

References

Actis, L. A., Tolmasky, M. E., & Crosa, J. H. (2011). *Vibriosis* CABI Publishing.

Adams, K., Osmundsen, B., & Gregory, W. T. (2013). Does fibromyalgia influence symptom bother from pelvic organ prolapse? *International Urogynecology Journal*, doi:10.1007/s00192-013-2280-y

INTRODUCTION AND HYPOTHESIS: Determine if women with fibromyalgia report increased bother from pelvic organ prolapse compared with women without fibromyalgia. METHODS: We performed a cross-sectional study of women with symptomatic prolapse on consultation with a private urogynecology practice within a 46-month period. After matching for age, women with a diagnosis of fibromyalgia were compared with a reference group of women without fibromyalgia. Demographic, POPQ examination, medical history, and pelvic floor symptom data (PFDI, PFIQ, and PISQ-12) were collected. Our primary outcome was to compare the mean Pelvic Floor Distress Inventory (PFDI) scores of women with and without fibromyalgia. RESULTS: The prevalence of fibromyalgia in women evaluated for initial urogynecology consultation during the study period was 114 out of 1,113 (7 %). Women with fibromyalgia reported significantly higher symptom bother scores related to pelvic organ prolapse, defecatory dysfunction, urinary symptoms, and sexual function: PFDI ($p = 0.005$), PFIQ ($p=0.010$), and PISQ ($p=0.018$). Women with fibromyalgia were found to have a higher BMI ($p=0.008$) and were more likely to report a history of sexual abuse, OR 3.1 (95 % CI 1.3, 7.9), and have levator myalgia on examination, OR 3.8 (95 % CI 1.5, 9.1). In a linear regression analysis, levator myalgia was found to be the significant factor associated with pelvic floor symptom bother. CONCLUSIONS: In women with symptomatic prolapse, fibromyalgia is associated with an increased risk of levator myalgia and 50 % more symptom bother from pelvic floor disorders.

Alexander, K. S., Kazmierczak, S. C., Snyder, C. K., Oberdorf, J. A., & Farrell, D. H. (2013). Prognostic utility of biochemical markers of cardiovascular risk: Impact of biological variability. *Clinical Chemistry and Laboratory Medicine*, 51(9), 1875-1882. doi:10.1515/cclm-2012-0750

Background: Although a variety of biochemical markers are used to help predict the risk of cardiovascular disease, the prognostic utility of any marker used as a risk assessment tool is

dependent on the long- and short-term biological variability that the marker shows in different individuals. Methods: We measured total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; triglycerides; high-sensitivity C-reactive protein (hsCRP); total fibrinogen; and γ fibrinogen in blood samples collected from 15 apparently healthy individuals over the course of 1 year. Repeated measures variation estimates were used to calculate short- and long-term intraclass correlation coefficients (ICC), within- and between-subject coefficients of variation (CVI and CVG, respectively), validity coefficients, and indices of individuality for each marker. Results: HDL cholesterol demonstrated the lowest variability profile, with an ICC of 0.84 and CVI of 11.1 (95% CI: 8.3, 17.0). hsCRP showed the highest levels of short- and long-term within-subject variability [CVI (95% CI): 54.8 (32.8, 196.3) and 77.1 (53.3, 141.3), respectively]. Stated differently, it would require five separate measurements of hsCRP, performed on samples collected over multiple days, to provide the risk assessment information provided by a single measurement of HDL cholesterol. γ Fibrinogen demonstrated an ICC of 0.79 and CVI of 14.3 (95% CI: 10.6, 21.9). Conclusions: hsCRP showed very high biological variability, such that a single measurement of hsCRP lacks sufficient clinical utility to justify routine measurement. The variability profile of γ fibrinogen was not markedly different than HDL cholesterol, necessitating only a limited number of measurements to establish an individual's risk of cardiovascular disease.

Amato, P., Tachibana, M., Sparman, M., & Mitalipov, S. (2014). Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases. *Fertility and Sterility*, *101*(1), 31-35. doi:10.1016/j.fertnstert.2013.11.030; 10.1016/j.fertnstert.2013.11.030

The exchange of nuclear genetic material between oocytes and embryos offers a novel reproductive option for the prevention of inherited mitochondrial diseases. Mitochondrial dysfunction has been recognized as a significant cause of a number of serious multiorgan diseases. Tissues with a high metabolic demand, such as brain, heart, muscle, and central nervous system, are often affected. Mitochondrial disease can be due to mutations in mitochondrial DNA or in nuclear genes involved in mitochondrial function. There is no curative treatment for patients with mitochondrial disease. Given the lack of treatments and the limitations of prenatal and preimplantation diagnosis, attention has focused on prevention of

transmission of mitochondrial disease through germline gene replacement therapy. Because mitochondrial DNA is strictly maternally inherited, two approaches have been proposed. In the first, the nuclear genome from the pronuclear stage zygote of an affected woman is transferred to an enucleated donor zygote. A second technique involves transfer of the metaphase II spindle from the unfertilized oocyte of an affected woman to an enucleated donor oocyte. Our group recently reported successful spindle transfer between human oocytes, resulting in blastocyst development and embryonic stem cell derivation, with very low levels of heteroplasmy. In this review we summarize these novel assisted reproductive techniques and their use to prevent transmission of mitochondrial disorders. The promises and challenges are discussed, focusing on their potential clinical application.

Amling, C. L. (2013). Editorial Comment. *The Journal of Urology*, doi:10.1016/j.juro.2013.09.096; 10.1016/j.juro.2013.09.096

Arnold, B., Friedrichsen, L., & Nishiyama, M. (2013). Creating your master mind: Personal and professional development through MasterMind groups. *50th ACM Annual Conference on Special Interest Group on University and College Computing Services, SIGUCCS 2013*, Chicago, IL. 123-126. doi:10.1145/2504776.2504791

Do you find it easier or more enjoyable to pursue your personal or professional goals in concert with other like-minded people? If so, a "MasterMind group" might be just the resource you have been searching for. A MasterMind group, as described by the business author Napoleon Hill, is "The coordination of knowledge and effort of two or more people, who work toward a definite purpose, in the spirit of harmony." By gathering regularly with a like-minded set of people, one can find camaraderie, advice, differing points of view, and perhaps most importantly, accountability. Within a peer mentorship environment, members are willing to hold each other responsible for their growth and progress. The MasterMind group stands in contrast to a mentor/mentee relationship because in the former, each participant stands to gain from the relationship equally. Copyright © 2013 ACM.

Arnold, D. E., Hattamer, S., & Hicks, J. S. (2014). Characteristics of a High-quality Anesthesia Practice. *International Anesthesiology Clinics*, 52(1), 15-41.

doi:10.1097/AIA.0000000000000007; 10.1097/AIA.0000000000000007

Artornsombudh, P., Pistilli, M., Foster, C. S., Pujari, S. S., Gangaputra, S. S., Jabs, D. A., . . .

Kempen, J. H. (2013). Factors Predictive of Remission of New-Onset Anterior Uveitis.

Ophthalmology, doi:10.1016/j.ophtha.2013.09.041; 10.1016/j.ophtha.2013.09.041

PURPOSE: To identify factors predictive of remission of inflammation in new-onset anterior uveitis cases treated at tertiary uveitis care facilities. DESIGN: Retrospective cohort study.

PARTICIPANTS: Patients seeking treatment at participating academic uveitis clinics within 90 days of initial diagnosis of anterior uveitis. METHODS: Retrospective cohort study based on

standardized chart review. MAIN OUTCOME MEASURES: Factors predictive of remission (no

disease activity without corticosteroid or immunosuppressive treatments at all visits during a 90-day period). RESULTS: Nine hundred ninety eyes (687 patients) had a first-ever diagnosis of

anterior uveitis within 90 days before initial presentation and had follow-up visits thereafter. The median follow-up time was 160 days. Systemic diagnoses with juvenile idiopathic arthritis (JIA;

adjusted hazard ratio [aHR], 0.38; 95% confidence interval [CI], 0.19-0.74) and Behcet's disease (aHR, 0.10; 95% CI, 0.01-0.85) were associated with a lower incidence of uveitis remission.

Cases of bilateral uveitis (aHR, 0.68; 95% CI, 0.54-0.87) and those with a history of cataract surgery before presentation (aHR, 0.51; 95% CI, 0.29-0.87) also had a lower incidence of

remission. Regarding clinical findings at the initial visit, a high degree of vitreous cells at initial presentation was associated with a lower incidence of remission (for 1+ or more vs. none: aHR,

0.72; 95% CI, 0.55-0.95). An initial visual acuity of 20/200 or worse, with respect to 20/40 or better, also was predictive of a lower incidence of remission (aHR, 0.52; 95% CI, 0.32-0.86).

CONCLUSIONS: Factors associated with a lower incidence of remission among new-onset anterior uveitis cases included diagnosis with JIA, Behcet's disease, bilateral uveitis, history of cataract

surgery, findings of 1+ or more vitreous cells at presentation, and an initial visual acuity of 20/200 or worse. Patients with these risk factors seem to be at higher risk of persistent

inflammation; reciprocally, patients lacking these factors would be more likely to experience

remission. Patients with risk factors for nonremission of uveitis should be managed taking into

account the higher probability of a chronic inflammatory course. FINANCIAL DISCLOSURE(S):
Proprietary or commercial disclosure may be found after the references.

Aslam, M. I., Hettmer, S., Abraham, J., Latocha, D., Soundararajan, A., Huang, E. T., . . . Keller, C. (2013). Dynamic and nuclear expression of PDGFR α and IGF-1R in alveolar rhabdomyosarcoma. *Molecular Cancer Research*, 11(11), 1303-1313. doi:10.1158/1541-7786.MCR-12-0598

Since the advent of tyrosine kinase inhibitors as targeted therapies in cancer, several receptor tyrosine kinases (RTK) have been identified as operationally important for disease progression. Rhabdomyosarcoma (RMS) is a malignancy in need of new treatment options; therefore, better understanding of the heterogeneity of RTKs would advance this goal. Here, alveolar RMS (aRMS) tumor cells derived from a transgenic mouse model expressing two such RTKs, platelet-derived growth factor (PDGFR) α and insulin-like growth factor (IGF)-1R, were investigated by fluorescence-activated cell sorting (FACS). Sorted subpopulations that were positive or negative for PDGFR α and IGF-1R dynamically altered their cell surface RTK expression profiles as early as the first cell division. Interestingly, a difference in total PDGFR α expression and nuclear IGF-1R expression was conserved in populations. Nuclear IGF-1R expression was greater than cytoplasmic IGF-1R in cells with initially high cell surface IGF-1R, and cells with high nuclear IGF-1R established tumors more efficiently in vivo. RNA interference-mediated silencing of IGF-1R in the subpopulation of cells initially harboring higher cell surface and total IGF-1R resulted in significantly reduced anchorage-independent colony formation as compared with cells with initially lower cell surface and total IGF-1R expression. Finally, in accordance with the findings observed in murine aRMS, human aRMS also had robust expression of nuclear IGF-1R. Implications: RTK expression status and subcellular localization dynamics are important considerations for personalized medicine. © 2013 American Association for Cancer Research.

Asquith, M., Pasala, S., Engelmann, F., Haberthur, K., Meyer, C., Park, B., . . . Messaoudi, I. (2013). Chronic Ethanol Consumption Modulates Growth Factor Release, Mucosal Cytokine Production, and MicroRNA Expression in Nonhuman Primates. *Alcoholism, Clinical and Experimental Research*, doi:10.1111/acer.12325; 10.1111/acer.12325

BACKGROUND: Chronic alcohol consumption has been associated with enhanced susceptibility to

both systemic and mucosal infections. However, the exact mechanisms underlying this enhanced susceptibility remain incompletely understood. METHODS: Using a nonhuman primate model of ethanol (EtOH) self-administration, we examined the impact of chronic alcohol exposure on immune homeostasis, cytokine, and growth factor production in peripheral blood, lung, and intestinal mucosa following 12 months of chronic EtOH exposure. RESULTS: EtOH exposure inhibited activation-induced production of growth factors hepatocyte growth factor (HGF), granulocyte colony-stimulating factor (G-CSF), and vascular-endothelial growth factor (VEGF) by peripheral blood mononuclear cells (PBMC). Moreover, EtOH significantly reduced the frequency of colonic Th1 and Th17 cells in a dose-dependent manner. In contrast, we did not observe differences in lymphocyte frequency or soluble factor production in the lung of EtOH-consuming animals. To uncover mechanisms underlying reduced growth factor and Th1/Th17 cytokine production, we compared expression levels of microRNAs in PBMC and intestinal mucosa. Our analysis revealed EtOH-dependent up-regulation of distinct microRNAs in affected tissues (miR-181a and miR-221 in PBMC; miR-155 in colon). Moreover, we were able to detect reduced expression of the transcription factors STAT3 and ARNT, which regulate expression of VEGF, G-CSF, and HGF and contain targets for these microRNAs. To confirm and extend these observations, PBMC were transfected with either mimics or antagomirs of miR-181 and miR-221, and protein levels of the transcription factors and growth factors were determined. Transfection of microRNA mimics led to a reduction in both STAT3/ARNT as well as VEGF/HGF/G-CSF levels. The opposite outcome was observed when microRNA antagomirs were transfected. CONCLUSIONS: Chronic EtOH consumption significantly disrupts both peripheral and mucosal immune homeostasis, and this dysregulation may be mediated by changes in microRNA expression.

Austin, J. C. (2011). *Disorders of elimination: Constipation* Springer London. doi:10.1007/978-1-84996-366-4_13

Constipation is commonly seen in pediatric patients. It is a frequent complaint seen by pediatric gastroenterologists as well as primary care providers. Constipation is very relevant to pediatric urology patients as it is seen frequently in patients presenting with urinary tract infections and/or voiding dysfunction. Dysfunctional elimination is the combination of bowel and bladder

dysfunction that was initially described in patients with recurrent urinary tract infections and vesicoureteral reflux. It is important to seek out symptoms of bowel dysfunction in patients seen with urinary complaints and vice versa. The treatment of constipation is an integral part of the treatment regimen in children with voiding dysfunction. Encopresis, or fecal incontinence associated with constipation and chronic fecal impaction may also be present in patients with voiding dysfunction and recurrent urinary tract infections. In children with constipation an organic cause should be sought out during the evaluation including neurologic, endocrine, or anatomic causes. In 95% of patients no etiology is found and they are classified as having functional constipation. © Springer-Verlag London Limited 2011.

Avenarius, M. R., Saylor, K. W., Lundeberg, M. R., Wilmarth, P. A., Shin, J. B., Spinelli, K. J., . . .

Barr-Gillespie, P. G. (2013). Correlation of Actin Crosslinker and Capper Expression Levels with Stereocilia Growth Phases. *Molecular & Cellular Proteomics : MCP*, doi:10.1074/mcp.M113.033704

During development of the chick cochlea, actin crosslinkers and barbed-end cappers presumably influence growth and remodeling of the actin paracrystal of hair cell stereocilia. We used mass spectrometry to identify and quantify major actin-associated proteins of the cochlear sensory epithelium from E14 to E21, when stereocilia widen and lengthen. Tight actin crosslinkers (i.e., fascins, plastins, and espin) are expressed dynamically during cochlear epithelium development between E7 and E21, with FSCN2 replacing FSCN1 and plastins remaining low in abundance. Capping protein (CAPZ), a barbed-end actin capper, is located at stereocilia tips; it is abundant during growth phase II, when stereocilia have ceased elongating and are increasing in diameter. CAPZ levels then decline during growth phase III, when stereocilia reinitiate barbed-end elongation. Although actin crosslinkers are readily detected by electron microscopy in developing chick cochlea stereocilia, quantitative mass spectrometry of stereocilia isolated from E21 chick cochlea indicated that tight crosslinkers are present there in stoichiometric ratios relative to actin that are much lower than their ratios for vestibular stereocilia. These results demonstrate the value of quantitation of global protein expression in chick cochlea during stereocilia development.

Bächinger, H. P., & Engel, J. (2008). *The Thermodynamics and Kinetics of Collagen Folding* Wiley-VCH Verlag GmbH. doi:10.1002/9783527619498.ch30

Ballabh, P., & Back, S. A. (2013). Advances in Neonatal Neurology. *Clinics in Perinatology*, doi:10.1016/j.clp.2013.11.002

Barewal, R. M., & Hagen, C. C. (2014). Management of snoring and obstructive sleep apnea with mandibular repositioning appliances: A prosthodontic approach. *Dental Clinics of North America*, 58(1), 159-180. doi:10.1016/j.cden.2013.09.010

Dentists are becoming increasingly aware of the importance of the detection and management of obstructive sleep apnea. The anatomic and neuromuscular risk factors in the pathogenesis of obstructive sleep apnea are reviewed with particular emphasis on oral findings. Mandibular repositioning appliances hold an important role in the treatment of this condition; however, knowledge of indications and contraindications for treatment, potential areas of oropharyngeal obstruction, appliance design, and treatment steps are vital to ensure maximum treatment success. A review of the steps involved in treatment and management with particular emphasis on collaborative care with physicians is presented. © 2014 Elsevier Inc.

Barker, D., Barker, M., Fleming, T., & Lampl, M. (2013). Support mothers to secure future public health. *Nature*, 504(7479), 209-211. doi:10.1038/504209a

Barkley-Levenson, A. M., & Crabbe, J. C. (2013). High Drinking in the Dark Mice: A genetic model of drinking to intoxication. *Alcohol (Fayetteville, N.Y.)*, doi:10.1016/j.alcohol.2013.10.007; 10.1016/j.alcohol.2013.10.007

Drinking to intoxication is a critical component of risky drinking behaviors in humans, such as binge drinking. Previous rodent models of alcohol consumption largely failed to demonstrate that animals were patterning drinking in such a way as to experience intoxication. Therefore, few rodent models of binge-like drinking and no specifically genetic models were available to study possible predisposing genes. The High Drinking in the Dark (HDID) selective breeding project was started to help fill this void, with HDID mice selected for reaching high blood alcohol levels in a limited access procedure. HDID mice now represent a genetic model of drinking to intoxication

and can be used to help answer questions regarding predisposition toward this trait as well as potential correlated responses. They should also prove useful for the eventual development of better therapeutic strategies.

Barnett, C. M., Heinrich, M. C., Lim, J., Nelson, D., Beadling, C., Warrick, A., . . . Beer, T. M. (2013).

Genetic Profiling to Determine Risk of Relapse Free Survival in High-risk Localized Prostate Cancer. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, doi:10.1158/1078-0432.CCR-13-1775

PURPOSE: The characterization of actionable mutations in human tumors is a prerequisite for the development of individualized, targeted therapy. We examined the prevalence of potentially therapeutically actionable mutations in patients with high risk clinically localized prostate cancer.

EXPERIMENTAL DESIGN: 48 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 ERG translocations were examined using

immunohistochemistry 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 vs. 106 months ($p = .01$). 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. While 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.

Baru, A., Kerns, E. S., & Cohen, D. M. (2013). A reversible cause of 'end-stage renal disease':

discrepant findings in serial duplex ultrasonograms in a suspected occlusion of a renal arterial

bypass graft. *BMJ Case Reports*, 2013, 10.1136/bcr-2013-201600. doi:10.1136/bcr-2013-201600; 10.1136/bcr-2013-201600

Duplex ultrasonography may be inaccurate due to a number of variables in operator and patient characteristics. We describe a 40-year-old woman who presented with acute kidney injury after prior complex abdominal aortic surgery that had left her with an essentially solitary functional kidney. On the basis of normal Doppler findings, she was started on dialysis. Owing to high clinical suspicion and a failure of renal function to return, a second Doppler study was performed 3 weeks after the first, revealing the characteristic tardus-parvus waveform of renal artery stenosis. The patient underwent urgent renal arterial angioplasty and stent placement. She experienced an immediate increase in urinary output, required no further dialysis, and the creatinine improved to 1.7 mg/dL (her prior renal baseline). The case illustrates an important complication of abdominal aortic aneurysm repair, draws attention to a potential source of error in the Doppler measurement, and underscores the limitations of duplex ultrasonography for excluding renal artery stenosis in the presence of high pretest probability.

Bascom, P. B. (2013). Inadvertent Ophthalmic Administration of Atropine Drops in a Hospice Patient. *American Journal of Hospice and Palliative Medicine*, 30(8), 793-794.

doi:10.1177/1049909112467363

This case report describes a patient who had atropine ophthalmic drops prescribed and dispensed by hospice to be administered sublingually as needed for control of secretions at the end of life. However, even as she stabilized and discharged from hospice, these remained on her medication list. At a subsequent hospitalization, this order was misinterpreted and the drops were ordered to be administered in both the eyes 3 times a day while in the hospital and were included in her discharge medication list. The patient experienced severe blurring of vision until the error was corrected. This case highlights the potential risks of the common practice in hospice of using alternate routes of administration for medications designed for another purpose. © The Author(s) 2012.

Bayly, P. V., Taber, L. A., & Kroenke, C. D. (2014). Mechanical forces in cerebral cortical folding: A review of measurements and models. *Journal of the Mechanical Behavior of Biomedical Materials*,

29, 568-581. doi:10.1016/j.jmbbm.2013.02.018

Folding of the cerebral cortical surface is a critical process in human brain development, yet despite decades of indirect study and speculation the mechanics of the process remain incompletely understood. Leading hypotheses have focused on the roles of circumferential expansion of the cortex, radial growth, and internal tension in neuronal fibers (axons). In this article, we review advances in the mathematical modeling of growth and morphogenesis and new experimental data, which together promise to clarify the mechanical basis of cortical folding. Recent experimental studies have illuminated not only the fundamental cellular and molecular processes underlying cortical development, but also the stress state and mechanical behavior of the developing brain. The combination of mathematical modeling and biomechanical data provides a means to evaluate hypothesized mechanisms objectively and quantitatively, and to ensure that they are consistent with physical law, given plausible assumptions and reasonable parameter values. © 2013 Elsevier Ltd.

Belcik, J. T., & Lindner, J. R. (2009). *Myocardial contrast echocardiography in the emergency department* Springer London. doi:10.1007/978-1-84882-027-2_28

Emergency departments across the United States annually treat close to 6 million patients who present with chest pain (CP).¹ Only a minority of these patients (10-30%) are ultimately diagnosed as having an acute myocardial infarction or acute coronary syndrome (ACS).^{2, 3} Yet, many patients with noncardiac CP are admitted to the hospital or to observation units incurring enormous burden to the health-care system. It has been estimated that the majority of patients admitted to the hospital with CP have a noncardiac etiology.¹ Of those who do have ACS, the standard diagnostic algorithms that are currently employed are frequently nondiagnostic, leading to a delayed or even missed diagnosis.²⁻⁴ © 2009 Springer-Verlag London.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Dagli, M. L., Fryer, A. D., . . . Sipes, I. G. (2013). A toxicological and dermatological assessment of alkyl cyclic ketones when used as fragrance ingredients. *Food and Chemical Toxicology*, 62, S1-S44. doi:10.1016/j.fct.2013.09.033

The alkyl cyclic ketone (ACK) fragrance ingredients are a diverse group of structures with similar metabolic and toxicity profiles. ACK fragrance materials demonstrate low acute toxicity. Upon

repeat dose testing, some adverse effects in biochemical and hematological parameters, and slightly increased liver and kidney weights were reported, primarily at high doses, resulting from adaptive effects. Developmental effects occurred only in the presence of maternal toxicity. Assays in bacteria and mammalian cell systems and the mouse micronucleus assay did not demonstrate genotoxicity. ACK fragrance ingredients are considered non-irritating to the skin of humans; results showed few reactions, most of which were equivocal or involved doses greater than those in consumer products. Mild to moderate eye irritation in animal tests was observed with most compounds; however, full recovery was usually observed. Human sensitization studies indicate that ACK fragrance ingredients have a low sensitization potential. Diagnostic patch-tests indicated low sensitizing potential in humans; except for fragrance materials which caused reactions at 1% or 5%. Phototoxicity and photosensitization were not demonstrated in humans, and, with the possible exception of acetyl cedrene, would not be expected. It is concluded that ACK materials do not present a safety concern at current levels of use as fragrance ingredients. © 2013 Elsevier Ltd.

Berrekouw, E., & He, G. -. (2006). *Bilateral versus unilateral internal thoracic artery in coronary bypass grafting* Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8_13

The long-term event-free survival after coronary bypass surgery is related to the preoperative status of the patient, progression of atherosclerotic disease in the native coronary arteries and patency of the conduits used [1]. In comparison to the saphenous vein, it has been shown that the left internal thoracic artery (LITA) has a superior patency and leads to a better (event-free) survival after 10 years [2]. The LITA is now widely accepted as the standard conduit for making an anastomosis with the left anterior descending artery (LAD) [2]. Use of the right internal thoracic artery (RITA) so far has been less widespread. Although it took a longer time to prove, the additional benefit of using bilateral internal thoracic arteries (BITA) is now more evident. In this chapter, we will focus on the differences in inhospital and late outcome between the BITA and LITA in coronary artery bypass grafting (CABG). © Springer-Verlag Berlin Heidelberg 2006.

Bethell, C. D. (2013). Engaging Families (and Ourselves) in Quality Improvement: An Optimistic and Developmental Perspective. *Academic Pediatrics, 13*(6 Suppl), S9-S11.

doi:10.1016/j.acap.2013.08.003; 10.1016/j.acap.2013.08.003

Bharadwaj, A. S., Schewitz-Bowers, L. P., Wei, L., Lee, R. W., & Smith, J. R. (2013). Intercellular adhesion molecule 1 mediates migration of Th1 and Th17 cells across human retinal vascular endothelium. *Investigative Ophthalmology & Visual Science, 54*(10), 6917-6925.

doi:10.1167/iovs.13-12058; 10.1167/iovs.13-12058

PURPOSE: Autoimmune inflammation of the retina causes vision loss in the majority of affected individuals. Th1 or Th17 cells initiate the disease on trafficking from the circulation into the eye across the retinal vascular endothelium. We investigated the ability of human Th1- and Th17-polarized cells to cross a simulated human retinal endothelium, and examined the role of IgG superfamily members in this process. **METHODS:** Th1- and Th17-polarized cell populations were generated from human peripheral blood CD4(+) T cells, using two Th1- and Th17-polarizing protocols. Transendothelial migration assays were performed over 18 hours in Boyden chambers, after seeding the transwell membrane with human retinal endothelial cells. In some assays intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), or activated leukocyte cell adhesion molecule (ALCAM) blocking antibody, or isotype- and concentration-matched control antibody, was added to the upper chambers. **RESULTS:** Th1- and Th17-polarized cells migrated equally efficiently across the human retinal endothelial monolayer. The percentage of IL-17(+) IFN-gamma(-) Th17-polarized cells was reduced following migration. Blocking ICAM-1, but not VCAM-1 or ALCAM, significantly reduced migration of Th1- and Th17-polarized cells for a majority of human donors. **CONCLUSIONS:** Taken in the context of other literature on transendothelial migration, our results illustrate the importance of investigating the specific tissue and vascular endothelium when considering helper T cell migration in autoimmune inflammation. Our findings further indicate that while generalizations about involvement of specific adhesion molecules in uveitis and other autoimmune disease may be possible, these may not apply to individual patients universally. The observations are relevant to the use of adhesion blockade for therapeutic purposes.

Bielawska, B., Day, A. G., Lieberman, D. A., & Hookey, L. C. (2014). Risk factors for early colonoscopic perforation include non-gastroenterologist endoscopists: A multivariable analysis. *Clinical Gastroenterology and Hepatology*, 12(1), 85-92. doi:10.1016/j.cgh.2013.06.030

Background & Aims: Bowel perforation is a rare but serious complication of colonoscopy. Its prevalence is increasing with the rapidly growing volume of procedures performed. Although colonoscopies have been performed for decades, the risk factors for perforation are not completely understood. We investigated risk factors for perforation during colonoscopy by assessing variables that included sedation type and endoscopist specialty and level of training.

Methods: We performed a retrospective multivariate analysis of risk factors for early perforation (occurring at any point during the colonoscopy but recognized during or immediately after the procedure) in adult patients by using the Clinical Outcomes Research Initiative National Endoscopic Database. Risk factors were determined from published articles. Additional variables assessed included endoscopist specialty and years of experience, trainee involvement, and sedation with propofol.

Results: We identified 192 perforation events during 1,144,900 colonoscopies from 85 centers entered into the database from January 2000-March 2011. On multivariate analysis, increasing age, American Society of Anesthesia class, female sex, hospital setting, any therapy, and polyps >10 mm were significantly associated with increased risk of early perforation. Colonoscopies performed by surgeons and endoscopists of unknown specialty had higher rates of perforation than those performed by gastroenterologists (odds ratio, 2.00; 95% confidence interval, 1.30-3.08). Propofol sedation did not significantly affect risk for perforation.

Conclusions: In addition to previously established risk factors, non-gastroenterologist specialty was found to affect risk for perforations detected during or immediately after colonoscopy. This finding could result from differences in volume and style of endoscopy training. Further investigation into these observed associations is warranted. © 2014 AGA Institute.

Bitton, A., Pereira, A. G., Smith, C. S., Babbott, S. F., & Bowen, J. L. (2013). The EFECT framework for interprofessional education in the patient centered medical home. *Healthcare*, 1(3-4), 63-68. doi:10.1016/j.hjdsi.2013.08.003

The very nature of the Patient-Centered Medical Home (PCMH) necessitates new instructional models that prepare learners for the roles they will have to assume in these transformed primary

care practices. In this manuscript we describe a new instructional framework that seeks to blend the goals of patient-centered care and inter-professional education, and can be implemented in existing training environments while practice transformation continues to proceed. We propose a 5-step process, the EFECT framework, which is simultaneously a sequence of tasks for effective patient care and a guide for the learners and faculty in teaching and evaluating that care delivery. These steps include: (1) Eliciting a patient-centered narrative, (2) Facilitating an inter-professional team discussion, (3) Evaluating clinical evidence, (4) Creating a shared care plan, and (5) Tracking outcomes. We then report preliminary descriptive outcomes from the first EFECT pilot. Our proposed framework supports learners' abilities to construct a patient-centered narrative from multiple professional perspectives as the basis for developing an evidence-based, integrated care plan between the patient and the inter-professional care team and deliberately following up on outcomes. We present this framework to stimulate a process for creating new curricula and evaluative tools to measure and promote learner functioning in medical home environments. © 2013.

Biundo, J. J., Roberts, W. N., & Deodhar, A. (2009). *Regional musculoskeletal complaints* Springer London. doi:10.1007/978-1-84800-934-9_44

This chapter is divided into sections based upon the anatomic sites: shoulder, elbow, wrist, hand, coccyx, hip, knee, ankle, and foot. Before focusing on specific musculoskeletal regions, however, we provide one introductory Pearl and then some general comments on the performance of arthro-centesis and joint injection. Some specific pointers on arthro-centesis and the injection of individual joints are found within the appropriate section. Introductory Pearl: "The number of rheumatologists doing procedures equals the number of different ways of performing them.." (Gardner 2007). Comment: It is true: there are many ways to skin a cat, and there are also many ways to perform most of the procedures described in this chapter. The preferences of the authors are emphasized herein, but other approaches may also work. © 2010 Springer-Verlag London.

Blauvelt, A. (2008). *HIV disease and AIDS* Springer London. doi:10.1007/978-1-84800-165-7_21

The two major glycoprotein subunits on the HIV envelope that interact with target cell surface

receptors are gp120 and gp41. CD4, as well as co-receptors, on the target cell surface interacts with gp120 to initiate infection. The co-receptor used by HIV on T cell targets is primarily CXCR4. The co-receptor used by HIV on macrophage targets is primarily CCR5. Mucocutaneous manifestations of HIV can be the result of primary infection, but are usually due to opportunistic infections, neoplasia, or various inflammatory conditions. Highly active antiretroviral therapy (HAART) includes inhibitors of viral reverse transcriptase, protease, and integrase, as well as blockers of fusion and co-receptors (e.g., CCR5). © 2008 Springer London.

Bloom, J. D., & Buckley, M. C. (2013). The Oregon psychiatric security review board: 1978-2012. *The Journal of the American Academy of Psychiatry and the Law*, 41(4), 560-567.

This commentary describes the functioning of the Oregon Psychiatric Security Review Board (PSRB) from 1978 through 2011, when the Oregon Legislature altered the authority of the PSRB in regard to certain hospitalized insanity acquittees. Following the Hinckley verdict, the American Psychiatric Association recognized the PSRB as a possible future model for the management and treatment of insanity acquittees. The commentary provides an overview of the board from administrative and empirical viewpoints over this 34-year period and discusses the changes made in PSRB statutes in 2012 and the implication of these changes for the future management of insanity acquittees in Oregon.

Blucher, A. S., & McWeeney, S. K. (2014). Challenges in secondary analysis of high throughput screening data. *Pacific Symposium on Biocomputing*. *Pacific Symposium on Biocomputing*, 19, 114-124.

Repurposing an existing drug for an alternative use is not only a cost effective method of development, but also a faster process due to the drug's previous clinical testing and established pharmacokinetic profiles. A potentially rich resource for computational drug repositioning approaches is publically available high throughput screening data, available in databases such as PubChem Bioassay and ChemBank. We examine statistical and computational considerations for secondary analysis of publicly available high throughput screening (HTS) data with respect to metadata, data quality, and completeness. We discuss developing methods and best practices that can help to ameliorate these issues.

Bodhankar, S., Chen, Y., Vandembark, A. A., Murphy, S. J., & Offner, H. (2013). IL-10-producing B-cells limit CNS inflammation and infarct volume in experimental stroke. *Metabolic Brain Disease*, 28(3), 375-386. doi:10.1007/s11011-013-9413-3

Clinical stroke induces inflammatory processes leading to cerebral injury. 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 increased numbers of activated T-cells, monocytes and microglial cells in the brain, thus implicating a regulatory role of B-cell subpopulations in limiting CNS damage from stroke. The aim of this study was to determine whether the IL-10-producing regulatory B-cell subset can limit CNS inflammation and reduce infarct volume following ischemic stroke in B-cell deficient (μ MT^{-/-}) mice. Five million IL-10-producing B-cells were obtained from IL-10-GFP reporter mice and transferred i.v. to μ MT^{-/-} mice. After 24 h following this transfer, recipients were subjected to 60 min of middle cerebral artery occlusion (MCAO) followed by 48 h of reperfusion. Compared to vehicle-treated controls, the IL-10⁺ B-cell-replenished μ MT^{-/-} mice had reduced infarct volume and fewer infiltrating activated T-cells and monocytes in the affected brain hemisphere. These effects in CNS were accompanied by significant increases in regulatory T-cells and expression of the co-inhibitory receptor, PD-1, with a significant reduction in the proinflammatory milieu in the periphery. These novel observations provide the first proof of both immunoregulatory and protective functions of IL-10-secreting B-cells in MCAO that potentially could impart significant benefit for stroke patients in the clinic. © 2013 Springer Science+Business Media New York.

Bolkan, S. S., & Matthew Lattal, K. (2013). Opposing effects of D-cycloserine on fear despite a common extinction duration: Interactions between brain regions and behavior. *Neurobiology of Learning and Memory*, doi:10.1016/j.nlm.2013.12.009; 10.1016/j.nlm.2013.12.009

A number of studies have reported that D-cycloserine (DCS), a partial agonist of the N-methyl-D-aspartate glutamate receptor, can facilitate the loss of conditioned fear if it is administered during an extinction trial. Here we examine the effects of DCS injected into the hippocampus or amygdala on extinction of context-evoked freezing after contextual fear conditioning in C57BL/6 mice. We find that DCS administered prior to an extinction session decreased freezing from the outset of the session regardless of which brain region was targeted. Retention tests revealed

opposite effects on fear expression despite identical behavioral treatments: intra-hippocampal DCS inhibited fear expression while intra-amygdala DCS potentiated fear expression. Following post-extinction session injections of DCS, we found a similar though less pronounced effect. Closer inspection of the data revealed that the effects of DCS interacted with the behavior of the subjects during extinction. Intra-hippocampal injections of DCS enhanced extinction in those mice that showed the greatest amount of within-session extinction, but had less pronounced effects on mice that showed the least within-session extinction. Intra-amygdala injections of DCS impaired extinction in those mice that showed the least within-session, but there was some evidence that the effect in the amygdala did not depend on behavior during extinction. These findings demonstrate that even with identical extinction preparations and trial durations, the effects of DCS administered into the hippocampus and amygdala can heavily depend on the organism's behavior during the extinction session. The broader implication of these findings is that the effects of pharmacological treatments designed to enhance extinction by targeting hippocampal or amygdalar processes may depend greatly on the responsivity of the subject to the behavioral treatment.

