalmology,*

PURPOSE: To evaluate the benefits and complications of periocular depot corticosteroid injections in patients with ocular inflammatory disorders. DESIGN: Multicenter, retrospective cohort study. PARTICIPANTS: A total of 914 patients (1192 eyes) who had received >/=1 periocular corticosteroid injection at 5 tertiary uveitis clinics in the United States. METHODS: Patients were identified from the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study. Demographic and clinical characteristics were obtained at every visit via medical record review by trained reviewers. MAIN OUTCOME MEASURES: Control of inflammation, improvement of visual acuity (VA) to >/=20/40, improvement of VA loss attributed to macular edema (ME), incident cataract affecting VA, cataract surgery, ocular hypertension, and glaucoma surgery. RESULTS: Among 914 patients (1192 eyes) who received >/=1 periocular injection during follow-up, 286 (31.3%) were classified as having anterior uveitis, 303 (33.3%) as intermediate uveitis, and 324 (35.4%) as posterior or panuveitis. Cumulatively by /=20/40. Among the subset with VA /=20/40. By 12 months, the cumulative incidence of >/=1 visits with an intraocular pressure of >/=24 mmHg and >/=30 mmHg was 34.0% (95% CI, 24.8-45.4) and 15.0% (95% CI, 11.8-19.1) respectively; glaucoma surgery was performed in 2.4% of eyes (95% CI, 1.4-3.9). Within

12 months, among phakic eyes initially >/=20/40, the incidence of a reduction in VA to <20/40 attributed to cataract was 20.2% (95% CI, 15.9-25.6); cataract surgery was performed within 12 months in 13.8% of the initially phakic eyes (95% CI, 11.1-17.2). CONCLUSION: Periocular injections were effective in treating active intraocular inflammation and in improving reduced VA attributed to ME in a majority of patients. The response pattern was similar across anatomic locations of uveitis. Overall, VA improved in one half of the patients at some point within 6 months. However, cataract and ocular hypertension occurred in a substantial minority.

Shahidi, A. M., Patel, S. R., Huang, D., Tan, O., Flanagan, J. G., & Hudson, C. (2014). Assessment of total retinal blood flow using doppler fourier domain optical coherence tomography during systemic hypercapnia and hypocapnia. *Physiological Reports, 2*(7), 10.14814/phy2.12046. Print 2014 Jul 1.

The purpose of this study was to investigate changes in total retinal blood flow (RBF) using Doppler Fourier Domain Optical Coherence Tomography (Doppler FD-OCT) in response to the manipulation of systemic partial pressure of CO2 (PETCO2). Double circular Doppler blood flow scans were captured in nine healthy individuals (mean age +/- standard deviation: 27.1 +/- 4.1, six males) using the RTVue() FD-OCT (Optovue). PETCO2 was manipulated using a custom-designed computer-controlled gas blender (RespirAct()) connected to a sequential gas delivery rebreathing circuit. Doppler FD-OCT measurements were captured at baseline, during stages of hypercapnia (+5/+10/+15 mmHg PETCO2), return to baseline and during stages of hypocapnia (-5/-10/-15 mmHg PETCO2). Repeated measures analysis of variance (reANOVA) and Tukey's post hoc analysis were used to compare Doppler FD-OCT measurements between the various PETCO2 levels relative to baseline. The effect of PETCO2 on TRBF was also investigated using linear regression models. The average RBF significantly increased by 15% ($P < 0.0001$) with an increase in PETCO2 and decreased significantly by 10% with a decrease in PETCO2 ($P = 0.001$). Venous velocity significantly increased by 3.11% from baseline to extreme hypercapnia ($P < 0.001$) and reduced significantly by 2.01% at extreme hypocapnia ($P = 0.012$). No significant changes were found in the average venous area measurements under hypercapnia ($P = 0.36$) or hypocapnia ($P = 0.40$). Overall, increased and decreased PETCO2 values had a significant effect

on RBF outcomes (P < 0.002). In healthy individuals, altered end-tidal CO2 levels significantly changed RBF as measured by Doppler FD-OCT.

Sharma, M., Zhang, M. J., Zhong, X., Abidi, M. H., Akpek, G., Bacher, U., et al. (2014). Older patients with myeloma derive similar benefit from autologous transplantation. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,* Autologous hematopoietic cell transplant (AHCT) for plasma cell myeloma (PCM) is performed less often in >70 year olds. We analyzed 11,430 AHCT recipients for PCM prospectively reported to the CIBMTR between 2008 and 2011 representing the majority of US AHCT activity during this period. Survival (OS) was compared in 3 cohorts; ages 18-59 years (N=5818), 60-69 years (N= 4666) and >70 years (N=946). Median OS was not reached for any cohort. In multivariate analysis, increasing age was associated with mortality (p=0.0006). Myeloma specific mortality was similar at 12% indicating age related effect on non-myeloma mortality. Analyses were performed in a representative subgroup comparing relapse rate (RR), progression free survival (PFS) and non-relapse mortality (NRM). 1-year NRM was 0% for age >70 years and 2% for other ages (p = NS). 3-year RR were 56% in age 18-59 years, 61% in age 60-69 years and 63% age >70 (p = NS). 3 year PFS was similar at 42% in age 18-59 years, 38% in age 60-69 years, and 33% in age >70 years (p=NS). Post-relapse survival (PRS) was significantly worse for the older cohort (p=0.03). Older subjects selected for AHCT derived similar anti-myeloma benefit without worse NRM, RR or PFS.

Shen, H. -., Sun, H., Hanthorn, M. M., Zhi, Z., Lan, J. -., Poulsen, D. J., et al. (2014). Overexpression of adenosine kinase in cortical astrocytes and focal neocortical epilepsy in mice: Laboratory investigation. *Journal of Neurosurgery, 120*(3), 628-638.
Object. New experimental models and diagnostic methods are needed to better understand the pathophysiology of focal neocortical epilepsies in a search for improved epilepsy treatment options. The authors hypothesized that a focal disruption of adenosine homeostasis in the neocortex might be sufficient to trigger electrographic seizures. They further hypothesized that a focal disruption of adenosine homeostasis might affect microcirculation and thus offer a diagnostic opportunity for the detection of a seizure focus located in the neocortex. Methods.

Focal disruption of adenosine homeostasis was achieved by injecting an adeno-associated virus (AAV) engineered to overexpress adenosine kinase (ADK), the major metabolic clearance enzyme for the brain's endogenous anticonvulsant adenosine, into the neocortex of mice. Eight weeks following virus injection, the affected brain area was imaged via optical microangiography (OMAG) to detect changes in microcirculation. After completion of imaging, cortical electroencephalography (EEG) recordings were obtained from the imaged brain area. Results. Viral expression of the Adk cDNA in astrocytes generated a focal area (~ 2 mm in diameter) of ADK overexpression within the neocortex. OMAG scanning revealed a reduction in vessel density within the affected brain area of approximately 23% and 29% compared with control animals and the contralateral hemisphere, respectively. EEG recordings revealed electrographic seizures within the focal area of ADK overexpression at a rate of 1.3 ± 0.2 seizures per hour (mean ± SEM). Conclusions. The findings of this study suggest that focal adenosine deficiency is sufficient to generate a neocortical focus of hyperexcitability, which is also characterized by reduced vessel density. The authors conclude that their model constitutes a useful tool to study neocortical epilepsies and that OMAG constitutes a noninvasive diagnostic tool for the imaging of seizure foci with disrupted adenosine homeostasis. ©AANS, 2014.

Shen, I., & Campbell, D. N. (2004). *Congenital septal defects* Elsevier Inc.

Sibley, C., Yazici, Y., Tascilar, K., Khan, N., Bata, Y., Yazici, H., et al. (2014). Behçet syndrome manifestations and activity in the united states versus turkey - A cross-sectional cohort comparison. *Journal of Rheumatology, 41*(7), 1379-1384.

Objective. To compare clinical manifestations and activity of Behçet syndrome (BS) in the United States versus Turkey using validated outcome measures. Methods. Consecutive patients with BS from the US National Institutes of Health (NIH), New York University, and the University of Istanbul were evaluated. Disease activity was measured using the Behçet's Syndrome Activity Scale (BSAS) and the Behçet's Disease Current Activity Form (BDCAF) with quality of life measured by the Behçet Disease Quality of Life (BDQOL) form. One-way ANOVA, t-tests, and multivariate regression analyses were performed. Results. Mean age did not differ between sites; however, more women were seen in the United States versus in Turkey ($p < 0.001$), and disease

duration was longer in the United States (p = 0.02). Organ manifestations were similar for oral and genital ulcers, skin disease, arthralgia, eye disease, and thrombosis. However, more gastrointestinal (p < 0.001) and neurologic disease (p = 0.003) was seen in the United States. BSAS and BDCAF scores were worse in the United States compared to Turkey (p = 0.013 and < 0.001, respectively). Worse mean BDQOL scores were observed at the NIH compared to Istanbul (not significant). Multivariable regression models showed worse scores in ethnically atypical patients for BSAS and BDCAF (p = 0.04 and p = 0.001), American patients for BDCAF (p = 0.01), older age for BDCAF (p = 0.005), and women for BDQOL (p = 0.01). Conclusion. Demographic and clinical manifestations of BS differ between sites with higher disease activity in the United States compared to Turkey. Referral patterns, age, sex, ethnicity, and country of origin may be important in these differences. These observations raise the question of whether pathogenic mechanisms differ in Turkish and American patients.

Silverberg, J. I., & Simpson, E. L. (2014). Association between obesity and eczema prevalence, severity and poorer health in US adolescents. *Dermatitis : Contact, Atopic, Occupational, Drug, 25*(4), 172-181.