Bornstein, S., Young, K., Tanyi, J., & Holland, J. (2013). Heavy PETting: Reducing Radiation Exposure From Intradepartment Positron Emission Tomography Scans. *International Journal of Radiation Oncology, Biology, Physics*, doi:10.1016/j.ijrobp.2013.11.015; 10.1016/j.ijrobp.2013.11.015

Bottomly, D., Ryabinin, P. A., Tyner, J. W., Chang, B. H., Loriaux, M. M., Druker, B. J., . . . Wilmot, B. (2013). Comparison of methods to identify aberrant expression patterns in individual patients: augmenting our toolkit for precision medicine. *Genome Medicine*, 5(11), 103. doi:10.1186/gm509

BACKGROUND: Patient-specific aberrant expression patterns in conjunction with functional screening assays can guide elucidation of the cancer genome architecture and identification of therapeutic targets. Since most statistical methods for expression analysis are focused on differences between experimental groups, the performance of approaches for patient-specific expression analyses are currently less well characterized. A comparison of methods for the identification of genes that are dysregulated relative to a single sample in a given set of experimental samples, to our knowledge, has not been performed. METHODS: We systematically

evaluated several methods including variations on the nearest neighbor based outlying degree method, as well as the Zscore and a robust variant for their suitability to detect patient-specific events. The methods were assessed using both simulations and expression data from a cohort of pediatric acute B lymphoblastic leukemia patients. RESULTS: We first assessed power and false discovery rates using simulations and found that even under optimal conditions, high effect sizes (>4 unit differences) were necessary to have acceptable power for any method (>0.9) though high false discovery rates (>0.1) were pervasive across simulation conditions. Next we introduced a technical factor into the simulation and found that performance was reduced for all methods and that using weights with the outlying degree could provide performance gains depending on the number of samples and genes affected by the technical factor. In our use case that highlights the integration of functional assays and aberrant expression in a patient cohort (the identification of gene dysregulation events associated with the targets from a siRNA screen), we demonstrated that both the outlying degree and the Zscore can successfully identify genes dysregulated in one patient sample. However, only the outlying degree can identify genes dysregulated across several patient samples. CONCLUSION: Our results show that outlying degree methods may be a useful alternative to the Zscore or Rscore in a personalized medicine context especially in small to medium sized (between 10 and 50 samples) expression datasets with moderate to high sample-to-sample variability. From these results we provide guidelines for detection of aberrant expression in a precision medicine context.

Bourdette, D., & Naismith, R. T. (2014). BCG vaccine for clinically isolated syndrome and MS:

Infections and protective immunity. *Neurology*, 82(1), 15-16.

doi:10.1212/01.wnl.0000438232.40847.c3; 10.1212/01.wnl.0000438232.40847.c3

Infections may be harmful for people with multiple sclerosis (MS), resulting in fever, "pseudo-exacerbations," and increased risk of relapses.(1) Can infections ever be beneficial for MS? The long-held yet unproven "hygiene hypothesis" proposes that certain infections early in life might reduce the risk of developing autoimmune diseases by inducing protective immunity.(2) In addition, parasitic intestinal infections in people with MS may reduce disease activity.(3) It follows that better sanitation and common use of disinfectants and antibiotics may account in part for the increased prevalence of MS and other autoimmune diseases in North America and

much of Europe, compared with Africa, South America, and parts of Asia. If true, might we harness this natural phenomenon to develop new treatments for MS?

Bowman, G. L., Dodge, H. H., Mattek, N., Barbey, A. K., Silbert, L. C., Shinto, L., . . . Quinn, J. F. (2013). Plasma omega-3 PUFA and white matter mediated executive decline in older adults. *Frontiers in Aging Neuroscience, 5*, 92. doi:10.3389/fnagi.2013.00092; 10.3389/fnagi.2013.00092

Introduction: Cross-sectional studies have identified long chain omega-3 polyunsaturated fatty acids (eicosapentaenoic acid 20:5n-3 and docosahexaenoic acid 22:6n-3 (O3PUFA) in association with fewer white matter lesions and better executive function in older adults. We hypothesized that O3PUFA are associated with less executive decline over time and that total white matter hyperintensity volume (WMH) mediates this association. Methods: Eighty-six non-demented older adults were followed over 4 years after measurement of plasma O3PUFA with annual evaluations of cognitive function. A subset of these participants also had brain MRI of total WMH available to conduct a formal mediation analysis of a putative relationship between O3PUFA and cognitive function. Results: Mean age at baseline was 86, 62% were female and 11% carried the APOE4 allele. Each 100 mug/ml increase in plasma O3PUFA associated with 4 s less change in executive decline per year of aging ($p = 0.02$, fully adjusted model). O3PUFA was not associated with verbal memory or global cognitive changes. The significance of the association between O3PUFA and better executive function was lost once WMH was added to the regression model. Conclusion: Executive decline with age appears to be a cognitive domain particularly sensitive to plasma O3PUFA in longitudinal examination. O3PUFA may modulate executive functioning by mechanisms underlying the development of WMH, a biologically plausible hypothesis that warrants further investigation.

Brace, R. A., Cheung, C. Y., & Anderson, D. F. (2013). Inhibitor of Intramembranous Absorption in Ovine Amniotic Fluid. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology*, doi:10.1152/ajpregu.00469.2013

Intramembranous absorption increases during intra-amniotic infusion of physiological saline solutions. The increase may be due partly to the concomitant elevation in fetal urine production

as fetal urine contains a stimulator of intramembranous absorption. In this study, we hypothesized that the increase in intramembranous absorption during intra-amniotic infusion is due in part to dilution of a non-renal inhibitor of intramembranous absorption that is present in amniotic fluid. In late gestation fetal sheep, amniotic fluid volume and the 4 primary amniotic inflows and outflows were determined over 2-day intervals under 3 conditions: 1) control conditions when fetal urine entered the amniotic sac, 2) during intra-amniotic infusion of 2 liters/day of lactated Ringer's solution when urine entered the amniotic sac, and 3) during the same intra-amniotic infusion when fetal urine was continuously replaced with lactated Ringer's solution. Amniotic fluid volume, fetal urine production, swallowed volume, and intramembranous absorption rate increased during the infusions independent of fetal urine entry into the amniotic sac or its replacement. Lung liquid secretion rate was unchanged during infusion. Because fetal membrane stretch has been shown to be not involved and because urine replacement did not alter the response, we conclude that the increase in intramembranous absorption that occurs during intra-amniotic infusions is due primarily to dilution of a non-renal inhibitor of intramembranous absorption that is normally present in amniotic fluid. This result combined with our previous study suggests that a non-renal inhibitor(s) together with a renal stimulator(s) interact to regulate intramembranous absorption rate and hence amniotic fluid volume.

Braun, T. A., Mullins, R. F., Wagner, A. H., Andorf, J. L., Johnston, R. M., Bakall, B. B., . . . Stone, E. M. (2013). Non-exonic and synonymous variants in ABCA4 are an important cause of Stargardt disease. *Human Molecular Genetics*, 22(25), 5136-5145. doi:10.1093/hmg/ddt367

Mutations in ABCA4 cause Stargardt disease and other blinding autosomal recessive retinal disorders. However, sequencing of the complete coding sequence in patients with clinical features of Stargardt diseasesometimes fails to detectone or both mutations. For example,among208 individuals with clear clinical evidence of ABCA4 disease ascertained at a single institution, 28 had only one disease-causing allele identified in the exons and splice junctions of the primary retinal transcript of the gene. Haplotype analysis of these 28 probands revealed 3 haplotypes shared among ten families, suggesting that 18 of the 28 missing alleles were rare enough to be present only once in the cohort. We hypothesized that mutations near rare alternate splice junctions in ABCA4might causediseasebyincreasing the probability of mis-splicingat these sites. Next-

generationsequencing of RNAextracted from human donor eyes revealed more than a dozen alternate exons that are occasionally incorporated into the ABCA4 transcript in normal human retina. We sequenced the genomic DNA containing 15 of these minor exons in the 28 one-allele subjects and observed five instances of two different variations in the splice signals of exon 36.1 that were not present in normal individuals ($P < 10^{-6}$). Analysis ofRNAobtained from the keratinocytes of patients with these mutations revealed the predicted alternate transcript. This study illustrates the utility ofRNAsequence analysis of human donor tissue and patient-derived cell lines to identify mutations that would be undetectable by exome sequencing. © The Author 2013.

Brazil, R. M., & Fan, G. (2007). *B-cell lymphomas* Springer New York. doi:10.1007/978-0-387-33227-7_32

The B-cell lymphomas (BCLs) represent 80% to 90% of non-Hodgkin lymphomas in the Western world and include multiple lymphoma subtypes with different biologies, natural histories, morphologic characteristics, immunophenotypes, genetic features, prognoses, and responses to therapy.¹ Numerous subtypes of B-cell malignancies are defined according to the World Health Organization (WHO) classification (Table 32-1). Accurate subclassification of these BCLs has always been a challenge for pathologists, resulting in early application of new techniques in genetic analysis to these tumors to improve diagnostic accuracy. Today, the genetic features of BCLs are used not only to aid in rendering an accurate primary diagnosis, but also to predict prognosis, to assess for minimal residual disease after therapy, and even to help determine optimal therapy. © 2007 Springer Science+Business Media, LLC.

Britt, L. D., Trunkey, D. D., & Feliciano, D. V. (2007). *Acute care surgery: Principles and practice* Springer New York. doi:10.1007/978-0-387-69012-4

The practice of general and trauma surgery frequently involves a broad range of emergency situations. Surgeons must be familiar with diagnosis and operative management principles in the fast-paced environment of the emergency setting. *Acute Care Surgery: Principles and Practice* comprehensively presents the full spectrum of surgical emergencies, including trauma and non-traumatic acute surgical diseases of the abdominal, pelvic, and cardiothoracic organs as well as

the extremities, skin and soft tissue, and head and neck. Management of surgical infections is also discussed. Edited by an internationally renowned trio of experts, *Acute Care Surgery* is the ideal reference text for surgical trainees as well as practicing surgeons. Authoritative, comprehensive, and user-friendly, the text features over 40 chapters complete with case studies as well as question and answer commentaries. Every chapter begins with a box highlighting the key points and current areas of controversy. The text is augmented by more than 500 tables and illustrations. *Acute Care Surgery* is destined to be the gold-standard reference for surgeons faced with split-second decisions. © 2007 Springer Science+Business Media, LLC. All rights reserved.

Broberg, C. S. (2009). *Left Ventricular Outflow Tract Obstruction* Blackwell Publishing Ltd.

doi:10.1002/9781444311846.ch7

Broberg, C. S., Van Woerkom, R. C., Swallow, E., Dimopoulos, K., Diller, G. P., Allada, G., & Gatzoulis,

M. A. (2013). Lung function and gas exchange in Eisenmenger syndrome and their impact on exercise capacity and survival. *International Journal of Cardiology*,

doi:10.1016/j.ijcard.2013.11.047; 10.1016/j.ijcard.2013.11.047

BACKGROUND: Eisenmenger physiology may contribute to abnormal pulmonary mechanics and gas exchange and thus impaired functional capacity. We explored the relationship between lung function and gas exchange parameters with exercise capacity and survival. METHODS: Stable adult patients with Eisenmenger syndrome (N=32) were prospectively studied using spirometry, lung volumes, diffusion capacity, and blood gas analysis, as well as same day measurement of 6-minute walk distance and cardiopulmonary maximal treadmill exercise. Patients were followed prospectively to determine survival (7.4±0.5years). Abnormalities were identified and appropriate comparisons were made between affected and unaffected individuals between respiratory mechanics, exercise function, and survival. RESULTS: Obstruction (FEV1/FVC ratio <0.70) was found in 13 patients (41%), who were older but not otherwise different. Restriction was uncommon. Diffusion transfer coefficient, which was <80% in half the patients, correlated with exercise duration (r=0.542, P=0.005), and was worse in non-survivors (N=6). Nearly all patients had a compensated respiratory alkalosis (PaCO₂ 32±4.4mmHg). PaCO₂ was less reduced in older patients (r=0.438, P=0.022), and correlated independently with exercise

duration ($R=-0.463$, $P=0.03$), yet PaO₂, not PaCO₂, was associated with survival.

CONCLUSIONS: Eisenmenger patients show evidence of obstructive lung disease, diffusion abnormalities, and hypocapnia; likely from hyperventilation. Understanding expected lung mechanics and gas exchange may facilitate more appropriate clinical management.

Bryans, L., Palmer, A. D., Schindler, J. S., Andersen, P. E., & Cohen, J. I. (2013). Subjective and objective parameters of the adult female voice after cricotracheal resection and dilation. *The Annals of Otolaryngology, Rhinology, and Laryngology*, 122(11), 707-716.

OBJECTIVES: We compared the voice outcomes after cricotracheal resection (CTR) and airway dilation in adult women. METHODS: We performed long-term comprehensive voice assessments in 23 adult women treated for laryngotracheal stenosis, including acoustic and perceptual measurements of voice, videostroboscopy, the Voice Handicap Index, and an open-ended subjective questionnaire. RESULTS: Voice measures were abnormal in both groups. Objective pitch and loudness measurements were significantly more impaired after CTR than after dilation. Perceptual ratings of voice were worse after CTR than after dilation, particularly with regard to breathiness, pitch, and loudness. The CTR group was more likely to report a voice disorder, reported significantly more voice symptoms, and had higher voice handicap scores. Videostroboscopy was frequently abnormal in both groups, with more evidence of vocal hyperfunction after CTR. Self-ratings of breathing and swallowing were generally high in both groups, but voice satisfaction was rated lower after CTR. CONCLUSIONS: Voice was more significantly negatively impacted by CTR than by dilation. Surprisingly, many individuals in both groups reported improvements--a finding that possibly highlights the impact of laryngotracheal stenosis on airflow and vocal function before surgery. The importance of patient selection and preoperative counseling is emphasized, along with the potential need for voice therapy.

Brzana, J., Yedinak, C. G., Gultekin, S. H., Delashaw, J. B., & Fleseriu, M. (2013). Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: A large single center experience. *Pituitary*, 16(4), 490-498. doi:10.1007/s11102-012-0445-1

Acromegaly is associated with serious morbidity and mortality, if not well controlled. Approved

somatostatin receptor ligands (SRLs) are a mainstay of medical therapy and exhibit preferential affinity for somatostatin receptor (SSTR) subtype 2. Our objective was to assess whether characteristic features of individual growth hormone (GH)-secreting adenomas at diagnosis, correlated with SRL sensitivity, using defined tumor markers. A retrospective review of 86 consecutive acromegaly surgeries (70 patients) performed between January 2006 and December 2011 was undertaken. Patients with any preoperative medical treatment were excluded. Response to SRL therapy was defined as normalization of insulin-like growth factor 1 (IGF1) and random GH < 1.0 ng/dl. Immunohistochemical staining pattern: sparsely granulated, densely granulated, mixed growth hormone-prolactin (GH/PRL) and SSTR2 positivity (+) were correlated with clinicopathologic features, adenoma recurrence, and SRL treatment response. Two-tailed t test, univariate ANOVA, Kruskal-Wallis and bivariate correlation were performed using PAWS 18. The cohort eligible for analysis comprised 59 patients (41 female and 18 male). Based on pre-surgery adenoma imaging dimensions, 81.3 % (48) were macroadenomas and average maximum tumor diameter was 18.1 ± 9.9 mm. Patients on SRLs were followed for 13.4 ± 15.8 (mean \pm SD) months. Sparsely granulated adenomas were significantly larger at diagnosis, exhibited lower SSTR2 positivity and had a lower rate of biochemical normalization to SRLs. Densely granulated adenomas were highly responsive to SRLs. Overall, patients with SSTR2A+ adenomas responded more favorably to SRL treatment than those with SSTR2A- adenomas. Eighty-one percent of patients with SSTR2A+ adenomas were biochemically controlled (both GH and IGF1) on SRL treatment, e.g. a much higher normalization rate than that reported in the unselected acromegaly population (20-30 %). Detailed knowledge of adenoma GH granularity and the immunohistochemical SSTR2A+ status is a predictor of SRL response. These immunoreactive markers should be assessed routinely on surgical specimens to assess subsequent SRL responsiveness and potential need for adjunctive therapy after surgery. © 2012 Springer Science+Business Media New York.

Bubalo, J., Warden, B. A., Wiegel, J. J., Nishida, T., Handel, E., Svoboda, L. M., . . . Edillo, P. N. (2013). Does applying technology throughout the medication use process improve patient safety with antineoplastics? *Journal of Oncology Pharmacy Practice : Official Publication of the International Society of Oncology Pharmacy Practitioners*, doi:10.1177/1078155213514469

Purpose Medical errors, in particular medication errors, continue to be a troublesome factor in the delivery of safe and effective patient care. Antineoplastic agents represent a group of medications highly susceptible to medication errors due to their complex regimens and narrow therapeutic indices. As the majority of these medication errors are frequently associated with breakdowns in poorly defined systems, developing technologies and evolving workflows seem to be a logical approach to provide added safeguards against medication errors. Summary This article will review both the pros and cons of today's technologies and their ability to simplify the medication use process, reduce medication errors, improve documentation, improve healthcare costs and increase provider efficiency as relates to the use of antineoplastic therapy throughout the medication use process. Several technologies, mainly computerized provider order entry (CPOE), barcode medication administration (BCMA), smart pumps, electronic medication administration record (eMAR), and telepharmacy, have been well described and proven to reduce medication errors, improve adherence to quality metrics, and/or improve healthcare costs in a broad scope of patients. The utilization of these technologies during antineoplastic therapy is weak at best and lacking for most. Specific to the antineoplastic medication use system, the only technology with data to adequately support a claim of reduced medication errors is CPOE. In addition to the benefits these technologies can provide, it is also important to recognize their potential to induce new types of errors and inefficiencies which can negatively impact patient care. CONCLUSION: /st>The utilization of technology reduces but does not eliminate the potential for error. The evidence base to support technology in preventing medication errors is limited in general but even more deficient in the realm of antineoplastic therapy. Though CPOE has the best evidence to support its use in the antineoplastic population, benefit from many other technologies may have to be inferred based on data from other patient populations. As health systems begin to widely adopt and implement new technologies it is important to critically assess their effectiveness in improving patient safety.

Burchill, L. J., Mertens, L., & Broberg, C. S. (2014). Imaging for the assessment of heart failure in congenital heart disease. Ventricular function and beyond. *Heart Failure Clinics*, 10(1), 9-22. doi:10.1016/j.hfc.2013.09.013

Although heart failure is a diagnosis made on clinical grounds, cardiac imaging remains essential

for quantifying ventricular remodeling and function, and for identifying potentially reversible causes of heart failure. Various nongeometric methods for the assessment of ventricular function have been developed, and 3-dimensional imaging is also gaining ground in its clinical applications. This review focuses on the application of noninvasive imaging strategies in the assessment of heart failure in congenital heart disease, specifically echocardiography, cardiac magnetic resonance imaging, and computed tomography. Both traditional and emerging techniques are discussed, and their potential applications and limitations explored. © 2014 Elsevier Inc.

Burke, W., Brown Trinidad, S., & Press, N. A. (2013). Essential elements of personalized medicine.

Urologic Oncology: Seminars and Original Investigations, doi:10.1016/j.urolonc.2013.09.002

Objectives: Genomic information has been promoted as the basis for "personalized" health care.

We considered the benefits provided by genomic testing in context of the concept of personalized medicine. Materials and Methods: We evaluated current and potential uses of genomic testing in health care, using prostate cancer as an example, and considered their implications for individualizing or otherwise improving health care.

Results and Conclusions: Personalized medicine is most accurately seen as a comprehensive effort to tailor health care to the individual, spanning multiple dimensions. While genomic tests will offer many potential opportunities to improve the delivery of care, including the potential for genomic research to offer opportunities to improve prostate cancer screening and treatment, such advances do not in themselves constitute a paradigm shift in the delivery of health care. Rather, personalized medicine is based on a partnership between clinician and patient that utilizes shared decision making to determine the best health care options among the available choices, weighing the patient's personal values and preferences together with clinical findings. This approach is particularly important for difficult clinical decisions involving uncertainty and trade-offs, such as those involved in prostate cancer screening and management. The delivery of personalized medicine also requires adequate health care access and assurance that basic health needs have been met. Substantial research investment will be needed to identify how genomic tests can contribute to this effort. © 2013 Elsevier Inc. All rights reserved.

Chan, C. J., & Coussens, L. M. (2013). Poker face no more: cancer recurrence reveals its hand. *Nature Medicine*, 19(12), 1569-1570. doi:10.1038/nm.3410; 10.1038/nm.3410

Cheng, Y. W., Snowden, J. M., King, T., & Caughey, A. B. (2013). Reply to "Planned home or hospital delivery: what outcomes provide valid comparisons?". *American Journal of Obstetrics and Gynecology*, doi:10.1016/j.ajog.2013.12.015; 10.1016/j.ajog.2013.12.015

Cherala, G., Pearson, J., Maslen, C., & Edelman, A. (2013). An Ethinyl Estradiol-levonorgestrel Containing Oral Contraceptives Does Not Alter Cytochrome P4502C9 In Vivo Activity. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, doi:10.1124/dmd.113.054346

Oral contraceptives have been in wide use for more than 50 years. Levonorgestrel, a commonly employed progestin component of combined oral contraceptives, was implicated in drug-drug interactions mediated via cytochrome P4502C9 (CYP2C9). While in vitro studies refuted this interaction, there are no confirmatory in vivo studies. In the current study, we have examined the phenotypic status of CYP2C9 using low dose (125mg) Tolbutamide, pre- and post- oral contraceptive use in reproductive age women. Blood was collected 24 hr post Tolbutamide oral dose, plasma isolated, and Tolbutamide concentration (C24) was measured using liquid chromatography- mass spectrometry. The natural logarithm of Tolbutamide C24, a metric for CYP2C9 phenotype, was found to be similar between pre- and post- oral contraceptive use. In conclusion, levonorgestrel containing oral contraceptives, the most commonly used form of oral contraception, does not affect the status of CYP2C9 enzyme. This suggests that it is safe to co-administer levonorgestrel containing oral contraceptives and CYP2C9 substrates which includes a wide array of drugs.

Chia, S. H., Gross, N. D., & Richmon, J. D. (2013). Surgeon experience and complications with transoral robotic surgery (TORS). *Otolaryngology - Head and Neck Surgery (United States)*, 149(6), 885-892. doi:10.1177/0194599813503446

Objective. To investigate surgeon preferences for perioperative management of transoral robotic surgery (TORS) and explore the frequency of postoperative complications. Study Design. Retrospective survey. Setting. Multi-institutional. Subjects and Methods. An electronic survey was sent to over 300 TORS-trained surgeons in the United States identified by Intuitive Surgical, Inc.

Participation was voluntary and solicited by email invitations to participate 3 times over a 1-month period. Results. A total of 2015 procedures were reported by 45 respondent TORS-trained surgeons: 67% academic, 33% nonacademic. A minority of TORS procedures (n = 214, 10.6%) were performed on previously irradiated patients. Neck dissections were performed concurrently (58%) or staged (42%). Fewer than 6% of TORS procedures required tracheotomy or reconstruction. Most surgeons (62%) initiated oral intake on postoperative day 0-1. Of the patients who required readmission, bleeding (n = 62, 3.1%) was the most common cause followed by dehydration (n = 26, 1.3%). Other complications of surgery included tooth injury (n = 29, 1.4%), percutaneous endoscopic gastrostomy (PEG) dependency .6 months (n = 21, 1.0%), temporary hypoglossal nerve injury (n = 18, 0.9%), and lingual nerve injury (n = 11, 0.6%). A total of 6 deaths (0.3%) were reported within 30 days of TORS. All reported deaths were due to postoperative hemorrhage. The complication rate decreased significantly with higher surgeon case volume (.50 cases). Conclusions. TORS is associated with a low major complication rate, early initiation of oral intake, and a low rate of long-term PEG dependency. Postoperative hemorrhage was the most common cause of hospital readmission and postoperative mortality. © American Academy of Otolaryngology - Head and Neck Surgery Foundation 2013.

Cho, S., & von Gersdorff, H. (2013). Neuroscience: Faster than kiss-and-run. *Nature*, *504*(7479), 220-221. doi:10.1038/nature12842; 10.1038/nature12842

Choo, E. K., & Tabas, J. A. (2009). *Obstacles to Teaching in the Emergency Department* Wiley-Blackwell. doi:10.1002/9781444303636.ch2

Chou, R. (2013). In response. *Annals of Internal Medicine*, *159*(10), 718-719.

Chou, S., Komazin-Meredith, G., Williams, J. D., & Bowlin, T. L. (2013). Cytomegalovirus mutants resistant to ganciclovir and cidofovir differ in susceptibility to synguanol and its 6-ether and 6-thioether derivatives. *Antimicrobial Agents and Chemotherapy*, doi:10.1128/AAC.02544-13
The methylenecyclopropane nucleoside (MCPN) analogs synguanol and its 6-alkoxy (MBX2168) and 6-alkylthio (MBX1616) derivatives retained good in vitro activity against several common ganciclovir-resistant UL97 kinase mutants of human cytomegalovirus. Foscarnet-MCPN cross-

resistance was observed among UL54 polymerase mutants. UL54 exonuclease domain ganciclovir-cidofovir dual-resistant mutants were remarkably more hypersensitive to these MCPNs than to cyclopropavir, with some EC50 ratios <0.1x wild type. Different categories of MCPNs may have therapeutically exploitable mechanistic differences in viral DNA polymerase inhibition.

Chugh, S. S. (2008). *Novel predictors of sudden cardiac death* Springer London. doi:10.1007/978-1-84628-854-8_30

Despite recent advances in resuscitation science, survival from sudden cardiac arrest (SCA) remains low, and sudden cardiac death (SCD) remains a public health problem of significant proportions. Estimates of the annual incidence of SCD in the United States range from 200,000 to 400,000.¹⁻⁴ Currently, severe left ventricular (LV) dysfunction is the best available predictor of SCD risk and is the major indication for primary prevention with the implantable cardioverter defibrillator (ICD).⁵⁻⁸ Based on this indication, it is estimated that there will be at least 50,000 potential ICD recipients per year among the U.S. Medicare population alone, which is likely to translate into \$3-5 billion per year for implantation and follow-up of ICDs.⁹ However, using severe LV dysfunction as the criterion for a prophylactic ICD, it takes approximately 10 ICD recipients to save one life during an intermediate follow-up period, indicating that there is significant scope for enhancement of risk stratification.^{5,8} Therefore, there is a need to extend beyond the LV ejection fraction, and to identify novel predictors of SCD. This chapter will discuss the utility and limitations of severe LV systolic dysfunction as a risk predictor of SCD, other predictors in the process of being evaluated, and finally, the promise that new genomic predictors may also contribute to the process of SCD risk stratification. Wherever possible, predictors of SCD will be discussed in the context of the overall population, as opposed to population subgroups that can have variable risk. © 2008 Springer-Verlag London Limited.

Cohen, A. M., Demner-Fushman, D., Iorio, A., Sim, I., & Smalheiser, N. R. (2013). Tools for Identifying Reliable Evidence and Implementing it in Everyday Clinical Care. *AMIA Summits on Translational Science Proceedings AMIA Summit on Translational Science, 2013*, 42-44. Just as translational medicine follows a long winding path from bench-to-bedside, so can

Evidence-Based Medicine be envisioned as comprising a multi-step pipeline, from building evidence from raw data through synthesizing best practices and providing clinical decision support in a process described as the "evidence pyramid".¹ At one end, a heterogeneous mix of clinical and experimental studies including clinical trials, case reports, animal models and retrospective analyses are published as new knowledge. Then, experts collect and assess high-quality relevant evidence on specific issues and publish their conclusions (e.g., regarding efficacy and safety of treatments) as systematic reviews and meta-analyses. Finally, when an expert consensus has been reached, this must reach the attention of policy makers within the profession, the government and insurance companies, resulting in new practice guidelines and altered clinical practice within hospitals and clinics. At each stage, this process requires a large investment of time and effort from many individuals with a wide range of expertise. Our panel will discuss the variety of innovative approaches that are being taken by different informatics research groups to improve each step within the evidence based medicine pipeline. These approaches are, in part, devoted to making existing data collection and synthesis practices faster and more efficient, but they also involve re-imagining and re-engineering the processes by which evidence is accumulated, evaluated and applied.

Cohen, J. D., Aspry, K. E., Brown, A. S., Foody, J. M., Furman, R., Jacobson, T. A., . . . Ito, M. K. (2013). Use of health information technology (HIT) to improve statin adherence and low-density lipoprotein cholesterol goal attainment in high-risk patients: Proceedings from a workshop. *Journal of Clinical Lipidology*, 7(6), 573-609. doi:10.1016/j.jacl.2013.10.002

The workshop discussions focused on how low-density lipoprotein cholesterol (LDL-C) goal attainment can be enhanced with the use of health information technology (HIT) in different clinical settings. A gap is acknowledged in LDL-C goal attainment, but because of the passage of the American Recovery & Reinvestment Act and the Health Information Technology for Economic and Clinical Health Acts there is now reason for optimism that this gap can be narrowed. For HIT to be effectively used to achieve treatment goals, it must be implemented in a setting in which the health care team is fully committed to achieving these goals. Implementation of HIT alone has not resulted in reducing the gap. It is critical to build an effective management strategy into the HIT platform without increasing the overall work/time burden on staff. By enhancing

communication between the health care team and the patient, more timely adjustments to treatment plans can be made with greater opportunity for LDL-C goal attainment and improved efficiency in the long run. Patients would be encouraged to take a more active role. Support tools are available. The National Lipid Association has developed a toolkit designed to improve patient compliance and could be modified for use in an HIT system. The importance of a collaborative approach between nongovernmental organizations such as the National Lipid Association, National Quality Forum, HIT partners, and other members of the health care industry offers the best opportunity for long-term success and the real possibility that such efforts could be applied to other chronic conditions, for example, diabetes and hypertension. © 2013 National Lipid Association. All rights reserved.

Costantino, L., Sotiriou, S. K., Rantala, J. K., Magin, S., Mladenov, E., Helleday, T., . . . Halazonetis, T. D. (2013). Break-Induced Replication Repair of Damaged Forks Induces Genomic Duplications in Human Cells. *Science*, , 1-8. doi:10.1126/science.1243211

In budding yeast, one-ended DNA double-strand breaks (DSBs) and damaged replication forks are repaired by break-induced replication (BIR), a homologous recombination pathway that requires the Pol32 subunit of DNA polymerase delta. DNA replication stress is prevalent in cancer, but BIR has not been characterized in mammals. In a cyclin E overexpression model of DNA replication stress, POLD3, the human ortholog of POL32, was required for cell cycle progression and processive DNA synthesis. Segmental genomic duplications induced by cyclin E overexpression were also dependent on POLD3, as were BIR-mediated recombination events captured with a specialized DSB repair assay. We propose that BIR repairs damaged replication forks in mammals, accounting for the high frequency of genomic duplications in human cancers.

Courcoulas, A. P., Christian, N. J., Belle, S. H., Berk, P. D., Flum, D. R., Garcia, L., . . . Wolfe, B. M. (2013). Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA - Journal of the American Medical Association*, 310(22), 2416-2425. doi:10.1001/jama.2013.280928

IMPORTANCE: Severe obesity (body mass index [BMI] ≥ 35) is associated with a broad range of health risks. Bariatric surgery induces weight loss and short-term health improvements, but little

is known about long-term outcomes of these operations. **OBJECTIVE:** To report 3-year change in weight and select health parameters after common bariatric surgical procedures. **DESIGN AND SETTING:** The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium is a multicenter observational cohort study at 10 US hospitals in 6 geographically diverse clinical centers. **PARTICIPANTS AND EXPOSURE:** Adults undergoing first-time bariatric surgical procedures as part of routine clinical care by participating surgeons were recruited between 2006 and 2009 and followed up until September 2012. Participants completed research assessments prior to surgery and 6 months, 12 months, and then annually after surgery. **MAIN OUTCOMES AND MEASURES:** Three years after Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB), we assessed percent weight change from baseline and the percentage of participants with diabetes achieving hemoglobin A1c levels less than 6.5% or fasting plasma glucose values less than 126mg/dL without pharmacologic therapy. Dyslipidemia and hypertension resolution at 3 years was also assessed. **RESULTS:** At baseline, participants (N = 2458) were 18 to 78 years old, 79% were women, median BMI was 45.9 (IQR, 41.7-51.5), and median weight was 129 kg (IQR, 115-147). For their first bariatric surgical procedure, 1738 participants underwent RYGB, 610 LAGB, and 110 other procedures. At baseline, 774 (33%) had diabetes, 1252 (63%) dyslipidemia, and 1601 (68%) hypertension. Three years after surgery, median actual weight loss for RYGB participants was 41 kg (IQR, 31-52), corresponding to a percentage of baseline weight lost of 31.5% (IQR, 24.6%-38.4%). For LAGB participants, actual weight loss was 20 kg (IQR, 10-29), corresponding to 15.9% (IQR, 7.9%-23.0%). The majority of weight loss was evident 1 year after surgery for both procedures. Five distinct weight change trajectory groups were identified for each procedure. Among participants who had diabetes at baseline, 216 RYGB participants (67.5%) and 28 LAGB participants (28.6%) experienced partial remission at 3 years. The incidence of diabetes was 0.9% after RYGB and 3.2% after LAGB. Dyslipidemia resolved in 237 RYGB participants (61.9%) and 39 LAGB participants (27.1%); remission of hypertension occurred in 269 RYGB participants (38.2%) and 43 LAGB participants (17.4%). **CONCLUSIONS AND RELEVANCE:** Among participants with severe obesity, there was substantial weight loss 3 years after bariatric surgery, with the majority experiencing maximum weight change during the first year. However, there was variability in the amount and trajectories of weight loss and in

diabetes, blood pressure, and lipid outcomes. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00465829. Copyright 2013 American Medical Association. All rights reserved.

Coyne, B., Sproat, R., & Hirschberg, J. (2010). Spatial relations in text-to-scene conversion. *Workshop on Computational Models of Spatial Language Interpretation at Spatial Cognition 2010, COSLI 2010*, Portland, OR. , 620 9-16.

Spatial relations play an important role in our understanding of language. In particular, they are a crucial component in descriptions of scenes in the world. WordsEye (www.wordseye.com) is a system for automatically converting natural language text into 3D scenes representing the meaning of that text. Natural language offers an interface to scene generation that is intuitive and immediately approachable by anyone, without any special skill or training. WordsEye has been used by several thousand users on the web to create approximately 15,000 fully rendered scenes. We describe how the system incorporates geometric and semantic knowledge about objects and their parts and the spatial relations that hold among these in order to depict spatial relations in 3D scenes.

Cukier, P., Wright, H., Rulfs, T., Silveira, L. F. G., Teles, M. G., Mendonca, B. B., . . . Brito, V. N. (2013). Molecular and gene network analysis of thyroid transcription factor 1 (TTF1) and enhanced at puberty (EAP1) genes in patients with GnRH-dependent pubertal disorders. *Hormone Research in Paediatrics*, 80(4), 257-266. doi:10.1159/000354643

Background/Aim: TTF1 and EAP1 are transcription factors that modulate gonadotropin-releasing hormone expression. We investigated the contribution of TTF1 and EAP1 genes to central pubertal disorders. Patients and Methods: 133 patients with central pubertal disorders were studied: 86 with central precocious puberty and 47 with normosmic isolated hypogonadotropic hypogonadism. The coding region of TTF1 and EAP1 were sequenced. Variations of polyglutamine and polyalanine repeats in EAP1 were analyzed by GeneScan software. Association of TTF1 and EAP1 to genes implicated in timing of puberty was investigated by meta-network framework GeneMANIA and Cytoscape software. Results: Direct sequencing of the TTF1 did not reveal any mutation or polymorphisms. Four EAP1 synonymous variants were identified with similar frequencies among groups. The most common EAP1 5'-distal polyalanine genotype was the

homozygous 12/12, but the genotype 12/9 was identified in 2 central precocious puberty sisters without functional alteration in EAP1 transcriptional activity. TTF1 and EAP1 were connected, via genetic networks, to genes implicated in the control of menarche. Conclusion: No TTF1 or EAP1 germline mutations were associated with central pubertal disorders. TTF1 and EAP1 may affect puberty by changing expression in response to other members of puberty-associated gene networks, or by differentially affecting the expression of gene components of these networks. © 2013 S. Karger AG, Basel.

Curtis, J., Tanner, P., Judd, C., Childs, B., Hull, C., & Leachman, S. (2013). Acrylic nail curing UV lamps: High-intensity exposure warrants further research of skin cancer risk. *Journal of the American Academy of Dermatology*, 69(6), 1069-1070. doi:10.1016/j.jaad.2013.08.032

Dantes, R., Mu, Y., Belflower, R., Aragon, D., Dumyati, G., Harrison, L. H., . . . Fridkin, S. (2013). National burden of invasive methicillin-resistant *Staphylococcus aureus* infections, United States, 2011. *JAMA Internal Medicine*, 173(21), 1970-1979. doi:10.1001/jamainternmed.2013.10423

IMPORTANCE: Estimating the US burden of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is important for planning and tracking success of prevention strategies. OBJECTIVE: To describe updated national estimates and characteristics of health care- and community-associated invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in 2011.

DESIGN, SETTING, AND PARTICIPANTS: Active laboratory-based case finding identified MRSA cultures in 9 US metropolitan areas from 2005 through 2011. Invasive infections (MRSA cultured from normally sterile body sites) were classified as health care-associated community-onset (HACO) infections (cultured ≤ 3 days after admission and/or prior year dialysis, hospitalization, surgery, long-term care residence, or central vascular catheter presence ≤ 2 days before culture); hospital-onset infections (cultured > 3 days after admission); or community-associated infections if no other criteria were met. National estimates were adjusted using US census and US Renal Data System data. MAIN OUTCOMES AND MEASURES: National estimates of invasive HACO, hospital-onset, and community-associated MRSA infections using US census and US Renal Data System data as the denominator. RESULTS: An estimated 80 461 (95% CI, 69 515-93 914) invasive MRSA infections occurred nationally in 2011. Of these, 48 353 (95% CI, 40 195-58 642)

were HACO infections; 14 156 (95% CI, 10 096-20 440) were hospital-onset infections; and 16 560 (95% CI, 12 806-21 811) were community-associated infections. Since 2005, adjusted national estimated incidence rates decreased among HACO infections by 27.7% and hospital-onset infections decreased by 54.2%; community-associated infections decreased by only 5.0%. Among recently hospitalized community-onset (nondialysis) infections, 64% occurred 3 months or less after discharge, and 32% of these were admitted from long-term care facilities.

CONCLUSIONS AND RELEVANCE: An estimated 30 800 fewer invasive MRSA infections occurred in the United States in 2011 compared with 2005; in 2011 fewer infections occurred among patients during hospitalization than among persons in the community without recent health care exposures. Effective strategies for preventing infections outside acute care settings will have the greatest impact on further reducing invasive MRSA infections nationally. © 2013 American Medical Association. All rights reserved.

David, S. V., & Shamma, S. A. (2013). Integration over Multiple Timescales in Primary Auditory Cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 33(49), 19154-19166. doi:10.1523/JNEUROSCI.2270-13.2013; 10.1523/JNEUROSCI.2270-13.2013

Speech and other natural vocalizations are characterized by large modulations in their sound envelope. The timing of these modulations contains critical information for discrimination of important features, such as phonemes. We studied how depression of synaptic inputs, a mechanism frequently reported in cortex, can contribute to the encoding of envelope dynamics. Using a nonlinear stimulus-response model that accounted for synaptic depression, we predicted responses of neurons in ferret primary auditory cortex (A1) to stimuli with natural temporal modulations. The depression model consistently performed better than linear and second-order models previously used to characterize A1 neurons, and it produced more biologically plausible fits. To test how synaptic depression can contribute to temporal stimulus integration, we used nonparametric maximum a posteriori decoding to compare the ability of neurons showing and not showing depression to reconstruct the stimulus envelope. Neurons showing evidence for depression reconstructed stimuli over a longer range of latencies. These findings suggest that

variation in depression across the cortical population supports a rich code for representing the temporal dynamics of natural sounds.

Davis, S. C., Gibbs, S. L., Gunn, J. R., & Pogue, B. W. (2013). Topical dual-stain difference imaging for rapid intra-operative tumor identification in fresh specimens. *Optics Letters*, 38(23), 5184-5187. doi:10.1364/OL.38.005184

Assessing tumor margin status during surgery is critical to ensure complete resection of cancer tissue; however, current approaches are ineffective and often result in repeat surgery. We present an optical imaging approach for margin assessment using topical application of two fluorescent stains, one targeted to a tumor biomarker and the other a nontargeted reference, to freshly excised specimens. Computing a normalized difference image from fluorescence images of the targeted and untargeted stains suppresses the confounding effects of nonspecific uptake. Applying this approach in excised breast tumor models produced promising tumor-to-normal tissue contrasts that were significantly higher than single-targeted-stain imaging. © 2013 Optical Society of America.

Dean, J. M., Bennet, L., Back, S. A., McClendon, E., Riddle, A., & Gunn, A. J. (2013). What brakes the preterm brain? An arresting story. *Pediatric Research*, doi:10.1038/pr.2013.189; 10.1038/pr.2013.189

Children surviving premature birth have a high risk of cognitive and learning disabilities and attention deficit. In turn, adverse outcomes are associated with persistent reductions in cerebral growth on magnetic resonance imaging (MRI). It is striking that modern care has been associated with a dramatic reduction in the risk of cystic white matter damage, but modest improvements in terms of neurodevelopmental impairment. This review will explore the hypothesis that the disability is primarily associated with impaired neural connectivity rather than cell death alone. Very preterm infants exhibit reduced thalamocortical connectivity and cortical neuroplasticity compared with term-born controls. In preterm fetal sheep, moderate cerebral ischemia with no neuronal loss, but significant diffuse failure of maturation of cortical pyramidal neurons, was associated with impaired dendritic growth and synapse formation, consistent with altered connectivity. These changes were associated with delayed decline in cortical fractional anisotropy

(FA) on MRI. Supporting these preclinical findings, preterm human survivors showed similar enduring impairment of microstructural development of the cerebral cortex defined by FA, consistent with delayed formation of neuronal processes. These findings offer the promise that better understanding of impairment of neural connectivity may allow us to promote normal development and growth of the cortex after preterm birth. *Pediatric Research* (2013); doi:10.1038/pr.2013.189.

Decker, M. R., Bronson, N. W., Greenberg, C. C., Dolan, J. P., Kent, K. C., & Hunter, J. G. (2013). The general surgery job market: Analysis of current demand for general surgeons and their specialized skills. *Journal of the American College of Surgeons*, 217(6), 1133-1139. doi:10.1016/j.jamcollsurg.2013.07.400

Background The majority of general surgery residents pursue fellowships. However, the relative demand for general surgical skills vs more specialization is not understood. Our objective was to describe the current job market for general surgeons and compare the skills required by the market with those of graduating trainees. Study Design Positions for board eligible/certified general surgeons in Oregon and Wisconsin from 2011 to 2012 were identified by review of job postings and telephone calls to hospitals, private practice groups, and physician recruiters. Data were gathered on each job to determine if fellowship training or specialized skills were required, preferred, or not requested. Information on resident pursuit of fellowship training was obtained from all residency programs within the represented states. Results Of 71 general surgery positions available, 34% of positions required fellowship training. Rural positions made up 46% of available jobs. Thirty-five percent of positions were in nonacademic metropolitan settings and 17% were in academic metropolitan settings. Fellowship training was required or preferred for 18%, 28%, and 92% of rural, nonacademic, and academic metropolitan positions, respectively. From 2008 to 2012, 67% of general surgery residents pursued fellowship training. Conclusions Most general surgery residents pursue fellowship despite the fact that the majority of available jobs do not require fellowship training. The motivation for fellowship training is unclear, but residency programs should tailor training to the skills needed by the market with the goal of improving access to general surgical services. © 2013 by the American College of Surgeons.

Delamater, A. R., & Matthew Lattal, K. (2013). The study of associative learning: Mapping from psychological to neural levels of analysis. *Neurobiology of Learning and Memory*, doi:10.1016/j.nlm.2013.12.006; 10.1016/j.nlm.2013.12.006

One of the major achievements of the last century of research in experimental psychology is the identification of a coherent set of theories and principles to characterize the nature of simple forms of associative learning. Major advances are also currently being made at a rapid pace in the neurobiology of associative learning, and, interestingly, we are beginning to see how a mapping from a psychological level of analysis to underlying neurobiological mechanisms is possible. This collection of papers honors the illustrative careers of four major learning theorists from the experimental psychology tradition (Robert Rescorla, Allan Wagner, Nicholas Mackintosh, Anthony Dickinson) who have helped shape our understanding of behavioral principles. The collection of works in this special issue reflect common interests among researchers working at both psychological and neurobiological levels of analysis towards a more comprehensive understanding of basic associative learning processes as they relate to several key issues identified and intensively studied by these influential learning theorists. These consist of the questions regarding (1) the critical conditions enabling learning, (2) the content of learning, and (3) the rules that translate learning into performance. In one way or another, the separate contributions in this issue address these fundamental questions as they relate to a wide variety of currently exciting topics in the study of the neurobiology of learning and memory.

Deodhar, A. (2013). Update in rheumatology: evidence published in 2012. *Annals of Internal Medicine*, 158(12), 903-906. doi:10.7326/0003-4819-158-12-201306180-00107; 10.7326/0003-4819-158-12-201306180-00107

DeVon, H. A., Rosenfeld, A., & Daya, M. (2013). Cardiac symptoms in women and men. *JAMA Internal Medicine*, 173(20), 1927-1928. doi:10.1001/jamainternmed.2013.9779

Disch, J., Tilden, V., Mason, D. J., Naylor, M., & Cox, K. (2013). Nursing's perspective on the national campaign for choosing wisely. *Nursing Outlook*, 61(6), 471-472. doi:10.1016/j.outlook.2013.10.004

Dobek, J., Winters-Stone, K. M., Bennett, J. A., & Nail, L. (2013). Musculoskeletal changes after 1 year of exercise in older breast cancer survivors. *Journal of Cancer Survivorship : Research and Practice*, doi:10.1007/s11764-013-0313-7

INTRODUCTION: We have previously reported that 1 year of supervised resistance + impact training stopped bone loss and built muscle strength in older breast cancer survivors. The purpose of this study was to determine whether these benefits persisted 1 year after completion of the intervention. METHODS: Sixty-seven women from the original trial completed baseline and post-intervention body composition and muscle strength tests, and 44 women were available 1 year later for follow-up assessments. Bone mineral density (grams per square centimeter) of the hip and spine, muscle mass (kilograms), and fat mass (kilograms) were measured by dual-energy X-ray absorptiometry and maximal upper and lower body strength were measured by one-repetition maximum tests (kilograms). We compared between group changes across baseline (pre-intervention), 1 (post-intervention), and 2 years (1 year follow up) on study outcomes using repeated-measures analysis of covariance, adjusting for age. RESULTS: Significant group by time interactions were found for spine bone mineral density (BMD) ($p < 0.01$) and lower body muscle strength ($p < 0.05$), with a trend for upper body muscle strength ($p = 0.05$). Spine BMD remained stable across intervention and follow-up periods in exercisers compared with continuous losses in controls across 1- and 2-year periods. In contrast, lower body strength increased in exercisers across the intervention, but decreased to near-baseline levels during follow-up compared with no change over either time period in controls. CONCLUSIONS: Our data suggest that spine BMD can be preserved in older breast cancer survivors even after formal exercise training stops; however, muscle strength is not similarly maintained and may require continued participation in a supervised exercise program. IMPLICATIONS FOR CANCER SURVIVORS: Exercise programs aimed at improving musculoskeletal health should be considered in the long-term care plan for breast cancer survivors.

Donaldson, M., & Goodchild, J. H. (2013). Local and systemic effects of mechanico-chemical retraction. *Compendium of Continuing Education in Dentistry (Jamesburg, N.J.: 1995)*, 34(8), 1-8.

The process of recording an acceptable fixed prosthodontic impression must include appropriate

tissue management. This article reviews the effects of mechanical and chemical tissue retraction for fixed prosthodontics, specifically discussing the use of retraction cord with or without chemicals to control sulcular hemorrhage and moisture. Common astringents, hemostatics, and vasoconstrictors used in dentistry as gingival retraction agents are discussed, and recommendations for modification of patient and treatment management are provided.

Donaldson, M., Goodchild, J. H., & Ziegler, J. (2014). Dental considerations for patients taking weight-loss medications. *Journal of the American Dental Association (1939)*, 145(1), 70-74.

doi:10.14219/jada.2013.3; 10.14219/jada.2013.3

BACKGROUND: In this article, the authors examine prescription weight-loss medications and related dental considerations for oral health care professionals (OHCPs). The authors focus on the most common prescription weight-loss drugs and their potential interactions with medications frequently used in dental practice, and they include recommendations for modification in patient care.

METHODS: The authors reviewed the literature regarding interactions between weight-loss drugs and medications commonly used in dentistry, including patient-treatment considerations. They also address the interactions of greatest clinical concern that have a high-quality evidence-based foundation in either randomized controlled clinical trials or meta-analyses.

CONCLUSIONS: Dental treatment can be performed and medications commonly used in dentistry can be administered safely to patients taking orlistat, an inhibitor of fat absorption. The same may not be true, however, for other weight-loss medications that modify the central nervous system neurotransmission of norepinephrine, dopamine or serotonin. OHCPs should be aware of the potential theoretical and pharmacokinetic risks relative to the actual clinical and reported risks for hypertension and cardiotoxicity in particular. Practical Implications Recognition and avoidance of potential weight-loss drug interactions, especially those with medications commonly used in dentistry, can help clinicians optimize patient treatment while emphasizing patient safety.

Dougados, M., Soubrier, M., Antunez, A., Balint, P., Balsa, A., Buch, M. H., . . . Kay, J. (2014).

Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: Results of an international, cross-sectional study (COMORA). *Annals of the Rheumatic Diseases*, 73(1), 62-

68. doi:10.1136/annrheumdis-2013-204223

Background Patients with rheumatoid arthritis (RA) are at increased risk of developing comorbid conditions. Objectives To evaluate the prevalence of comorbidities and compare their management in RA patients from different countries worldwide. Methods Study design: international, cross-sectional. Patients: consecutive RA patients. Data collected: demographics, disease characteristics (activity, severity, treatment), comorbidities (cardiovascular, infections, cancer, gastrointestinal, pulmonary, osteoporosis and psychiatric disorders). Results Of 4586 patients recruited in 17 participating countries, 3920 were analysed (age, 56 ± 13 years; disease duration, 10 ± 9 years (mean \pm SD); female gender, 82%; DAS28 (Disease Activity Score using 28 joints)-erythrocyte sedimentation rate, 3.7 ± 1.6 (mean \pm SD); Health Assessment Questionnaire, 1.0 ± 0.7 (mean \pm SD); past or current methotrexate use, 89%; past or current use of biological agents, 39%. The most frequently associated diseases (past or current) were: depression, 15%; asthma, 6.6%; cardiovascular events (myocardial infarction, stroke), 6%; solid malignancies (excluding basal cell carcinoma), 4.5%; chronic obstructive pulmonary disease, 3.5%. High intercountry variability was observed for both the prevalence of comorbidities and the proportion of subjects complying with recommendations for preventing and managing comorbidities. The systematic evaluation of comorbidities in this study detected abnormalities in vital signs, such as elevated blood pressure in 11.2%, and identified conditions that manifest as laboratory test abnormalities, such as hyperglycaemia in 3.3% and hyperlipidaemia in 8.3%. Conclusions Among RA patients, there is a high prevalence of comorbidities and their risk factors. In this multinational sample, variability among countries was wide, not only in prevalence but also in compliance with recommendations for preventing and managing these comorbidities. Systematic measurement of vital signs and laboratory testing detects otherwise unrecognised comorbid conditions.

Druzinsky, R., Mungall, C., Haendel, M., Lapp, H., & Mabee, P. (2013). What is an anatomy ontology? *Anatomical Record*, 296(12), 1797-1799. doi:10.1002/ar.22805

D'souza, S. L., Elmunzer, B. J., & Scheiman, J. M. (2013). Long-term Follow-up of Asymptomatic Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type I Syndrome. *Journal of*

BACKGROUND AND AIMS:: Pancreatic neuroendocrine tumors (PNETs) in asymptomatic patients may contribute to mortality. Endoscopic ultrasound (EUS) is the most accurate test to identify and monitor tumor size. The aim of this study was to examine the rate of growth and development of new tumors in multiple endocrine neoplasia type I (MEN 1). **MATERIALS AND METHODS::** A retrospective cohort study in a tertiary academic center. Patients identified in endoscopic databases were included if they had 2 or more EUS examinations with untreated asymptomatic tumors identified. The growth rate and incidence of new lesions was analyzed. **RESULTS::** A total of 11 patients were studied (7 female, 4 male). Initially, 18 lesions with an average size of 10.3 mm (range, 5 to 24 mm) were found. Mean surveillance was 79 months (range, 18 to 134 mo). The growth rate of index lesions was 1.32 mm/y; 11 lesions exhibited stability or a decrease in size. Twelve new lesions were identified in 7 patients during the surveillance period with an average growth rate of 3.0 mm/y. The earliest new lesion was identified at 12 months and the latest at 70 months after index EUS. New lesions had a faster growth rate than those seen on initial EUS ($P=0.01$). **CONCLUSIONS::** Multiple endocrine neoplasia type I patients exhibit an overall low rate of growth of pancreatic neuroendocrine tumors. Growth rate of newly diagnosed lesions was significantly faster, suggesting a variation in phenotypic expression of the disease. Therapy should be individualized based upon the tumor size and location, symptoms, overall clinical status, and operative risk.

Dusi, S., Valletta, L., Haack, T. B., Tsuchiya, Y., Venco, P., Pasqualato, S., . . . Tiranti, V. (2013).

Exome Sequence Reveals Mutations in CoA Synthase as a Cause of Neurodegeneration with Brain Iron Accumulation. *American Journal of Human Genetics*, doi:10.1016/j.ajhg.2013.11.008; 10.1016/j.ajhg.2013.11.008

Neurodegeneration with brain iron accumulation (NBIA) comprises a clinically and genetically heterogeneous group of disorders with progressive extrapyramidal signs and neurological deterioration, characterized by iron accumulation in the basal ganglia. Exome sequencing revealed the presence of recessive missense mutations in COASY, encoding coenzyme A (CoA) synthase in one NBIA-affected subject. A second unrelated individual carrying mutations in COASY was identified by Sanger sequence analysis. CoA synthase is a bifunctional enzyme

catalyzing the final steps of CoA biosynthesis by coupling phosphopantetheine with ATP to form dephospho-CoA and its subsequent phosphorylation to generate CoA. We demonstrate alterations in RNA and protein expression levels of CoA synthase, as well as CoA amount, in fibroblasts derived from the two clinical cases and in yeast. This is the second inborn error of coenzyme A biosynthesis to be implicated in NBIA.

Dyer, K. A., & Thompson, C. D. (2001). Medical internet ethics: A field in evolution. *10th World Congress on Medical Informatics, MEDINFO 2001*, London. , 84 1287-1291. doi:10.3233/978-1-60750-928-8-1287

As in any new field, the merger of medicine, e-commerce and the Internet raises many questions pertaining to ethical conduct. Key issues include defining the essence of the patient provider relationship, establishing guidelines and training for practicing online medicine and therapy, setting standards for ethical online research, determining guidelines for providing quality healthcare information and requiring ethical conduct for medical and health websites. Physicians who follow their professional code of ethics are obligated not to exploit the relationship they have with patients, nor allow anyone else working with them to do so. Physicians and therapists are obligated to serve those who place trust in them for treatment, whether in face-to-face or online Internet encounters with patients or clients. This ethical responsibility to patients and clients is often in direct conflict with the business model of generating profits. Healthcare professionals involved in Medical Internet Ethics need to define the scope of competent medical and healthcare on the Internet. The emerging ethical issues facing medicine on the Internet, the current state of medical ethics on the Internet and questions for future directions of study in this evolving field are reviewed in this paper. © 2001 IMIA. All right reserved.

Eichenfield, L. F., Tom, W. L., Chamlin, S. L., Feldman, S. R., Hanifin, J. M., Simpson, E. L., . . .

Sidbury, R. (2013). Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. *Journal of the American Academy of Dermatology*, doi:10.1016/j.jaad.2013.10.010

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults. This guideline addresses important clinical questions that arise

in the management and care of AD, providing updated and expanded recommendations based on the available evidence. In this first of 4 sections, methods for the diagnosis and monitoring of disease, outcomes measures for assessment, and common clinical associations that affect patients with AD are discussed. Known risk factors for the development of disease are also reviewed. © 2013 American Academy of Dermatology, Inc.

Eigenmann, D. E., Xue, G., Kim, K. S., Moses, A. V., Hamburger, M., & Oufir, M. (2013). Comparative study of four immortalized human brain capillary endothelial cell lines, hCMEC/D3, hBMEC, TY10, and BB19, and optimization of culture conditions, for an in vitro blood-brain barrier model for drug permeability studies. *Fluids and Barriers of the CNS*, 10(1) doi:10.1186/2045-8118-10-33

Background: Reliable human in vitro blood-brain barrier (BBB) models suitable for high-throughput screening are urgently needed in early drug discovery and development for assessing the ability of promising bioactive compounds to overcome the BBB. To establish an improved human in vitro BBB model, we compared four currently available and well characterized immortalized human brain capillary endothelial cell lines, hCMEC/D3, hBMEC, TY10, and BB19, with respect to barrier tightness and paracellular permeability. Co-culture systems using immortalized human astrocytes (SVG-A cell line) and immortalized human pericytes (HBPCT cell line) were designed with the aim of positively influencing barrier tightness. Methods: Tight junction (TJ) formation was assessed by transendothelial electrical resistance (TEER) measurements using a conventional epithelial voltohmmeter (EVOM) and an automated CellZscope system which records TEER and cell layer capacitance (CCL) in real-time. Paracellular permeability was assessed using two fluorescent marker compounds with low BBB penetration (sodium fluorescein (Na-F) and lucifer yellow (LY)). Conditions were optimized for each endothelial cell line by screening a series of 24-well tissue culture inserts from different providers. For hBMEC cells, further optimization was carried out by varying coating material, coating procedure, cell seeding density, and growth media composition. Biochemical characterization of cell type-specific transmembrane adherens junction protein VE-cadherin and of TJ proteins ZO-1 and claudin-5 were carried out for each endothelial cell line. In addition, immunostaining for ZO-1 in hBMEC cell line was performed. Results: The four cell lines all expressed the endothelial cell type-specific adherens junction protein VE-cadherin. The TJ protein

ZO-1 was expressed in hCMEC/D3 and in hBMEC cells. ZO-1 expression could be confirmed in hBMEC cells by immunocytochemical staining. Claudin-5 expression was detected in hCMEC/D3, TY10, and at a very low level in hBMEC cells. Highest TEER values and lowest paracellular permeability for Na-F and LY were obtained with mono-cultures of hBMEC cell line when cultivated on 24-well tissue culture inserts from Greiner Bio-one® (transparent PET membrane, 3.0 µm pore size). In co-culture models with SVG-A and HBPCT cells, no increase of TEER could be observed, suggesting that none of the investigated endothelial cell lines responded positively to stimuli from immortalized astrocytic or pericytic cells. Conclusions: Under the conditions examined in our experiments, hBMEC proved to be the most suitable human cell line for an in vitro BBB model concerning barrier tightness in a 24-well mono-culture system intended for higher throughput. This BBB model is being validated with several compounds (known to cross or not to cross the BBB), and will potentially be selected for the assessment of BBB permeation of bioactive natural products. © 2013 Eigenmann et al.; licensee BioMed Central Ltd.

Eisen, G. M., & Hoda, K. M. (2009). *Management of Anticoagulation and Antiplatelet Agents* Wiley-Blackwell. doi:10.1002/9781444316902.ch8

El-Gohary, M., Pearson, S., McNames, J., Mancini, M., Horak, F., Mellone, S., & Chiari, L. (2013).

Continuous monitoring of turning in patients with movement disability. *Sensors (Basel, Switzerland)*, 14(1), 356-369. doi:10.3390/s140100356; 10.3390/s140100356

Difficulty with turning is a major contributor to mobility disability and falls in people with movement disorders, such as Parkinson's disease (PD). Turning often results in freezing and/or falling in patients with PD. However, asking a patient to execute a turn in the clinic often does not reveal their impairments. Continuous monitoring of turning with wearable sensors during spontaneous daily activities may help clinicians and patients determine who is at risk of falls and could benefit from preventative interventions. In this study, we show that continuous monitoring of natural turning with wearable sensors during daily activities inside and outside the home is feasible for people with PD and elderly people. We developed an algorithm to detect and characterize turns during gait, using wearable inertial sensors. First, we validate the turning algorithm in the laboratory against a Motion Analysis system and against a video analysis of 21

PD patients and 19 control (CT) subjects wearing an inertial sensor on the pelvis. Compared to Motion Analysis and video, the algorithm maintained a sensitivity of 0.90 and 0.76 and a specificity of 0.75 and 0.65, respectively. Second, we apply the turning algorithm to data collected in the home from 12 PD and 18 CT subjects. The algorithm successfully detects turn characteristics, and the results show that, compared to controls, PD subjects tend to take shorter turns with smaller turn angles and more steps. Furthermore, PD subjects show more variability in all turn metrics throughout the day and the week.

Eriksson, J. G., Kajantie, E., Lampl, M., Osmond, C., & Barker, D. J. P. (2014). Small head circumference at birth and early age at adiposity rebound. *Acta Physiologica*, *210*(1), 154-160. doi:10.1111/apha.12142

Aims: The adiposity rebound is the age in childhood when body mass index is at a minimum before increasing again. The age at rebound is highly variable. An early age is associated with increased obesity in later childhood and adult life. We have reported that an early rebound is predicted by low weight gain between birth and 1 year of age and resulting low body mass index at 1 year. Here, we examine whether age at adiposity rebound is determined by influences during infancy or is a consequence of foetal growth. Our hypothesis was that measurements of body size at birth are related to age at adiposity rebound. Methods: Longitudinal study of 2877 children born in Helsinki, Finland, during 1934-1944. Results: Early age at adiposity rebound was associated with small head circumference and biparietal diameter at birth, but not with other measurements of body size at birth. The mean age at adiposity rebound rose from 5.8 years in babies with a head circumference of ≤ 33 cm to 6.2 in babies with a head circumference of > 36 cm (P for trend = 0.007). The association between thinness in infancy and early rebound became apparent at 6 months of age. It was not associated with adverse living conditions. In a simultaneous regression, small head circumference at birth, high mother's body mass index and tall maternal stature each had statistically significant trends with early adiposity rebound (P = 0.002, < 0.001 , 0.004). Conclusion: We hypothesize that the small head size at birth that preceded an early adiposity rebound was the result of inability to sustain a rapid intra-uterine growth trajectory initiated in association with large maternal body size. This was followed by

catch-up growth in infancy, and we hypothesize that this depleted the infant's fat stores. © 2013 Scandinavian Physiological Society.

Feigerlova, E., Swinyard, M., Derr, M. A., Farnsworth, J., Andrew, S. F., Rosenfeld, R. G., & Hwa, V. (2013). A Novel GHR Intronic Variant, c.266+83G>T, Activates a Cryptic 5' Splice Site Causing Severe GHR Deficiency and Classical GH Insensitivity Syndrome. *Hormone Research in Paediatrics*, doi:10.1159/000355404

Background/Aims: Mutations in the human growth hormone receptor gene (GHR) are the most common cause of growth hormone insensitivity (GHI) syndrome and insulin-like growth factor (IGF-1) deficiency. The extracellular domain of GHR (encoded by exons 2-7 of the GHR gene) can be proteolytically cleaved to circulate as GH-binding protein (GHBP). Methods: We evaluated the cause of classical GHI (Laron) phenotypes in 3 siblings. Results: Two brothers (aged 16.5 and 14.9 years) and their half-brother (aged 11.3 years) presented with extreme short stature (height standard deviation score, SDS, of -7.05, -6.34 and -8.02, respectively). The parents were consanguineous and of normal stature. Serum GHBP levels of probands were undetectable and circulating IGF-1 and IGF-binding protein-3 were abnormally low, but GH concentrations were elevated. Molecular analysis of the GHR gene revealed homozygous deletion of exon 3, a common polymorphism, and a novel c.266+83G>T variant within intron 4 which generated a 5' donor splice site. Splicing events from this cryptic 5' donor site resulted in retention of 81 intronic nucleotides in the GHR mRNA. Long-term rhIGF-1 therapy combined with leuprolide depot increased height by +2 to +3 SDS. Conclusion: The c.266+83G>T is the second intronic GHR mutation identified that activates a cryptic 5' donor splice site. The abnormal splicing event led to early protein termination and undetectable serum GHBP concentrations. (c) 2013 S. Karger AG, Basel.

Fennerty, M. B. (2007). *Chromoendoscopy in Barrett's Esophagus* Blackwell Publishing Ltd. doi:10.1002/9780470987513.ch14

Fenske, T. S., Zhang, M. J., Carreras, J., Ayala, E., Burns, L. J., Cashen, A., . . . Hari, P. N. (2013). Autologous or Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Sensitive Mantle-Cell Lymphoma: Analysis of Transplantation Timing and

Modality. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, doi:10.1200/JCO.2013.49.2454

PURPOSE: To examine the outcomes of patients with chemotherapy-sensitive mantle-cell lymphoma (MCL) following a first hematopoietic stem-cell transplantation (HCT), comparing outcomes with autologous (auto) versus reduced-intensity conditioning allogeneic (RIC allo) HCT and with transplantation applied at different times in the disease course. **PATIENTS AND METHODS:** In all, 519 patients who received transplantations between 1996 and 2007 and were reported to the Center for International Blood and Marrow Transplant Research were analyzed. The early transplantation cohort was defined as those patients in first partial or complete remission with no more than two lines of chemotherapy. The late transplantation cohort was defined as all the remaining patients. **RESULTS:** Auto-HCT and RIC allo-HCT resulted in similar overall survival from transplantation for both the early (at 5 years: 61% auto-HCT v 62% RIC allo-HCT; $P = .951$) and late cohorts (at 5 years: 44% auto-HCT v 31% RIC allo-HCT; $P = .202$). In both early and late transplantation cohorts, progression/relapse was lower and nonrelapse mortality was higher in the allo-HCT group. Overall survival and progression-free survival were highest in patients who underwent auto-HCT in first complete response. Multivariate analysis of survival from diagnosis identified a survival benefit favoring early HCT for both auto-HCT and RIC allo-HCT. **CONCLUSION:** For patients with chemotherapy-sensitive MCL, the optimal timing for HCT is early in the disease course. Outcomes are particularly favorable for patients undergoing auto-HCT in first complete remission. For those unable to achieve complete remission after two lines of chemotherapy or those with relapsed disease, either auto-HCT or RIC allo-HCT may be effective, although the chance for long-term remission and survival is lower.

Fink, H. A., Kuskowski, M. A., & Marshall, L. M. (2014). Association of stressful life events with incident falls and fractures in older men: The osteoporotic fractures in men (MrOS) Study. *Age and Ageing*, 43(1), 103-108. doi:10.1093/ageing/aft117

Background: small, retrospective studies suggest that major life events and/or sudden emotional stress may increase fall and fracture risk. The current study examines these associations prospectively. **Methods:** a total of 5,152 men aged ≥ 65 years in the Osteoporotic Fractures in Men study self-reported data on stressful life events for 1 year prior to study Visit 2. Incident falls

and fractures were ascertained for 1 year after Visit 2. Fractures were centrally confirmed. Results: a total of 2,932 (56.9%) men reported ≥ 1 type of stressful life event. In men with complete stressful life event, fall and covariate data ($n = 3,949$), any stressful life event was associated with a 33% increased risk of incident fall [relative risk (RR) 1.33, 95% confidence interval (CI) 1.19-1.49] and 68% increased risk of multiple falls (RR = 1.68, 95% CI = 1.40-2.01) in the year following Visit 2 after adjustment for age, education, Parkinson's disease, diabetes, stroke, instrumental activities of daily living (IADL) impairment, chair stand time, walk speed, multiple past falls, depressive symptoms and antidepressant use. Risk increased with the number of types of stressful life events. Though any stressful life event was associated with a 58% increased age-adjusted risk for incident fracture, this association was attenuated and no longer statistically significant after additional adjustment for total hip bone mineral density, fracture after age 50, Parkinson's disease, stroke and IADL impairment. Conclusions: in this cohort of older men, stressful life events significantly increased risk of incident falls independent of other explanatory variables, but did not independently increase incident fracture risk. © The Author 2013. Published by Oxford University Press on behalf of the British Geriatrics Society. All rights reserved.

Fitzgerald, J., Holden, P., & Hansen, U. (2013). The expanded collagen VI family: New chains and new questions. *Connective Tissue Research*, 54(6), 345-350. doi:10.3109/03008207.2013.822865

Collagen VI is a component of the extracellular matrix of almost all connective tissues, including cartilage, bone, tendon, muscles and cornea, where it forms abundant and structurally unique microfibrils organized into different suprastructural assemblies. The precise role of collagen VI is not clearly defined although it is most abundant in the interstitial matrix of tissues and often found in close association with basement membranes. Three genetically distinct collagen VI chains, $\alpha 1(VI)$, $\alpha 2(VI)$ and $\alpha 3(VI)$, encoded by the COL6A1, COL6A2 and COL6A3 genes, were first described more than 20 years ago. Their molecular assembly and role in congenital muscular dystrophy has been broadly characterized. In 2008, three additional collagen VI genes arrayed in tandem at a single gene locus on chromosome 3q in humans, and chromosome 9 in mice, were described. Following the naming scheme for collagens the new genes were designated COL6A4, COL6A5 and COL6A6 encoding the $\alpha 4(VI)$, $\alpha 5(VI)$ and $\alpha 6(VI)$ chains, respectively. This review will

focus on the current state of knowledge of the three new chains. © 2013 Informa Healthcare USA, Inc.

Ford, E. R., & Zeigen, L. (2013). In Woodsworth A., & Penniman W.D.(Eds.), *Interinstitutional library collaboration: Support for a joint master of public health program* doi:10.1108/S0065-2830(2013)0000037007

Library-related and resource access issues confronting students enrolled in an interinstitutional joint master's degree program in public health are addressed in this chapter. It details a cross-institutional collaborative effort to identify and provide research resources to interinstitutional joint degree students and faculty and analyzes the program through the lens of literature on collaboration in higher education and in library instruction. Reports on findings from qualitative feedback and quantitative card sort analysis data were gathered to inform development of content for, and organization of, a library research guide. Bureaucratic structures and policies often affect library services to students and faculty in interinstitutional joint degree programs. Therefore, more salient information about library policies, services, and resources was needed in order for the affected libraries to coordinate instruction, collections, and services to best support such programs. One of the limitations of the case study was that limited qualitative and quantitative feedback was received. Also there was no prior formal needs assessment. Nevertheless, the chapter provides insight to challenges facing libraries and librarians supporting interinstitutional joint degree programs. It also points to administrative opportunities to create rich library collaborations. Existing literature does not adequately address obstacles of in-person interinstitutional joint degree programs. The contribution of this chapter is that it identifies the complications of access, library policies, and administrative procedure that will need to be address by two or more libraries that want to support joint degree programs at the college or university level. © 2013 by Emily R. Ford and Laura Zeigen.