BACKGROUND: Identification of modifiable risk factors for the development of eczema is of major public health significance. OBJECTIVE: This study aimed to determine the effects of obesity in adolescence on the prevalence, severity, and quality of life of patients with eczema. METHODS: We used the 2007-2008 National Survey of Children's Health, including a nationally representative sample of 45,897 adolescents aged 10 to 17 years. Caregiver report of eczema, health status, height, weight, number of health conditions, use of health services, and sociodemographics were assessed. RESULTS: The prevalences of overweight (20.3% vs 15.4%) and obesity (16.8% vs 15.4%) were increased in adolescents with eczema compared with adolescents without eczema (Rao-Scott chi, P /=2 conditions; P </= 0.003), and used more health services than most children of the same age compared with nonobese children (31.2% vs 21.5%; P = 0.01). CONCLUSIONS: Obesity in adolescence is associated with increased eczema prevalence and severity, poorer overall health, and increased chronic health conditions and health care utilization.

Simerly, C., Tachibana, M., Mitalipov, S., & Schatten, G. (2013). *Cloning primates* Elsevier Inc.

The promise of nuclear transfer (NT) in producing patient-specific embryonic stem cells for regenerative medicine holds great interest for the treatment of human diseases, whether as tools for "disease in a dish" discoveries or as replacement cells in patient therapies. With the discovery of induced pluripotent stem cells, current debates flourish over whether human NT is necessary, given the limitations of burdensome technical, ethical, and legal issues. Non-human primates (NHP) are superior models for understanding the stepwise events of successful primate NT and could provide easier extrapolations to events in humans than rodent cloning model. Early challenges to producing cloned NHP blastocysts using traditional NT technologies successful in rodent and cows were overcome by modifications to enucleation, artificial activation, and embryo culture in monkeys. Regardless, adoption of these technical advances in human NT has yet to produce stable human pluripotent embryonic stem cells, and recent reports suggest that human meiotic spindle removal as the first step in the cloning process remains detrimental to producing viable human ESC lines. This chapter provides a review on challenges in nuclear transfer in primates - non-human and human alike.

Simpson, B., Foster, S., Ku, J. H., Simpson, E. L., & Ehst, B. D. (2014). Triple antibiotic combination therapy may improve but not resolve granuloma annulare. *Dermatologic Therapy,*

Granuloma annulare is a fairly common entity yet lacks reliable treatment options especially when multiple lesions or dissemination exists. A recent case series suggests that a regimen of three oral antibiotics may prove to be an effective treatment. Our objective is to evaluate the efficacy of once monthly triple antibiotic therapy for granuloma annulare. We conducted an open-label prospective study of subjects with at least five lesions of granuloma annulare who received once monthly rifampin, ofloxacin, and minocycline for 6 months. Improvement was measured with a novel objective Granuloma Annulare Severity Index (GASI) scoring system. Twenty-one subjects enrolled. Ten subjects (48%) achieved at least a 50% reduction in their GASI, including three subjects (14%) who reached 75% improvement and one subject (5%) whose skin cleared. Six subjects (29%) had no change or worsening of their granuloma annulare. Median GASI scores decreased significantly by 15 points ($p < 0.01$), although the clinical significance of this result is unclear. As this was a small open-label study without a control group, we cannot determine if the

results simply reflect the natural course of the disease. The GASI is not a validated assessment tool. Once monthly triple antibiotic use may improve but not clear granuloma annulare over 6 months. Randomized trials may be warranted to further assess this therapy.

Simpson, B. M., Foster, S. K., Chapman, C. N., & Simpson, E. L. (2014). The effectiveness of grenz ray therapy for chronic dermatoses of the hands and feet. *Dermatitis : Contact, Atopic, Occupational, Drug, 25*(4), 205-208.

BACKGROUND: Grenz ray therapy (GRT) has been used for inflammatory and neoplastic dermatologic diseases for over 100 years. Its use is declining, possibly because of the difficulties maintaining radiation certification and insurance coverage. OBJECTIVE: The aim of this study is to evaluate the safety and effectiveness of GRT in chronic inflammatory dermatoses of the hands and feet. METHODS: We performed a retrospective chart review of patients treated with GRT at the Oregon Health & Science University from 2006 to 2009. Candidates identified for the study were then mailed questionnaires to supplement data acquired from chart review. RESULTS: Most patients (73%; 95% confidence interval [CI], 65%-80%) experienced at least moderate improvement. This improvement persisted for at least 1 month in 66% of patients (95% CI, 57%-74%), with 18 patients (23%; 95% CI, 15%-33%) clear for over 1 year. Minimal adverse effects were reported, and most patients (63%; 95% CI, 52%-72%) stated that they would repeat GRT if available. CONCLUSIONS: Grenz ray therapy seems to be a safe and effective modality for chronic hand and foot dermatoses with some patients experiencing prolonged remissions. Grenz ray therapy, when available, should be considered before the use of systemic agents, which are often associated with higher costs and potential toxicities.

Sinclair, S., Cunnington, M., Messenheimer, J., Weil, J., Cragan, J., Lowensohn, R., et al. (2014). Advantages and problems with pregnancy registries: Observations and surprises throughout the life of the international lamotrigine pregnancy registry. *Pharmacoepidemiology and Drug Safety,*

Purpose: The International Lamotrigine Pregnancy Registry monitored for a signal of a substantial increase in the frequency of major congenital malformations associated with lamotrigine exposures in pregnancy over an 18-year period. Key methodological lessons are discussed. Methods: The strengths and weaknesses of the Registry were assessed using quantifiable

methodological and operational parameters including enrollment, completeness of exposure and outcome data reporting, and lost to follow-up. The choice of comparator groups and stopping rules for registry closure were critically evaluated. Results: The reliance on voluntary reporting was associated with a clustered geographical distribution of registered pregnancies. The enrollment rate increased over time with new approvals and indications for lamotrigine and publication of interim data. Reporter burden was minimized through a streamlined data collection approach resulting in a high level of completeness of exposure and primary outcome data. Lost to follow-up rates were high (28.5% overall) representing a major limitation; incentives to increase the completeness of reporting failed to reduce rates. A lack of an internal comparator group complicated data interpretation; but external comparisons with multiple external groups allowed an assessment of consistency of outcome data across multiple data sources. A lack of a priori closure criteria prolonged the life of the Registry, and consideration of regulatory guidelines on this subject is encouraged at the time of conception of future registries. Conclusions: A successful pregnancy exposure registry requires ongoing flexibility and continuous re-assessment of enrollment, recruitment, and retention methods and the availability of comparison data, throughout its lifecycle. © 2014 John Wiley & Sons, Ltd.

Sittig, D. F., Ash, J. S., & Singh, H. (2014). The SAFER guides: Empowering organizations to improve the safety and effectiveness of electronic health records. *American Journal of Managed Care, 20*(5), 418-423.

Electronic health records (EHRs) have potential to improve quality and safety of healthcare. However, EHR users have experienced safety concerns from EHR design and usability features that are not optimally adapted for the complex work flow of real-world practice. Few strategies exist to address unintended consequences from implementation of EHRs and other health information technologies. We propose that organizations equipped with EHRs should consider the strategy of "proactive risk assessment" of their EHR-enabled healthcare system to identify and address EHR-related safety concerns. In this paper, we describe the conceptual underpinning of an EHR-related self-assessment strategy to provide institutions a foundation upon which they could build their safety efforts. With support from the Office of the National Coordinator for Health Information Technology (ONC), we used a rigorous, iterative process to develop a set of 9

self-assessment tools to optimize the safety and safe use of EHRs. These tools, referred to as the Safety Assurance Factors for EHR Resilience (SAFER) guides, could be used to self-assess safety and effectiveness of EHR implementations, identify specific areas of vulnerability, and create solutions and culture change to mitigate risks. A variety of audiences could conduct these assessments, including frontline clinicians or care teams in different practices, or clinical, quality, or administrative leaders within larger institutions. The guides use a multifaceted systems-based approach to assess risk and empower organizations to work with internal or external stakeholders (eg, EHR developers) on optimizing EHR functionality and using EHRs to drive improvements in the quality and safety of healthcare.

Smith, A. W., Rønnekleiv, O. K., & Kelly, M. J. (2014). Gq-mER signaling has opposite effects on hypothalamic orexigenic and anorexigenic neurons. *Steroids, 81*, 31-35.

Two populations of cells within the hypothalamus exert opposite actions on food intake: proopiomelanocortin (POMC) neurons decrease it, while neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons increase it. 17β-Estradiol (E2) is a potent anorexigenic hormone that exerts both genomic and non-genomic, rapid actions on these metabolic neurons. This review focuses on the rapid membrane effects of E2 in both POMC and NPY/AgRP neurons and how these combined effects mediate the anorexigenic effects of this steroid.

Smith, N. R., Anderson, E. C., Davies, P. S., & Wong, M. H. (2014). *Building blocks for engineering the small intestine* Elsevier Inc.

Bowel transplantation represents the current standard of care for patients suffering from severe intestinal disorders such as short bowel syndrome. Despite improvements in surgical procedures, there remains an approximate 50% 5-year survival rate for intestinal transplant patients [55]. Currently, the primary barriers to successful organ transplantation are the lack of transplantable tissue, the potential for transplant rejection, and the requirement of lifelong immunosuppression [35]. These challenges highlight the need to fully explore the developing field of intestinal epithelial stem cell biology and their ability for ex vivo expansion of tissue in order to reach the

ultimate goal of engineering personalized transplantable intestine from patient-derived cells.

Sonnenberg, A. (2014). Ubiquitous occurrence of birth-cohort patterns in inflammatory bowel disease. *European Journal of Gastroenterology & Hepatology, 26*(8), 888-893.