Fox, L., Friedrichsen, L., & Nishiyama, M. (2013). The art of productive meetings. *50th ACM Annual Conference on Special Interest Group on University and College Computing Services, SIGUCCS 2013*, Chicago, IL. 181-183. doi:10.1145/2504776.2504783

Meetings are a necessary part of working in higher education. This presentation will cover the

fine points of planning, preparing, and participating in effective meetings. We will also discuss remote attendance, scheduling, formal vs. informal meetings, and etiquette. Copyright 2013 ACM.

Fraunfelder, F. W. (2007). *Ocular Side Effects of Prescription Medications* John Wiley & Sons, Ltd.
doi:10.1002/9780470059210.ch36

Freeman, M. D., Eriksson, A., & Leith, W. (2014). Head and neck injury patterns in fatal falls:

Epidemiologic and biomechanical considerations. *Journal of Forensic and Legal Medicine*, 21, 64-70. doi:10.1016/j.jflm.2013.08.005; 10.1016/j.jflm.2013.08.005

Fatal falls often involve a head impact, which are in turn associated with a fracture of the skull or cervical spine. Prior authors have noted that the degree of inversion of the victim at the time of impact is an important predictor of the distribution of skull fractures, with skull base fractures more common than skull vault fractures in falls with a high degree of inversion. The majority of fatal fall publications have focused on skull fractures, and no research has described the association between fall circumstances and the distribution of fractures in the skull and neck. In the present study, we accessed data regarding head and neck fractures resulting from fatal falls from a Swedish autopsy database for the years 1992-2010, for the purposes of examining the relationships between skull and cervical spine fracture distribution and the circumstances of the fatal fall. Out of 102,310 medico-legal autopsies performed there were 1008 cases of falls associated with skull or cervical spine fractures. The circumstances of the falls were grouped in 3 statistically homogenous categories; falls occurring at ground level, falls from a height of ≤ 3 m. Only head and neck injuries and fractures that were associated with the fatal CNS injuries were included for study, and categorized as skull vault and skull base fractures, upper cervical injuries (C0-C1 dislocation, C1 and C2 fractures), and lower cervical fractures. Logistic regression modeling revealed increased odds of skull base and lower cervical fracture in the middle and upper fall severity groups, relative to ground level falls (lower cervical ≤ 3 m falls, OR = 2.23 [0.98, 5.08]; skull base ≤ 3 m falls, OR = 2.30 [1.55, 3.40]). C0-C1 dislocations were strongly related to fall height, with an OR of 8.3 for $> \leq 3$ m falls versus ground level. The findings of increased odds of skull base and lower cervical spine fracture in falls from a height are consistent

with prior observations that the risk of such injuries is related to the degree of victim inversion at impact. The finding that C0-C1 dislocations are most common in falls from more than 3 m is unique, an indication that the injuries likely result from high energy shear forces rather than pure tension, as previously thought.

Furukawa, R., Driessnack, M., & Colclough, Y. (2013). A committee approach maintaining cultural originality in translation. *Applied Nursing Research : ANR*, doi:10.1016/j.apnr.2013.11.011; 10.1016/j.apnr.2013.11.011

Various methods have been used to translate existing assessment tools and clinical nursing materials from one language to another. The method of choice depends on the research objectives, availability of translators, budget, and time. We highlight our experience using the committee approach to translation. This less commonly used approach introduces the concept of cultural consensus building early in the translation process, which is particularly appropriate when languages are culturally and linguistically distant. Our experience centers on the translation of the Primary Communication Inventory (PCI), from English to Japanese, to study first-time parents in Japan.

Galon, J., Mlecnik, B., Bindea, G., Angell, H. K., Berger, A., Lagorce, C., . . . Pagès, F. (2014).

Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. *Journal of Pathology*, 232(2), 199-209. doi:10.1002/path.4287

The American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TNM staging system provides the most reliable guidelines for the routine prognostication and treatment of colorectal carcinoma. This traditional tumour staging summarizes data on tumour burden (T), the presence of cancer cells in draining and regional lymph nodes (N) and evidence for distant metastases (M). However, it is now recognized that the clinical outcome can vary significantly among patients within the same stage. The current classification provides limited prognostic information and does not predict response to therapy. Multiple ways to classify cancer and to distinguish different subtypes of colorectal cancer have been proposed, including morphology, cell origin, molecular pathways, mutation status and gene expression-based stratification. These parameters rely on tumour-cell characteristics. Extensive literature has

investigated the host immune response against cancer and demonstrated the prognostic impact of the in situ immune cell infiltrate in tumours. A methodology named 'Immunoscore' has been defined to quantify the in situ immune infiltrate. In colorectal cancer, the Immunoscore may add to the significance of the current AJCC/UICC TNM classification, since it has been demonstrated to be a prognostic factor superior to the AJCC/UICC TNM classification. An international consortium has been initiated to validate and promote the Immunoscore in routine clinical settings. The results of this international consortium may result in the implementation of the Immunoscore as a new component for the classification of cancer, designated TNM-I (TNM-Immune). © 2013 The Authors. Journal of Pathology published by John Wiley & Sons Ltd on behalf of Pathological Society of Great Britain and Ireland. © 2013 The Authors. Journal of Pathology published by John Wiley & Sons Ltd on behalf of Pathological Society of Great Britain and Ireland.

Garami, A., Almeida, M. C., Nucci, T. B., Hew-Butler, T., Soriano, R. N., Pakai, E., . . . Romanovsky, A. A. (2010). *The TRPV1 Channel in Normal Thermoregulation: What Have We Learned from Experiments Using Different Tools?* John Wiley & Sons, Inc. doi:10.1002/9780470588284.ch14

Gatzoulis, M. A., Swan, L., Therrien, J., & Pantely, G. A. (2007). *Adult Congenital Heart Disease: A Practical Guide* Blackwell Publishing Ltd. doi:10.1002/9780470750544

Congenital heart disease with its worldwide incidence of 1% is the most common inborn defect. Increasingly, patients are living into adulthood, with ongoing congenital heart and other medical needs. Sadly, only a small minority have specialist follow-up. However, all patients see their family doctor and may also seek advice from other health professionals. This practical guide with its straightforward a,b,c approach is written for those professionals. Special features of this book:

- Introduces the principles of congenital heart disease and tells you whom and when to refer for specialist care
- Discusses common congenital heart lesions in a practical, easy-to-follow way, with an emphasis on diagnosis and management issues
- Includes an extensive chapter on 'Pregnancy and Contraception' (by Philip J. Steer), essential both for family planning and for managing safely the pregnant woman with congenital heart disease
- Includes chapters on non-cardiac surgery and lifestyle issues such as work, insurability, travel and driving
- Provides invaluable information on dealing with common emergencies; what to do and what not to do

With

a wealth of illustrations (including diagrams, EKGs, CXRs, Echos and cardiac MRIs) and with key point tables, this is an essential guide for all health care professionals managing patients with adult congenital heart disease. © 2005 by Blackwell Publishing Ltd.

Gatzoulis, M. A., Swan, L., Therrien, J., & Pantely, G. A. (2007). Preface. *Adult Congenital Heart Disease: A Practical Guide*, doi:10.1002/9780470750544

Gerber, L. M., Chiu, Y. -, Carney, N., Härtl, R., & Ghajar, J. (2013). Marked reduction in mortality in patients with severe traumatic brain injury: Clinical article. *Journal of Neurosurgery*, 119(6), 1583-1590. doi:10.3171/2013.8.JNS13276

Object. In spite of evidence that use of the Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury (Guidelines) would dramatically reduce morbidity and mortality, adherence to these Guidelines remains variable across trauma centers. The authors analyzed 2-week mortality due to severe traumatic brain injury (TBI) from 2001 through 2009 in New York State and examined the trends in adherence to the Guidelines. Methods. The authors calculated trends in adherence to the Guidelines and age-adjusted 2-week mortality rates between January 1, 2001, and December 31, 2009. Univariate and multivariate logistic regression analyses were performed to evaluate the effect of time period on case-fatality. Intracranial pressure (ICP) monitor insertion was modeled in a 2-level hierarchical model using generalized linear mixed effects to allow for clustering by different centers. Results. From 2001 to 2009, the case-fatality rate decreased from 22% to 13% ($p < 0.0001$), a change that remained significant after adjusting for factors that independently predict mortality (adjusted OR 0.52, 95% CI 0.39-0.70; $p < 0.0001$). Guidelines adherence increased, with the percentage of patients with ICP monitoring increasing from 56% to 75% ($p < 0.0001$). Adherence to cerebral perfusion pressure treatment thresholds increased from 15% to 48% ($p < 0.0001$). The proportion of patients having an ICP elevation greater than 25 mm Hg dropped from 42% to 29% ($p = 0.0001$). Conclusions. There was a significant reduction in TBI mortality between 2001 and 2009 in New York State. Increase in Guidelines adherence occurred at the same time as the pronounced decrease in 2-week mortality and decreased rate of intracranial hypertension, suggesting a causal relationship between Guidelines adherence and improved outcomes. Our

findings warrant future investigation to identify methods for increasing and sustaining adherence to evidence-based Guidelines recommendations. ©AANS, 2013.

Gold, R., Whitlock, E. P., Patnode, C. D., Mcginnis, P. S., Buckley, D. I., & Morris, C. (2013).

Prioritizing research needs based on a systematic evidence review: A pilot process for engaging stakeholders. *Health Expectations*, 16(4), 338-350. doi:10.1111/j.1369-7625.2011.00716.x

Background/context Systematic evidence reviews (SERs) identify knowledge gaps in the literature, a logical starting place for prioritizing future research. Varied methods have been used to elicit diverse stakeholders' input in such prioritization. Objective To pilot a simple, easily replicable process for simultaneously soliciting consumer, clinician and researcher input in the identification of research priorities, based on the results of the 2009 SER on screening adults for depression in primary care. Methods We recruited 20 clinicians, clinic staff, researchers and patient advocates to participate in a half-day event in October 2009. We presented SER research methods and the results of the 2009 SER. Participants took part in focus groups, organized by profession; broad themes from these groups were then prioritized in a formal exercise. The focus group content was also subsequently analysed for specific themes. Results Focus group themes generally reacted to the evidence presented; few were articulated as research questions. Themes included the need for resources to respond to positive depression screens, the impact of depression screening on delivery systems, concerns that screening tools do not address comorbid or situational causes of depression and a perceived 'disconnect' between screening and treatment. The two highest-priority themes were the system effects of screening for depression and whether depression screening effectively leads to improved treatment. Conclusion We successfully piloted a simple, half-day, easily replicable multi-stakeholder engagement process based on the results of a recent SER. We recommend a number of potential improvements in future endeavours to replicate this process. © 2011 John Wiley & Sons Ltd.

Greenstein, A. J., Dolan, J. P., & Hunter, J. G. (2011). *Surgical management of non-acid reflux unresponsive to medical therapy* Springer London. doi:10.1007/978-1-84996-492-0_29

Gastroesophageal reflux disease (GERD), the most common upper gastrointestinal disorder in the United States, is typically treated medically. Referral for surgery has traditionally been reserved

for those with complications of reflux, inability to tolerate medication or refractory symptoms despite medication. With the evolution of laparoscopic antireflux surgery (LARS) as a durable, safe and successful option, confidence in the procedure has increased and its popularity has risen to the point that it is considered a reasonable alternative to chronic medical therapy when performed by experienced surgeons.^{1,2} In order to maintain viability of this surgical option, good outcomes must be maintained, one aspect of which is appropriate patient selection. © Springer-Verlag London Limited 2011.

Gupta, S., & Casterella, P. J. (2009). *Antiplatelet Therapy Resistance: Definition, Diagnosis, and Clinical Implications* Wiley-Blackwell. doi:10.1002/9781444306347.ch37

Gustafson, E. C., Morgans, C. W., Tekmen, M., Sullivan, S. J., Esguerra, M., Konno, R., & Miller, R. F. (2013). Retinal NMDA receptor function and expression are altered in a mouse lacking D-amino acid oxidase. *Journal of Neurophysiology*, *110*(12), 2718-2726. doi:10.1152/jn.00310.2013

D-serine is present in the vertebrate retina and serves as a coagonist for the N-methyl-D-aspartate (NMDA) receptors of ganglion cells. Although the enzyme D-amino acid oxidase (DAO) has been implicated as a pathway for D-serine degradation, its role in the retina has not been established. In this study, we investigated the role of DAO in regulating D-serine levels using a mutant mouse line deficient in DAO (ddY/DAO⁻) and compared these results with their wild-type counterparts (ddY/DAO⁺). Our results show that DAO is functionally present in the mouse retina and normally serves to reduce the background levels of D-serine. The enzymatic activity of DAO was restricted to the inner plexiform layer as determined by histochemical analysis. Using capillary electrophoresis, we showed that mutant mice had much higher levels of D-serine. Whole cell recordings from identified retinal ganglion cells demonstrated that DAO-deficient animals had light-evoked synaptic activity strongly biased toward a high NMDA-to-AMPA receptor ratio. In contrast, recordings from wild-type ganglion cells showed a more balanced ratio between the two receptor subclasses. Immunostaining for AMPA and NMDA receptors was carried out to compare the two receptor ratios by quantitative immunofluorescence. These studies revealed that the mutant mouse had a significantly higher representation of NMDA receptors compared with the wild-type controls. We conclude that 1) DAO is an important regulatory enzyme and normally

functions to reduce D-serine levels in the retina, and 2) D-serine levels play a role in the expression of NMDA receptors and the NMDA-to-AMPA receptor ratio. © 2013 the American Physiological Society.

Guydish, J., Campbell, B. K., Manuel, J. K., Delucchi, K. L., Le, T., Peavy, K. M., & McCarty, D. (2014).

Does treatment fidelity predict client outcomes in 12-Step Facilitation for stimulant abuse? *Drug and Alcohol Dependence*, *134*, 330-336. doi:10.1016/j.drugalcdep.2013.10.020;

10.1016/j.drugalcdep.2013.10.020

OBJECTIVE: This study examined the relationships between treatment fidelity and treatment outcomes in a community-based trial of a 12-Step Facilitation (TSF) intervention. METHOD: In a prior multi-site randomized clinical trial, 234 participants in 10 outpatient drug treatment clinics were assigned to receive the Stimulant Abuser Groups to Engage in 12-Step (STAGE-12) intervention. A secondary analysis reviewed and coded all STAGE-12 sessions for fidelity to the protocol, using the Twelve Step Facilitation Adherence Competence Empathy Scale (TSF ACES). Linear mixed-effects models tested the relationship between three fidelity measures (adherence, competence, empathy) and six treatment outcomes (number of days of drug use and five Addiction Severity Index (ASI) composite scores) measured at 3 months post-baseline. RESULTS: Adherence, competence and empathy were robustly associated with improved employment status at follow up. Empathy was inversely associated with drug use, as was competence in a non-significant trend ($p=.06$). Testing individual ASI drug composite score items suggested that greater competence was associated with fewer days of drug use and, at the same time, with an increased sense of being troubled or bothered by drug use. CONCLUSIONS: Greater competence and empathy in the delivery of a TSF intervention were associated with better drug use and employment outcomes, while adherence was associated with employment outcomes only. Higher therapist competence was associated with lower self-report drug use, and also associated with greater self-report concern about drug use. The nature of TSF intervention may promote high levels of concern about drug use even when actual use is low.

Hameed, N., Yedinak, C. G., Brzana, J., Gultekin, S. H., Coppa, N. D., Dogan, A., . . . Fleseriu, M.

(2013). Remission rate after transsphenoidal surgery in patients with pathologically confirmed

Cushing's disease, the role of cortisol, ACTH assessment and immediate reoperation: A large single center experience. *Pituitary*, 16(4), 452-458. doi:10.1007/s11102-012-0455-z

Postoperative serum cortisol is used as an indicator of Cushing's disease (CD) remission following transsphenoidal surgery (TSS) and guides (controversially) the need for immediate adjuvant treatment for CD. We investigated postoperative cortisol and adrenocorticotrophic hormone (ACTH) levels as predictors of remission/recurrence in CD in a large retrospective cohort of patients with pathologically confirmed CD, over 6 years at a single institution. Midnight and morning cortisol, and ACTH at 24-48 h postoperatively (>24 h after last hydrocortisone dose) were measured. Remission was defined as normal 24-h urine free cortisol, normal midnight salivary cortisol, a normal dexamethasone-corticotropin releasing hormone (CRH) test or continued need for hydrocortisone, assessed periodically. Statistical analysis was performed using PASW 18. Follow up data was available for 52 patients (38 females and 14 males), median follow up was 16.5 month (range 2-143 months), median age was 45 years (range 21-72 years), 28 tumors were microadenomas and 16 were macroadenomas, and in eight cases no tumor was observed on magnetic resonance imaging. No patient with postoperative cortisol levels >10 mcg/dl were found to be in remission. Ten of the 52 patients with cortisol >10 mcg/dl by postoperative day 1-2 underwent a second TSS within 7 days. Forty-three patients (82.7 %) achieved CD remission (36 after one TSS and 7 after a second early TSS) and six patients suffered disease recurrence (mean 39.2 ± 52.4 months). An immediate second TSS induced additional hormonal deficiencies (diabetes insipidus) in three patients with no surgical complications. Persistent disease was noted in nine patients despite three patients having an immediate second TSS. Positive predictive value for remission of cortisol 10 mcg/dl were observed to have delayed remission; all required additional treatment. There was no significant difference in age, body mass index, tumor size and length of follow-up between postoperative cortisol groups: cortisol ≤2 mcg/dl, cortisol >5 mcg/dl and cortisol >10 mcg/dl. Immediate postoperative cortisol levels should routinely be obtained in CD patients post TSS, until better tools to identify early remission are available. Immediate repeat TSS could be beneficial in patients with cortisol >10 mcg/dl and positive CD pathology: our combined (micro- and macroadenomas) remission rate with this approach was 82.7 %. ACTH measurements correlate well with cortisol. However, because no single cortisol or ACTH cutoff value excludes all

recurrences, patients require long-term clinical and biochemical follow-up. Further research is needed in this area. © 2012 Springer Science+Business Media New York.

Hamilton, B., Liu, S., Simon, J. H., & Bourdette, D. (2013). Response to comment on letter for Prevalence of brain magnetic resonance imaging meeting Barkhof and Mc Donald criteria for dissemination in space among headache patients. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, doi:10.1177/1352458513515960

Handel, D. J., Kleit, S. A., & Handel, D. A. (2013). The Development and Maturation of a Statewide Academic Health Care System: Clarian Health Partners/Indiana University Health. *Academic Medicine : Journal of the Association of American Medical Colleges*, doi:10.1097/ACM.0000000000000093

As health care reform continues, health care organizations are evolving both structurally and operationally to position themselves to meet the challenges ahead. Academic medical centers (i.e., teaching hospitals) particularly need an effective strategy that will allow them to meet their tripartite missions in patient care, education, and research in this time of increasing competition and resource constraints. Clarian Health Partners, recently renamed Indiana University Health, is a health care entity that developed from a partnership of the Indiana University Hospitals and Methodist Hospital of Indiana. This case study explores the history behind the development of Clarian Health Partners, the model employed, and the lessons learned. It discusses the governance and management models implemented, the steps taken to integrate the two partners in the new system, and the specific challenges of physician partnerships and collaborations. As mergers and consolidations continue in an era of health care reform, the lessons learned from previous endeavors, such as that of Clarian Health Partners, may be applicable.

Hanna, C. B., & Hennebold, J. D. (2014). Ovarian germline stem cells: an unlimited source of oocytes? *Fertility and Sterility*, 101(1), 20-30. doi:10.1016/j.fertnstert.2013.11.009; 10.1016/j.fertnstert.2013.11.009

While there has been progress in directing the development of embryonic stem cells and induced pluripotent stem cells toward a germ cell state, their ability to serve as a source of functional oocytes in a clinically relevant model or situation has yet to be established. Recent studies

suggest that the adult mammalian ovary is not endowed with a finite number of oocytes, but instead possesses stem cells that contribute to their renewal. The ability to isolate and promote the growth and development of such ovarian germline stem cells (GSCs) would provide a novel means to treat infertility in women. Although such ovarian GSCs are well characterized in nonmammalian model organisms, the findings that support the existence of adult ovarian GSCs in mammals have been met with considerable evidence that disputes their existence. This review details the lessons provided by model organisms that successfully utilize ovarian GSCs to allow for a continual and high level of female germ cell production throughout their life, with a specific focus on the cellular mechanisms involved in GSC self-renewal and oocyte development. Such an overview of the role that oogonial stem cells play in maintaining fertility in nonmammalian species serves as a backdrop for the data generated to date that supports or disputes the existence of GSCs in mammals as well as the future of this area of research in terms of its potential for any application in reproductive medicine.

Harding, C. O. (2013). Seeking a cure for the royal pain. *Human Gene Therapy*, 24(12), 968-969.
doi:10.1089/hum.2013.2522; 10.1089/hum.2013.2522

Harper, L. M., Caughey, A. B., Roehl, K. A., Odibo, A. O., & Cahill, A. G. (2013). Defining an Abnormal First Stage of Labor based on Maternal and Neonatal Outcomes. *American Journal of Obstetrics and Gynecology*, doi:10.1016/j.ajog.2013.12.027; 10.1016/j.ajog.2013.12.027

OBJECTIVE: To determine the threshold for defining abnormal labor that is associated with adverse maternal and neonatal outcomes. STUDY DESIGN: Retrospective cohort of all consecutive women admitted ≥ 37.0 weeks gestation from 2004-2008 who reached the second stage of labor. The 90th, 95th, and 97th percentile for progress in first stage of labor was determined specific for parity & labor onset. Women with first stage above & below each centile were compared. Maternal outcomes were cesarean delivery in second stage, operative delivery, prolonged second stage, post-partum hemorrhage, & maternal fever. Neonatal outcomes were a composite of: admission to level 2 or 3 nursery, 5-minute Apgar ≤ 97 th percentile. Longer labors were associated with an increased risk of prolonged second stage, maternal fever, the composite neonatal outcome, shoulder dystocia and admission to level 2 or 3 nursery ($p < 0.01$). Depending

on the cutoff used, 29-30 cesarean deliveries would need to be performed to prevent one shoulder dystocia. CONCLUSIONS: Although women who experience labor dystocia may ultimately deliver vaginally, a longer first stage of labor is associated with adverse maternal and neonatal outcomes, in particular shoulder dystocia. This risk must be balanced against the risks of cesarean delivery for labor arrest.

Hartung, D. M., Middleton, L., McFarland, B. H., Haxby, D. G., McDonagh, M. S., & McConnell, J. (2013). Use of administrative data to identify off-label use of second-generation antipsychotics in a medicaid population. *Psychiatric Services, 64*(12), 1236-1242. doi:10.1176/appi.ps.005482012

Objective: The use of second-generation antipsychotics for conditions not approved by the U.S. Food and Drug Administration (FDA) is a prevalent phenomenon with important implications. The objective of this study was to determine the accuracy of administrative claims for identifying off-label use of second-generation antipsychotics in a Medicaid population in 2009. Methods: The authors estimated the sensitivity, specificity, positive predictive values (PPV), and negative predictive values of Medicaid claims data for detecting off-label use of second-generation antipsychotics in the electronic health records of 788 patients. Separate estimates were calculated for patients without schizophrenia and bipolar disorder, the two most long-standing FDA indications for use of second-generation antipsychotics, and for a subset of patients using a second-generation antipsychotic with indications for treatment-resistant depression. Results: Medicaid claims determined a lack of schizophrenia and bipolar disorder in the medical record with a sensitivity of 72% and a specificity of 85%. The prevalence of identifying neither diagnosis was 83%, which was associated with a predictive ability (PPV) of 96%. Among those using a second-generation antipsychotic with an indication for treatment-resistant depression, the sensitivity, specificity, and PPV of Medicaid claims for identifying off-label use were 41%, 86%, and 87%, respectively. Conclusions: Medicaid claims data had high predictive ability for identifying users of second-generation antipsychotics who did not have documentation of schizophrenia or bipolar disorder in the medical record. The predictive utility of the claims was diminished when the analyses were limited to patients using a second-generation antipsychotic with an indication for treatment-resistant depression.

Haviland, J. A., Reiland, H., Butz, D. E., Tonelli, M., Porter, W. P., Zucchi, R., . . . Assadi-Porter, F. M.

(2013). NMR-based metabolomics and breath studies show lipid and protein catabolism during low dose chronic T1AM treatment. *Obesity*, 21(12), 2538-2544. doi:10.1002/oby.20391

Objective 3-Iodothyronamine (T1AM), an analog of thyroid hormone, is a recently discovered fast-acting endogenous metabolite. Single high-dose treatments of T1AM have produced rapid short-term effects, including a reduction of body temperature, bradycardia, and hyperglycemia in mice. Design and Methods The effect of daily low doses of T1AM (10 mg/kg) for 8 days on weight loss and metabolism in spontaneously overweight mice was monitored. The experiments were repeated twice (n = 4). Nuclear magnetic resonance (NMR) spectroscopy of plasma and real-time analysis of exhaled ¹³CO₂ in breath by cavity ring down spectroscopy (CRDS) were used to detect T1AM-induced lipolysis. Results CRDS detected increased lipolysis in breath shortly after T1AM administration that was associated with a significant weight loss but independent of food consumption. NMR spectroscopy revealed alterations in key metabolites in serum: valine, glycine, and 3-hydroxybutyrate, suggesting that the subchronic effects of T1AM include both lipolysis and protein breakdown. After discontinuation of T1AM treatment, mice regained only 1.8% of the lost weight in the following 2 weeks, indicating lasting effects of T 1AM on weight maintenance. Conclusions CRDS in combination with NMR and ¹³C-metabolic tracing constitute a powerful method of investigation in obesity studies for identifying in vivo biochemical pathway shifts and unanticipated debilitating side effects. Copyright © 2013 The Obesity Society.

He, G. -. (2006). *Arterial grafting for coronary artery bypass surgery: Second edition* Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8

The second edition of this book provides updated knowledge about the biological characteristics and clinical use of arterial grafts for coronary artery bypass surgery. The reader will find first-hand information on arterial grafts as well as vein grafts with regard to biological characteristics, clinical use including off-pump coronary bypass grafting surgery, results, and future developments. Written by world-renowned cardiac surgeons and cardiovascular research scientists working in this area, the book will be invaluable both as a practical guide and as a stimulus for further improvement of arterial grafting techniques and technology. © Springer-Verlag Berlin Heidelberg 2006. All rights are reserved.

He, G. -. (2006). *Considerations in the choice of arterial grafts* Springer Berlin Heidelberg.

doi:10.1007/3-540-30084-8_9

Various arterial grafts have been used for coronary artery bypass grafting (CABG), but a unanimous opinion as to the best use of these grafts has not yet been formed, except for the internal mammary artery (IMA), which has been accepted as the first choice, usually for the left anterior descending artery (LAD) if the artery needs to be grafted [1, 2]. As to the patency of the right internal mammary artery (RIMA), early reports gave conflicting results: the angiographic patency was 98% for the RIMA and 93% for the LIMA in 50 patients [3], pedicled RIMA patency rates equaled those of pedicled LIMA (95.1 vs 96.7, NS) and the grafted vessel did not alter the patency rates of IMA [4]. Dietl [5] reported that the prevalence of perioperative myocardial infarction in the right coronary artery distribution was significantly higher, and the reoperation rate for graft failure and the prevalence of deep sternal wound infection in diabetics was significantly higher for RIMA than for the right gastroepiploic artery (GEA). However, the most recent reports from large series in Melbourne in 2,127 arterial to coronary conduits over 15 years clearly showed [6] that the LIMA patency at 5 years was 98%, at 10 years it was 95%, and at 15 years it was 88%. The right internal thoracic artery (RITA) patency at 5 years was 96%, at 10 years it was 81%, and at 15 years it was 65%, and the interval from operation to angiogram was not associated with IMA patency (96% patency for LITA and 88% patency for RITA, remaining stable when studied at ≤ 1 , 1-4, 5-9, 10-14 and 15 years) [7]. Based on the superior long-term results of the IMA [1, 2], other arteries have been used in CABG [8-14]. Such conduits include the radial artery [8], the GEA [9], the inferior epigastric artery (IEA) [10, 11], the splenic artery [12], the subscapular artery [13], and the inferior mesenteric artery [14], the descending branch of the lateral femoral circumflex artery [15], and the ulnar artery [16]. In addition, the intercostal artery [17] has also been suggested to be used as a graft. The long-term patency rates for IMA are well established as mentioned above. Although there are few reports on other arterial conduits with a relatively small number of patients, the long-term patencies for GEA and radial artery (RA) have recently been established. Suma [18, 19] recently reported that the cumulative patency rate estimated by the Kaplan-Meier method for GEA was 96.6% at 1 month, 91.4% at 1 year, 80.5% at 5 years, and 62.5% at 10 years. Causes of late occlusion were primary anastomotic stenosis and anastomosis to a less critically stenosed coronary artery. Voutilainers

and associates [20] reported that 82.1%(23/26) of the GEA grafts were patent at 5 years. From these studies, the patency of the GEA, as a Type II artery, is acceptable but not as superior as the IMA, the patency of which was 95%at 10 years and 88% at 15 years [21]. The patency rate of the RA is more dramatic. There was a disappointing 35%incidence of narrowing or occlusion of the RA [22].With modified technique, avoiding skeletonization and using calcium antagonists, the early patency increased to 93.5% at 9 months in Acar's group [23] and to 93.1-95.7% in other groups [24, 25] at 3-21 months in the early stage of the use of RA. Latterly, Acar and colleagues reported that the patency rate of the radial artery grafts was 83% at 5 years [26]. In addition, Tatoulis and associates reported that the radial artery patency at 1 year was 96%and at 4 years it was 89%[6]. Interestingly, similar to the right IMA, for the radial artery there was a higher patency with greater coronary stenosis. Arterial grafts are not uniform in their biological characteristics (see Chaps. 3, 4). The difference in the perioperative behavior of the grafts and in the longterm patency may be related to different characteristics. These should be taken into account in the use of arterial grafts, some of which are subjected to more active pharmacological intervention during and after operation to obtain satisfactory results. Clinical choice of graftsmust be based on the general condition of the patient, the biological characteristics of the graft, the anatomy of the coronary artery, the match between the coronary artery and the graft, and the technical considerations including antispastic management. © Springer-Verlag Berlin Heidelberg 2006.

He, G. -. (2006). *Endothelial function and interaction between the endothelium and smooth muscle in arterial grafts* Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8_2

He, G. -. (2006). Preface. *Arterial Grafting for Coronary Artery Bypass Surgery: Second Edition*, IX-X. doi:10.1007/3-540-30084-8

He, G. -. (2006). *Role of venous grafts in combination with arterial grafting* Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8_38

Since the first successful coronary artery bypass grafting (CABG) was performed using a saphenous vein graft at the Cleveland Clinic, the saphenous vein has become widely used as a coronary artery bypass graft [1]. From 1968, the internal mammary artery (IMA) became more

widely applied as new surgical techniques evolved. Green [2] and Favaloro [3, 4] used a combination of single and bilateral IMA grafting, alone and in combination with saphenous vein grafting (SVG). However, the patency rates of SVG in the early reports were unsatisfactory. The occlusion rate of SVG in the first year is 10~26% [5, 6]. By 10 years, 50% of grafts are occluded [7-9] and of the grafts still patent, 50% show marked atherosclerotic changes [7]. In contrast, in an early study, the patency of the IMA within 5 years of operation was 97% with only 2% occlusion and 2% stenosis, compared to the patency rate of 82%, 5% stenosis or irregular, and 13% occlusion in SVG [9]. These reports confirmed the superior patency of arterial grafting and promoted the search for arterial conduits other than the IMA. Most recent reports from large series continuously support the superiority of IMA grafting. A report by Tatoulis and colleagues in Melbourne [10] has clearly shown in 2,127 arterial to coronary conduits over 15 years a LIMA patency at 5 years of 98%, 95% at 10 years, and 88% at 15 years. On the other hand, the average number of grafts in a patient is 3~4. Although the LIMA has been established as the first choice of the graft for coronary artery, other arterial grafts such as the right IMA, the gastroepiploic artery (GEA), the inferior epigastric artery (IEA), and the radial artery (RA) are routinely used by fewer surgeons. This means that SVG is still widely used in combination with arterial grafts. Recognizing the lower patency of SVG compared to arterial grafts, surgeons are more cautious with the protection of the SVG during harvesting and in the careful choice of the target vessel. A number of techniques have been developed to protect the graft particularly the endothelium of the graft [11]. With these improved techniques, the patency rate for SVG has been reported to be better than that reported previously. Further, with the most important coronary branch - the LAD grafted by LIMA, the SVG is often grafted to other branches. Under such circumstances, the patient's survival is improved [12]. The role of SVG in the current practice of CABG should therefore be updated. © Springer-Verlag Berlin Heidelberg 2006.

He, G. -, & Yang, C. -. (2006). *Clinical classification of arterial grafts* Springer Berlin Heidelberg.
doi:10.1007/3-540-30084-8_4

Various arterial grafts have been used for coronary artery bypass grafting. However, except for the internal mammary artery (IMA), which has been regarded as the choice for left anterior descending artery (LAD) grafting, so far there is no unanimous opinion as to the best use of other

grafts. Arterial grafts, on the one hand, are all conductance arteries and therefore have features in common compared with venous grafts (see Chap. 3). On the other hand, they are found in different parts of the body and have a different physiological role because the organs they perfuse have a different physiological role. To meet the physiological requirements, these arteries have a different anatomic structure (see Chap. 1) and a different physiological and pharmacological reactivity to vasoactive substances. Furthermore, they are of different embryological origin [1]. Arterial grafts are therefore not uniform in their biological characteristics. As discussed in Chap. 3, the difference in the perioperative behavior of the grafts and in the long-term patency may be related to different characteristics. These should be taken into account in the use of arterial grafts, some of which require more active pharmacological intervention during and after operation to obtain satisfactory results. To better understand the biological behavior of the grafts, their common features and differences, a clinical classification may be useful for the practicing surgeon. © Springer-Verlag Berlin Heidelberg 2006.

He, G. -, & Yang, C. -. (2006). *Pharmacological studies and guidelines for the use of vasodilators for arterial grafts* Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8_5

Heeman, P. A., Meshorer, T., Kun, A. L., Palinko, O., & Medenica, Z. (2013). Estimating cognitive load using pupil diameter during a spoken dialogue task. *5th International Conference on Automotive User Interfaces and Interactive Vehicular Applications, AutomotiveUI 2013*, Eindhoven. 242-245. doi:10.1145/2516540.2516570

We explore the feasibility of using pupil diameter to estimate how the cognitive load of the driver changes during a spoken dialogue task with a remote conversant. The conversants play a series of Taboo games, which do not follow a structured turn-taking nor initiative protocol. We contrast the driver's pupil diameter when the remote conversant begins speaking with the diameter right before the driver responds. Although we find a significant difference in pupil diameter for the first pair in each game, subsequent pairs show little difference. We speculate that this is due to the less structured nature of the task, where there are no set time boundaries on when the conversants work on the task. This suggests that spoken dialogue systems for in-car use might

better manage the driver's cognitive load by using a more structured interaction, such as system-initiative dialogues. © 2013 ACM.

Hersh, W., Junium, K., Mailhot, M., & Tidmarsh, P. (2001). Implementation and evaluation of a distance learning introductory course in medical informatics. *10th World Congress on Medical Informatics, MEDINFO 2001*, London, , 84 1023-1027. doi:10.3233/978-1-60750-928-8-1023

Context: There is a growing interest in and need for continuing education in medical informatics delivered by distance learning. Objectives: Implement and evaluate a distance learning introductory course in medical informatics. Methods: A Web-based version of our on-campus 'Introduction to Medical Informatics' course was implemented using streaming audio lectures, threaded discussion boards, and several other teaching modalities. Evaluation was performed using an adaptation of our on-campus course evaluation instrument. Results: The course was implemented with no major technological or pedagogical problems. Student satisfaction with teaching modalities and other course modalities was high. Conclusions: The learning technologies used in this course were implemented successfully and a Graduate Certificate Program is planned to further meet educational needs in medical informatics. © 2001 IMIA. All right reserved.

Herting, M. M., Colby, J. B., Sowell, E. R., & Nagel, B. J. (2013). White matter connectivity and aerobic fitness in male adolescents. *Developmental Cognitive Neuroscience, 7C*, 65-75. doi:10.1016/j.dcn.2013.11.003; 10.1016/j.dcn.2013.11.003

Exercise has been shown to have positive effects on the brain and behavior throughout various stages of the lifespan. However, little is known about the impact of exercise on neurodevelopment during the adolescent years, particularly with regard to white matter microstructure, as assessed by diffusion tensor imaging (DTI). Both tract-based spatial statistics (TBSS) and tractography-based along-tract statistics were utilized to examine the relationship between white matter microstructure and aerobic exercise in adolescent males, ages 15-18. Furthermore, we examined the data by both (1) grouping individuals based on aerobic fitness self-reports (high fit (HF) vs. low fit (LF)), and (2) using VO₂ peak as a continuous variable across the entire sample. Results showed that HF youth had an overall higher number of streamline counts compared to LF peers, which was driven by group differences in corticospinal

tract (CST) and anterior corpus callosum (Fminor). In addition, VO2 peak was negatively related to FA in the left CST. Together, these results suggest that aerobic fitness relates to white matter connectivity and microstructure in tracts carrying frontal and motor fibers during adolescence. Furthermore, the current study highlights the importance of considering the environmental factor of aerobic exercise when examining adolescent brain development.

Hoffmann, S., & Ash, J. (2001). A survey of academic and industry professionals regarding the preferred skillset of graduates of medical informatics programs. *10th World Congress on Medical Informatics, MEDINFO 2001*, London. , 84 1028-1032. doi:10.3233/978-1-60750-928-8-1028

Identification of the skills needed by graduates of medical informatics masters degree programs is needed so that students will know what is desired in the workplace and curriculum designers can assure that courses cover relevant areas. We conducted a mail survey of representatives of the informatics job market to discover what they think is most important. A survey instrument was designed after analyses of job ads and curricula in the U.S. and interviews with representative employers. The survey was mailed to 1000 randomly selected members of AMIA and HIMMS plus EMR vendors. Respondents were asked to rank skills and groups of skills according to perceived utility. The results indicate higher rankings for organizational and interpersonal skills than for more technical credentials. Statistical analysis indicates the existence of relatively few underlying constructs to the skill list. © 2001 IMIA. All right reserved.

Hsieh, M. J., Tang, S. C., Chiang, W. C., Huang, K. Y., Chang, A. M., Ko, P. C., . . . Ma, M. H. (2013). Utilization of emergency medical service increases chance of thrombolytic therapy in patients with acute ischemic stroke. *Journal of the Formosan Medical Association = Taiwan Yi Zhi*, doi:10.1016/j.jfma.2013.10.020; 10.1016/j.jfma.2013.10.020

BACKGROUND/PURPOSE: To determine whether utilization of emergency medical service (EMS) can increase use and expedite delivery of the thrombolytic therapy in acute ischemic stroke patients. METHODS: We analyzed consecutive patients presenting to the emergency department (ED) with an ischemic stroke within 72 hours of symptom onset from a prospective stroke registry. Variables associated with early ED arrival (within 3 hours of stroke onset) and administration of intravenous thrombolytic therapy were analyzed. RESULTS: From January 1,

2010 to July 31, 2011, there were 1081 patients (62.3% men, age 69.6 +/- 13 years) included in this study. Among them, 289 (26.7%) arrived in the ED within 3 hours, and 88 (8.1%) received thrombolytic therapy. Patients who arrived at the ED by EMS (n = 279, 25.8%) were independently associated with earlier ED arrival (adjusted odds ratio = 3.68, 95% confidence interval = 2.54-5.33), and higher chance of receiving thrombolytic therapy (adjusted odds ratio = 3.89, 95% confidence interval = 1.86-8.17). Furthermore, utilization of EMS significantly decreased onset-to-needle time by 26 minutes in patients receiving thrombolytic therapy.

CONCLUSIONS: Utilization of EMS can not only help acute ischemic stroke patients in early presentation to ED, but also effectively facilitate thrombolytic therapy and shorten the onset-to-needle time.

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., . . . Zubieta, J. -. (2013). Response of the μ -opioid system to social rejection and acceptance. *Molecular Psychiatry*, 18(11), 1211-1217. doi:10.1038/mp.2013.96

The endogenous opioid system, which alleviates physical pain, is also known to regulate social distress and reward in animal models. To test this hypothesis in humans (n=18), we used an μ -opioid receptor (MOR) radiotracer to measure changes in MOR availability in vivo with positron emission tomography during social rejection (not being liked by others) and acceptance (being liked by others). Social rejection significantly activated the MOR system (i.e., reduced receptor availability relative to baseline) in the ventral striatum, amygdala, midline thalamus and periaqueductal gray (PAG). This pattern of activation is consistent with the hypothesis that the endogenous opioids have a role in reducing the experience of social pain. Greater trait resiliency was positively correlated with MOR activation during rejection in the amygdala, PAG and subgenual anterior cingulate cortex (sgACC), suggesting that MOR activation in these areas is protective or adaptive. In addition, MOR activation in the pregenual ACC was correlated with reduced negative affect during rejection. In contrast, social acceptance resulted in MOR activation in the amygdala and anterior insula, and MOR deactivation in the midline thalamus and sgACC. In the left ventral striatum, MOR activation during acceptance predicted a greater desire for social interaction, suggesting a role for the MOR system in social reward. The ventral striatum, amygdala, midline thalamus, PAG, anterior insula and ACC are rich in MORs and comprise a

pathway by which social cues may influence mood and motivation. MOR regulation of this pathway may preserve and promote emotional well being in the social environment. © 2013 Macmillan Publishers Limited.

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., . . . Zubieta, J. -. (2013). Social feedback activates the endogenous opioid system. *Molecular Psychiatry*, *18*(11), 1147. doi:10.1038/mp.2013.139

Huang, J., Parks, S. B., & Press, R. D. (2006). *Diagnostic molecular pathology* Humana Press. doi:10.1007/978-1-60327-173-8_1

Huang, R. J., Chun, C. L., Friday, K., & Triadafilopoulos, G. (2013). Manometric abnormalities in the postural orthostatic tachycardia syndrome: A case series. *Digestive Diseases and Sciences*, *58*(11), 3207-3211. doi:10.1007/s10620-013-2865-9

Background: Postural orthostatic tachycardia syndrome (POTS) is a rare disease that is believed to be mediated by dysautonomia. Gastrointestinal complaints in POTS patients are common and disturbing but not well characterized. Aims: We hypothesized that gastrointestinal dysmotility may be contributory to these symptoms. Methods: We studied 12 POTS patients who presented with gastrointestinal symptoms to a tertiary referral center. Gastrointestinal symptoms were quantified using a previously validated symptom questionnaire. All patients underwent gastroduodenal manometry (GDM); select patients also underwent further testing including esophageal manometry (EM), anorectal manometry (ARM), plain abdominal radiography (AXR), abdominal computed tomography (CT), gastric emptying studies (GES), and colonic transit time (CTT) studies. Results: The four most common symptoms were bloating, constipation, abdominal pain, and nausea/vomiting, all experienced by greater than 70 % of patients. On GDM testing, 93 % of patients demonstrated signs of neuropathy, and the most common abnormalities observed included bursts of uncoordinated phasic activity in both fasting (59 %) and post-prandial (42 %) states, low contractility in the post-prandial state (67 %), and lack of post-prandial pattern (42 %). A total of 67 % of patients undergoing EM and 86 % of those undergoing ARM demonstrated abnormalities consistent with dysmotility. On AXR or CT, 58 % demonstrated either dilated intestinal loops or air-fluid levels. On CTT 80 % demonstrated delayed colonic transit, while on

GES 60 % demonstrated delayed gastric emptying. Conclusions: In this cohort of POTS patients with gastrointestinal symptoms, there is a high prevalence of abnormal manometric and radiographic findings suggestive of dysmotility. © 2013 Springer Science+Business Media New York.

Hyman, R. W., Fukushima, M., Jiang, H., Fung, E., Rand, L., Johnson, B., . . . Giudice, L. C. (2014). Diversity of the vaginal microbiome correlates with preterm birth. *Reproductive Sciences*, *21*(1), 32-40. doi:10.1177/1933719113488838

Reproductive tract infection is a major initiator of preterm birth (PTB). The objective of this prospective cohort study of 88 participants was to determine whether PTB correlates with the vaginal microbiome during pregnancy. Total DNA was purified from posterior vaginal fornix swabs during gestation. The 16S ribosomal RNA gene was amplified using polymerase chain reaction primers, followed by chain-termination sequencing. Bacteria were identified by comparing contig consensus sequences with the Ribosomal Database Project. Dichotomous responses were summarized via proportions and continuous variables via means \pm standard deviation. Mean Shannon Diversity index differed by Welch t test ($P = .00016$) between caucasians with PTB and term gestation. Species diversity was greatest among African Americans ($P = .0045$). Change in microbiome/Lactobacillus content and presence of putative novel/noxious bacteria did not correlate with PTB. We conclude that uncultured vaginal bacteria play an important role in PTB and race/ethnicity and sampling location are important determinants of the vaginal microbiome. © The Author(s) 2013.

Iltis, A. S., Misra, S., Dunn, L. B., Brown, G. K., Campbell, A., Earll, S. A., . . . Du Bois, J. M. (2013). Addressing risks to advance mental health research. *JAMA Psychiatry*, *70*(12), 1363-1371. doi:10.1001/jamapsychiatry.2013.2105

IMPORTANCE: Risk communication and management are essential to the ethical conduct of research, yet addressing risks may be time consuming for investigators and institutional review boards may reject study designs that seem too risky. This can discourage needed research, particularly in higher-risk protocols or those enrolling potentially vulnerable individuals, such as those with some level of suicidality. Improved mechanisms for addressing research risks may

facilitate much needed psychiatric research. OBJECTIVE: To provide mental health researchers with practical approaches to (1) identify and define various intrinsic research risks, (2) communicate these risks to others (eg, potential participants, regulatory bodies, and society), (3) manage these risks during the course of a study, and (4) justify the risks. EVIDENCE REVIEW: As part of a National Institute of Mental Health-funded scientific meeting series, a public conference and a closed-session expert panel meeting were held on managing and disclosing risks in mental health clinical trials. The expert panel reviewed the literature with a focus on empirical studies and developed recommendations for best practices and further research on managing and disclosing risks in mental health clinical trials. No institutional review board-review was required because there were no human subjects. FINDINGS Challenges, current data, practical strategies, and topics for future research are addressed for each of 4 key areas pertaining to management and disclosure of risks in clinical trials: identifying and defining risks, communicating risks, managing risks during studies, and justifying research risks. CONCLUSIONS AND RELEVANCE: Empirical data on risk communication, managing risks, and the benefits of research can support the ethical conduct of mental health research and may help investigators better conceptualize and confront risks and to gain institutional review board-approval. © Copyright 2013 American Medical Association. All rights reserved.

Inaba, Y., Davidson, B. P., Kim, S., Liu, Y. N., Packwood, W., Belcik, J. T., . . . Lindner, J. R. (2013).

Echocardiographic Evaluation of the Effects of Stem Cell Therapy on Perfusion and Function in Ischemic Cardiomyopathy. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography*, doi:10.1016/j.echo.2013.10.011; 10.1016/j.echo.2013.10.011

BACKGROUND: Small animal models of ischemic left ventricular (LV) dysfunction are important for the preclinical optimization of stem cell therapy. The aim of this study was to test the hypothesis that temporal changes in LV function and regional perfusion after cell therapy can be assessed in mice using echocardiographic imaging. METHODS: Wild-type mice (n = 25) were studied 7 and 28 days after permanent ligation of the left anterior descending coronary artery. Animals were randomized to receive closed-chest ultrasound-guided intramyocardial delivery of saline (n = 13) or 5 x 10⁵ multipotential adult progenitor cells (MAPCs; n = 12) on day 7. LV

end-diastolic and end-systolic volumes, LV ejection fraction, and stroke volume were measured using high-frequency echocardiography. Multiplanar assessments of perfusion and defect area size were made using myocardial contrast echocardiography. RESULTS: Between days 7 and 28, MAPC-treated animals had 40% to 50% reductions in defect size ($P < .001$) and 20% to 30% increases in total perfusion ($P < .01$). Perfusion did not change in nontreated controls. Both LV end-diastolic and end-systolic volumes increased between days 7 and 28 in both groups, but LV end-systolic volume increased to a lesser degree in MAPC-treated compared with control mice ($+4.2 \pm 7.9$ vs $+19.2 \pm 22.0$ μL , $P < .05$). LV ejection fraction increased in the MAPC-treated mice and decreased in control mice ($+3.0 \pm 4.3\%$ vs $-5.6 \pm 5.9\%$, $P < .01$). There was a significant linear relation between the change in LV ejection fraction and the change in either defect area size or total perfusion. CONCLUSIONS: High-frequency echocardiography and myocardial contrast echocardiography in murine models of ischemic LV dysfunction can be used to assess the response to stem cell therapy and to characterize the relationship among spatial flow, ventricular function, and ventricular remodeling.

Irwin, R. P., & Allen, C. N. (2013). Simultaneous electrophysiological recording and calcium imaging of suprachiasmatic nucleus neurons. *Journal of Visualized Experiments : JoVE*, (82). doi(82), 10.3791/50794. doi:10.3791/50794; 10.3791/50794

Simultaneous electrophysiological and fluorescent imaging recording methods were used to study the role of changes of membrane potential or current in regulating the intracellular calcium concentration. Changing environmental conditions, such as the light-dark cycle, can modify neuronal and neural network activity and the expression of a family of circadian clock genes within the suprachiasmatic nucleus (SCN), the location of the master circadian clock in the mammalian brain. Excitatory synaptic transmission leads to an increase in the postsynaptic Ca^{2+} concentration that is believed to activate the signaling pathways that shifts the rhythmic expression of circadian clock genes. Hypothalamic slices containing the SCN were patch clamped using microelectrodes filled with an internal solution containing the calcium indicator bis-fura-2. After a seal was formed between the microelectrode and the SCN neuronal membrane, the membrane was ruptured using gentle suction and the calcium probe diffused into the neuron filling both the soma and dendrites. Quantitative ratiometric measurements of the intracellular

calcium concentration were recorded simultaneously with membrane potential or current. Using these methods it is possible to study the role of changes of the intracellular calcium concentration produced by synaptic activity and action potential firing of individual neurons. In this presentation we demonstrate the methods to simultaneously record electrophysiological activity along with intracellular calcium from individual SCN neurons maintained in brain slices.

Islam, M., Gor, J., Perkins, S. J., Ishikawa, Y., Bächinger, H. P., & Hohenester, E. (2013). The concave face of decorin mediates reversible dimerization and collagen binding. *Journal of Biological Chemistry*, 288(49), 35526-35533. doi:10.1074/jbc.M113.504530

Background: In the crystal structure of decorin, the concave faces of two monomers interact to form a tight dimer. Results: The decorin dimer in solution is in equilibrium with stable monomers, and mutations on the concave face abolish collagen binding. Conclusion: Decorin binds collagen as a monomer. Significance: These findings help resolve the controversy about the functional oligomeric state of decorin. © 2013 by The American Society for Biochemistry and Molecular Biology, Inc.

Ito, M. K., Maki, K. C., Brinton, E. A., Cohen, J. D., & Jacobson, T. A. (2013). Muscle symptoms in statin users, associations with cytochrome P450, and membrane transporter inhibitor use: A subanalysis of the USAGE study. *Journal of Clinical Lipidology*, doi:10.1016/j.jacl.2013.10.006

Background: Drug interactions have been identified as a risk factor for muscle-related side effects in statin users. Objectives: The aim was to assess whether use of medications that inhibit cytochrome P450 (CYP450) isozymes, organic anion transporting polypeptide 1B1 (OATP1B1), or P-glycoprotein (P-gp) are associated with muscle-related symptoms among current and former statin users. Methods: Persons (n = 10,138) from the Understanding Statin Use in America and Gaps in Education (USAGE) internet survey were categorized about whether they ever reported new or worsening muscle pain while taking a statin (n = 2935) or ever stopped a statin because of muscle pain (n = 1516). Univariate and multivariate logistic regression models were used to assess associations between use of concomitant therapies that inhibit CYP450 isozymes, OATP1B1, P-gp, or a combination and muscle-related outcomes. Results: In multivariate analyses, concomitant use of a CYP450 inhibitor was associated with increased odds for new or

worse muscle pain (odds ratio [OR] = 1.42; P < .001) or ever having stopped a statin because of muscle pain (OR = 1.28; P = .037). Concomitant use of medication known to inhibit both OATP1B1 and P-gp was also associated with increased odds (OR = 1.80; P = .030) of ever having stopped a statin because of muscle pain. Conclusions: Concomitant use of medication(s) that inhibit statin metabolism was associated with increased odds of new or worse muscle pain while taking a statin and having previously stopped a statin because of muscle symptoms. These data emphasize the importance of enhancing the capabilities of clinicians and health systems for identifying and reducing statin drug interactions. © 2013 National Lipid Association.

Jacobs, A. C., Calkins, M. J., Jadhav, A., Dorjsuren, D., Maloney, D., Simeonov, A., . . . Lloyd, R. S. (2013). Inhibition of DNA Glycosylases via Small Molecule Purine Analogs. *PLoS One*, 8(12), e81667. doi:10.1371/journal.pone.0081667; 10.1371/journal.pone.0081667

Following the formation of oxidatively-induced DNA damage, several DNA glycosylases are required to initiate repair of the base lesions that are formed. Recently, NEIL1 and other DNA glycosylases, including OGG1 and NTH1 were identified as potential targets in combination chemotherapeutic strategies. The potential therapeutic benefit for the inhibition of DNA glycosylases was validated by demonstrating synthetic lethality with drugs that are commonly used to limit DNA replication through dNTP pool depletion via inhibition of thymidylate synthetase and dihydrofolate reductase. Additionally, NEIL1-associated synthetic lethality has been achieved in combination with Fanconi anemia, group G. As a prelude to the development of strategies to exploit the potential benefits of DNA glycosylase inhibition, it was necessary to develop a reliable high-throughput screening protocol for this class of enzymes. Using NEIL1 as the proof-of-principle glycosylase, a fluorescence-based assay was developed that utilizes incision of site-specifically modified oligodeoxynucleotides to detect enzymatic activity. This assay was miniaturized to a 1536-well format and used to screen small molecule libraries for inhibitors of the combined glycosylase/AP lyase activities. Among the top hits of these screens were several purine analogs, whose postulated presence in the active site of NEIL1 was consistent with the paradigm of NEIL1 recognition and excision of damaged purines. Although a subset of these small molecules could inhibit other DNA glycosylases that excise oxidatively-induced DNA adducts, they could not inhibit a pyrimidine dimer-specific glycosylase.

Jaganath, D., Zalwango, S., Okware, B., Nsereko, M., Kisingo, H., Malone, L., . . . Mupere, E. (2013).

Contact investigation for active tuberculosis among child contacts in Uganda. *Clinical Infectious Diseases*, 57(12), 1685-1692. doi:10.1093/cid/cit645

Background. Tuberculosis is a large source of morbidity and mortality among children. However, limited studies characterize childhood tuberculosis disease, and contact investigation is rarely implemented in high-burden settings. In one of the largest pediatric tuberculosis contact investigation studies in a resource-limited setting, we assessed the yield of contact tracing on childhood tuberculosis and indicators for disease progression in Uganda. Methods. Child contacts aged <15 years in Kampala, Uganda, were enrolled from July 2002 to June 2009 and evaluated for tuberculosis disease via clinical, radiographic, and laboratory methods for up to 24 months. Results. Seven hundred sixty-one child contacts were included in the analysis. Prevalence of tuberculosis in our child population was 10%, of which 71% were culture-confirmed positive. There were no cases of disseminated tuberculosis, and 483 of 490 children (99%) started on isoniazid preventative therapy did not develop disease. Multivariable testing suggested risk factors including human immunodeficiency virus (HIV) status (odds ratio [OR], 7.90; $P < .001$), and baseline positive tuberculin skin test (OR, 2.21; $P = .03$); BCG vaccination was particularly protective, especially among children aged ≤ 5 years (OR, 0.23; $P < .001$). Adult index characteristics such as sex, HIV status, and extent or severity of disease were not associated with childhood disease. Conclusions. Contact tracing for children in high-burden settings is able to identify a large percentage of culture-confirmed positive tuberculosis cases before dissemination of disease, while suggesting factors for disease progression to identify who may benefit from targeted screening. © The Author 2013. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved.

Janovick, J. A., Stewart, M. D., Jacob, D., Martin, L. D., Deng, J. M., Stewart, C. A., . . . Conn, P. M.

(2013). Restoration of testis function in hypogonadotropic hypogonadal mice harboring a misfolded GnRHR mutant by pharmacoperone drug therapy. *Proceedings of the National Academy of Sciences of the United States of America*, 110(52), 21030-21035.

doi:10.1073/pnas.1315194110; 10.1073/pnas.1315194110

Mutations in receptors, ion channels, and enzymes are frequently recognized by the cellular

quality control system as misfolded and retained in the endoplasmic reticulum (ER) or otherwise misrouted. Retention results in loss of function at the normal site of biological activity and disease. Pharmacoperones are target-specific small molecules that diffuse into cells and serve as folding templates that enable mutant proteins to pass the criteria of the quality control system and route to their physiologic site of action. Pharmacoperones of the gonadotropin releasing hormone receptor (GnRHR) have efficacy in cell culture systems, and their cellular and biochemical mechanisms of action are known. Here, we show the efficacy of a pharmacoperone drug in a small animal model, a knock-in mouse, expressing a mutant GnRHR. This recessive mutation (GnRHR E(90)K) causes hypogonadotropic hypogonadism (failed puberty associated with low or apulsatile luteinizing hormone) in both humans and in the mouse model described. We find that pulsatile pharmacoperone therapy restores E(90)K from ER retention to the plasma membrane, concurrently with responsiveness to the endogenous natural ligand, gonadotropin releasing hormone, and an agonist that is specific for the mutant. Spermatogenesis, proteins associated with steroid transport and steroidogenesis, and androgen levels were restored in mutant male mice following pharmacoperone therapy. These results show the efficacy of pharmacoperone therapy in vivo by using physiological, molecular, genetic, endocrine and biochemical markers and optimization of pulsatile administration. We expect that this newly appreciated approach of protein rescue will benefit other disorders sharing pathologies based on misrouting of misfolded protein mutants.

Janson, C., Marks, G., Buist, S., Gnatiuc, L., Gislason, T., McBurnie, M. A., . . . Burney, P. (2013). The impact of COPD on health status: Findings from the BOLD study. *European Respiratory Journal*, 42(6), 1472-1483. doi:10.1183/09031936.00153712

The aim of this study was to describe the impact of chronic obstructive pulmonary disease (COPD) on health status in the Burden of Obstructive Lung Disease (BOLD) populations. We conducted a cross-sectional, general population-based survey in 11 985 subjects from 17 countries. We measured spirometric lung function and assessed health status using the Short Form 12 questionnaire. The physical and mental health component scores were calculated. Subjects with COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity <0.70, n=2269) had lower physical component scores (44 ± 10 versus 48 ± 10 units, p<0.0001)

and mental health component scores (51 ± 10 versus 52 ± 10 units, $p=0.005$) than subjects without COPD. The effect of reported heart disease, hypertension and diabetes on physical health component scores (-3 to -4 units) was considerably less than the effect of COPD Global Initiative for Chronic Obstructive Lung Disease grade 3 (-8 units) or 4 (-11 units). Dyspnoea was the most important determinant of a low physical and mental health component scores. In addition, lower forced expiratory volume in 1 s, chronic cough, chronic phlegm and the presence of comorbidities were all associated with a lower physical health component score. COPD is associated with poorer health status but the effect is stronger on the physical than the mental aspects of health status. Severe COPD has a greater negative impact on health status than self-reported cardiovascular disease and diabetes. Copyright © ERS 2013.

Jensen, R. L., Mumert, M. L., Gillespie, D. L., Kinney, A. Y., Schabel, M. C., & Salzman, K. L. (2013).

Preoperative dynamic contrast-enhanced MRI correlates with molecular markers of hypoxia and vascularity in specific areas of intratumoral microenvironment and is predictive of patient outcome. *Neuro-Oncology*, doi:10.1093/neuonc/not148

Background Measures of tumor vascularity and hypoxia have been correlated with glioma grade and outcome. Dynamic contrast-enhanced (DCE) MRI can noninvasively map tumor blood flow, vascularity, and permeability. In this prospective observational cohort pilot study, preoperative imaging was correlated with molecular markers of hypoxia, vascularity, proliferation, and progression-free and overall patient survival. Methods Pharmacokinetic modeling methods were used to generate maps of tumor blood flow, extraction fraction, permeability-surface area product, transfer constant, washout rate, interstitial volume, blood volume, capillary transit time, and capillary heterogeneity from preoperative DCE-MRI data in human glioma patients. Tissue was obtained from areas of peritumoral edema, active tumor, hypoxic penumbra, and necrotic core and evaluated for vascularity, proliferation, and expression of hypoxia-regulated molecules. DCE-MRI parameter values were correlated with hypoxia-regulated protein expression at tissue sample sites. Results Patient survival correlated with DCE parameters in 2 cases: capillary heterogeneity in active tumor and interstitial volume in areas of peritumoral edema. Statistically significant correlations were observed between several DCE parameters and tissue markers. In addition, MIB-1 index was predictive of overall survival ($P = .044$) and correlated with vascular

endothelial growth factor expression in hypoxic penumbra ($r = 0.7933$, $P = .0071$) and peritumoral edema ($r = 0.4546$). Increased microvessel density correlated with worse patient outcome ($P = .026$). Conclusions Our findings suggest that DCE-MRI may facilitate noninvasive preoperative predictions of areas of tumor with increased hypoxia and proliferation. Both imaging and hypoxia biomarkers are predictive of patient outcome. This has the potential to allow unprecedented prognostic decisions and to guide therapies to specific tumor areas.

John McConnell, K., Marie Chang, A., Cohen, D. J., Wallace, N., Chernew, M. E., Kautz, G., . . . Smith, J. (2013). Oregon's Medicaid transformation: An innovative approach to holding a health system accountable for spending growth. *Healthcare*, doi:10.1016/j.hjdsi.2013.11.002

In 2012, Oregon initiated a significant transformation of its Medicaid program, catalyzed in part through an innovative arrangement with the Centers for Medicare and Medicaid Services (CMS), which provided an upfront investment of \$1.9 billion to the state. In exchange, Oregon agreed to reduce the rate of Medicaid spending by 2 percentage points without degrading quality. A failure to meet these targets triggers penalties on the order of hundreds of millions of dollars from CMS. We describe the novel arrangement with CMS and how the CCO structure compares to Accountable Care Organizations (ACOs) and managed care organizations (MCOs). © 2013 Elsevier Inc. All rights reserved.

Kansagara, D., Dyer, E., Englander, H., Fu, R., Freeman, M., & Kagen, D. (2013). Treatment of anemia in patients with heart disease: A systematic review. *Annals of Internal Medicine*, 159(11), 746-757.

Background: The benefits of anemia treatment in patients with heart disease are uncertain. Purpose: To evaluate the benefits and harms of treatments for anemia in adults with heart disease. Data Sources: MEDLINE, EMBASE, and Cochrane databases; clinical trial registries; reference lists; and technical advisors. Study Selection: English-language trials of blood transfusions, iron, or erythropoiesis-stimulating agents in adults with anemia and congestive heart failure or coronary heart disease and observational studies of transfusion. Data Extraction: Data on study design, population characteristics, hemoglobin levels, and health outcomes were extracted. Trials were assessed for quality. Data Synthesis: Low-strength evidence from 6 trials

and 26 observational studies suggests that liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols (combined relative risk among trials, 0.94 [95% CI, 0.61 to 1.42]; I² = 16.8%), although decreased mortality rates occurred in a small trial of patients with the acute coronary syndrome (1.8% vs. 13.0%; P = 0.032).

Moderate-strength evidence from 3 trials of intravenous iron found improved short-term exercise tolerance and quality of life in patients with heart failure. Moderate- to high-strength evidence from 17 trials of erythropoiesis-stimulating agent therapy found they offered no consistent benefits, but their use may be associated with harms, such as venous thromboembolism.

Limitations: Few trials have examined transfusions in patients with heart disease, and observational studies are potentially confounded by indication. Data supporting iron use come mainly from 1 large trial, and long-term effects are unknown. Conclusion: Higher transfusion thresholds do not consistently improve mortality rates, but large trials are needed. Intravenous iron may help to alleviate symptoms in patients with heart failure and iron deficiency and also warrants further study. Erythropoiesis-stimulating agents do not seem to benefit patients with mild to moderate anemia and heart disease and may be associated with serious harms. Primary Funding Source: U.S. Department of Veterans Affairs.

Kaplan, M. S., Huguet, N., Feeny, D., McFarland, B. H., Caetano, R., Bernier, J., . . . Ross, N. A. (2014). The association between alcohol use and long-term care placement among older Canadians: A 14-year population-based study. *Addictive Behaviors, 39*(1), 219-224. doi:10.1016/j.addbeh.2013.09.031

Studies have shown that moderate alcohol use confers protection against some of the dominant predictors of long-term care placement, including diminished cognitive functioning, physical disability, and injury. But little is known about the association between alcohol use and the likelihood of placement in long-term care facilities. A nationally representative sample of 5404 community-dwelling Canadians ages 50. years and older at baseline (1994/95) was obtained from the longitudinal National Population Health Survey. Alcohol use categories were developed based on the quantity and frequency of use in the 12. months before the interview. Cox proportional hazards models were used to estimate the association between alcohol use at baseline and subsequent placement in long-term care facilities after adjusting for covariates

measured at baseline. During the 14-year follow-up period, 14% of lifetime abstainers, 10% of former drinkers, 7% of infrequent drinkers, 4% of moderate drinkers, and 3% of heavy drinkers were placed in long-term care facilities. Furthermore, the multivariate analysis revealed that abstainers, former drinkers, and infrequent drinkers were more than twice as likely to be placed in long-term care as moderate drinkers. Moderate drinking was protective against placement in long-term care facilities even after adjusting for an array of well-known confounders. The strong protective effect of moderate alcohol use on long-term care entry is likely due to a complex mix of physical, cognitive and psychosocial health factors. © 2013 Elsevier Ltd.

Kehr, E., Stenzel, P., Xu, G., & Kelemen, K. (2010). Leukemic phase of hepatosplenic T cell lymphoma: A case report and review of the literature. *Journal of Hematopathology*, 3(2), 101-107. doi:10.1007/s12308-010-0066-4

Kellermann, A. L., Saultz, J. W., Mehrotra, A., Jones, S. S., & Dalal, S. (2013). Primary care technicians: A solution to the primary care workforce gap. *Health Affairs*, 32(11), 1893-1898. doi:10.1377/hlthaff.2013.0481

Efforts to close the primary care workforce gap typically employ one of three basic strategies: train more primary care physicians; boost the supply of nurse practitioners or physician assistants, or both; or use community health workers to extend the reach of primary care physicians. In this article we briefly review each strategy and the barriers to its success. We then propose a new approach adapted from the widely accepted model of emergency medical services. Translating this model to primary care and leveraging the capabilities of modern health information technology, it should be possible to create primary care technicians who can dramatically expand the impact and reach of patient-centered medical homes by providing basic preventive, minor illness, and stable chronic disease care in rural and resource-deprived communities. © 2013 Project HOPE - The People-to-People Health Foundation, Inc.

Kieburtz, R. B. (2006). Programmed strategies for program verification. *Electronic Notes in Theoretical Computer Science*, , 1.

Plover is an automated property-verifier for Haskell programs that has been under development for the past three years as a component of the Programatica project. In Programatica, predicate

definitions and property assertions written in P-logic, a programming logic for Haskell, can be embedded in the text of a Haskell program module. P-logic properties refine the type system of Haskell but cannot be verified by type-checking alone; a more powerful logical verifier is needed. Plover codes the proof rules of P-logic, and additionally, embeds strategies and decision procedures for their application and discharge. It integrates a reduction system that implements a rewriting semantics for Haskell terms with a congruence-closure algorithm that supports reasoning with equality. It can employ splitting strategies to explore alternative valuations of expressions of type Bool or other finite data types, but these strategies lead to exponential growth of terms and must be employed cautiously. Plover itself is written in Stratego, which has proven to be a powerful language in which to write a verifier. This talk will explain the design and implementation of some of the strategies that enable Plover to comprehend Haskell and to discharge some valid property assertions.

Kikuchi, K., Taniguchi, E., Chen, H. - H., Svalina, M. N., Abraham, J., Huang, E. T., . . . Keller, C. (2013). Rb1 loss modifies but does not initiate alveolar rhabdomyosarcoma. *Skeletal Muscle*, 3(1) doi:10.1186/2044-5040-3-27

Background: Alveolar rhabdomyosarcoma (aRMS) is a myogenic childhood sarcoma frequently associated with a translocation-mediated fusion gene, Pax3:Foxo1a. Methods: We investigated the complementary role of Rb1 loss in aRMS tumor initiation and progression using conditional mouse models. Results: Rb1 loss was not a necessary and sufficient mutational event for rhabdomyosarcomagenesis, nor a strong cooperative initiating mutation. Instead, Rb1 loss was a modifier of progression and increased anaplasia and pleomorphism. Whereas Pax3:Foxo1a expression was unaltered, biomarkers of aRMS versus embryonal rhabdomyosarcoma were both increased, questioning whether these diagnostic markers are reliable in the context of Rb1 loss. Genome-wide gene expression in Pax3:Foxo1a,Rb1 tumors more closely approximated aRMS than embryonal rhabdomyosarcoma. Intrinsic loss of pRb function in aRMS was evidenced by insensitivity to a Cdk4/6 inhibitor regardless of whether Rb1 was intact or null. This loss of function could be attributed to low baseline Rb1, pRb and phospho-pRb expression in aRMS tumors for which the Rb1 locus was intact. Pax3:Foxo1a RNA interference did not increase pRb or improve Cdk inhibitor sensitivity. Human aRMS shared the feature of low and/or heterogeneous

tumor cell pRb expression. Conclusions: Rb1 loss from an already low pRb baseline is a significant disease modifier, raising the possibility that some cases of pleomorphic rhabdomyosarcoma may in fact be Pax3:Foxo1a-expressing aRMS with Rb1 or pRb loss of function. © 2013 Kikuchi et al.; licensee BioMed Central Ltd.

Kimani, S., Moterroso, V., Lasarev, M., Kipruto, S., Bukachi, F., Maitai, C., . . . Tshala-Katumbay, D. (2013). Carbamylation correlates of cyanate neuropathy and cyanide poisoning: relevance to the biomarkers of cassava cyanogenesis and motor system toxicity. *Springerplus*, 2, 647-1801-2-647. doi:10.1186/2193-1801-2-647; 10.1186/2193-1801-2-647

We sought to elucidate the protein carbamylation patterns associated with cyanate neuropathy relative to cyanide poisoning. We hypothesized that under a diet deficient in sulfur amino acids (SAA), the carbamylation pattern associated with cyanide poisoning is similar to that of cyanate neuropathy. Male rats (6-8 weeks old) were fed a diet with all amino acids (AAA) or 75%-deficiency in SAA and treated with 2.5 mg/kg/body weight (bw) NaCN, or 50 mg/kg/bw NaOCN, or 1 ml/g/bw saline, for up to 6 weeks. Albumin and spinal cord proteins were analyzed using liquid chromatography mass spectrometry (LC-MS/MS). Only NaOCN induced motor deficits with significant levels of carbamylation. At Day 14, we found a diet-treatment interaction effect on albumin carbamylation ($p = 0.07$). At Day 28, no effect was attributed to diet ($p = 0.71$). Mean number of NaCN-carbamoylated sites on albumin was 47.4% higher relative to vehicle (95% CI:16.7-86.4%). Only NaOCN carbamoylated spinal cord proteins, prominently, under SAA-restricted diet. Proteins targets included myelin basic and proteolipid proteins, neurofilament light and glial fibrillary acidic proteins, and 2', 3' cyclic-nucleotide 3'-phosphodiesterase. Under SAA deficiency, chronic but not acute cyanide toxicity may share biomarkers and pathogenetic similarities with cyanate neuropathy. Prevention of carbamylation may protect against the neuropathic effects of cyanate.