BACKGROUND AND AIMS: The aim of the present study was to demonstrate the ubiquitous occurrence of the birth-cohort phenomenon of inflammatory bowel disease among US whites and nonwhites, as well as males and females. METHODS: Mortality from Crohn's disease and ulcerative colitis in the USA between 1950 and 2010 were analyzed to discern underlying birth-cohort patterns affecting both their time trends. Age-standardized cohort mortality ratio was used as a summary statistic to represent the overall mortality associated with consecutive birth-cohorts. RESULTS: The cohort-age contours of Crohn's disease aligned to form one hyperbola with an initial rise between 1865 and 1935 and a subsequent decline. This pattern was confirmed by the time trends of the corresponding standardized cohort mortality ratio values. In ulcerative colitis, the individual cohort-age contours also aligned into one hyperbola that appeared shifted towards earlier generations by about 30 years when compared with Crohn's disease. Similar trends were observed in men and women or whites and nonwhites analyzed separately. CONCLUSION: The birth-cohort patterns indicate that exposure to two separate risk factors must have occurred in both diseases during an early period of life. In the USA, these exposures have changed over historical times similarly in both sexes and different ethnic groups.

Sorror, M. L., Martin, P. J., Storb, R. F., Bhatia, S., Maziarz, R. T., Pulsipher, M. A., et al. (2014). Pretransplant comorbidities predict severity of acute graft-versus-host disease and subsequent mortality. *Blood, 124*(2), 287-295.

Whether the hematopoietic cell transplantation comorbidity index (HCT-CI) can provide prognostic information about development of acute graft-versus-host disease (GVHD) and subsequent mortality is unknown. Five institutions contributed information on 2985 patients given human leukocyte antigen-matched grafts to address this question. Proportional hazards models were used to estimate the hazards of acute GVHD and post-GVHD mortality after adjustment for known risk variables. Higher HCT-CI scores predicted increased risk of grades 3 to

4 acute GVHD (P < .0001 and c-statistic of 0.64), and tests of interaction suggested that this association was consistent among different conditioning intensities, donor types, and stem cell sources. Probabilities of grades 3 to 4 GVHD were 13%, 18%, and 24% for HCT-CI risk groups of 0, 1 to 4, and ≥5. The HCT-CI was statistically significantly associated with mortality rates following diagnosis of grade 2 (hazard ratio [HR] = 1.24; P < .0001) or grades 3 to 4 acute GVHD (HR = 1.19; P < .0001). Patients with HCT-CI scores of ≥3 who developed grades 3 to 4 acute GVHD had a 2.63-fold higher risk of mortality than those with scores of 0 to 2 and did not develop acute GVHD. Thus, pretransplant comorbidities are associated with the development and severity of acute GVHD and with post-GVHD mortality. The HCT-CI could be useful in designing trials for GVHD prevention and could inform expectations for GVHD treatment trials.

Sorwell, K. G., Kohama, S. G., & Urbanski, H. F. (2014). Testosterone increases circulating dehydroepiandrosterone sulfate levels in the male rhesus macaque. *Frontiers in Endocrinology, 5*, 101.

The adrenal steroid dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are two of the most abundant hormones in the human circulation. Furthermore, they are released in a circadian pattern and show a marked age-associated decline. Adult levels of DHEA and DHEAS are significantly higher in males than in females, but the reason for this sexual dimorphism is unclear. In the present study, we administered supplementary androgens [DHEA, testosterone and 5alpha-dihydrotestosterone (DHT)] to aged male rhesus macaques (Macaca mulatta). While this paradigm increased circulating DHEAS immediately after DHEA administration, an increase was also observed following either testosterone or DHT administration, resulting in hormonal profiles resembling levels observed in young males in terms of both amplitude and circadian pattern. This stimulatory effect was limited to DHEAS, as an increase in circulating cortisol was not observed. Taken together, these data demonstrate an influence of the hypothalamo-pituitary-testicular axis on adrenal function in males, possibly by sensitizing the zona reticularis to the stimulating action of adrenocorticopic hormone. This represents a plausible mechanism to explain sex differences in circulating DHEA and DHEAS levels, and may have important implications in the development of hormone therapies designed for elderly men and women.

Spellman, P. T., Stuart, J., & Gray, J. W. (2015). *Understanding and using information about cancer genomes* Elsevier Inc.

Srinivasan, N. K., & Zahorik, P. (2014). Enhancement of speech intelligibility in reverberant rooms: Role of amplitude envelope and temporal fine structure. *Journal of the Acoustical Society of America, 135*(6), EL239-EL245.

The temporal envelope and fine structure of speech make distinct contributions to the perception of speech in normal-hearing listeners, and are differentially affected by room reverberation. Previous work has demonstrated enhanced speech intelligibility in reverberant rooms when prior exposure to the room was provided. Here, the relative contributions of envelope and fine structure cues to this intelligibility enhancement were tested using an open-set speech corpus and virtual auditory space techniques to independently manipulate the speech cues within a simulated room. Intelligibility enhancement was observed only when the envelope was reverberant, indicating that the enhancement is envelope-based. © 2014 Acoustical Society of America.

Stauber, B. D., Arthur, A., & Baron, S. (2013). Stenting for brachial artery dissection and stenosis. *Vascular Disease Management, 10*(4), 79-81.

Purpose. To report percutaneous transluminal angioplasty and stenting in a patient with brachial artery dissection and stenosis. Case report. A 79-year-old woman with a history of coronary artery disease and hypertension 10 months post 2-vessel coronary artery bypass surgery presented with pain, numbness, and weakness in her right hand that had been increasing in severity for several months. Her brachial, radial, and ulnar pulses were not palpable and a Doppler ultrasound was consistent with brachial artery stenosis. She was taken for angiography, which revealed a dissection of her right brachial artery with concomitant severe stenosis. Her right brachial artery was stented with two LifeStent FlexStar XL vascular stents (Bard Peripheral Vascular), with symptomatic relief and no evidence of restenosis at 1 year. Conclusion. Percutaneous angioplasty and stenting can be a viable option to treat patients with symptomatic upperextremity stenosis. © 2010 HMP Communications.

Swafford, K. L., Miller, L. L., Herr, K., Forcucci, C., Kelly, A. M., & Bakerjian, D. (2014). Geriatric pain competencies and knowledge assessment for nurses in long term care settings. *Geriatric Nursing (New York, N.Y.),*

Pain in older adults is a prevalent problem that affects quality of life and challenges nurses, particularly those caring for older adults living in long term care settings. Despite the national priority of pain management, insufficient knowledge of nurses about geriatric pain is a documented barrier to effective geriatric pain management in all long term care settings. To address this knowledge gap, a website (GeriatricPain.org) was developed by the National Geriatric Pain Collaborative with a grant from the MayDay Fund to provide a single site for evidenced-based, easy-to-use, downloadable resources on pain management. This paper describes the development of the most recent addition to the website, a set of evidence-based core geriatric pain management competencies and a geriatric pain knowledge assessment, and discusses their potential uses in improving pain care for older adults. Geriatric Pain Competencies and Knowledge Assessment for Nurses in Long Term Care Settings.

Takahashi, C., Mass, M., Hamilton, B., Humayun Guletkin, S., & Bourdette, D. (2014). Microbial DNA testing for inflammatory diseases of the brain of uncertain etiology. *Neurology: Clinical Practice, 4*(3), 192-198.

Neurologists may be confronted with patients who present with inflammatory brain lesions where the diagnosis cannot be made through history and physical examination alone. Molecular testing for bacterial infections, tuberculosis, and fungal infections may aid in the diagnosis. Since the treatments for these disorders are different and delays can result in permanent neurologic disability and death, rapid and accurate diagnoses are critical. This review provides the neurologist with testing options and recommends ways to enhance sensitivity and specificity. © 2014 American Academy of Neurology.

Tan, W. C., Bourbeau, J., Aaron, S., FitzGerald, J. M., Hernandez, P., Cowie, R., et al. (2014). Exacerbations in non-COPD patients: Truth or myth-authors' response. *Thorax,*

Tarr, M. E., Rivard, C., Petzel, A. E., Summers, S., Mueller, E. R., Rickey, L. M., et al. (2014). Robotic objective structured assessment of technical skills: A randomized multicenter dry laboratory

training pilot study. *Female Pelvic Medicine & Reconstructive Surgery, 20*(4), 228-236.

STUDY OBJECTIVE: The goal of this study was to determine if a robotic dry laboratory curriculum for gynecology and urology residents improved their basic robotic skills. METHODS: After the institution-specific institutional review board approval or exemption, 165 residents from 8 gynecology and/or urology programs were enrolled. Residents underwent standardized robotic orientation followed by dry laboratory testing on 4 unique robotic tasks. Residents were block randomized by program to unstructured or structured training programs. Regardless of group, residents were expected to practice for 15 minutes twice monthly over 7 months. Errors, time to completion, and objective structured assessment of technical skills global rating scores were recorded for each task before and after the training period. Statistics were calculated using the Student t tests, Pearson correlation, and analysis of variance with STATA systems (version 11.2). RESULTS: A total of 99 residents completed both the pretraining and posttraining testing. A mean of 4 (range, 0-15) 15-minute training sessions per resident was self-reported. The structured group had faster posttraining times on the transection task, although the unstructured group had higher posttraining scores on the knot-tying task. CONCLUSIONS: Overall, the residents' robotic skills improved after participating in a dry laboratory curriculum; however, robotic availability, duty hour restrictions, and clinical responsibilities limit the curriculum implementation.

Terr, L. C., Beitchman, J. H., Braslow, K., Fox, F., Metcalf, A., Pease, M., et al. (2007). *Children's turn-arounds in psychotherapy: The doctor's gesture* Yale University Press.