Kimani, S., Sinei, K., Bukachi, F., Tshala-Katumbay, D., & Maitai, C. (2013). Memory deficits associated with sublethal cyanide poisoning relative to cyanate toxicity in rodents. *Metabolic Brain Disease*, , 1-8. doi:10.1007/s11011-013-9459-2

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 μ l/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 ($F_{2, 19} = 4.57$, $p < 0.05$), higher working memory errors (WME) ($F_{2, 19} = 5.09$, $p < 0.05$) 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 ($F_{2, 19} = 7.45$, $p < 0.01$) and increased working memory errors ($F_{2, 19} = 9.35$, $p < 0.05$) 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. © 2013 Springer Science+Business Media New York.

Kisby, G. E., Moore, H., & Spencer, P. S. (2013). Animal models of brain maldevelopment induced by cycad plant genotoxins. *Birth Defects Research Part C - Embryo Today: Reviews*, 99(4), 247-255. doi:10.1002/bdrc.21052

Cycads are long-lived tropical and subtropical plants that contain azoxyglycosides (e.g., cycasin, macrozamin) and neurotoxic amino acids (notably β -N-methylamino-L-alanine L-BMAA), toxins that have been implicated in the etiology of a disappearing neurodegenerative disease, amyotrophic lateral sclerosis and parkinsonism-dementia complex that has been present in high incidence among three genetically distinct populations in the western Pacific. The neuropathology of amyotrophic lateral sclerosis/parkinsonism-dementia complex includes features suggestive of brain maldevelopment, an experimentally proven property of cycasin attributable to the genotoxic action of its aglycone methylazoxymethanol (MAM). This property of MAM has been exploited by neurobiologists as a tool to study perturbations of brain development. Depending on the neurodevelopmental stage, MAM can induce features in laboratory animals that model certain characteristics of epilepsy, schizophrenia, or ataxia. Studies in DNA repair-deficient mice show

that MAM perturbs brain development through a DNA damage-mediated mechanism. The brain DNA lesions produced by systemic MAM appear to modulate the expression of genes that regulate neurodevelopment and contribute to neurodegeneration. Epigenetic changes (histone lysine methylation) have also been detected in the underdeveloped brain after MAM administration. The DNA damage and epigenetic changes produced by MAM and, perhaps by chemically related substances (e.g., nitrosamines, nitrosoureas, hydrazines), might be an important mechanism by which early-life exposure to genotoxicants can induce long-term brain dysfunction. © 2013 Wiley Periodicals, Inc.

Kobus, A. M., Heintzman, J., & Garvin, R. D. (2013). Use of standardised patients in the evaluation of a residency mood disorders curriculum: a brief report. *Mental Health in Family Medicine*, 10(1), 45-51.

Background and objectives The purpose of this paper is to describe the use of resident performance on an observed structured clinical examination (OSCE) as a tool to refine a mood disorders curriculum, and to disseminate a mood disorders OSCE for use in other residency settings. **Methods** A depression-focused OSCE and a direct observation evaluation tool were developed and implemented. A total of 24 first-year family medicine residents (PGY1) participated in the OSCE, and their performance was used to direct changes in a mood disorders curriculum. **Results** Residents performed well on general interview behaviours, and 67% were able to uncover depression in a patient presenting with headaches. Less than 50% of the residents asked about suicidal ideation and recreational drug use. Curriculum was added that addressed the latter deficiencies. **Conclusions** Tracking of resident performance on specific behaviours during OSCE sessions can be used for curriculum evaluation purposes. The mood disorders curriculum in additional family medicine residency programmes can now be evaluated using our depression-focused OSCE and Clinical Performance Checklist.

Koehler, S. A., & Freeman, M. D. (2013). Forensic epidemiology: a method for investigating and quantifying specific causation. *Forensic Science, Medicine, and Pathology*, , 1-6.

doi:10.1007/s12024-013-9513-8

The field of forensic epidemiology was initially introduced as a systematic approach to the

investigation of acts of bioterrorism. In recent years, however, the applications of forensic epidemiology have expanded greatly, covering a wide range of medicolegal issues routinely encountered in both criminal and civil court settings. Forensic epidemiology provides a method of evaluating causation in groups and individuals based in the application of the Hill Criteria, with conclusions given in terms of relative or comparative risk, or as a Probability of Causation. The purpose of this paper is to give a brief overview of the methods and applications of forensic epidemiology. © 2013 Springer Science+Business Media New York.

Krahn, G. L., Horner-Johnson, W., Hall, T. A., Roid, G. H., Andresen, E. M., Fujiura, G. T., . . .

Peterson, J. J. (2014). Development and psychometric assessment of the function-neutral health-related quality of life measure. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists*, 93(1), 56-74. doi:10.1097/PHM.0b013e3182a517e6; 10.1097/PHM.0b013e3182a517e6

OBJECTIVE: The aim of this study was to determine the conceptual framework, item pool, and psychometric properties of a new function-neutral measure of health-related quality-of-life (HRQOL). DESIGN: This is an expert panel review of existing measures of HRQOL and development of a conceptual model, core constructs, and item pool and a validation by experts in specific disabilities and in cultural competence. Items were cognitively tested, pilot tested for functional bias, field tested with a national sample of adults with various limitations, and reliability tested via repeat administration. Final item selection was based on analyses of factor structure, demographic bias, variance in likelihood of endorsement, and item-total correlation. Psychometric properties were demonstrated through differential item functioning analyses, factor analyses, correlations, and item response theory analyses. RESULTS: The results supported a four-domain conceptual model of HRQOL (physical health, mental health, social health, and life satisfaction and beliefs) for a 42-item HRQOL measure with an ancillary 15-item environment scale. The measure has strong internal consistency ($\alpha = 0.88-0.97$), known-groups validity, and test-retest reliability ($r = 0.83-0.91$). Tests of convergent and divergent validity confirmed the ability of the Function-Neutral Health-Related Quality of Life to measure health while being relatively free of content assessing function. CONCLUSIONS: A conceptually grounded four-

domain, function-neutral measure of HRQOL that is appropriate for use with persons with and without various functional limitations was developed.

Landewé, R., Braun, J., Deodhar, A., Dougados, M., Maksymowych, W. P., Mease, P. J., . . . Sieper, J. (2014). Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Annals of the Rheumatic Diseases*, 73(1), 39-47. doi:10.1136/annrheumdis-2013-204231

Objectives To evaluate the efficacy and safety of certolizumab pegol (CZP) after 24 weeks in RAPIDaxSpA (NCT01087762), an ongoing Phase 3 trial in patients with axial spondyloarthritis (axSpA), including patients with ankylosing spondylitis (AS) and nonradiographic axSpA (nr-axSpA). Methods Patients with active axSpA were randomised 1:1:1 to placebo, CZP 200 mg every 2 weeks (Q2W) or CZP 400 mg every 4 weeks (Q4W). In total 325 patients were randomised. Primary endpoint was ASAS20 (Assessment of SpondyloArthritis international Society 20) response at week 12. Secondary outcomes included change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) linear. Results Baseline disease activity was similar between AS and nr-axSpA. At week 12, ASAS20 response rates were significantly higher in CZP 200 mg Q2W and CZP 400 mg Q4W arms versus placebo (57.7 and 63.6 vs 38.3, $p \leq 0.004$). At week 24, combined CZP arms showed significant ($p < 0.001$) differences in change from baseline versus placebo in BASFI (-2.28 vs -0.40), BASDAI (-3.05 vs -1.05), and BASMI (-0.52 vs -0.07). Improvements were observed as early as week 1. Similar improvements were reported with CZP versus placebo in both AS and nr-axSpA subpopulations. Adverse events were reported in 70.4% vs 62.6%, and serious adverse events in 4.7% vs 4.7% of All CZP versus placebo groups. No deaths or malignancies were reported. Conclusions CZP rapidly reduced the signs and symptoms of axSpA, with no new safety signals observed compared to the safety profile of CZP in RA. Similar improvements were observed across CZP dosing regimens, and in AS and nr-axSpA patients.

Lathan, C., Frank, D. A., & Humphrey, L. L. (2013). Review: Low-dose CT screening reduces lung cancer and mortality in current or former smokers. *Annals of Internal Medicine*, 159(10)
doi:10.7326/0003-4819-159-10-201311190-02003

Le, D. E., Pascotto, M., Leong-Poi, H., Sari, I., Micari, A., & Kaul, S. (2013). Anti-inflammatory and pro-angiogenic effects of beta blockers in a canine model of chronic ischemic cardiomyopathy: Comparison between carvedilol and metoprolol. *Basic Research in Cardiology*, 108(6)
doi:10.1007/s00395-013-0384-7

There is controversy regarding the superiority of carvedilol (C) over metoprolol (M) in congestive heart failure. We hypothesized that C is superior to M in chronic ischemic cardiomyopathy because of its better anti-inflammatory and pro-angiogenic effects. In order to test our hypothesis we used a chronic canine model of multivessel ischemic cardiomyopathy where myocardial microcatheters were placed from which interstitial fluid was collected over time to measure leukocyte count and cytokine levels. After development of left ventricular dysfunction, the animals were randomized into four groups: sham (n = 7), placebo (n = 8), M (n = 11), and C (n = 10), and followed for 3 months after treatment initiation. Tissue was examined for immunohistochemistry, oxidative stress, and capillary density. At 3 months both rest and stress wall thickening were better in C compared to the other groups. At the end of 3 months of treatment end-systolic wall stress also decreased the most in C. Similarly resting myocardial blood flow (MBF) improved the most in C as did the stress endocardial/epicardial MBF. Myocardial interstitial fluid showed greater attenuation of leukocytosis with C compared to M, which was associated with less fibrosis and oxidative stress. C also had higher IL-10 level and capillary density. In conclusion, in a chronic canine model of multivessel ischemic cardiomyopathy we found 3 months of C treatment resulted in better resting global and regional function as well as better regional function at stress compared to M. These changes were associated with higher myocardial levels of the anti-inflammatory cytokine IL-10 and less myocardial oxidative stress, leukocytosis, and fibrosis. Capillary density and MBF were almost normalized. Thus in the doses used in this study, C appears to be superior to M in a chronic canine model of ischemic cardiomyopathy from beneficial effects on inflammation and angiogenesis. Further studies are

required for comparing additional doses of these drugs. © 2013 Springer-Verlag Berlin Heidelberg.

Lee, C. S., Gelow, J. M., Mudd, J. O., Green, J. K., Hiatt, S. O., Chien, C., & Riegel, B. (2013). Profiles of self-care management versus consulting behaviors in adults with heart failure. *European Journal of Cardiovascular Nursing : Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology*, doi:10.1177/1474515113519188

Introduction: Patients with heart failure (HF) vary in their ability to respond to symptoms when they occur. The goal of this study was to classify common patterns of symptom response behaviors among adults with HF and identify biobehavioral determinants thereof. Methods: Consulting behaviors (i.e. contacting a provider for guidance) were measured using the European Heart Failure Self-care Behavior Scale consulting behaviors subscale, and self-care management (i.e. recognizing and engaging in self-initiated treatment of symptoms) was measured with the Self-Care of HF Index self-care management scale in a prospective cohort study. Latent class mixture modeling was used to identify distinct profiles of consulting and of self-care management behaviors. Results: The mean age (n=146) was 57+/-13 years, 30% were female, and 59% had class III/IV HF. Two distinct profiles of consulting behaviors (novice and expert) and three distinct profiles of self-care management (novice, inconsistent and expert) were identified. There was a weak association between profiles of consulting behaviors and self-care management (Kendall's tau-b=0.211). Higher levels of anxiety were associated with worse consulting behaviors (beta=1.67+/-0.60) and worse self-care management (beta= -5.82+/-3.12) and lower odds of exhibiting expert level consulting behaviors (odds ratio (OR)=0.50; 95% confidence interval (CI)=0.26-0.95) and self-care management (OR=0.47; 95% CI=0.24-0.92) (all p<0.05). Higher levels of physical symptoms were associated with better self-care management (beta=0.50+/-0.12; OR =1.02, 95% CI=1.00-1.05; both p<0.05). Conclusions: Expertise in consulting behaviors does not necessarily confer expertise in symptom self-care management and vice versa. Physical and psychological symptoms are strong determinants of symptom response behaviors.

Levin, M. H., Pistilli, M., Daniel, E., Gangaputra, S. S., Nussenblatt, R. B., Rosenbaum, J. T., . . .

Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study. (2013). Incidence of Visual Improvement in Uveitis Cases with Visual Impairment Caused by Macular Edema.

Ophthalmology, doi:10.1016/j.ophtha.2013.09.023; 10.1016/j.ophtha.2013.09.023

PURPOSE: Among cases of visually significant uveitic macular edema (ME), to estimate the incidence of visual improvement and identify predictive factors. DESIGN: Retrospective cohort study. PARTICIPANTS: Eyes with uveitis, seen at 5 academic ocular inflammation centers in the United States, for which ME was documented to be currently present and the principal cause of reduced visual acuity (≥ 0.2 base 10 logarithm of visual acuity decimal fraction-equivalent; risk factors for such visual improvement. RESULTS: We identified 1510 eyes (of 1077 patients) with visual impairment to a level ≥ 2 lines of visual acuity improvement in affected eyes was 52% (95% confidence interval [CI], 49%-55%). Vision reduced by ME was more likely to improve by 2 lines in eyes initially with poor visual acuity ($\leq 20/200$; adjusted hazard ratio [HR] 1.5; 95% CI, 1.3-1.7), active uveitis (HR, 1.3; 95% CI, 1.1-1.5), and anterior uveitis as opposed to intermediate (HR, 1.2), posterior (HR, 1.3), or panuveitis (HR, 1.4; overall $P = 0.02$). During follow-up, reductions in anterior chamber or vitreous cellular activity or in vitreous haze each led to significant improvements in visual outcome ($P < 0.001$ for each). Conversely, snowbanking (HR, 0.7; 95% CI, 0.4-0.99), posterior synechiae (HR, 0.8; 95% CI, 0.6-0.9), and hypotony (HR, 0.2; 95% CI, 0.06-0.5) each were associated with lower incidence of visual improvement with respect to eyes lacking each of these attributes at a given visit. CONCLUSIONS: These results suggest that many, but not all, patients with ME causing low vision in a tertiary care setting will enjoy meaningful visual recovery in response to treatment. Evidence of significant ocular damage from inflammation (posterior synechiae and hypotony) portends a lower incidence of visual recovery. Better control of anterior chamber or vitreous activity is associated with a greater incidence of visual improvement, supporting an aggressive anti-inflammatory treatment approach for ME cases with active inflammation. FINANCIAL DISCLOSURE(S): Proprietary or commercial disclosure may be found after the references.

Levitt, E. S., Hunnicutt, B. J., Knopp, S. J., Williams, J. T., & Bissonnette, J. M. (2013). A selective 5-HT_{1a} receptor agonist improves respiration in a mouse model of Rett syndrome. *Journal of*

Applied Physiology, 115(11), 1626-1633. doi:10.1152/jappphysiol.00889.2013

Rett syndrome is a neurological disorder caused by loss of function mutations in the gene that encodes the DNA binding protein methyl-CpG-binding protein 2 (Mecp2). A prominent feature of the syndrome is disturbances in respiration characterized by frequent apnea and an irregular interbreath cycle. 8-Hydroxy-2-dipropylaminotetralin has been shown to positively modulate these disturbances (Abdala AP, Dutschmann M, Bissonnette JM, Paton JF, Proc Natl Acad Sci U S A 107: 18208-18213, 2010), but the mode of action is not understood. Here we show that the selective 5-HT_{1a} biased agonist 3-chloro-4-fluorophenyl-(4-fluoro-4-[(5-methylpyrimidin-2-ylmethyl)-amino]-methyl)-piperidin-1-yl)-methanone (F15599) decreases apnea and corrects irregularity in both heterozygous Mecp2-deficient female and in Mecp2 null male mice. In whole cell voltage-clamp recordings from dorsal raphe neurons, F15599 potently induced an outward current, which was blocked by barium, reversed at the potassium equilibrium potential, and was antagonized by the 5-HT_{1a} antagonist WAY100135. This is consistent with somatodendritic 5-HT_{1a} receptor-mediated activation of G protein-coupled inwardly rectifying potassium channels (GIRK). In contrast, F15599 did not activate 5-HT_{1b/d} receptors that mediate inhibition of glutamate release from terminals in the nucleus accumbens by a presynaptic mechanism. Thus F15599 activated somatodendritic 5-HT_{1a} autoreceptors, but not axonal 5-HT_{1b/d} receptors. In unanesthetized Mecp2-deficient heterozygous female mice, F15599 reduced apnea in a dose-dependent manner with maximal effect of $74.5 \pm 6.9\%$ at 0.1 mg/kg and improved breath irregularity. Similarly, in Mecp2 null male mice, apnea was reduced by $62 \pm 6.6\%$ at 0.25 mg/kg, and breathing became regular. The results indicate respiration is improved with a 5-agonist that activates GIRK channels without affecting neurotransmitter release. Copyright © 2013 the American Physiological Society.

Levy-Clarke, G., Jabs, D. A., Read, R. W., Rosenbaum, J. T., Vitale, A., & Van Gelder, R. N. (2013).

Expert Panel Recommendations for the Use of Anti-Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders. *Ophthalmology*,

doi:10.1016/j.ophtha.2013.09.048; 10.1016/j.ophtha.2013.09.048

PURPOSE: To provide recommendations for the use of anti-tumor necrosis factor alpha (TNF-alpha) biologic agents in patients with ocular inflammatory disorders. BACKGROUND: Ocular

inflammatory diseases remain a leading cause of vision loss worldwide. Anti-TNF-alpha agents are used widely in treatment of rheumatologic diseases. A committee of the American Uveitis Society performed a systematic review of literature to generate guidelines for use of these agents in ocular inflammatory conditions. METHODS: A systematic review of published studies was performed. Recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation group criteria. RESULTS: Numerous studies including controlled clinical trials have demonstrated that anti-TNF-alpha biologic agents (in particular infliximab and adalimumab) are effective in the treatment of severe ocular inflammatory disease. Based on these studies, the expert panel makes the following recommendations. CONCLUSIONS: Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behcet's disease. Infliximab and adalimumab can be considered as second-line immunomodulatory agents for the treatment of uveitis associated with juvenile arthritis. Infliximab and adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthropathy, and scleritis in patients requiring immunomodulation in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation. Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success. FINANCIAL DISCLOSURE(S): Proprietary or commercial disclosure may be found after the references.

Lewinsohn, D. M., & Flynn, J. L. (2006). *Immunodominance in Tuberculosis* Wiley-VCH Verlag GmbH & Co. KGaA. doi:10.1002/3527608028.ch8

Lieberman, D. (2008). *Measuring Utilization of Colonoscopy in Clinical Practice* Blackwell Publishing Ltd. doi:10.1002/9780470692189.ch22

Lieberman, D. (2009). *Screening Colonoscopy: Rationale and Performance* Wiley-Blackwell. doi:10.1002/9781444316902.ch17

Lin, J. S., O'Connor, E., Rossom, C., Perdue, L. A., & Eckstrom, E. (2013). Screening for cognitive impairment in older adults: A systematic review for the U.S. preventive services task force. *Annals of Internal Medicine*, 159(9), 601-612.

Background: Earlier identification of cognitive impairment may reduce patient and caregiver morbidity. Purpose: To systematically review the diagnostic accuracy of brief cognitive screening instruments and the benefits and harms of pharmacologic and nonpharmacologic interventions for early cognitive impairment. Data Sources: MEDLINE, PsycINFO, and the Cochrane Central Register of Controlled Trials through December 2012; systematic reviews; clinical trial registries; and experts. Study Selection: English-language studies of fair to good quality, primary care-feasible screening instruments, and treatments aimed at persons with mild cognitive impairment or mild to moderate dementia. Data Extraction: Dual quality assessment and abstraction of relevant study details. Data Synthesis: The Mini-Mental State Examination (k = 25) is the most thoroughly studied instrument but is not available for use without cost. Publicly available instruments with adequate test performance to detect dementia include the Clock Drawing Test (k = 7), Mini-Cog (k = 4), Memory Impairment Screen (k = 5), Abbreviated Mental Test (k = 4), Short Portable Mental Status Questionnaire (k = 4), Free and Cued Selective Reminding Test (k = 2), 7-Minute Screen (k = 2), and Informant Questionnaire on Cognitive Decline in the Elderly (k = 5). Medications approved by the U.S. Food and Drug Administration for Alzheimer disease (k = 58) and caregiver interventions (k = 59) show a small benefit of uncertain clinical importance for patients and their caregivers. Small benefits are also limited by common adverse effects of acetylcholinesterase inhibitors and limited availability of complex caregiver interventions. Although promising, cognitive stimulation (k = 6) and exercise (k = 10) have limited evidence to support their use in persons with mild to moderate dementia or mild cognitive impairment. Limitation: Limited studies in persons with dementia other than Alzheimer disease and sparse reporting of important health outcomes. Conclusion: Brief instruments to screen for cognitive impairment can adequately detect dementia, but there is no empirical evidence that screening improves decision making. Whether interventions for patients or their caregivers have a clinically significant effect in persons with earlier detected cognitive impairment is still unclear. Primary Funding Source: Agency for Healthcare Research and Quality. © 2013 American College of Physicians.

Lind, S. E., Williams, D. M., Raber, J., Peel, A., & Bowler, D. M. (2013). Spatial navigation impairments among intellectually high-functioning adults with autism spectrum disorder: Exploring relations with theory of mind, episodic memory, and episodic future thinking. *Journal of Abnormal Psychology, 122*(4), 1189-1199. doi:10.1037/a0034819; 10.1037/a0034819

Research suggests that spatial navigation relies on the same neural network as episodic memory, episodic future thinking, and theory of mind (ToM). Such findings have stimulated theories (e.g., the scene construction and self-projection hypotheses) concerning possible common underlying cognitive capacities. Consistent with such theories, autism spectrum disorder (ASD) is characterized by concurrent impairments in episodic memory, episodic future thinking, and ToM. However, it is currently unclear whether spatial navigation is also impaired. Hence, ASD provides a test case for the scene construction and self-projection theories. The study of spatial navigation in ASD also provides a test of the extreme male brain theory of ASD, which predicts intact or superior navigation (purportedly a systemizing skill) performance among individuals with ASD. Thus, the aim of the current study was to establish whether spatial navigation in ASD is impaired, intact, or superior. Twenty-seven intellectually high-functioning adults with ASD and 28 sex-, age-, and IQ-matched neurotypical comparison adults completed the memory island virtual navigation task. Tests of episodic memory, episodic future thinking, and ToM were also completed. Participants with ASD showed significantly diminished performance on the memory island task, and performance was positively related to ToM and episodic memory, but not episodic future thinking. These results suggest that (contra the extreme male brain theory) individuals with ASD have impaired survey-based navigation skills—that is, difficulties generating cognitive maps of the environment—and adds weight to the idea that scene construction/self-projection are impaired in ASD. The theoretical and clinical implications of these results are discussed. (PsycINFO Database Record (c) 2013 APA, all rights reserved).

Livingston, C., Cozzens, J., & Hamilton, A. (2013). Treatments for symptoms of the common cold. *American Family Physician, 88*(12), Online.

Lockwood, M. B., Saunders, M. R., Lee, C. S., Becker, Y. T., Josephson, M. A., & Chon, W. J. (2013). Kidney transplant and the digital divide: is information and communication technology a barrier

or a bridge to transplant for African Americans? *Progress in Transplantation* (Aliso Viejo, Calif.), 23(4), 302-309. doi:10.7182/pit2013869; 10.7182/pit2013869

Context-Barriers to kidney transplant for African Americans are well documented in the literature. Little information on ownership of information and communication technology and use of such technology in transplant populations has been published. Objective-To characterize racial differences related to ownership and use of information and communication technology in kidney transplant patients. Design-A single-center, cross-sectional survey study. Setting-An urban Midwestern transplant center. Participants-78 pretransplant patients and 177 transplant recipients. Main Outcomes Measures-The survey consisted of 6 demographic questions, 3 disease-related questions, and 9 technology-related questions. Dichotomous (yes/no) and Likert-scale items were the basis for the survey. Results-Cell phone use was high and comparable between groups (94% in African Americans, 90% in whites, $P = .22$). A vast majority (75% of African Americans and 74% of whites) reported being "comfortable" sending and receiving text messages. Computer ownership (94.3% vs 79.3%) and Internet access (97.7% vs 80.7%) were greater among whites than African Americans (both $P < .01$). Fewer African Americans were frequent users of the Internet (27.1% vs 56.3%) and e-mail (61.6% vs 79.3%) than whites (both $P < .01$). More African Americans than whites preferred education in a classroom setting (77% vs 60%; $P < .005$) and educational DVDs (66% vs 46%; $P < .002$). Conclusion-The use of cell phone technology and text messaging was ubiquitous and comparable between groups, but computer and Internet access and frequency of use were not. Reaching out to the African American community may best be accomplished by using cell phone/text messaging as opposed to Internet-based platforms.

Lynn Loriaux, D. (2009). Endocrinology, the Hertz Brothers, and the History of Cancer. *Clinical Endocrine Oncology: Second Edition*, , xvi-xx. doi:10.1002/9781444300222

Macey, T. A., Weimer, M. B., Grimaldi, E. M., Dobscha, S. K., & Morasco, B. J. (2013). Patterns of care and side effects for patients prescribed methadone for treatment of chronic pain. *Journal of Opioid Management*, 9(5), 325-333. doi:10.5055/jom.2013.0175; 10.5055/jom.2013.0175

OBJECTIVES: This manuscript evaluates physician monitoring practices and incidence of cardiac

side effects following initiation of methadone for treatment of chronic pain as compared to patients who began treatment for chronic pain with morphine sustained release (SR). DESIGN: We retrospectively reviewed medical record data on all new initiations of methadone and compared results of physician monitoring practices to patients with new initiations of morphine SR. A standardized chart tool was used to capture clinical data. Data related to health service utilization and clinical diagnoses were obtained from the VA clinical information system. SETTING: A single VA Medical Center in the Pacific Northwest. PATIENTS: Chronic pain patients prescribed methadone (n = 92) or morphine (n = 90) in the calendar year 2008. RESULTS: There was no difference between patients prescribed methadone versus patients prescribed morphine SR in the likelihood of receiving an electrocardiogram (ECG) prior to initiating medication (53 percent versus 54 percent) or in the year after opioid initiation (37 percent versus 40 percent). The two groups also did not differ in rates of developing prolonged rate-corrected (QTc) intervals (>450 ms) (11 percent versus 17 percent). Seventy-two percent of all patients discontinued their long-acting opioid regimens before 90 days due to adverse effects or insufficient pain relief. CONCLUSION: Despite recommendations for standardized assessment and cardiac risk monitoring, few patients prescribed methadone received an ECG, and this occurred at a rate that did not differ from patients prescribed morphine SR. Patients discontinued both medications at high rates. Further research is needed to evaluate the clinical significance of QTc prolongation in patients treated with methadone.

Makhlouf, M. A., Clifton, R. G., Roberts, J. M., Myatt, L., Hauth, J. C., Leveno, K. J., . . . for the Eunice Kennedy Shriver National Institute of Child Health Human Development Maternal-Fetal Medicine Units Network. (2013). Adverse Pregnancy Outcomes among Women with Prior Spontaneous or Induced Abortions. *American Journal of Perinatology*, doi:10.1055/s-0033-1358771

Objective The aim of the article is to determine whether prior spontaneous abortion (SAB) or induced abortion (IAB), or the interpregnancy interval are associated with subsequent adverse pregnancy outcomes in nulliparous women. Methods We performed a secondary analysis of data collected from nulliparous women enrolled in a completed trial of vitamins C and E or placebo for preeclampsia prevention. Adjusted odds ratios (ORs) for maternal and fetal outcomes were determined for nulliparous women with prior SABs and IABs as compared with primigravid

participants. Results Compared with primigravidas, women with one prior SAB were at increased risk for perinatal death (adj. OR, 1.5; 95% CI, 1.1-2.3) in subsequent pregnancies. Two or more SABs were associated with an increased risk for spontaneous preterm birth (PTB) (adj. OR, 2.6, 95% CI, 1.7-4.0), preterm premature rupture of membranes (PROM) (adj. OR, 2.9; 95% CI, 1.6-5.3), and perinatal death (adj. OR, 2.8; 95% CI, 1.5-5.3). Women with one previous IAB had higher rates of spontaneous PTB (adj. OR, 1.4; 95% CI, 1.0-1.9) and preterm PROM (OR, 2.0; 95% CI, 1.4-3.0). An interpregnancy interval less than 6 months after SAB was not associated with adverse outcomes. Conclusion Nulliparous women with a history of SAB or IAB, especially multiple SABs, are at increased risk for adverse pregnancy outcomes.

Mansberger, S. L., Gleitsmann, K., Gardiner, S., Sheppler, C., Demirel, S., Wooten, K., & Becker, T. M. (2013). Comparing the effectiveness of telemedicine and traditional surveillance in providing diabetic retinopathy screening examinations: A randomized controlled trial. *Telemedicine and e-Health, 19*(12), 942-948. doi:10.1089/tmj.2012.0313

Objective: To determine the effectiveness of telemedicine for providing diabetic retinopathy screening examinations compared with the effectiveness of traditional surveillance in community health clinics with a high proportion of minorities, including American Indian/Alaska Natives. Subjects and Methods: We conducted a multicenter, randomized controlled trial and assigned diabetic participants to one of two groups: (1) telemedicine with a nonmydriatic camera or (2) traditional surveillance with an eye care provider. For those receiving telemedicine, the criteria for requiring follow-up with an eye care provider were (1) moderate nonproliferative diabetic retinopathy or higher, (2) presence of clinically significant macular edema, or (3) "unable to grade" result for diabetic retinopathy or macular edema. Results: The telemedicine group (n=296) was more likely to receive a diabetic retinopathy screening examination within the first year of enrollment compared with the traditional surveillance group (n=271) (94% versus 56%, $p < 0.001$). The overall prevalence of diabetic retinopathy at baseline was 21.4%, and macular edema was present in 1.4% of participants. In the telemedicine group, 20.5% would require further evaluation with an eye care provider, and 86% of these referrals were because of poor-quality digital images. Conclusions: Telemedicine using nonmydriatic cameras increased the proportion of participants who obtained diabetic retinopathy screening examinations, and most

did not require follow-up with an eye care provider. Telemedicine may be a more effective way to screen patients for diabetic retinopathy and to triage further evaluation with an eye care provider. Methods to decrease poor quality imaging would improve the effectiveness of telemedicine for diabetic retinopathy screening examinations. © 2013 Mary Ann Liebert, Inc.

Martim, G. C., Detomini, T. R., Schuquel, I. T. A., Radovanovic, E., Pfeifer, C. S., & Giroto, E. M. (2013). A urethane-based multimethacrylate mixture and its use in dental composites with combined high-performance properties. *Dental Materials*, doi:10.1016/j.dental.2013.11.002

Objectives: To synthesize and characterize different molar weight urethane multimethacrylates with a single stage (one-pot) procedure. To prepare and characterize the properties of related composites. Methods: Two methacrylate precursors were initially synthesized. Then, these precursors and the multimethacrylate system formed by their coupling were characterized by FTIR and ¹H NMR. The final product was used as a matrix (with TEGDMA and SiO₂ silanized microparticles) in the preparation of composites and their physical and mechanical properties were compared to those of a bis-GMA-based resin. Water sorption and solubility measurements of the composites were also performed. Results: FTIR and NMR suggested that the proposed synthesis route yields a mixture of mainly urethane-di, -tri, and tetramethacrylates. The composites presented low polymerization shrinkage (e.g. $1.88 \pm 0.08\%$ for a resin with 70% of SiO₂) and high flexural strength (e.g. 124.74 ± 9.68 MPa for a resin with 65% of SiO₂) when compared to the bis-GMA based resin and other composites found to date. Water sorption and solubility results show that the composites were deemed compliant with ISO 4049 requirements. Significance: The mixture containing different molar weight of urethane multimethacrylates showed to be an excellent substitute for bis-GMA, achieving an equilibrium of properties (unlike reports elsewhere which show the enhancement of some parameters in detriment to others) and composites with low polymerization shrinkage, suitable microhardness and degree of conversion, and up to standard water sorption/solubility and flexural strength. © 2013 Academy of Dental Materials.

Matafonov, A., Cheng, Q., Geng, Y., Verhamme, I. M., Umunakwe, O., Tucker, E. I., . . . Gailani, D. (2013). Evidence for factor IX-independent roles for factor XIa in blood coagulation. *Journal of*

Thrombosis and Haemostasis, 11(12), 2118-2127. doi:10.1111/jth.12435

Summary: Background: Factor XIa is traditionally assigned a role in FIX activation during coagulation. However, recent evidence suggests this protease may have additional plasma substrates. Objective: To determine whether FXIa promotes thrombin generation and coagulation in plasma in the absence of FIX, and to determine whether FXI-deficiency produces an antithrombotic effect in mice independently of FIX. Methods: FXIa, FXIa variants and anti-FXIa antibodies were tested for their effects on plasma coagulation and thrombin generation in the absence of FIX, and for their effects on the activation of purified coagulation factors. Mice with combined FIX and FXI deficiency were compared with mice lacking either FIX or FXI in an arterial thrombosis model. Results: In FIX-deficient plasma, FXIa induced thrombin generation, and anti-FXIa antibodies prolonged clotting times. This process involved FXIa-mediated conversion of FX and FV to their active forms. Activation of FV by FXIa required the A3 domain on the FXIa heavy chain, whereas activation of FX did not. FX activation by FXIa, unlike FIX activation, was not a calcium-dependent process. Mice lacking both FIX and FXI were more resistant to ferric chloride-induced carotid artery occlusion than FXI-deficient or FIX-deficient mice. Conclusion: In addition to its predominant role as an activator of FIX, FXIa may contribute to coagulation by activating FX and FV. As the latter reactions do not require calcium, they may make important contributions to in vitro clotting triggered by contact activation. The reactions may be relevant to FXIa's roles in hemostasis and in promoting thrombosis. © 2013 International Society on Thrombosis and Haemostasis.

Mayberry, J. C., & Trunkey, D. D. (2007). *Chest wall* Springer New York. doi:10.1007/978-0-387-69012-4_23

A 31-year-old man is involved in a single-car accident, which occurred when he lost control of his car and hit a tree. The airbag did not deploy, and it was reported that the steering wheel was bent. The evaluation of this patient reveals a sternal fracture. Chest x-ray demonstrates a normal cardiac silhouette, no hemothorax, and no pneumothorax. The patient has had no dysrhythmias, and the electrocardiogram is normal. However, the patient continues to complain of chest pain, located at the site of the fracture. Which of the following should be the management plan? (A) Pain control and observation (B) Admission to the intensive care unit (C) Obtain an

echocardiogram (D) Sedate patient for cardiac catheterization (E) Administer prophylactic antidysrhythmic drugs © 2007 Springer-Verlag New York.

McCarroll, M. N., & Nechiporuk, A. V. (2013). Fgf3 and fgf10a work in concert to promote maturation of the epibranchial placodes in zebrafish. *PLoS One*, 8(12), e85087.

doi:10.1371/journal.pone.0085087; 10.1371/journal.pone.0085087

Essential cellular components of the paired sensory organs of the vertebrate head are derived from transient thickenings of embryonic ectoderm known as cranial placodes. The epibranchial (EB) placodes give rise to sensory neurons of the EB ganglia that are responsible for relaying visceral sensations from the periphery to the central nervous system. Development of EB placodes and subsequent formation of EB ganglia is a multistep process regulated by various extrinsic factors, including fibroblast growth factors (Fgfs). We discovered that two Fgf ligands, Fgf3 and Fgf10a, cooperate to promote EB placode development. Whereas EB placodes are induced in the absence of Fgf3 and Fgf10a, they fail to express placode specific markers Pax2a and Sox3. Expression analysis and mosaic rescue experiments demonstrate that Fgf3 signal is derived from the endoderm, whereas Fgf10a is emitted from the lateral line system and the otic placode. Further analyses revealed that Fgf3 and Fgf10a activities are not required for cell proliferation or survival, but are required for placodal cells to undergo neurogenesis. Based on these data, we conclude that a combined loss of these Fgf factors results in a failure of the EB placode precursors to initiate a transcriptional program needed for maturation and subsequent neurogenesis. These findings highlight the importance and complexity of reiterated Fgf signaling during cranial placode formation and subsequent sensory organ development.

McDonagh, M. S., Selph, S., Ozpinar, A., & Foley, C. (2013). Systematic Review of the Benefits and Risks of Metformin in Treating Obesity in Children Aged 18 Years and Younger. *JAMA Pediatrics*, doi:10.1001/jamapediatrics.2013.4200; 10.1001/jamapediatrics.2013.4200

IMPORTANCE Childhood obesity is an important public health problem with increasing prevalence. Because treatment often has limited success, new approaches must be identified. **OBJECTIVE** To evaluate the effectiveness and safety of metformin for treating obesity in children aged 18 years and younger without a diagnosis of diabetes mellitus. **EVIDENCE REVIEW** We included

randomized clinical trials identified through searches of MEDLINE, the Cochrane Library, and ClinicalTrials.gov. Our primary outcome measure was change in body mass index (BMI, calculated as weight in kilograms divided by height in meters squared). We assessed study quality, pooled data using a random-effects model, and performed subgroup and sensitivity analyses. FINDINGS Fourteen randomized clinical trials were eligible. For BMI, moderate-strength evidence indicated a reduction of -1.38 (95% CI, -1.93 to -0.82) from baseline compared with control at 6 months. A similar, if less dramatic, effect was observed in studies less than 6 months, but the pooled estimate from studies of 1 year of treatment was not statistically significant. Subgroup analyses indicated smaller, but significant, effects for those with baseline BMI below 35, those of Hispanic ethnicity, those with acanthosis nigricans, those who had tried and failed diet and exercise programs, and in studies with more girls or higher mean age (adolescents). Moderate-strength evidence indicated that with metformin, 26% reported a gastrointestinal event compared with 13% in control groups (relative risk, 2.05; 95% CI, 1.19-3.54), although there was no difference in discontinuations due to adverse events. No serious adverse events were reported. CONCLUSIONS AND RELEVANCE Metformin provides a statistically significant, but very modest reduction in BMI when combined with lifestyle interventions over the short term. A large trial is needed to determine the benefits to subgroups or impacts of confounders. In the context of other options for treating childhood obesity, metformin has not been shown to be clinically superior.

McGregor, A. J., Choo, E. K., Poznanski, S., Hendrickson, R. G., & Greenberg, M. R. (2013). Gender-specific emergency care: Part two. *Academic Emergency Medicine*, 20(11), 1182.

doi:10.1111/acem.12240

McGregor, J. C., & Harris, A. D. (2014). The need for advancements in the field of risk adjustment for healthcare-associated infections. *Infection Control and Hospital Epidemiology : The Official Journal of the Society of Hospital Epidemiologists of America*, 35(1), 8-9. doi:10.1086/674412;

10.1086/674412

McLain, A. T., Carman, G. W., Fullerton, M. L., Beckstrom, T. O., Gensler, W., Meyer, T. J., . . . Batzer, M. A. (2013). Analysis of western lowland gorilla (*Gorilla gorilla gorilla*) specific Alu repeats.

Mobile DNA, 4(1) doi:10.1186/1759-8753-4-26

Background: Research into great ape genomes has revealed widely divergent activity levels over time for Alu elements. However, the diversity of this mobile element family in the genome of the western lowland gorilla has previously been uncharacterized. Alu elements are primate-specific short interspersed elements that have been used as phylogenetic and population genetic markers for more than two decades. Alu elements are present at high copy number in the genomes of all primates surveyed thus far. The AluY subfamily and its derivatives have been recognized as the evolutionarily youngest Alu subfamily in the Old World primate lineage. Results: Here we use a combination of computational and wet-bench laboratory methods to assess and catalog AluY subfamily activity level and composition in the western lowland gorilla genome (gorGor3.1). A total of 1,075 independent AluY insertions were identified and computationally divided into 10 subfamilies, with the largest number of gorilla-specific elements assigned to the canonical AluY subfamily. Conclusions: The retrotransposition activity level appears to be significantly lower than that seen in the human and chimpanzee lineages, while higher than that seen in orangutan genomes, indicative of differential Alu amplification in the western lowland gorilla lineage as compared to other Hominae. © 2013 McLain et al.; licensee BioMed Central Ltd.

Meade, C. S., Bevilacqua, L. A., Moore, E. D., Griffin, M. L., Gardin II, J. G., Potter, J. S., . . . Weiss, R. D. (2014). Concurrent substance abuse is associated with sexual risk behavior among adults seeking treatment for prescription opioid dependence. *American Journal on Addictions*, 23(1), 27-33. doi:10.1111/j.1521-0391.2013.12057.x

Background Increasingly, new HIV infections among people who use drugs are attributed to sexual risk behavior. However, HIV prevention research targeting persons with opioid dependence continues to focus on drug injection practices. Moreover, despite the rising prevalence of prescription opioid dependence in the United States, little is known about HIV risk in this population. Methods This study examined the prevalence of sexual risk behavior among patients with opioid dependence who primarily use prescription opioids for non-medical purposes. As part of a multi-site clinical trial, participants (N = 653) completed a baseline assessment that included the Risk Behavior Survey. Results In the past month, 74% were sexually active. Of these, most had opposite sex partners (97.3%) and vaginal intercourse (97.1%); anal

intercourse was uncommon (3.1%). The majority reported unprotected intercourse (76.5%), but few had multiple partners (11.3%). Unprotected intercourse was associated with history of other substance dependence (adjusted odds ratio [AOR] = 1.73), and having multiple partners was associated with concurrent cocaine use (AOR = 2.54). Injection drug use in the past month was rare (2.5%).

Conclusions While the majority of sexually active participants engaged in unprotected intercourse, the proportion with multiple sex partners was low relative to other samples of persons who use illicit drugs. Among persons with non-medical prescription opioid dependence, those who concurrently use other substances may be at elevated risk for HIV infection. Comprehensive assessment of substance abuse history among individuals dependent upon prescription opioids is critical for identifying patients who may require additional clinical interventions to reduce HIV sexual risk behavior. © American Academy of Addiction Psychiatry.

Mease, P. J., Fleischmann, R., Deodhar, A. A., Wollenhaupt, J., Khraishi, M., Kielar, D., . . . Van Der Heijde, D. (2014). Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Annals of the Rheumatic Diseases*, 73(1), 48-55. doi:10.1136/annrheumdis-2013-203696

Objectives To evaluate the efficacy and safety of certolizumab pegol (CZP) after 24 weeks in RAPID-PsA (NCT01087788), an ongoing Phase 3 trial in patients with psoriatic arthritis (PsA).

Methods Patients were randomised 1:1:1 to placebo, 200 mg CZP every 2 weeks (Q2W) or 400 mg CZP every 4 weeks (Q4W). Patients could have had exposure to one previous tumour necrosis factor (TNF) inhibitor therapy. Primary endpoints were American College of Rheumatology 20% (ACR20) response at week 12 and modified Total Sharp Score change from baseline at week 24. Secondary endpoints included; Psoriatic Arthritis Response Criteria (PsARC) score, Health Assessment Questionnaire Disability Index (HAQ-DI), Psoriasis Area and Severity Index, Leeds Enthesitis Index, Leeds Dactylitis Index, and Modified Nail Psoriasis Severity Index.

Results Of 409 patients randomised, 368 completed 24 weeks of treatment. ACR20 response was significantly greater in CZP 200 mg Q2W and 400 mg Q4W-treated patients than placebo (58.0% and 51.9% vs 24.3% ($p < 0.001$)) at week 12, with improvements observed by week 1. There was a statistically significant improvement in physical function from baseline, measured by HAQ-DI in CZP patients compared with placebo (-0.50 vs -0.19, $p < 0.001$) and more patients treated

with CZP 200 mg Q2W and CZP 400 mg achieved an improvement in PsARC at week 24 than placebo (78.3% and 77.0% vs 33.1% ($p < 0.001$)). Sustained improvements were observed in psoriatic skin involvement, enthesitis, dactylitis and nail disease. Higher ACR20 response with CZP was independent of prior TNF inhibitor exposure. No new safety signals were observed. Conclusions Rapid improvements in the signs and symptoms of PsA, including joints, skin, enthesitis, dactylitis and nail disease were observed across both CZP dosing regimens.

Mellbin, L. G., Rydén, L., Riddle, M. C., Probstfield, J., Rosenstock, J., Díaz, R., . . . Gerstein, H. C.

(2013). Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Bioinformatics*, 29(24), 3137-3144. doi:10.1093/eurheartj/ehs332

Aims Hypoglycaemia caused by glucose-lowering therapy has been linked to cardiovascular (CV) events. The ORIGIN trial provides an opportunity to further assess this relationship. Methods and results A total of 12 537 participants with dysglycaemia and high CV-risk were randomized to basal insulin glargine titrated to a fasting glucose of ≤ 5.3 mmol/L (95 mg/dL) or standard glycaemic care. Non-severe hypoglycaemia was defined as symptoms confirmed by glucose ≤ 54 mg/dL and severe hypoglycaemia as a requirement for assistance or glucose ≤ 36 mg/dL.

Outcomes were: (i) the composite of CV death, non-fatal myocardial infarction or stroke; (ii) mortality; (iii) CV mortality; and (iv) arrhythmic death. Hazards were estimated before and after adjustment for a hypoglycaemia propensity score. During a median of 6.2 years (IQR: 5.8-6.7), non-severe hypoglycaemic episodes occurred in 41.7 and 14.4% glargine and standard group participants, respectively, while severe episodes occurred in 5.7 and 1.8%, respectively.

Nonsevere hypoglycaemia was not associated with any outcome following adjustment.

Conversely, severe hypoglycaemia was associated with a greater risk for the primary outcome (HR: 1.58; 95% CI: 1.24-2.02, $P < 0.001$), mortality (HR: 1.74; 95% CI: 1.39-2.19, $P < 0.001$), CV death (HR: 1.71; 95% CI: 1.27-2.30, $P < 0.001$) and arrhythmic death (HR: 1.77; 95% CI: 1.17-2.67, $P = 0.007$). Similar findings were noted for severe nocturnal hypoglycaemia for the primary outcome and mortality. The severe hypoglycaemia hazard for all four outcomes was higher with standard care than with insulin glargine. Conclusion Severe hypoglycaemia is associated with an increased risk for CV outcomes in people at high CV risk and dysglycaemia.

Although allocation to insulin glargine vs. standard care was associated with an increased risk of

severe and non-severe hypoglycaemia, the relative risk of CV outcomes with hypoglycaemia was lower with insulin glargine-based glucose-lowering therapy than with the standard glycaemic control.

Melnick, A. L. (2007). *Biological, chemical, and radiological terrorism: Emergency preparedness and response for the primary care physician* Springer New York. doi:10.1007/978-0-387-47232-4

This book provides sought-after guidance to primary care physicians on preparing for and responding to terrorist events. Chapters offer a fundamental understanding of the epidemiology and relevant clinical aspects of diseases caused by biological agents (anthrax, plague, smallpox, botulism, tularemia, and hemorrhagic viruses), chemical agents (nerve and blister), and radiological agents. The text details how to detect terrorist-caused illness as early as possible, how to provide defensive or preventive therapy, and how to triage and treat ill patients. Emphasis is placed on addressing both the physical and psychological impact on patients and providers. The author also examines how to work effectively with public health officials at the local, state, and national levels on the delivery of preventive and therapeutic measures. Surveillance activities, plans for handling mass casualties, and responding to concerns about risk are discussed as well. The practical approach is also applicable to accidental and natural disasters. This timely resource is invaluable for primary care physicians who want to better understand their role for patients and the public in emergency preparedness. © 2008 Springer Science+Business Media, LLC. All rights reserved.

Metzger, R., & Milas, M. (2014). Inherited cancer syndromes and the thyroid: an update. *Current Opinion in Oncology*, 26(1), 51-61. doi:10.1097/CCO.0000000000000030;
10.1097/CCO.0000000000000030

PURPOSE OF REVIEW: Knowledge related to hereditary thyroid cancer syndromes has expanded enormously. This review identifies contributions that have changed approaches to diagnosis and broadened treatment options for patients with hereditary medullary and nonmedullary thyroid cancers related to multiple endocrine neoplasia type 2 (MEN2), Cowden syndrome, and familial adenomatous polyposis (FAP). RECENT FINDINGS: A new risk-stratification scheme based on type of RET gene mutation informs the age at which prophylactic thyroidectomy and diagnostic

screening for MEN-associated endocrine diseases should occur. Two new US Food and Drug Administration-approved targeted medical therapies are now available for medullary thyroid cancer. There is better understanding of more aggressive clinical features and increased lifetime cancer risks for patients with well differentiated thyroid cancers as part of families with and without Cowden syndrome or FAP. This has led to a clearer appreciation for the role and timing of thyroid ultrasound screening in these populations. It has also informed the appropriate extent of thyroid surgery and the circumstances in which prophylactic thyroidectomy is reasonable to consider as part of hereditary syndromes other than MEN2. SUMMARY: Recognition and early diagnosis of these syndromes allows for comprehensive medical care and may improve thyroid cancer-related outcomes. Ultrasound-based screening programs to detect thyroid disease are advised for patients and family members with hereditary cancer syndromes.

Mitalipov, S., & Wolf, D. P. (2014). Clinical and ethical implications of mitochondrial gene transfer. *Trends in Endocrinology and Metabolism: TEM*, 25(1), 5-7. doi:10.1016/j.tem.2013.09.001; 10.1016/j.tem.2013.09.001

Inherited diseases caused by mitochondrial gene (mtDNA) mutations affect at least 1 in 5000-10000 children and are associated with severe clinical symptoms. Novel reproductive techniques designed to replace mutated mtDNA in oocytes or early embryos have been proposed to prevent transmission of disease from parents to their children. Here we review the efficacy and safety of these approaches and their associated ethical and regulatory issues.

Mohr, C., Kolotushkina, O., Kaplan, J. S., Welsh, J., Daunais, J. B., Grant, K. A., & Rossi, D. J. (2013). Primate cerebellar granule cells exhibit a tonic GABAAR conductance that is not affected by alcohol: a possible cellular substrate of the low level of response phenotype. *Frontiers in Neural Circuits*, 7, 189. doi:10.3389/fncir.2013.00189; 10.3389/fncir.2013.00189

In many rodent brain regions, alcohol increases vesicular release of GABA, resulting in an increase in the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) and the magnitude of tonic GABA_A receptor (GABAAR) currents. A neglected issue in translating the rodent literature to humans is the possibility that phylogenetic differences alter the actions of alcohol. To address this issue we made voltage-clamp recordings from granule cells (GCs) in

cerebellar slices from the non-human primate (NHP), *Macaca fascicularis*. We found that similar to Sprague Dawley rats (SDRs), NHP GCs exhibit a tonic conductance generated by alpha6delta subunit containing GABAARs, as evidenced by its blockade by the broad spectrum GABAAR antagonist, GABAzine (10 μ M), inhibition by alpha6 selective antagonist, furosemide (100 μ M), and enhancement by THDOC (10-20 nM) and THIP (500 nM). In contrast to SDR GCs, in most NHP GCs (~60%), application of EtOH (25-105 mM) did not increase sIPSC frequency or the tonic GABAAR current. In a minority of cells (~40%), EtOH did increase sIPSC frequency and the tonic current. The relative lack of response to EtOH was associated with reduced expression of neuronal nitric oxide synthase (nNOS), which we recently reported mediates EtOH-induced enhancement of vesicular GABA release in rats. The EtOH-induced increase in tonic GABAAR current was significantly smaller in NHPs than in SDRs, presumably due to less GABA release, because there were no obvious differences in the density of GABAARs or GABA transporters between SDR and NHP GCs. Thus, EtOH does not directly modulate alpha6delta subunit GABAARs in NHPs. Instead, EtOH enhanced GABAergic transmission is mediated by enhanced GABA release. Further, SDR GC responses to alcohol are only representative of a subpopulation of NHP GCs. This suggests that the impact of EtOH on NHP cerebellar physiology will be reduced compared to SDRs, and will likely have different computational and behavioral consequences.

Morasco, B. J., Cavanagh, R., Gritzner, S., & Dobscha, S. K. (2013). Care management practices for chronic pain in veterans prescribed high doses of opioid medications. *Family Practice, 30*(6), 671-678. doi:10.1093/fampra/cmt038

Background.: There is growing interest in the primary care management of patients with chronic non-cancer pain (CNCP) who are prescribed long-term opioid therapy. Objective.: The aim of this study was to examine the care management practices and medical utilization of patients prescribed high doses of opioids relative to patients prescribed traditional doses of opioids.

Methods.: We conducted a retrospective cohort study of veterans who had CNCP in 2008 and reviewed medical care for the prior 2 years. Patients with CNCP who were prescribed high-dose opioid therapy (≥ 180 mg morphine equivalent per day for 90+ consecutive days; n = 60) were compared with patients prescribed traditional dose opioid therapy (5-179mg morphine equivalent per day for 90+ consecutive days; n = 60). Results.: Patients in the high-dose group had several

aspects of documented care that differed from patients in the traditional dose group, including more medical visits, attempting an opioid taper, receiving a urine drug screen and developing a pain goal. The majority of variables that were assessed did not differ between groups, including documented assessments of functional status or co-morbid psychopathology, opioid rotation, discussion of treatment side effects, non-pharmacological treatments or collaboration with mental health or pain specialists. Conclusions.: Further work is needed to identify mechanisms for optimizing care management for patients with CNCP who are prescribed high doses of opioid medications. Published by Oxford University Press 2013.

Morasco, B. J., Lovejoy, T. I., Turk, D. C., Crain, A., Hauser, P., & Dobscha, S. K. (2013).

Biopsychosocial factors associated with pain in veterans with the hepatitis C virus. *Journal of Behavioral Medicine*, , 1-10. doi:10.1007/s10865-013-9549-y

Little research has examined etiological factors associated with pain in patients with the hepatitis C virus (HCV). The purpose of this study was to evaluate the relationship between biopsychosocial factors and pain among patients with HCV. Patients with HCV and pain (n = 119) completed self-report measures of pain, mental health functioning, pain-specific psychosocial variables (pain catastrophizing, self-efficacy for managing pain, social support), prescription opioid use, and demographic characteristics. In multivariate models, biopsychosocial factors accounted for 37 % of the variance in pain severity and 56 % of the variance in pain interference. In adjusted models, factors associated with pain severity include pain catastrophizing and social support, whereas variables associated with pain interference were age, pain intensity, prescription opioid use, and chronic pain self-efficacy (all p values <0.05). The results provide empirical support for incorporating the biopsychosocial model in evaluating and treating chronic pain in patients with HCV. © 2013 Springer Science+Business Media New York (outside the USA).

Morasco, B. J., O'neil, M. E., Duckart, J. P., & Ganzini, L. (2013). Comparison of Health Service Use Among Veterans With Methamphetamine Versus Alcohol Use Disorders. *Journal of Addiction Medicine*, doi:10.1097/ADM.0000000000000005

OBJECTIVES:: Methamphetamine use disorders (MUD) are associated with severe health effects

and psychiatric comorbidities, but little is known about the health care utilization of patients with MUD. The goal of this study was to describe health service use among veterans with MUD relative to a group of veterans with an alcohol use disorder (AUD). METHODS:: Using Veterans Affairs (VA) administrative data, we identified 718 patients who were diagnosed with MUD and had confirmatory drug testing. Data were compared with those of 744 patients who had diagnoses of an AUD also with confirmatory testing. We examined diagnoses and medical utilization for 5 years after their index date. RESULTS:: Patients with MUD and laboratory-confirmed recent use were younger and more likely to be diagnosed with a mood disorder, posttraumatic stress disorder, and a psychotic-spectrum disorder (all P values < 0.05). After statistical controls, patients with MUD were more likely to have an inpatient hospitalization (80% vs 70%, odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.4-2.3), discharge from an inpatient admission against medical advice (23.4% vs 8.3%, OR = 2.6, 95% CI = 1.9-3.7), receive care at 3 or more VA medical centers (13.1% vs 5.4%, OR = 2.3, 95% CI = 1.5-3.5), have a behavioral flag in the medical record (5.6% vs 1.1%, OR = 4.6, 95% CI = 2.1-10.6), and have more total missed appointments in the 5-year study period (M = 33.1 vs M = 23.5, P < 0.001). CONCLUSIONS:: Among veterans with substance use disorders, those with MUD and laboratory-confirmed recent use have additional behavioral, health care utilization, and psychiatric characteristics that need to be considered in developing programs of care.

Musicant, S. E., Roullet, J. -, Edwards, J. M., & Moneta, G. L. (2007). *Physiology of Vasospastic Disorders* Blackwell Publishing. doi:10.1002/9780470987094.ch7

Nazar-Stewart, V. (2006). *Lung Cancer* John Wiley & Sons, Inc. doi:10.1002/0471758043.ch13

Nelson, H. D., Walker, M., Zakher, B., & Mitchell, J. (2013). Re: Menopausal hormone therapy for the primary prevention of chronic conditions: A systematic review to update the U.S. preventive services task force recommendations. *Journal of Urology*, 190(6), 2168-2169.
doi:10.1016/j.juro.2013.05.116

Nguyen, B. T., Shih, G., & Turok, D. K. (2014). Putting the man in contraceptive mandate. *Contraception*, 89(1), 3-5. doi:10.1016/j.contraception.2013.10.001

Nguyen, T., Peng, J., & Jiang, J. (2014). Fence methods for backcross experiments. *Journal of*

Statistical Computation and Simulation, 84(3), 644-662. doi:10.1080/00949655.2012.721885

Model search strategies play an important role in finding simultaneous susceptibility genes that are associated with a trait. More particularly, model selection via the information criteria, such as the BIC with modifications, have received considerable attention in quantitative trait loci mapping. However, such modifications often depend upon several factors, such as sample size, prior distribution, and the type of experiment, for example, backcross, intercross. These changes make it difficult to generalize the methods to all cases. The fence method avoids such limitations with a unified approach, and hence can be used more broadly. In this article, this method is studied in the case of backcross experiments throughout a series of simulation studies. The results are compared with those of the modified BIC method as well as some of the most popular shrinkage methods for model selection. © 2012 Taylor & Francis.

Nguyen, T. N., Malisch, T., Castonguay, A. C., Gupta, R., Sun, C. H., Martin, C. O., . . . Zaidat, O. O.

(2014). Balloon guide catheter improves revascularization and clinical outcomes with the solitaire device: analysis of the north american solitaire acute stroke registry. *Stroke; a Journal of Cerebral Circulation*, 45(1), 141-145. doi:10.1161/STROKEAHA.113.002407;

10.1161/STROKEAHA.113.002407

BACKGROUND AND PURPOSE: Efficient and timely recanalization is an important goal in acute stroke endovascular therapy. Several studies demonstrated improved recanalization and clinical outcomes with the stent retriever devices compared with the Merci device. The goal of this study was to evaluate the role of the balloon guide catheter (BGC) and recanalization success in a substudy of the North American Solitaire Acute Stroke (NASA) registry. METHODS: The investigator-initiated NASA registry recruited 24 clinical sites within North America to submit demographic, clinical, site-adjudicated angiographic, and clinical outcome data on consecutive patients treated with the Solitaire Flow Restoration device. BGC use was at the discretion of the treating physicians. RESULTS: There were 354 patients included in the NASA registry. BGC data were reported in 338 of 354 patients in this subanalysis, of which 149 (44%) had placement of a BGC. Mean age was 67.3+/-15.2 years, and median National Institutes of Health Stroke Scale score was 18. Patients with BGC had more hypertension (82.4% versus 72.5%; P=0.05), atrial

fibrillation (50.3% versus 32.8%; $P=0.001$), and were more commonly administered tissue plasminogen activator (51.6% versus 38.8%; $P=0.02$) compared with patients without BGC. Time from symptom onset to groin puncture and number of passes were similar between the 2 groups. Procedure time was shorter in patients with BGC (120+/-28.5 versus 161+/-35.6 minutes; $P=0.02$), and less adjunctive therapy was used in patients with BGC (20% versus 28.6%; $P=0.05$). Thrombolysis in cerebral infarction 3 reperfusion scores were higher in patients with BGC (53.7% versus 32.5%; $P<0.001$). Distal emboli and emboli in new territory were similar between the 2 groups. Discharge National Institutes of Health Stroke Scale score (mean, 12+/-14.5 versus 17.5+/-16; $P=0.002$) and good clinical outcome at 3 months were superior in patients with BGC compared with patients without (51.6% versus 35.8%; $P=0.02$). Multivariate analysis demonstrated that the use of BGC was an independent predictor of good clinical outcome (odds ratio, 2.5; 95% confidence interval, 1.2-4.9). CONCLUSIONS: Use of a BGC with the Solitaire Flow Restoration device resulted in superior revascularization results, faster procedure times, decreased need for adjunctive therapy, and improved clinical outcome.

Nigg, J. T. (2013). Attention deficits and hyperactivity-impulsivity: What have we learned, what next? *Development and Psychopathology*, 25(4 Pt 2), 1489-1503. doi:10.1017/S0954579413000734; 10.1017/S0954579413000734

The domains of self-regulation, self-control, executive function, inattention, and impulsivity cut across broad swathes of normal and abnormal development. Attention-deficit/hyperactivity disorder is a common syndrome that encompasses a portion of these domains. In the past 25 years research on attention-deficit/hyperactivity disorder has been characterized by dramatic advances in genetic, neural, and neuropsychological description of the syndrome as well as clarification of its multidimensional phenotypic structure. The limited clinical applicability of these research findings poses the primary challenge for the next generation. It is likely that clinical breakthroughs will require further refinement in describing heterogeneity or clinical/biological subgroups, renewed focus on the environment in the form of etiological events as well as psychosocial contexts of development, and integration of both with biological understanding.

Nolan, B., & Wei, K. (2009). *Contrast echocardiography in acute coronary syndromes* Springer London. doi:10.1007/978-1-84882-027-2_9

The term acute coronary syndrome (ACS) encompasses a wide array of diagnoses from unstable angina to ST segment elevation myocardial infarction. Apart from its diversity, an ACS is a diagnosis that can be challenging to make because many other disease processes present with chest pain and confirmatory serology may take many hours to become positive. © 2009 Springer-Verlag London.

Nyendak, M. R., Park, B., Null, M. D., Baseke, J., Swarbrick, G., Mayanja-Kizza, H., . . . Tuberculosis Research Unit and the Tuberculosis Trials Consortium. (2013). Mycobacterium tuberculosis Specific CD8(+) T Cells Rapidly Decline with Antituberculosis Treatment. *PloS One*, 8(12), e81564. doi:10.1371/journal.pone.0081564; 10.1371/journal.pone.0081564

RATIONALE: Biomarkers associated with response to therapy in tuberculosis could have broad clinical utility. We postulated that the frequency of Mycobacterium tuberculosis (Mtb) specific CD8(+) T cells, by virtue of detecting intracellular infection, could be a surrogate marker of response to therapy and would decrease during effective antituberculosis treatment.

OBJECTIVES: We sought to determine the relationship of Mtb specific CD4(+) T cells and CD8(+) T cells with duration of antituberculosis treatment. MATERIALS AND METHODS: We performed a prospective cohort study, enrolling between June 2008 and August 2010, of HIV-uninfected Ugandan adults (n = 50) with acid-fast bacillus smear-positive, culture confirmed pulmonary TB at the onset of antituberculosis treatment and the Mtb specific CD4(+) and CD8(+) T cell responses to ESAT-6 and CFP-10 were measured by IFN-gamma ELISPOT at enrollment, week 8 and 24. RESULTS: There was a significant difference in the Mtb specific CD8(+) T response, but not the CD4(+) T cell response, over 24 weeks of antituberculosis treatment ($p < 0.0001$), with an early difference observed at 8 weeks of therapy ($p = 0.023$). At 24 weeks, the estimated Mtb specific CD8(+) T cell response decreased by 58%. In contrast, there was no significant difference in the Mtb specific CD4(+) T cell during the treatment. The Mtb specific CD4(+) T cell response, but not the CD8(+) response, was negatively impacted by the body mass index.

CONCLUSIONS: Our data provide evidence that the Mtb specific CD8(+) T cell response declines with antituberculosis treatment and could be a surrogate marker of response to therapy.

Additional research is needed to determine if the Mtb specific CD8(+) T cell response can detect early treatment failure, relapse, or to predict disease progression.

O'Conner-Von, S., & Turner, H. N. (2013). American Society for Pain Management Nursing (ASPMN) Position Statement: Male Infant Circumcision Pain Management. *Pain Management Nursing : Official Journal of the American Society of Pain Management Nurses*, 14(4), 379-382.
doi:10.1016/j.pmn.2011.08.007; 10.1016/j.pmn.2011.08.007

Olson, C. R., & Mello, C. V. (2012). In Preedy V.R. (Ed.), *Vitamin a and brain function*

Oresanya, L., Makam, A. N., Belkin, M., Moneta, G. L., & Conte, M. S. (2013). Factors associated with primary vein graft occlusion in a multicenter trial with mandated ultrasound surveillance. *Journal of Vascular Surgery*, doi:10.1016/j.jvs.2013.10.096; 10.1016/j.jvs.2013.10.096

OBJECTIVE: Even in the setting of duplex ultrasound (DUS) surveillance, a significant number of lower extremity vein bypass grafts (LEVBGs) become occluded as a first event. We sought to identify factors that may contribute to these primary occlusions. METHODS: This was a retrospective analysis of the Project of Ex Vivo Graft Engineering via Transfection III (PREVENT III) multicenter randomized clinical trial, in which 1404 patients with critical limb ischemia (CLI) underwent LEVBG with 1-year follow-up. Subjects were to undergo DUS at regular intervals (1, 3, 6, and 12 months), with reintervention based on prespecified DUS criteria. Patients who had nontechnical graft occlusion as the initial graft-related event were identified, and multivariate analysis was used to determine factors associated with primary graft occlusion. RESULTS: Primary vein graft occlusion occurred in 200 subjects and accounted for 36% of all primary patency events and 64% of all graft occlusions in the trial. Primary occlusion events were evenly distributed throughout the first postoperative year. Rates of recurrent CLI, loss of secondary patency, and major amputation in those with primary occlusion were 55%, 79%, and 22% respectively as compared to 18%, 10%, and 10% for subjects without primary occlusion ($P < .001$). On multivariate analysis, African-American race (subdistribution hazard ratio [SHR], 1.50; 95% confidence interval [CI], 1.06-2.12), a graft diameter <3 mm (SHR, 2.31; 95% CI, 1.33-4.01), and nonadherence with ultrasound surveillance (SHR, 1.58; 95% CI, 1.10-2.27) were independently associated with primary graft occlusion. Of the 123 subjects who received their

last scheduled surveillance DUS prior to a primary occlusion event, 39 had a critical ultrasound abnormality identified but failed to undergo graft revision, while 84 had no critical ultrasound abnormality identified. Among these 84 subjects, female gender (SHR, 1.65; 95% CI, 1.07-2.54), and graft diameter <3 mm (SHR, 2.12; 95% CI, 1.03-4.37) were independent factors associated with unheralded graft occlusion. CONCLUSIONS: Among patients undergoing LEVVG for CLI, almost half of primary patency events are occlusions even in the setting of a DUS surveillance protocol. African Americans, patients with smaller-diameter grafts, and those who are nonadherent with surveillance ultrasound are at increased risk. Failure to intervene on critical findings, and lack of sensitivity of DUS threshold criteria to predict thrombosis, are also important contributors. These findings suggest that prevention of vein graft thrombosis requires further improvements in risk stratification, surveillance, and the timing of reinterventions.

Orhan, U., Erdogmus, D., Roark, B., Oken, B., & Fried-Oken, M. (2013). Offline analysis of context contribution to ERP-based typing BCI performance. *Journal of Neural Engineering*, 10(6) doi:10.1088/1741-2560/10/6/066003

Objective. We aim to increase the symbol rate of electroencephalography (EEG) based brain-computer interface (BCI) typing systems by utilizing context information. Approach. Event related potentials (ERP) corresponding to a stimulus in EEG can be used to detect the intended target of a person for BCI. This paradigm is widely utilized to build letter-by-letter BCI typing systems. Nevertheless currently available BCI typing systems still require improvement due to low typing speeds. This is mainly due to the reliance on multiple repetitions before making a decision to achieve higher typing accuracy. Another possible approach to increase the speed of typing while not significantly reducing the accuracy of typing is to use additional context information. In this paper, we study the effect of using a language model (LM) as additional evidence for intent detection. Bayesian fusion of an n-gram symbol model with EEG features is proposed, and a specifically regularized discriminant analysis ERP discriminant is used to obtain EEG-based features. The target detection accuracies are rigorously evaluated for varying LM orders, as well as the number of ERP-inducing repetitions. Main results. The results demonstrate that the LMs contribute significantly to letter classification accuracy. For instance, we find that a single-trial ERP detection supported by a 4-gram LM may achieve the same performance as using 3-trial ERP

classification for the non-initial letters of words. Significance. Overall, the fusion of evidence from EEG and LMs yields a significant opportunity to increase the symbol rate of a BCI typing system.

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Orwoll, E. S. (2009). *Osteoporosis in Men* John Wiley & Sons, Inc. doi:10.1002/9780470623992.ch62

Ozoh, O. B., Awokola, T., & Buist, S. A. (2014). Medical students' knowledge about the management of chronic obstructive pulmonary disease in Nigeria. *The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union Against Tuberculosis and Lung Disease*, 18(1), 117-121. doi:10.5588/ijtld.13.0453; 10.5588/ijtld.13.0453

SETTING: College of Medicine, University of Lagos, Nigeria. OBJECTIVE: To determine the level of knowledge of medical students regarding the management of chronic obstructive pulmonary disease (COPD). DESIGN: Descriptive cross-sectional survey using a structured questionnaire on risk factors for COPD and some of the diagnostic criteria recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and treatment options. RESULTS: Among 139 questionnaires analysed, the mean total score (maximum 14) was 8.35 +/- 2.75. Based on the opinion of pulmonologists in Nigeria who were considered an appropriate standard, 53 students (38.1%) had good (>=70%), 52 (37.4%) had fair (>=50 to <=30 to <50%) about COPD management; 76 (54.7%) students were familiar with the GOLD guidelines, and 111 (79.9%) knew that spirometry was the means of confirming a diagnosis of COPD. Most students (93.5%) recognised cigarette smoking as a risk factor for COPD; history of tuberculosis (20.1%) was least recognised as a risk factor for COPD. Thirty-nine (28.1%) students were aware that inhaled steroids and inhaled bronchodilators were the correct options for treatment of stable COPD. CONCLUSION: Knowledge about COPD management among medical students in Nigeria is modest, and familiarity with the content of the GOLD guidelines is inadequate for optimal COPD management. More rigorous training would better equip medical students for COPD management in their careers as doctors.

Pantely, G. A., & Gatzoulis, M. A. (2009). *Simple congenital heart defects* Springer London.

doi:10.1007/978-1-84882-293-1_26

Echocardiography plays a vital role in the diagnosis and management of these anomalies. This

chapter focuses on the essentials of the echocardiographic evaluation of these lesions. It does not cover the infinite variations that occur. © Springer-Verlag London Limited 2009.