Over the past year, a number of us have been examining the organizing principles behind dramatic turning points in the psychotherapies of children. We wondered whether any particular techniques or occurrences in therapy promoted childhood change. Method: One of us (L.T.) asked the health care professionals on the UCSF child psychiatry grand rounds email list and 50 colleagues across the United States and Canada to select key "moments," or turning points, in their treatments of young people. No organizing principles were suggested in the request letters. Over 3 months, 21 vignettes telling of major changes in children and adolescents arrived in San Francisco. Some of them came from psychotherapies-thers, from consultations or very brief therapies. Eleven are included in this paper. Results: Gestures from the psychotherapist were shown to effect dramatic turn-arounds in some young people. These shifts in the doctor's

emphasis or behavior included: (1) making an entirely unexpected statement; (2) advocating strongly for the youngster; (3) confessing personal flaws and/or frustrations to the patient; (4) feeding or rewarding the young patient; and (5) inquiring deeply into something personal with the child. A gesture never given-in this instance, an undelivered inquiry into incestis shown to have left an adolescent patient unchanged. The young people described in this report suffered from anxiety, trauma, neglect, cancer, anorexia, bulimia, and personality disorders. Two were institutionalized at the time of their dramatic changes. One had been previously hospitalized 4 times. Another small child had suffered a double amputation. These children came with a far broader spectrum of problems than the relatively mild disorders for which child-psychodynamic psychotherapy was originally tailored. Although we were not primarily concerned with the "ground" on which the doctor's gesture fell, in 5 of our cases there had been little to no therapeutic relationship prior to the gesture; in 4, the relationship had been primarily positive; and, in 2, it had been negative. Conclusions: Doctors' gestures are usually given on impulse and unexpectedly during psychotherapy. To the child, these gestures appear counter-intuitive and surprising. From the therapist's perspective, they first generate a brief sense of confusion in the patient, and then a strong sense of connection between the young person and the adult. In the cases we report, the physicians' gestures created a new alliance. The tone of the therapy switched, leading to a noticeable psychic shift in the child. Summary: A doctor's gesture may elicit a dramatic turn-around in a young patient. This therapeutic climax is implicitly understood between the two parties and then may be converted to consciousness and worked with explicitly. Therapeutic "moments" occur in a broad range of disorders, that in many cases are also being treated simultaneously with medications, and with family or institutional counseling. © 2006 by Robert A. King, Peter B. Neubauer, Samuel Abrams, and A. Scott Dowling.

Thomas, C. R., & Keepers, G. (2014). The milestones for general psychiatry residency training. *Academic Psychiatry, 38*(3), 255-260.

Thompson, E. M., Strong, M. J., Warren, G., Woltjer, R. L., & Selden, N. R. (2014). Clinical significance of imaging and histological characteristics of filum terminale in tethered cord syndrome: Clinical article. *Journal of Neurosurgery: Pediatrics, 13*(3), 255-259.

Object. The pathophysiology of tethered cord syndrome (TCS) is uncertain; however, it has been suggested that fibrous and fatty elements within the filum terminale (FT) play a role. The objective of this study was to describe the radiological and histological features of the FT in TCS and determine if there are associations between those features and clinical outcomes, complications, and urodynamics. Methods. In this retrospective study, histological, MRI, and clinical data obtained in 293 patients with TCS who underwent FT transection were reviewed and analyzed in a multivariate analysis. Results. The median patient age was 4.9 years (range 0.3-64.3 years). On MRI, a fatty filum was present in 65% of patients and a thickened filum (> 2 mm) was seen in 45%. Histologically, the FT contained prominent fibrous tissue in 95%, nerve twigs in 79%, adipose tissue in 59%, and vascular tissue in 36%. Histological features associated with a thickened filum on MR images were adipose tissue (OR 3.5, $p < 0.001$), nerve twigs (OR 2.2, $p = 0.028$), and vascular tissue (OR 0.5, $p = 0.025$). Adipose tissue was associated with a conus level below the L2-3 disc space (OR 2.3, $p = 0.031$) and with a fatty filum on imaging (OR 9.8, $p < 0.001$). Nerve twigs were associated with abnormal urodynamics (OR 10.9, $p = 0.049$). The only variable predictive of clinical improvement was conus level; patients with conus levels caudal to L-2 were less likely to improve postoperatively (OR 0.3, $p = 0.042$). Conclusions. Fibrous tissue was ubiquitous and may be important in the pathophysiology of TCS. Nerve twigs and adipose tissue were associated with abnormal urodynamics and low-lying coni, respectively. Although the majority of patients clinically improved, patients with normal conus levels had significantly better outcomes.

Thong, T., Colbert, A. P., & Larsen, A. P. (2009). An 8-channel skin impedance measurement system for acupuncture research. *Conference Proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society.IEEE Engineering in Medicine and Biology Society.Conference,* , 861-864.

An 8-channel skin impedance measurement system for acupuncture research has been developed. The underlying model of the skin used is a parallel R & C network. Pulses are used to measure the R and C values. The measurement circuit is time multiplexed across the 8 channels at the rate of 2 measurements per second, leading to a complete set of measurements every 4 seconds. In static tests, the system has been operational for over 2 days of continuous

measurements. In preliminary human tests, measurements over 2 hours have been collected per subject.

Thornburg, K. L., & Challis, J. R. (2014). How to build a healthy heart from scratch. *Advances in Experimental Medicine and Biology, 814*, 205-216.

By any of several measures, the health of the American population has been worsening over the last two decades. Obesity, type 2 diabetes and heart failure have risen dramatically. All the while, the average birthweight at all gestational ages has declined. The relationship between robust growth in the womb and lifelong health is now well established. Likewise, babies born at the low end of the birthweight scale are known to have highly elevated risks for ischemic heart disease, hypertension, stroke and metabolic disease. The biological mechanisms by which developmental plasticity becomes a risk for cardiovascular disease are only now being understood. Translating from animal and human studies, low birthweight babies are likely to have endothelial dysfunction, fewer nephrons, fewer pancreatic beta cells, less vascular elastin, fewer cardiomyocytes, increased sympathetic tone and liver-derived dyslipidemias. Only in the past few years, however, has it become known that maternal and placenta phenotypes are associated with adult onset cardiovascular disease. Helsinki Birth Cohort studies have been especially important in the discovery of these relationships. Sudden cardiac death is associated with a thin placenta and heart failure is associated with a small placenta in short mothers. Coronary heart disease is associated with three combinations of maternal-placental phenotypes. Because the diet is important in providing nutrients for the development of the female body before pregnancy and for providing nutrients during pregnancy, there is increasing evidence that the western diet is an underlying cause for the increase in metabolic disease in the American population. A large segment of the American population suffers from high calorie malnutrition. Scientists in this field now have a responsibility to educate the public on the topic of nutrition and health. This chapter honors Lawrence Longo for decades of work in bringing health to pregnant women and their babies.

Tilak, A., Nelsen, S. M., Kim, H. S., Donley, N., McKnite, A., Lee, H., et al. (2014). Simultaneous rather than ordered cleavage of two sites within the BMP4 prodomain leads to loss of ligand in

mice. *Development (Cambridge, England), 141*(15), 3062-3071.

ProBMP4 is generated as a latent precursor that is sequentially cleaved at two sites within the prodomain to generate an active ligand. An initial cleavage occurs adjacent to the ligand domain, which generates a non-covalently associated prodomain/ligand complex that is subsequently dissociated by cleavage at an upstream site. An outstanding question is whether the two sites need to be cleaved sequentially and in the correct order to achieve proper control of BMP4 signaling during development. In the current studies, we demonstrate that mice carrying a knock-in point mutation that causes simultaneous rather than sequential cleavage of both prodomain sites show loss of BMP4 function and die during mid-embryogenesis. Levels of mature BMP4 are severely reduced in mutants, although levels of precursor and cleaved prodomain are unchanged compared with wild type. Our biochemical analysis supports a model in which the transient prodomain/ligand complex that forms during sequential cleavage plays an essential role in prodomain-mediated stabilization of the mature ligand until it can acquire protection from degradation by other means. By contrast, simultaneous cleavage causes premature release of the ligand from the prodomain, leading to destabilization of the ligand and loss of signaling in vivo.

Tipps, M. E., Raybuck, J. D., Buck, K. J., & Lattal, K. M. (2014). Delay and trace fear conditioning in C57BL/6 and DBA/2 mice: Issues of measurement and performance. *Learning & Memory (Cold Spring Harbor, N.Y.), 21*(8), 380-393.

Strain comparison studies have been critical to the identification of novel genetic and molecular mechanisms in learning and memory. However, even within a single learning paradigm, the behavioral data for the same strain can vary greatly, making it difficult to form meaningful conclusions at both the behavioral and cellular level. In fear conditioning, there is a high level of variability across reports, especially regarding responses to the conditioned stimulus (CS). Here, we compare C57BL/6 and DBA/2 mice using delay fear conditioning, trace fear conditioning, and a nonassociative condition. Our data highlight both the significant strain differences apparent in these fear conditioning paradigms and the significant differences in conditioning type within each strain. We then compare our data to an extensive literature review of delay and trace fear conditioning in these two strains. Finally, we apply a number of commonly used baseline normalization approaches to compare how they alter the reported differences. Our findings

highlight three major sources of variability in the fear conditioning literature: CS duration, number of CS presentations, and data normalization to baseline measures.

Tommaso, C. L., Fullerton, D. A., Feldman, T., Dean, L. S., Hijazi, Z. M., Horlick, E., et al. (2014). SCAI/AATS/ACC/STS operator and institutional requirements for transcatheter valve repair and replacement: Part II. mitral valve. *Annals of Thoracic Surgery,*

Trounson, A., & Mitalipov, S. (2013). Foreword to the second edition. *Principles of Cloning: Second Edition,* , xi-xii.

Troxell, M. L., & Houghton, D. C. (2014). The basics of renal allograft pathology. *Surgical Pathology Clinics,*

Renal allograft biopsy provides critical information in the management of patients who receive renal transplantation. The histologic correlates of acute T-cell-mediated rejection are interstitial inflammation, tubulitis, and endothelialitis. Antibody-mediated rejection may be recognized by a constellation of features. Acute tubular injury/necrosis is a reversible cause of impaired graft function, especially in the immediate posttransplant period. Drug toxicity, recurrent disease, chronic injury, and other entities affecting both native and transplant kidneys must also be evaluated. Pathologic interpretation must be performed in the context of patient history, clinical and laboratory studies, and in close collaboration with the clinical team. © 2014 Elsevier Inc. All rights reserved.

Trudell, A. S., Louis, J. M., Tuuli, M. G., Caughey, A. B., Odibo, A. O., & Cahill, A. G. (2014). Use of a simple clinical tool for airway assessment to predict adverse pregnancy outcomes. *American Journal of Perinatology,*

Objective Obstructive sleep apnea (OSA) is a risk factor for adverse perinatal outcomes. We aimed to test the hypothesis that maternal Mallampati class (MC), as a marker for OSA, is associated with adverse perinatal outcomes. Study Design We performed a retrospective secondary analysis of a prospective cohort of term births (>/= 37 weeks). Fetal anomalies and aneuploidy were excluded. Primary outcome was small for gestational age (SGA). Secondary outcomes included preeclampsia, neonatal cord arterial blood gas pH < 7.10 and < 7.05, base

excess < - 8 and < - 12 mEq/L. Outcomes were compared between mothers with low MC airways and high MC airways using logistic regression. Results A total of 1,823 women met the inclusion criteria. No significant differences were found in the risk of SGA (adjusted odds ratio [aOR] 0.9, 95% confidence interval [CI] 0.6-1.2), preeclampsia (aOR 1.2, 95% CI 0.8-1.9) or neonatal acidemia (aOR 0.8, 95% CI 0.3-2.0), between high and low MC. Conclusion High MC is not associated with adverse perinatal outcomes.

Tyner, J. W. (2014). Functional genomics for personalized cancer therapy. *Science Translational Medicine, 6*(243), 243fs26.

Integration of functional and genomic screening strategies reveals clinically actionable genetic events that impact the effectiveness of cancer treatment regimens and the outcomes of cancer patients.

Ulrich, C. M., Rankin, C., Toriola, A. T., Makar, K. W., Altug-Teber, O., Benedetti, J. K., et al. (2014). Polymorphisms in folate-metabolizing enzymes and response to 5-fluorouracil among patients with stage II or III rectal cancer (INT-0144; SWOG 9304). *Cancer,*

BACKGROUND: Recurrence and toxicity occur commonly among patients with rectal cancer who are treated with 5-fluorouracil (5-FU). The authors hypothesized that genetic variation in folate-metabolizing genes could play a role in interindividual variability. The objective of the current study was to evaluate the associations between genetic variants in folate-metabolizing genes and clinical outcomes among patients with rectal cancer treated with 5-FU. METHODS: The authors investigated 8 functionally significant polymorphisms in 6 genes (methylenetetrahydrofolate reductase [MTHFR] [C667T, A1298C], SLC191A [G80A], SHMT1 [C1420T], dihydrofolate reductase [DHFR] [Del19bp], TS 1494del,and TSER) involved in folate metabolism in 745 patients with TNM stage II or III rectal cancer enrolled in a phase 3 adjuvant clinical trial of 3 regimens of 5-FU and radiotherapy (INT-0144 and SWOG 9304). RESULTS: There were no statistically significant associations noted between polymorphisms in any of the genes and overall survival, disease-free survival (DFS), and toxicity in the overall analyses. Nevertheless, there was a trend toward worse DFS among patients with the variant allele of MTHFR C677T compared with wild-type, particularly in treatment arm 2, in which patients with the MTHFR C677T TT genotype

had worse overall survival (hazards ratio, 1.76; 95% confidence interval, 1.06-2.93 [P=.03]) and DFS (hazards ratio, 1.84; 95% confidence interval, 1.12-3.03 [P=.02]) compared with those with homozygous wild-type. In addition, there was a trend toward reduced hematological toxicity among patients with variants of SLC19A1 G80A in treatment arm 1 (P for trend, .06) and reduced esophagitis/stomatitis noted among patients with variants of TSER in treatment arm 3 (P for trend, .06). CONCLUSIONS: Genetic variability in folate-metabolizing enzymes was found to be associated only to a limited degree with clinical outcomes among patients with rectal cancer treated with 5-FU. © 2014 American Cancer Society.

Underhill, S. M., Wheeler, D. S., Li, M., Watts, S. D., Ingram, S. L., & Amara, S. G. (2014). Amphetamine modulates excitatory neurotransmission through endocytosis of the glutamate transporter EAAT3 in dopamine neurons. *Neuron, 83*(2), 404-416.

Amphetamines modify the brain and alter behavior through mechanisms generally attributed to their ability to regulate extracellular dopamine concentrations. However, the actions of amphetamine are also linked to adaptations in glutamatergic signaling. We report here that when amphetamine enters dopamine neurons through the dopamine transporter, it stimulates endocytosis of an excitatory amino acid transporter, EAAT3, in dopamine neurons. Consistent with this decrease in surface EAAT3, amphetamine potentiates excitatory synaptic responses in dopamine neurons. We also show that the process of internalization is dynamin- and Rho-mediated and requires a unique sequence in the cytosolic C terminus of EAAT3. Introduction of a peptide based on this motif into dopamine neurons blocks the effects of amphetamine on EAAT3 internalization and its action on excitatory responses. These data indicate that the internalization of EAAT3 triggered by amphetamine increases glutamatergic signaling and thus contributes to the effects of amphetamine on neurotransmission.

Urben, L. M., Wiedmar, J., Boettcher, E., Cavallazzi, R., Martindale, R. G., & McClave, S. A. (2014). Bugs or drugs: Are probiotics safe for use in the critically ill? *Current Gastroenterology Reports, 16*(7)

Probiotics are living microorganisms which have demonstrated many benefits in prevention, mitigation, and treatment of various disease states in critically ill populations. These diseases

include antibiotic-associated diarrhea, Clostridium difficile diarrhea, ventilator-associated pneumonia, clearance of vancomycin-resistant enterococci from the GI tract, pancreatitis, liver transplant, major abdominal surgery, and trauma. However, their use has been severely limited due to a variety of factors including a general naïveté within the physician community, lack of regulation, and safety concerns. This article focuses on uses for probiotics in prevention and treatment, addresses current concerns regarding their use as well as proposing a protocol for safe use of probiotics in the critically ill patient.

Valenzuela, D. M., Behr, S., Coakley, F. V., Wang, Z. J., Webb, E. M., & Yeh, B. M. (2014). Computed tomography of iatrogenic complications of upper gastrointestinal endoscopy, stenting, and intubation. *Radiologic Clinics of North America,*

Intraluminal procedures for the gastrointestinal tract range from simple intubation for feeding or bowel decompression to endoscopic procedures including stenting and pancreatobiliary ductal catheterization. Each of these procedures and interventions carries a risk of iatrogenic injury, including bleeding, perforation, infection, adhesions, and obstruction. An understanding of how anatomy and function may predispose to injury, and the distinct patterns of injury, can help the radiologist identify and characterize iatrogenic injury rapidly at computed tomography (CT) imaging. Furthermore, selective use of intravenous or oral CT contrast material can help reveal injury and triage clinical management.

VanderWielen, L. M., Enurah, A. S., Rho, H. Y., Nagarkatti-Gude, D. R., Michelsen-King, P., Crossman, S. H., et al. (2014). Medical interpreters: Improvements to address access, equity, and quality of care for limited-english-proficient patients. *Academic Medicine : Journal of the Association of American Medical Colleges,*

Limited-English-proficient (LEP) patients in the United States experience a variety of health care disparities associated with language barriers, including reduced clinical encounter time and substandard medical treatment compared with their English-speaking counterparts. In most current U.S. health care settings, interpretation services are provided by personnel ranging from employed professional interpreters to untrained, ad hoc interpreters such as friends, family, or

medical staff. Studies have demonstrated that untrained individuals commit many interpretation errors that may critically compromise patient safety and ultimately prove to be life-threatening. Despite documented risks, the U.S. health care system lacks a required standardized certification for medical interpreters.The authors propose that the standardization of medical interpreter training and certification would substantially reduce the barriers to equitable care experienced by LEP patients in the U.S. health care system, including the occurrence of preventable clinical errors. Recent efforts of the U.S. federal court system are cited as a successful and realistic example of how these goals may be achieved. As guided by the evolution of the federal court interpreting certification program, subsequent research will be required to demonstrate the improvements and challenges that would result from national certification standards and policy for medical interpreters. Research should examine cost-effectiveness and ensure that certified interpreting services are appropriately used by health care practitioners. Ongoing commitment is required from lawmakers, health care providers, and researchers to remove barriers to care and to demand that equity remain a consistent goal of our health care system.

Verma, S., Kirigiti, M., Millar, R. P., Grove, K. L., & Smith, S. M. (2014). Endogenous kisspeptin tone is a critical excitatory component of spontaneous GnRH activity and the GnRH response to NPY and CART. *Neuroendocrinology,*

Background/Aims: Kisspeptin is the major excitatory regulator of GnRH neurons and is responsible for basal GnRH/LH release and the GnRH/LH surge. Although it is widely assumed, based on mutations in kisspeptin and Kiss1R, that kisspeptin acts to sustain basal GnRH neuronal activity, there have been no studies to investigate whether endogenous basal kisspeptin tone plays a direct role in basal spontaneous GnRH neuronal excitability. It is also of interest to examine possible interactions between endogenous kisspeptin tone and other neuropeptides that have direct effects on GnRH neurons, such as NPY or CART, since the activity of all these neuropeptides changes during states of negative energy balance. Methods: Loose cell-attached and whole cell current-clamp patch recordings were made from GnRH-GFP neurons in hypothalamic slices from female and male rats. Results: Kisspeptin activated GnRH neurons in a concentration dependent manner with an EC50 of 3.32 +/- 0.02 nM. Surprisingly, a kisspeptin antagonist, Peptide 347, suppressed spontaneous activity in GnRH neurons, demonstrating the

essential nature of the endogenous kisspeptin tone. Furthermore, inhibition of endogenous kisspeptin tone blocked the direct activation of GnRH cells that occurs in response to antagonism of NPY Y5R or by CART. Conclusions: Our electrophysiology studies suggest that basal endogenous kisspeptin tone is not only essential for spontaneous GnRH neuronal firing, but it is also required for the net excitatory effects of other neuropeptides, such as CART or NPY antagonism, on GnRH neurons. Therefore, endogenous kisspeptin tone could serve as the linchpin in GnRH activation or inhibition. (c) 2014 S. Karger AG, Basel.

Vetter, T. R., & Chou, R. (2013). *Clinical trial design methodology for pain outcome studies* Elsevier Inc.

Vinet, E., Pineau, C., Clarke, A., Fombonne, E., Platt, R., & Bernatsky, S. (2014). Neurodevelopmental disorders in children born to mothers with systemic lupus erythematosus. *Lupus,*
Children born to women with systemic lupus erythematosus seem to have a potentially increased risk of neurodevelopmental disorders compared to children born to healthy women. Recent experimental data suggest in utero exposure to maternal antibodies and cytokines as important risk factors for neurodevelopmental disorders. Interestingly, women with systemic lupus erythematosus display high levels of autoantibodies and cytokines, which have been shown, in animal models, to alter fetal brain development and induce behavioral anomalies in offspring. Furthermore, subjects with systemic lupus erythematosus and neurodevelopmental disorders share a common genetic predisposition, which could impair the fetal immune response to in utero immunologic insults. Moreover, systemic lupus erythematosus pregnancies are at increased risk of adverse obstetrical outcomes and medication exposures, which have been implicated as potential risk factors for neurodevelopmental disorders. In this article, we review the current state of knowledge on neurodevelopmental disorders and their potential determinants in systemic lupus erythematosus offspring.

Viswanathan, M., Carey, T. S., Belinson, S. E., Berliner, E., Chang, S. M., Graham, E., et al. (2014). A proposed approach may help systematic reviews retain needed expertise while minimizing bias from nonfinancial conflicts of interest. *Journal of Clinical Epidemiology,*
OBJECTIVES: Groups such as the Institute of Medicine emphasize the importance of attention to

financial conflicts of interest. Little guidance exists, however, on managing the risk of bias for systematic reviews from nonfinancial conflicts of interest. We sought to create practical guidance on ensuring adequate clinical or content expertise while maintaining independence of judgment on systematic review teams. STUDY DESIGN AND SETTING: Workgroup members built on existing guidance from international and domestic institutions on managing conflicts of interest. We then developed practical guidance in the form of an instrument for each potential source of conflict. RESULTS: We modified the Institute of Medicine's definition of conflict of interest to arrive at a definition specific to nonfinancial conflicts. We propose questions for funders and systematic review principal investigators to evaluate the risk of nonfinancial conflicts of interest. Once risks have been identified, options for managing conflicts include disclosure followed by no change in the systematic review team or activities, inclusion on the team along with other members with differing viewpoints to ensure diverse perspectives, exclusion from certain activities, and exclusion from the project entirely. CONCLUSION: The feasibility and utility of this approach to ensuring needed expertise on systematic reviews and minimizing bias from nonfinancial conflicts of interest must be investigated.

Walker, K. L., Kirillova, O., Gillespie, S. E., Hsiao, D., Pishchalenko, V., Kalsanka Pai, A., et al. (2014). Using the CER hub to ensure data quality in a multi-institution smoking cessation study. *Journal of the American Medical Informatics Association : JAMIA,*

Comparative effectiveness research (CER) studies involving multiple institutions with diverse electronic health records (EHRs) depend on high quality data. To ensure uniformity of data derived from different EHR systems and implementations, the CER Hub informatics platform developed a quality assurance (QA) process using tools and data formats available through the CER Hub. The QA process, implemented here in a study of smoking cessation services in primary care, used the 'emrAdapter' tool programmed with a set of quality checks to query large samples of primary care encounter records extracted in accord with the CER Hub common data framework. The tool, deployed to each study site, generated error reports indicating data problems to be fixed locally and aggregate data sharable with the central site for quality review. Across the CER Hub network of six health systems, data completeness and correctness issues were prevalent in the first iteration and were considerably improved after three iterations of the

QA process. A common issue encountered was incomplete mapping of local EHR data values to those defined by the common data framework. A highly automated and distributed QA process helped to ensure the correctness and completeness of patient care data extracted from EHRs for a multi-institution CER study in smoking cessation.

Wegmann, K. W., Archie Bouwer, H. G., Whitham, R. H., & Hinrichs, D. J. (2014). Eluding anaphylaxis allows peptide-specific prevention of the relapsing stage of experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology,*

We have used a peptide derived from Acanthamoeba castellanii (ACA) to treat the relapsing phase of EAE that develops in SJL mice following immunization with the PLP 139-151 peptide. The native sequence of the ACA 81-95 peptide that shares key residues with the PLP 139-151 peptide is weakly encephalitogenic in SJL mice but is not recognized by antiserum from SJL mice immunized with PLP 139-151. A single amino acid change to the ACA 81-95 peptide sequence significantly enhanced its encephalitogenicity. When administered to SJL mice as a nonlinear peptide octamer, the modified ACA peptide prevented relapsing episodes of EAE in SJL mice previously immunized with the PLP 139-151 encephalitogenic peptide.

Wiener, L., Baird, K., Crum, C., Powers, K., Carpenter, P., Baker, K. S., et al. (2014). Child and parent perspectives of the chronic graft-versus-host disease (cGVHD) symptom experience: A concept elicitation study. *Supportive Care in Cancer, 22*(2), 295-305.

Purpose: Chronic graft-versus-host disease (cGVHD) is a significant cause of mortality and morbidity after allogeneic hematopoietic cell transplant and is associated with a wide range of distressing symptoms. A pediatric measure of cGVHD-related symptoms is needed to advance clinical research. Our aim was to elicit descriptions of the cGVHD symptom experience directly from children and to compare the specific language used by children to describe their symptoms and the comprehension of symptom concepts across the developmental spectrum. Methods: We used qualitative methods to identify the phrases, terms, and constructs that children (ages 5-8 [n=8], 9-12 [n=8], and 13-17 [n=8]) with cGVHD employ when describing their symptoms. The symptom experience of each participant was determined through individual interviews with each participant and parent (5-7 year olds were interviewed together with a parent). Medical

practitioners with experience in evaluating cGVHD performed clinical assessments of each participant. Results: Pediatric transplant survivors and their parents identified a wide range of bothersome cGVHD symptoms, and common concepts and terminologies to describe these experiences emerged. Overall concordance between patient and parent reports was moderate (70-75%). No consistent pattern of child under- or over-reporting in comparison to the parent report was observed. Conclusion: These study results identify concepts and vocabulary to inform item generation for a new pediatric self-report measure of cGVHD symptoms for use in clinical research. The findings also confirm the prevalence and nature of symptom distress in pediatric patients with cGVHD and support implementation of systematic approaches to symptom assessment and intervention in routine clinical practice. © Springer-Verlag 2013.

Williams, J. T. (2014). Desensitization of functional micro-opioid receptors increases agonist off-rate. *Molecular Pharmacology, 86*(1), 52-61.

Desensitization of micro-opioid receptors (MORs) develops over 5-15 minutes after the application of some, but not all, opioid agonists and lasts for tens of minutes after agonist removal. The decrease in function is receptor selective (homologous) and could result from 1) a reduction in receptor number or 2) a decrease in receptor coupling. The present investigation used photolysis of two caged opioid ligands to examine the kinetics of MOR-induced potassium conductance before and after MOR desensitization. Photolysis of a caged antagonist, carboxynitroveratryl-naloxone (caged naloxone), blocked the current induced by a series of agonists, and the time constant of decline was significantly decreased after desensitization. The increase in the rate of current decay was not observed after partial blockade of receptors with the irreversible antagonist, beta-chlornaltrexamine (beta-CNA). The time constant of current decay after desensitization was never more rapid than 1 second, suggesting an increased agonist off-rate rather than an increase in the rate of channel closure downstream of the receptor. The rate of G protein-coupled K(+) channel (GIRK) current activation was examined using photolysis of a caged agonist, carboxynitrobenzyl-tyrosine-[Leu(5)]-enkephalin. After acute desensitization or partial irreversible block of MORs with beta-CNA, there was an increase in the time it took to reach a peak current. The decrease in the rate of agonist-induced GIRK conductance was receptor selective and dependent on receptor number. The results indicate that opioid receptor

desensitization reduced the number of functional receptor and that the remaining active receptors have a reduced agonist affinity.

Winters-Stone, K. M., & Beer, T. M. (2014). Review of exercise studies in prostate cancer survivors receiving androgen deprivation therapy calls for an aggressive research agenda to generate high-quality evidence and guidance for exercise as standard of care. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,*

Wiren, K. M. (2013). *Androgens and skeletal biology: Basic mechanisms* Elsevier Inc.

The obvious impact of the menopause on skeletal health has focused much of the research describing the general action of gonadal steroids on the specific effects of estrogen in bone. However, androgens clearly have important beneficial effects, in both men and women, on skeletal development and on the maintenance of bone mass. Thus it has been demonstrated that androgens (a) influence growth plate maturation and closure helping to determine longitudinal bone growth during development, (b) mediate regulation of trabecular (cancellous) and cortical bone mass in a fashion distinct from estrogen, leading to a sexually dimorphic skeleton, (c) modulate peak bone mass acquisition, and (d) inhibit bone loss. In castrated animals, replacement with nonaromatizable androgens (e.g., 5α-dihydrotestosterone (DHT)) yields beneficial effects that are clearly distinct from those observed with estrogen replacement. In intact females, blockade of the androgen receptor (AR) with the specific AR antagonist hydroxyflutamide results in osteopenia. Furthermore, treatment with nonaromatizable androgen alone in females results in improvements in bone mineral density (BMD). Finally, combination therapy with estrogen and androgen in postmenopausal women is more beneficial than either steroid alone, indicating complementary but nonparallel and distinct pathways of action. Combined, these reports illustrate the distinct actions of androgens and estrogens on the skeleton. Thus, in both men and women it is probable that androgens and estrogens each have important yet distinct functions during bone development, and in the subsequent maintenance of skeletal homeostasis. As is clear from the osteopenia that develops after androgen deprivation therapy (ADT) used for the treatment of prostate cancer and with the loss of sex steroids in older men, androgen signaling is important for bone health in the adult and during aging. With the

awareness of the importance of the effects of androgen on skeletal homeostasis, and the potential to make use of this information for the treatment of bone disorders, much remains to be learned.

Wolf, D. P., & Mitalipov, S. (2014). Mitochondrial replacement therapies can circumvent mtDNA-based disease transmission. *Cell Metabolism, 20*(1), 6-8.

Mitochondrial DNA diseases are relatively common, sometimes devastating, and transmitted exclusively through the egg to children of carrier mothers. A study in Cell by Wang et al. (2014) adds the exciting possibility of a new therapy for preventing mitochondrial disease transmission predicated on the use of polar body genomes in mice.

Wolinsky, F. D., Ayyagari, P., Malmstrom, T. K., Miller, J. P., Andresen, E. M., Schootman, M., et al. (2014). Lower extremity function trajectories in the african american health cohort. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 69*(8), 1004-1010.

Background. We addressed two understudied issues in estimating lower extremity functional trajectories in older adults-incorporating the effect of mortality and evaluating heterogeneity among African Americans. Methods. Data were taken from the 998 participants in the African American Health cohort. A highly reliable and valid 8-item lower extremity function scale was used at baseline and at the 1-, 2-, 3-, 4-, 7-, and 9-year follow-up interviews. Semiparametric (ie, discrete) group-based mixture modeling identified the trajectories, and multinomial logistic regression identified risk factors for differential trajectory groups. Results. When treating mortality as informative censoring, six discrete trajectories were observed with 45% of the participants belonging to three stable trajectories (good, fair, or poor function), and the remainder belonging to three declining trajectories (very high function with minimal improvement then minimal decline, very good function with a slow and modest decline, and very good function with a large and quick decline). Conclusion. Substantial heterogeneity in lower extremity function trajectories exists in the African American Health cohort, after appropriately treating mortality as informative censoring.

Wong, J., Tran, L. T., Magun, E. A., Magun, B. E., & Wood, L. J. (2014). Production of IL-1beta by bone marrow-derived macrophages in response to chemotherapeutic drugs: Synergistic effects of

doxorubicin and vincristine. *Cancer Biology & Therapy, 15*(10)

Cytotoxic chemotherapeutic drugs, especially when used in combination, are widely employed to treat a variety of cancers in patients but often lead to serious symptoms that negatively affect physical functioning and quality of life. There is compelling evidence that implicates cytotoxic chemotherapy-induced inflammation in the etiology of these symptoms. Because IL-1beta plays a central role as an initiator cytokine in immune responses, we compared doxorubicin, a drug known to induce IL-1beta production, with ten other commonly prescribed chemotherapeutic drugs in their ability to lead to processing and secretion of IL-1beta by primary mouse macrophages. Seven of them (melphalan, cisplatin, vincristine, etoposide, paclitaxel, methotrexate, and cytarabine) caused the production of IL-1beta in cells pretreated with lipopolysaccharide. When delivered in combination with doxorubicin, one of the drugs, vincristine, was also capable of synergistically activating the NLRP3-dependent inflammasome and increasing expression of IL-1beta, IL-6 and CXCL1. The absence of TNF-alpha and IL-1 signaling caused a partial reduction in the production of mature IL-1beta. Three small-molecule inhibitors known to suppress activity of kinases situated upstream of mitogen-activated kinases (MAPKs) inhibited the expression of IL-1beta, IL-6 and CXCL1 when doxorubicin and vincristine were used singly or together. Kinase inhibitors may be useful in reducing inflammation in patients receiving chemotherapy.

Wong, J. C., Foster, N. C., Maahs, D. M., Raghinaru, D., Bergenstal, R. M., Ahmann, A. J., et al. (2014). Real-time continuous glucose monitoring among participants in the T1D exchange clinic registry. *Diabetes Care,*

OBJECTIVE: To assess the frequency of continuous glucose monitoring (CGM) device use, factors associated with its use, and the relationship of CGM with diabetes outcomes (HbA1c, severe hypoglycemia [SH], and diabetic ketoacidosis [DKA]).RESEARCH DESIGN AND METHODS: Survey questions related to CGM device use 1 year after enrollment in the T1D Exchange clinic registry were completed by 17,317 participants. Participants were defined as CGM users if they indicated using real-time CGM during the prior 30 days.RESULTS: Nine percent of participants used CGM (6% of children /=26 years). CGM use was more likely with higher education, higher household income, private health insurance, longer duration of diabetes, and use of insulin pump (P /=26

years). CGM use was more likely with higher education, higher household income, private health insurance, longer duration of diabetes, and use of insulin pump (P /=26 years). CGM use was more likely with higher education, higher household income, private health insurance, longer duration of diabetes, and use of insulin pump (P /=6 days/week) was associated with lower mean HbA1c. Only 27% of users downloaded data from their device at least once per month, and <15% of users reported downloading their device at least weekly. Among participants who used CGM at baseline, 41% discontinued within 1 year.CONCLUSIONS: CGM use is uncommon but associated with lower HbA1c in some age-groups, especially when used more frequently. Factors associated with discontinuation and infrequent use of retrospective analysis of CGM data should be considered in developing next-generation devices and education on CGM use.

Wood, E., Kerr, T., Rowell, G., Montaner, J. S. G., Phillips, P., Korthuis, P. T., et al. (2014). Does this adult patient have early HIV infection? the rational clinical examination systematic review. *JAMA - Journal of the American Medical Association, 312*(3), 278-285.

IMPORTANCE: Timely identification of human immunodeficiency virus (HIV) infection in adults can contribute to reduced mortality and likelihood of further HIV transmission. During the first 6 months after infection, known as early HIV infection, patients often report a well-described constellation of symptoms and signs. However, the literature examining utility of the clinical examination in identifying early infection has not been systematically assessed. OBJECTIVE: To assess the accuracy of symptoms and signs in identifying early HIV infection among adults. DATA SOURCES: We searched MEDLINE and EMBASE (1981-May, 2014) for articles investigating symptoms and signs of early HIV infection in adults and searched reference lists of retrieved articles. STUDY SELECTION: We retained original studies that compared symptoms and signs among patients with early HIV infection in comparison to HIV-negative individuals. DATA EXTRACTION AND SYNTHESIS: Datawere extracted and used to calculate sensitivity, specificity, and likelihood ratios (LRs), and meta-analysis was used to calculate summary LRs. RESULTS: Of 1356 studies, 16 studies included data that were eligible for meta-analysis and included a total of 24 745 patients and 1253 cases of early HIV infection. Symptoms that increased the likelihood of early HIV infection the most included genital ulcers (LR, 5.4; 95% CI, 2.5-12), weight loss (LR, 4.7; 95% CI, 2.1-7.2), vomiting (LR, 4.6; 95% CI, 2.5-8.0), and swollen lymph nodes (LR, 4.6;

95% CI, 1.3-8.0). No symptoms had an LR that was 0.5 or lower, but the absence of recent fever (LR, 0.74; 95% CI, 0.64-0.84) slightly decreased the likelihood of early HIV infection. The presence of lymphadenopathy on physical examination was the most useful sign (LR, 3.1; 95% CI, 1.0-5.2). No sign had an LR of 0.5 or less, but the absence of lymphadenopathy slightly decreased the likelihood of early HIV infection (LR, 0.70, 95% CI, 0.49-0.92). Using data from studies that considered combinations of findings (range of possible findings, 4-17), the summary LR for individuals with 0 findings was 0.47 (95% CI, 0.38-0.58). CONCLUSIONS AND RELEVANCE: The limited utility of the clinical examination to detect or rule out early HIV infection highlights the importance of routine testing for HIV infection among adults. Copyright 2014 American Medical Association. All rights reserved.

Yao, H., Goldman, D. C., Nechiporuk, T., Kawane, S., McWeeney, S. K., Tyner, J. W., et al. (2014). Corepressor Rcor1 is essential for murine erythropoiesis. *Blood, 123*(20), 3175-3184.
The corepressor Rcor1 has been linked biochemically to hematopoiesis, but its function in vivo remains unknown. We show that mice deleted for Rcor1 are profoundly anemic and die in late gestation. Definitive erythroid cells from mutant mice arrest at the transition from proerythroblast to basophilic erythroblast. Remarkably, Rcor1 null erythroid progenitors cultured in vitro form myeloid colonies instead of erythroid colonies. The mutant proerythroblasts also aberrantly express genes of the myeloid lineage as well as genes typical of hematopoietic stem cells (HSCs) and/or progenitor cells. The colony-stimulating factor 2 receptor beta subunit (Csf2rb), which codes for a receptor implicated in myeloid cytokine signaling, is a direct target for both Rcor1 and the transcription repressor Gfi1b in erythroid cells. In the absence of Rcor1, the Csf2rb gene is highly induced, and Rcor1(-/-) progenitors exhibit CSF2-dependent phospho-Stat5 hypersensitivity. Blocking this pathway can partially reduce myeloid colony formation by Rcor1-deficient erythroid progenitors. Thus, Rcor1 promotes erythropoiesis by repressing HSC and/or progenitor genes, as well as the genes and signaling pathways that lead to myeloid cell fate.

Yehia, B. R., Herati, R. S., Fleishman, J. A., Gallant, J. E., Agwu, A. L., Berry, S. A., et al. (2014). Hepatitis C virus testing in adults living with HIV: A need for improved screening efforts. *PloS One, 9*(7), e102766.

OBJECTIVES: Guidelines recommend hepatitis C virus (HCV) screening for all people living with HIV (PLWH). Understanding HCV testing practices may improve compliance with guidelines and can help identify areas for future intervention. METHODS: We evaluated HCV screening and unnecessary repeat HCV testing in 8,590 PLWH initiating care at 12 U.S. HIV clinics between 2006 and 2010, with follow-up through 2011. Multivariable logistic regression examined the association between patient factors and the outcomes: HCV screening (>/=1 HCV antibody tests during the study period) and unnecessary repeat HCV testing (>/=1 HCV antibody tests in patients with a prior positive test result). RESULTS: Overall, 82% of patients were screened for HCV, 18% of those screened were HCV antibody-positive, and 40% of HCV antibody-positive patients had unnecessary repeat HCV testing. The likelihood of being screened for HCV increased as the number of outpatient visits rose (adjusted odds ratio 1.02, 95% confidence interval 1.01-1.03). Compared to men who have sex with men (MSM), patients with injection drug use (IDU) were less likely to be screened for HCV (0.63, 0.52-0.78); while individuals with Medicaid were more likely to be screened than those with private insurance (1.30, 1.04-1.62). Patients with heterosexual (1.78, 1.20-2.65) and IDU (1.58, 1.06-2.34) risk compared to MSM, and those with higher numbers of outpatient (1.03, 1.01-1.04) and inpatient (1.09, 1.01-1.19) visits were at greatest risk of unnecessary HCV testing. CONCLUSIONS: Additional efforts to improve compliance with HCV testing guidelines are needed. Leveraging health information technology may increase HCV screening and reduce unnecessary testing.

Young, K. H., Newell, P., Cottam, B., Friedman, D., Savage, T., Baird, J., et al. (2014). TGFbeta inhibition prior to hypofractionated radiation enhances efficacy in preclinical models. *Cancer Immunology Research,*

The immune infiltrate in colorectal cancer has been correlated with outcome, such that individuals with higher infiltrations of T cells have increased survival independent of disease stage. For those patients with poor immune infiltrates, overall survival is severely limited. Since the colorectal cancer patients studied received conventional cancer therapies, these data could be interpreted to mean that the pre-treatment tumor environment increases the efficacy of treatments such as chemotherapy, surgical resection and radiation therapy. This study was designed to test the hypothesis that an improved immune environment in the tumor at the time of treatment will

increase the efficacy of radiation therapy. We demonstrate that inhibition of TGFbeta using the orally available small molecule inhibitor SM16 improved the immune environment of tumors in mice and significantly improved the efficacy of subsequent radiation therapy. This effect was not due to changes in radiosensitivity, epithelial to mesenchymal transition or changes in vascular function in the tumor; rather, this effect was dependent on adaptive immunity and resulted in long-term protective immunity in cured mice. These data demonstrate that immunotherapy is an option to improve the immune status of patients with poor tumor infiltrates and that pre-treatment improves the efficacy of radiation therapy.

Yuan, Y., Van Allen, E. M., Omberg, L., Wagle, N., Amin-Mansour, A., Sokolov, A., et al. (2014). Assessing the clinical utility of cancer genomic and proteomic data across tumor types. *Nature Biotechnology, 32*(7), 644-652.

Molecular profiling of tumors promises to advance the clinical management of cancer, but the benefits of integrating molecular data with traditional clinical variables have not been systematically studied. Here we retrospectively predict patient survival using diverse molecular data (somatic copy-number alteration, DNA methylation and mRNA, microRNA and protein expression) from 953 samples of four cancer types from The Cancer Genome Atlas project. We find that incorporating molecular data with clinical variables yields statistically significantly improved predictions (FDR < 0.05) for three cancers but those quantitative gains were limited (2.2-23.9%). Additional analyses revealed little predictive power across tumor types except for one case. In clinically relevant genes, we identified 10,281 somatic alterations across 12 cancer types in 2,928 of 3,277 patients (89.4%), many of which would not be revealed in single-tumor analyses. Our study provides a starting point and resources, including an open-access model evaluation platform, for building reliable prognostic and therapeutic strategies that incorporate molecular data. © 2014 Nature America, Inc.

Zaninotto, G., & Hunter, J. G. (2014). Dysplastic barrett's esophagus. *World Journal of Surgery,*

Zelaya, J. E., Goenezen, S., Dargon, P. T., Azarbal, A. F., & Rugonyi, S. (2014). Improving the efficiency of abdominal aortic aneurysm wall stress computations. *PloS One, 9*(7), e101353.

An abdominal aortic aneurysm is a pathological dilation of the abdominal aorta, which carries a

high mortality rate if ruptured. The most commonly used surrogate marker of rupture risk is the maximal transverse diameter of the aneurysm. More recent studies suggest that wall stress from models of patient-specific aneurysm geometries extracted, for instance, from computed tomography images may be a more accurate predictor of rupture risk and an important factor in AAA size progression. However, quantification of wall stress is typically computationally intensive and time-consuming, mainly due to the nonlinear mechanical behavior of the abdominal aortic aneurysm walls. These difficulties have limited the potential of computational models in clinical practice. To facilitate computation of wall stresses, we propose to use a linear approach that ensures equilibrium of wall stresses in the aneurysms. This proposed linear model approach is easy to implement and eliminates the burden of nonlinear computations. To assess the accuracy of our proposed approach to compute wall stresses, results from idealized and patient-specific model simulations were compared to those obtained using conventional approaches and to those of a hypothetical, reference abdominal aortic aneurysm model. For the reference model, wall mechanical properties and the initial unloaded and unstressed configuration were assumed to be known, and the resulting wall stresses were used as reference for comparison. Our proposed linear approach accurately approximates wall stresses for varying model geometries and wall material properties. Our findings suggest that the proposed linear approach could be used as an effective, efficient, easy-to-use clinical tool to estimate patient-specific wall stresses.

Zhang, Z., Duckart, J., Slatore, C. G., Fu, Y., Petrik, A. F., Thorp, M. L., et al. (2014). Individuality of the plasma sodium concentration. *American Journal of Physiology - Renal Physiology, 306*(12), F1534-F1543.

Older literature has suggested that the plasma sodium concentration is not individual, that it is neither intrinsic to an individual nor reproducible, longitudinally. We recently observed that the plasma sodium concentration is heritable. Because demonstrable heritability requires individuality of the relevant phenotype, we hypothesized that the plasma sodium concentration was substantially individual. In two large health plan-based cohorts, we demonstrated individuality of the plasma sodium concentration over a 10-yr interval; the intraclass correlation coefficient (ICC) averaged 0.4-0.5. The individuality of plasma sodium increased significantly with age. Plasma sodium individuality was equal to or only slightly less than that for plasma glucose but was less

than the individuality for creatinine. The individuality of plasma sodium was further confirmed by comparing the Pearson correlation coefficient for within-individual versus between-individual pairs of sodium determinations and via application of the agreement index. Furthermore, the distribution of all sodium determinations for all participants within a population was similar to the distribution for the mean sodium concentration for individuals within that population. Therefore, the near-normal distribution of plasma sodium measurements within a population is likely not attributable to assay-specific factors but rather to genuine and durable biological variability in the osmotic set point. In aggregate, these data strongly support the individuality of the plasma sodium concentration. They further indicate that serial plasma sodium values for any given individual tend to cluster around a patient-specific set point and that these set points vary among individuals.

Zuckerman, K. E., Lindly, O. J., Bethell, C. D., & Kuhlthau, K. (2014). Family impacts among children with autism spectrum disorder: The role of health care quality. *Academic Pediatrics, 14*(4), 398-407.

OBJECTIVE: To compare health care quality and family employment and financial impacts among children with special health care needs (CSHCN) with autism spectrum disorder (CSHCN + ASD), CSHCN with functional limitations (CSHCN + FL), and CSHCN lacking these conditions (other CSHCN); to test whether high health care quality was associated with reduced family impacts among CSHCN + ASD. METHODS: Data from the 2009-2010 National Survey of CSHCN were used to compare 3025 CSHCN + ASD, 6505 CSHCN + FL, and 28,296 other CSHCN. Weighted multivariate logistic regression analyses examined 6 age-relevant, federally defined health care quality indicators and 5 family financial and employment impact indicators. Two composite measures were additionally used: 1) receipt of care that met all age-relevant quality indicators; and 2) had >/=2 of the 5 adverse family impacts. RESULTS: Across all health care quality indicators, CSHCN + ASD fared poorly, with only 7.4% meeting all age-relevant indicators. CSHCN + ASD had worse health care quality than other CSHCN, including CSHCN + FL. CSHCN + ASD also had high rates of adverse family impact, with over half experiencing >/=2 adverse impacts. Rates of adverse family impact were higher in CSHCN + ASD than other CSHCN, including CSHCN + FL. Among CSHCN + ASD, those whose health care that met federal quality

standards were less likely to have multiple adverse family impacts than CSHCN + ASD whose health care did not meet federal quality standards. CONCLUSIONS: CSHCN + ASD are more prone to experience poor health care quality and family impacts than other CSHCN, even CSHCN + FL. Receipt of care meeting federal quality standards may potentially lessen adverse family impacts for CSHCN + ASD.

Zuckerman, K. E., Mattox, K. M., Sinche, B. K., & Blaschke, G. S. (2014). Disparities in family health-related internet and email use in the general pediatrics setting. *Clinical Pediatrics,*