Park, H. J., Curry, J. N., & McCormick, J. A. (2013). Regulation of NKCC2 activity by inhibitory SPAK isoforms: KS-SPAK is a more potent inhibitor than SPAK2. *American Journal of Physiology - Renal Physiology*, 305(12), F1687-F1696. doi:10.1152/ajprenal.00211.2013

The cation cotransporters Na⁺-K⁺-2Cl⁻ cotransporter 1 and 2 (NKCC1 and NKCC2) and Na⁺-Cl cotransporter (NCC) are phosphorylated and activated by the kinases Ste20-related proline alanine-rich kinase (SPAK) and oxidative stress-responsive kinase (OSR1), and their targeted disruption in mice causes phenotypes resembling the human disorders Bartter syndrome and Gitelman syndrome, reflecting reduced NKCC2 and NCC activity, respectively. We previously cloned a kinase-inactive kidney-specific SPAK isoform, kidney-specific (KS)-SPAK, which lacks the majority of the kinase domain present in full-length SPAK. Another putative inactive SPAK isoform, SPAK2, which only lacks the initial portion of the kinase domain, is also highly expressed in kidney. The functional relevance of inactive SPAK isoforms is unclear. Here, we tested whether KS-SPAK and SPAK2 differentially affect cation cotransporter activity. While KS-SPAK and SPAK2 both strongly inhibited NKCC1 activity, SPAK2 was a much weaker inhibitor of NKCC2 activity. Removal of the catalytic loop from SPAK2 resulted in an inhibitory effect on NKCC2 similar to that of KS-SPAK. Full-length SPAK is phosphorylated and activated by members of the with-no-lysine[K] (WNK) kinase family. Mutation of a WNK phosphorylation in KS-SPAK did not alter its ability to inhibit NKCC2 activity. In contrast, we found that residues involved in KS-SPAK interactions with cation cotransporters are required for it to inhibit cotransporter activity. Finally, both KS-SPAK and SPAK2 associated with NKCC2, as demonstrated by coimmunoprecipitation. Together, these data identify the structural basis for the differential effects of KS-SPAK and SPAK2 on cation cotransporter activity that may be physiologically important. © 2013 the American Physiological Society.

Parthan, A., Kruse, M., Agodoa, I., Silverman, S., & Orwoll, E. (2014). Denosumab: A cost-effective alternative for older men with osteoporosis from a Swedish payer perspective. *Bone*, 59, 105-113. doi:10.1016/j.bone.2013.11.002

Objective: To assess the cost-effectiveness of denosumab versus other treatments in men with osteoporosis who are \geq 75 years old from a payer perspective in Sweden. Methods: A lifetime cohort Markov model was developed with seven health states: well, hip fracture, vertebral fracture, other osteoporotic fracture, post-hip fracture, post-vertebral fracture, and dead. During each cycle, patients could have a fracture, remain healthy, remain in a post-fracture state or die. Background fracture risks, mortality rates, persistence rates, utilities, medical and drug costs were derived using published sources. Estimates of fracture efficacy were drawn from available studies in post-menopausal osteoporotic (PMO) women as BMD improvements have been shown to be similar across male osteoporosis (MOP) and PMO populations, and a recent clinical trial suggested that the fracture risk reduction from bisphosphonate therapy in men is similar to that seen in women in comparable studies. Lifetime expected costs and quality-adjusted life-years (QALYs) were estimated for denosumab, generic alendronate, generic risedronate, ibandronate, zoledronate, strontium ranelate and teriparatide. On average, patients in the model were 78 years old, with bone mineral density T-score at the femoral neck of - 2.12. Prevalent vertebral fractures were present in 23% of patients. In the base-case, the model assumed that patients would experience treatment-related effects up to 2 years after discontinuation. Costs and QALYs were discounted at 3% annually. Extensive sensitivity analyses were conducted. Results: Total lifetime costs for denosumab, alendronate, strontium ranelate, zoledronate, risedronate, ibandronate and teriparatide were €31,004, €33,731, €34,788, €34,796, €34,826, €35,983 and €37,461, respectively. Total QALYs were 5.23, 5.15, 5.15, 5.17, 5.13, 5.12 and 5.22, respectively. Compared to other treatments, denosumab had the lowest costs and highest QALYs. In the one-way sensitivity analyses, when compared to alendronate (next least expensive strategy), the ICER for denosumab was most sensitive to the relative risk of hip fracture on denosumab. The probability of denosumab being cost-effective compared to the other treatments at a threshold of €66,000/QALY was 96.1%. Conclusion: Denosumab dominated all comparators, including generic bisphosphonates, in the treatment of osteoporosis in men who were \geq 75 years old in Sweden. © 2013 Elsevier Inc.

Paulson, L. M., Weaver, T. S., & Macarthur, C. J. (2013). Outcomes of tympanostomy tube placement in children with Down syndrome-A retrospective review. *International Journal of Pediatric*

Otorhinolaryngology, doi:10.1016/j.ijporl.2013.10.062; 10.1016/j.ijporl.2013.10.062

OBJECTIVES: Tympanostomy tubes are commonly used for treatment of chronic otitis media with effusion (COME) or recurrent acute otitis media (RAOM) in patients with Down syndrome, but hearing outcomes in this population have been mixed, and complications appear to be common. We aim to characterize outcomes and complications associated with tympanostomy tube placement in this population. **METHODS:** Retrospective review. All patients with Down syndrome presenting to a tertiary academic pediatric otolaryngology practice over a ten year period from 2002 to 2012 who received tympanostomy tubes for COME, RAOM, or hearing loss were reviewed. **RESULTS:** Long term follow up data was obtained in 102 patients, with average follow up 4.7 years. COME was the primary indication for tube placement in 100/102 (98%). Less than half of these patients (44%) initially failed their newborn hearing screen. Post operative hearing was found to be normal or near normal for the better hearing ear in 85/99 (85.9%), and normal to near normal in bilateral ears in 71/99 (71%). A majority (63.7%) of patients required two or more sets of tubes during the follow up period. Long term complications were common and were significantly increased if the patient required three or more sets of tubes, including chronic perforation (36.6% vs 8.2%, $p < 0.001$), atelectasis (29.3% vs 1.6%, $p < 0.0001$), and cholesteatoma (14.6% vs 0%, $p = 0.003$). **CONCLUSIONS:** COME is a frequent problem in Down syndrome, and the majority of patients will require two or more sets of tubes during their childhood and achieve normal postoperative hearing. Long term complications of otitis media appear to be more common in this population and appear to correlate with increasing number of tubes placed. More investigation is required to determine optimal treatment strategies for COME in patients with Down syndrome.

Pearson, S., Mancini, M., El-Gohary, M., McNames, J., & Horak, F. (2013). Turn detection and characterization with inertial sensors. *1st International Congress on Sports Science Research and Technology Support, icSPORTS 2013*, Vilamoura, Algarve. 19-22.

Powers, M. V., Valenti, M., Miranda, S., Maloney, A., Eccles, S. A., Thomas, G., . . . Workman, P. (2013). Mode of cell death induced by the HSP90 inhibitor 17-AAG (tanespimycin) is dependent on the expression of pro-apoptotic bax. *Oncotarget*, 4(11), 1963-1975.

Inhibitors of the molecular chaperone heat shock protein 90 (HSP90) are of considerable current interest as targeted cancer therapeutic agents because of the ability to destabilize multiple oncogenic client proteins. Despite their resulting pleiotropic effects on multiple oncogenic pathways and hallmark traits of cancer, resistance to HSP90 inhibitors is possible and their ability to induce apoptosis is less than might be expected. Using an isogenic model for BAX knockout in HCT116 human colon carcinoma cells, we demonstrate the induction of BAX-dependent apoptosis at pharmacologically relevant concentrations of the HSP90 inhibitor 17-AAG both in vitro and in tumor xenografts in vivo. Removal of BAX expression by homologous recombination reduces apoptosis in vitro and in vivo but allows a lower level of cell death via a predominantly necrotic mechanism. Despite reducing apoptosis, the loss of BAX does not alter the overall sensitivity to 17-AAG in vitro or in vivo. The results indicate that 17-AAG acts predominantly to cause a cytostatic antiproliferative effect rather than cell death and further suggest that BAX status may not alter the overall clinical response to HSP90 inhibitors. Other agents may be required in combination to enhance tumor-selective killing by these promising drugs. In addition, there are implications for the use of apoptotic endpoints in the assessment of the activity of molecularly targeted agents.

Press, O. W., Unger, J. M., Rimsza, L. M., Friedberg, J. W., Leblanc, M., Czuczman, M. S., . . . Fisher, R. I. (2013). A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab versus CHOP + 131iodine- tositumomab. *Clinical Cancer Research*, 19(23), 6624-6632. doi:10.1158/1078-0432.CCR-13-1120

Purpose: There is currently no consensus on optimal frontline therapy for patients with follicular lymphoma. We analyzed a phase III randomized intergroup trial comparing six cycles of CHOP-R (cyclophosphamide-Adriamycin-vincristine- prednisone (Oncovin)-rituximab) with six cycles of CHOP followed by iodine-131 tositumomab radioimmunotherapy (RIT) to assess whether any subsets benefited more from one treatment or the other, and to compare three prognostic models. Experimental Design: We conducted univariate and multivariate Cox regression analyses of 532 patients enrolled on this trial and compared the prognostic value of the FLIPI (follicular lymphoma international prognostic index), FLIPI2, and LDH + β 2M (lactate dehydrogenase + β 2-microglobulin) models. Results: Outcomes were excellent, but not

statistically different between the two study arms [5-year progression-free survival (PFS) of 60% with CHOP-R and 66% with CHOP-RIT (P = 0.11); 5-year overall survival (OS) of 92% with CHOP-R and 86% with CHOP-RIT (P = 0.08); overall response rate of 84% for both arms]. The only factor found to potentially predict the impact of treatment was serum β 2M; among patients with normal β 2M, CHOP-RIT patients had better PFS compared with CHOP-R patients, whereas among patients with high serum β 2M, PFS by arm was similar (interaction P value = 0.02). Conclusions: All three prognostic models (FLIPI, FLIPI2, and LDH + β 2M) predicted both PFS and OS well, though the LDH + β 2M model is easiest to apply and identified an especially poor risk subset. In an exploratory analysis using the latter model, there was a statistically significant trend suggesting that low-risk patients had superior observed PFS if treated with CHOP-RIT, whereas high-risk patients had a better PFS with CHOP-R. © 2013 American Association for Cancer Research.

Purnell, J. Q., Selzer, F., Smith, M. D., Berk, P. D., Courcoulas, A. P., Inabnet, W. B., . . . Patterson, E. J. (2013). Metabolic Syndrome Prevalence and Associations in a Bariatric Surgery Cohort from the Longitudinal Assessment of Bariatric Surgery-2 Study. *Metabolic Syndrome and Related Disorders*, doi:10.1089/met.2013.0116

Abstract Background: Metabolic syndrome is associated with higher risk for cardiovascular disease, sleep apnea, and nonalcoholic steatohepatitis, all common conditions in patients referred for bariatric surgery, and it may predict early postoperative complications. The objective of this study was to determine the prevalence of metabolic syndrome, defined using updated National Cholesterol Education Program criteria, in adults undergoing bariatric surgery and compare the prevalence of baseline co-morbid conditions and select operative and 30-day postoperative outcomes by metabolic syndrome status. Methods: Complete metabolic syndrome data were available for 2275 of 2458 participants enrolled in the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2), an observational cohort study designed to evaluate long-term safety and efficacy of bariatric surgery in obese adults. Results: The prevalence of metabolic syndrome was 79.9%. Compared to those without metabolic syndrome, those with metabolic syndrome were significantly more likely to be men, to have a higher prevalence of diabetes and prior cardiac events, to have enlarged livers and higher median levels of liver enzymes, a history of sleep

apnea, and a longer length of stay after surgery following laparoscopic Roux-en-Y gastric bypass (RYGB) and gastric sleeves but not open RYGB or laparoscopic adjustable gastric banding. Metabolic syndrome status was not significantly related to duration of surgery or rates of composite end points of intraoperative events and 30-day major adverse surgical outcomes. Conclusions: Nearly four in five participants undergoing bariatric surgery presented with metabolic syndrome. Establishing a diagnosis of metabolic syndrome in bariatric surgery patients may identify a high-risk patient profile, but does not in itself confer a higher risk for short-term adverse postsurgery outcomes.

Qaseem, A., Humphrey, L. L., Fitterman, N., Starkey, M., & Shekelle, P. (2013). Treatment of anemia in patients with heart disease: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, 159(11), 770-779.

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the treatment of anemia and iron deficiency in adult patients with heart disease. Methods: This guideline is based on published literature in the English language on anemia and iron deficiency from 1947 to July 2012 that was identified using MEDLINE and the Cochrane Library. Literature was reassessed in April 2013, and additional studies were included. Outcomes evaluated for this guideline included mortality; hospitalization; exercise tolerance; quality of life; and cardiovascular events (defined as myocardial infarction, congestive heart failure exacerbation, arrhythmia, or cardiac death) and harms, including hypertension, venous thromboembolic events, and ischemic cerebrovascular events. The target audience for this guideline includes all clinicians, and the target patient population is anemic or iron-deficient adult patients with heart disease. This guideline grades the evidence and recommendations using the ACP's clinical practice guidelines grading system. Recommendation 1: ACP recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease. (Grade: weak recommendation; low-quality evidence) Recommendation 2: ACP recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anemia and congestive heart failure or coronary heart disease. (Grade: strong recommendation; moderate-quality evidence) © 2013 American College of Physicians.

Qin, B., Chen, S., Brass, R., Li, Y., Tang, M., Zhang, X., . . . Huang, D. (2013). Keratoconus diagnosis with optical coherence tomography-based pachymetric scoring system. *Journal of Cataract and Refractive Surgery*, 39(12), 1864-1871. doi:10.1016/j.jcrs.2013.05.048

Purpose To develop an optical coherence tomography (OCT) pachymetry map-based keratoconus risk scoring system. Settings Doheny Eye Institute, University of Southern California, Los Angeles, California, and Brass Eye Center, New York, New York, USA; Department of Ophthalmology, Affiliated Eye Hospital of Wenzhou Medical College, Wenzhou, China. Design Cross-sectional study. Methods Fourier-domain OCT was used to acquire corneal pachymetry maps in normal and keratoconus subjects. Pachymetric variables were minimum, minimum-median, superior-inferior (S-I), superonasal-inferotemporal (SN-IT), and the vertical location of the thinnest cornea (Ymin). A logistic regression formula and a scoring system were developed based on these variables. Keratoconus diagnostic accuracy was measured by the area under the receiver operating characteristic (ROC) curve. Results One hundred thirty-three eyes of 67 normal subjects and 82 eyes from 52 keratoconus subjects were recruited. The keratoconus logistic regression formula = $0.543 \times \text{minimum} + 0.541 \times (S-I) - 0.886 \times (SN-IT) + 0.886 \times (\text{minimum-median}) + 0.0198 \times Y_{\text{min}}$. The formula gave better diagnostic power with the area under the ROC than the best single variable (formula = 0.975, minimum = 0.942; $P < .01$). The diagnostic power with the area under the ROC of the keratoconus risk score (0.949) was similar to that of the formula ($P = .08$). Conclusion The OCT corneal pachymetry map-based logistic regression formula and the keratoconus risk scoring system provided high accuracy in keratoconus detection. These methods may be useful in keratoconus screening. Financial Disclosure Oregon Health and Science University (OHSU) and Drs. Huang, Li, and Tang have a significant financial interest in Optovue, Inc., a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest has been reviewed and managed by OHSU. Dr. Brass receives speaker honoraria from Optovue, Inc. No other author has a financial or proprietary interest in any material or method mentioned. © 2013 ASCRS and ESCRS.

Rackham, D. M., C Herink, M., Stevens, I. G., Cardoza, N. M., & Singh, H. (2013). Evidence Behind FDA Alerts for Drugs with Adverse Cardiovascular Effects: Implications for Clinical Practice.

Pharmacotherapy, doi:10.1002/phar.1381; 10.1002/phar.1381

The U.S. Food and Drug Administration (FDA) periodically publishes Drug Safety Communications and Drug Alerts notifying health care practitioners and the general public of important information regarding drug therapies following FDA approval. These alerts can result in both positive and negative effects on patient care. Most clinical trials are not designed to detect long-term safety end points, and postmarketing surveillance along with patient reported events are often instrumental in signaling the potential harmful effect of a drug. Recently, many cardiovascular (CV) safety announcements have been released for FDA-approved drugs. Because a premature warning could discourage a much needed treatment or prompt a sudden discontinuation, it is essential to evaluate the evidence supporting these FDA alerts to provide effective patient care and to avoid unwarranted changes in therapy. Conversely, paying attention to these warnings in cases involving high-risk patients can prevent adverse effects and litigation. This article reviews the evidence behind recent FDA alerts for drugs with adverse CV effects and discusses the clinical practice implications.

Ramamoorthy, S., Wilson, T. M., Wu, T., & Nuttall, A. L. (2013). Non-uniform Distribution of Outer Hair Cell Transmembrane Potential Induced by Extracellular Electric Field. *Biophysical Journal*, 105(12), 2666-2675. doi:10.1016/j.bpj.2013.11.021; 10.1016/j.bpj.2013.11.021

Intracochlear electric fields arising out of sound-induced receptor currents, silent currents, or electrical current injected into the cochlea induce transmembrane potential along the outer hair cell (OHC) but its distribution along the cells is unknown. In this study, we investigated the distribution of OHC transmembrane potential induced along the cell perimeter and its sensitivity to the direction of the extracellular electric field (EEF) on isolated OHCs at a low frequency using the fast voltage-sensitive dye ANNINE-6plus. We calibrated the potentiometric sensitivity of the dye by applying known voltage steps to cells by simultaneous whole-cell voltage clamp. The OHC transmembrane potential induced by the EEF is shown to be highly nonuniform along the cell perimeter and strongly dependent on the direction of the electrical field. Unlike in many other cells, the EEF induces a field-direction-dependent intracellular potential in the cylindrical OHC. We predict that without this induced intracellular potential, EEF would not generate somatic electromotility in OHCs. In conjunction with the known heterogeneity of OHC membrane

microdomains, voltage-gated ion channels, charge, and capacitance, the EEF-induced nonuniform transmembrane potential measured in this study suggests that the EEF would impact the cochlear amplification and electropermeability of molecules across the cell.

Rasmussen, L. E. L. (2008). *Chemical, Tactile, and Taste Sensory Systems* Blackwell Publishing Ltd. doi:10.1002/9780470344484.ch32

Roark, B. (2009). *A Survey of Discriminative Language Modeling Approaches for Large Vocabulary Continuous Speech Recognition* John Wiley & Sons, Ltd. doi:10.1002/9780470742044.ch8

Roberts, L. E., Martin, W. H., & Bosnyak, D. J. (2011). *The prevention of tinnitus and noise-induced hearing loss* Springer New York. doi:10.1007/978-1-60761-145-5_69

Keypoints: 1. Although tinnitus is more common in older individuals, it can occur at any age. Because tinnitus in most individuals is associated with hearing impairment, prevalence may be increasing among youthful populations owing to exposure to environmental and recreational sound. 2. At present, there are no effective medical treatments for chronic tinnitus. Because hearing loss is a major risk factor, primary prevention is possible. Primary prevention is effective in other health domains, although it takes time for such programs to have impact. 3. Public education programs, role modeling by parents, cooperation from employers and industry, awareness campaigns, education of health professionals about avoidable risk factors, legislated standards for sound-emitting devices, and protection strategies that are acceptable to the young as well as adults, all have a role to play. 4. Dangerous Decibels is an example of a successful program aimed at reducing noise-induced hearing loss and tinnitus among school-aged children and young adults. 5. Epidemiological research tracking the prevalence of hearing loss and tinnitus at all ages, and research on intervention approaches, can provide essential information about effectiveness and long-term trends. © Springer Science+Business Media, LLC 2011.

Rodrigues, M., Oliveira, A., Costa, M., Fortunato, A. B., & Zhang, Y. (2009). Sensitivity analysis of an ecological model applied to the Ria de Aveiro. *Journal of Coastal Research*, (SPEC. ISSUE 56), 448-452.

Ecological models can be useful tools for understanding the dynamics of the estuarine and coastal

ecosystems. However, the application of these models in real systems requires the specification of many empirical input parameters, which are in general difficult to quantify for a specific site. This study presents a sensitivity analysis on the input parameters of the model ECO-SELFE applied to the Ria de Aveiro. ECO-SELFE is a three-dimensional, unstructured grid, fully-coupled hydrodynamic-ecological model. The sensitivity analysis is based on a previous analysis using the zero-dimensional ecological model, where one parameter was varied with the others being held constant. Results show that phytoplankton growth rate and zooplankton excretion and mortality rates are the parameters that influence the results the most. The degree of influence of these parameters depends on the local concentrations of zooplankton and phytoplankton. These two ecological variables are also most affected by the variations in the input parameters.

Rodriguez, S. (2014). Response. *Gastrointestinal Endoscopy*, 79(1), 182.

doi:10.1016/j.gie.2013.09.009; 10.1016/j.gie.2013.09.009

Rosenbaum, J. T., & Papaliodis, G. N. (2009). *Inflammatory eye disease* Springer London.

doi:10.1007/978-1-84800-934-9_38

The eye is frequently the target of immune-mediated inflammation, either as the sole organ involved or as part of a multiorgan system disease. Systemic inflammatory disorders tend to involve the eye in characteristic manners. As examples, disorders associated with HLA-B27 often cause a highly symptomatic anterior uveitis; Behcet's disease can cause a subclinical but ultimately vision-threatening posterior uveitis; and Wegener's granulomatosis is associated with scleritis, peripheral ulcerative keratitis, and orbital pseudotumor. The diagnosis of systemic disease can therefore be inferred from the specific types of ocular involvement. The uveal tract is divided into anterior, intermediate, and posterior segments. "Anterior uveitis" and "iritis" are synonyms. © 2010 Springer-Verlag London.

Rosenberg, J. H., Albrecht, J. S., Fromme, E. K., Noble, B. N., McGregor, J. C., Comer, A. C., & Furuno, J. P. (2013). Antimicrobial Use for symptom management in patients receiving hospice and palliative care: A systematic review. *Journal of Palliative Medicine*, 16(12), 1568-1574.

doi:10.1089/jpm.2013.0276

Background: Patients receiving hospice or palliative care often receive antimicrobial therapy;

however the effectiveness of antimicrobial therapy for symptom management in these patients is unknown. Objective: The study's objective was to systematically review and summarize existing data on the prevalence and effectiveness of antimicrobial therapy to improve symptom burden among hospice or palliative care patients. Design: Systematic review of articles on microbial use in hospice and palliative care patients published from January 1, 2001 through June 30, 2011. Measurements: We extracted data on patients' underlying chronic condition and health care setting, study design, prevalence of antimicrobial use, whether symptom response following antimicrobial use was measured, and the method for measuring symptom response. Results: Eleven studies met our inclusion criteria in which prevalence of antimicrobial use ranged from 4% to 84%. Eight studies measured symptom response following antimicrobial therapy. Methods of symptom assessment were highly variable and ranged from clinical assessment from patients' charts to the Edmonton Symptom Assessment Scale. Symptom improvement varied by indication, and patients with urinary tract infections (two studies) appeared to experience the greatest improvement following antimicrobial therapy (range 67% to 92%). Conclusion: Limited data are available on the use of antimicrobial therapy for symptom management among patients receiving palliative or hospice care. Future studies should systematically measure symptom response and control for important confounders to provide useful data to guide antimicrobial use in this population. © 2013 Mary Ann Liebert, Inc.

Ross, A., Hershberger, R. E., & Ellison, D. H. (2007). *Diuretics in Congestive Heart Failure* Blackwell Publishing. doi:10.1002/9780470994740.ch1

Ross, C. T., Weise, J. A., Bonnar, S., Nolin, D., Satkoski Trask, J., Smith, D. G., . . . Kanthaswamy, S. (2013). 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*, doi:10.1002/ajp.22235

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.

Ross, J., Roy, S. L., Mathers, W. D., Ritterband, D. C., Yoder, J. S., Ayers, T., . . . Brown, A. C.

(2013). Clinical Characteristics of Acanthamoeba Keratitis Infections in 28 States, 2008 to 2011. *Cornea*, doi:10.1097/ICO.000000000000014

PURPOSE:: The aim was to describe a geographically and clinically diverse sample of cases of Acanthamoeba keratitis (AK) and establish the risk factors for poor outcomes among patients with this disease. **METHODS::** We conducted a retrospective, population-based case series of 116 patients with AK identified through a national surveillance network. Data were collected via a medical record review by diagnosing ophthalmologists and by phone interviews with patients. Exact logistic regression modeling was used to determine risk factors for poor visual outcomes. **RESULTS::** Among patients with data available on contact lens use, it was found that 93.3% wore contact lenses. The median time from symptom onset to care seeking was 2 days, whereas the median time from symptom onset to diagnosis was 27 days. Keratoplasty was performed in 27 of 81 patients with available outcome data and was more likely in patients >40 years old [odds ratio (OR) 5.25, 95% confidence interval (CI) 1.49-21.92]. When adjusted for age, the risk factors for keratoplasty included the presence of a ring infiltrate (OR 40.00, 95% CI 3.58-447.0) or any sign of stromal invasion (OR 10.48, 95% CI 2.56-55.09). One-third of patients with available data on best-corrected visual acuity had a best-corrected visual acuity <20/200, with the presence of a ring infiltrate as the only significant predictor of this outcome when adjusted for age (aOR 3.45, 95% CI 1.01-12.31). **CONCLUSIONS::** AK remains challenging to diagnose. Consequently, patients with advanced disease are more likely to have poor outcomes, particularly if they are

older. The increasing awareness of AK among general eye care providers may shorten referral times and potentially improve outcomes.

Sabloff, M., Sobecks, R. M., Ahn, K. W., Zhu, X., de Lima, M., Brown, J. R., . . . Saber, W. (2013).

Does Total Body Irradiation Conditioning Improve Outcomes of Myeloablative Human Leukocyte Antigen-Identical Sibling Transplantations for Chronic Lymphocytic Leukemia? *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*, doi:10.1016/j.bbmt.2013.11.032; 10.1016/j.bbmt.2013.11.032

An allogeneic hematopoietic cell transplantation from an HLA-identical donor after high-dose (myeloablative) pretransplantation conditioning is an effective therapy for some people with chronic lymphocytic leukemia (CLL). Because CLL is a highly radiosensitive cancer, we hypothesized that total body irradiation (TBI) conditioning regimens may be associated with better outcomes than those without TBI. To answer this, we analyzed data from 180 subjects with CLL receiving myeloablative doses of TBI (n = 126) or not (n = 54), who received transplants from an HLA-identical sibling donor between 1995 and 2007 and reported to the Center for International Blood & Marrow Transplant Research. At 5 years, treatment-related mortality was 48% (95% confidence interval [CI], 39% to 57%) versus 50% (95% CI, 36% to 64%); P = NS. Relapse rates were 17% (95% CI, 11% to 25%) versus 22% (95% CI, 11% to 35%); P = NS. Five-year progression-free survival and overall survival were 34% (95% CI, 26% to 43%) versus 28% (95% CI, 15% to 42%); P = NS and 42% (95% CI, 33% to 51%) versus 33% (95% CI, 19% to 48%); P = NS, respectively. The single most common cause of death in both cohorts was recurrent/progressive CLL. No variable tested in the multivariate analysis was found to significantly affect these outcomes, including having failed fludarabine. Within the limitations of this study, we found no difference in HLA-identical sibling transplantation outcomes between myeloablative TBI and chemotherapy pretransplantation conditioning in persons with CLL.

Saborowski, A., Saborowski, M., Davare, M. A., Druker, B. J., Klimstra, D. S., & Lowe, S. W. (2013).

Mouse model of intrahepatic cholangiocarcinoma validates FIG-ROS as a potent fusion oncogene and therapeutic target. *Proceedings of the National Academy of Sciences of the United States of*

America, 110(48), 19513-19518. doi:10.1073/pnas.1311707110

Cholangiocarcinoma is the second most common primary liver cancer and responds poorly to existing therapies. Intrahepatic cholangiocarcinoma (ICC) likely originates from the biliary tree and develops within the hepatic parenchyma. We have generated a flexible orthotopic allograft mouse model of ICC that incorporates common genetic alterations identified in human ICC and histologically resembles the human disease. We examined the utility of this model to validate driver alterations in ICC and tested their suitability as therapeutic targets. Specifically, we showed that the fused-in-glioblastoma-c-ros-oncogene1 (FIG-ROS1(S); FIG-ROS) fusion gene dramatically accelerates ICC development and that its inactivation in established tumors has a potent antitumor effect. Our studies establish a versatile model of ICC that will be a useful preclinical tool and validate ROS1 fusions as potent oncoproteins and therapeutic targets in ICC and potentially other tumor types.

Sally, M. B., Ewing, T., Crutchfield, M., Patel, M. S., Raza, S., De La Cruz, S., . . . United Network for Organ Sharing (UNOS) Region 5 Donor Management Goals (DMG) Workgroup. (2014).

Determining optimal threshold for glucose control in organ donors after neurologic determination of death: A United Network for Organ Sharing Region 5 Donor Management Goals Workgroup prospective analysis. *The Journal of Trauma and Acute Care Surgery*, 76(1), 62-69.

doi:10.1097/TA.0b013e3182ab0d9b; 10.1097/TA.0b013e3182ab0d9b

BACKGROUND: The appropriate level of glucose control in organ donors after neurologic determination of death (DNDD) remains uncertain. We hypothesized that a glucose target of 180 mg/dL would be appropriate for optimizing organ transplantation rates and outcomes. METHODS: Demographic, critical care, organ transplantation, and graft outcome data were prospectively collected on all DNDDs in United Network for Organ Sharing (UNOS) Region 5 from 2010 to 2012. Glucose levels were assessed at four time points in the organ donation process. The primary outcome measure was having four or more organs transplanted per donor (OTPD). Univariate analyses were conducted to determine the relationship between glucose levels and OTPD, organ transplantation rates, and graft function. Multivariate analyses were performed to determine independent predictors of four or more OTPDs. Glucose levels were analyzed at the following cutoff points: 150 or less, 180, and 200 mg/dL. Results with a $p < 0.05$ are listed. RESULTS: A

total of 1,611 DNDDs had a mean (SD) age of 38 (17) years and 3.4 (1.7) OTPDs. Forty-one percent had four or more OTPDs. Glucose levels of 150 mg/dL or less were not associated with differences in organ use. Levels of 180 mg/dL or less were associated with more OTPDs (3.5 vs. 3.2), a higher rate of four or more OTPDs (42% vs. 34%), and more heart (34% vs. 28%), pancreas (18% vs. 11%), and kidney (85% vs. 81%) use. Levels of 200 mg/dL or less revealed similar results. However, only a level of 180 mg/dL or less was an independent predictor of four or more OTPDs (odds ratio, 1.4). All three levels were associated with higher kidney graft survival after a mean (SD) of 10 (6.0) months of follow-up (97% vs. 95%). CONCLUSION: Hyperglycemia is common in DNDDs and is associated with lower organ transplantation rates and worse graft outcomes. Targeting a glucose level of 180 mg/dL or less seems to preserve outcomes and is consistent with general critical care guidelines. LEVEL OF EVIDENCE: Therapeutic study, level II.

Samji, H., Cescon, A., Hogg, R. S., Modur, S. P., Althoff, K. N., Buchacz, K., . . . North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. (2013). Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada. *PLoS One*, 8(12), e81355. doi:10.1371/journal.pone.0081355; 10.1371/journal.pone.0081355

BACKGROUND: Combination antiretroviral therapy (ART) has significantly increased survival among HIV-positive adults in the United States (U.S.) and Canada, but gains in life expectancy for this region have not been well characterized. We aim to estimate temporal changes in life expectancy among HIV-positive adults on ART from 2000-2007 in the U.S. and Canada.

METHODS: Participants were from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), aged ≥ 20 years and on ART. Mortality rates were calculated using participants' person-time from January 1, 2000 or ART initiation until death, loss to follow-up, or administrative censoring December 31, 2007. Life expectancy at age 20, defined as the average number of additional years that a person of a specific age will live, provided the current age-specific mortality rates remain constant, was estimated using abridged life tables. RESULTS: The crude mortality rate was 19.8/1,000 person-years, among 22,937 individuals contributing 82,022 person-years and 1,622 deaths. Life expectancy increased from 36.1 [standard error (SE) 0.5] to

51.4 [SE 0.5] years from 2000-2002 to 2006-2007. Men and women had comparable life expectancies in all periods except the last (2006-2007). Life expectancy was lower for individuals with a history of injection drug use, non-whites, and in patients with baseline CD4 counts <350 cells/mm³. CONCLUSIONS: A 20-year-old HIV-positive adult on ART in the U.S. or Canada is expected to live into their early 70 s, a life expectancy approaching that of the general population. Differences by sex, race, HIV transmission risk group, and CD4 count remain.

Sampath, H., & Ntambi, J. M. (2013). The role of Stearoyl-CoA desaturase-1 in skin integrity and whole body energy balance. *The Journal of Biological Chemistry*, doi:10.1074/jbc.R113.516716

The skin is the largest single organ in humans serving as a major barrier to infection, water loss, and abrasion. The functional diversity of skin requires the synthesis of large amounts of lipids, such as cholesterol, phospholipids, triglycerides, ceramides, cholesterol esters, wax esters, and retinyl esters. Some of these lipids are used as cell membrane components, signaling molecules, and as a source of energy. An important class of lipid metabolism enzymes expressed in skin is the delta 9 desaturases, which catalyze the synthesis of delta-9 monounsaturated lipids, primarily oleoyl- (18:1n9) and palmitoyl-CoA (16:1n7), the major monounsaturated fatty acids of cutaneous lipids. Mice with a deletion of the delta-9 desaturase-1 isoform (SCD1) either globally (Scd1^{-/-}) or specifically in the skin (SKO) present with marked changes in cutaneous lipids and skin integrity. Interestingly, these mice also exhibit increased whole-body energy expenditure, protection against diet-induced adiposity, hepatic steatosis, and glucose intolerance. The increased energy expenditure in SKO mice is a surprising phenotype as it links cutaneous lipid homeostasis with whole body energy balance. This review summarizes the role of skin SCD1 in regulating skin integrity and whole body energy homeostasis and offers a discussion of potential pathways that may connect these seemingly disparate phenotypes.

Sanborn, R. E., Gonzalez, A. L., Ulbright, T. M., Sonpavde, G., & Sandler, A. B. (2006). *Primary Sarcomas of the Lung* John Wiley & Sons, Ltd. doi:10.1002/0470030542.ch22

Primary pulmonary sarcomas (PPSs) are a rare group of pulmonary malignancies, outnumbered by bronchogenic carcinomas by a factor of 500:1. These tumors are often difficult to differentiate and characterize on the basis of morphology alone, and diagnosis frequently depends on

immunohistochemical and ultrastructural analysis. PPSs are typically very advanced at the time of diagnosis, with symptoms relating to tumor invasion or postobstructive pneumonia commonly prompting evaluation. Some patients, however, are asymptomatic at the time of diagnosis, with an incidental finding on an imaging study. Clinical symptoms and radiographic findings can resemble a diverse collection of other disease entities; thus, PPS needs to be entertained in the differential diagnosis in the evaluation of other diseases. Complete surgical resection remains the only approach for cure, although many patients are not eligible for resection at the time of diagnosis. Chemotherapy and radiation therapy play only limited roles in treatment, and newer, more efficacious, therapeutic agents are needed. © 2006 John Wiley & Sons, Ltd.

Sano, M., Egelko, S., Donohue, M., Ferris, S., Kaye, J., Hayes, T. L., . . . Aisen, P. S. (2013).

Developing dementia prevention trials: Baseline report of the home-based assessment study. *Alzheimer Disease and Associated Disorders*, 27(4), 356-362.

doi:10.1097/WAD.0b013e3182769c05

This report describes the baseline experience of the multicenter, Home-Based Assessment study, designed to develop methods for dementia prevention trials using novel technologies for test administration and data collection. Nondemented individuals of 75 years of age or more were recruited and evaluated in-person using established clinical trial outcomes of cognition and function, and randomized to one of 3 assessment methodologies: (1) mail-in questionnaire/live telephone interviews [mail-in/phone (MIP)]; (2) automated telephone with interactive voice recognition; and (3) internet-based computer Kiosk. Brief versions of cognitive and noncognitive outcomes were adapted to each methodology and administered at baseline and repeatedly over a 4-year period. "Efficiency" measures assessed the time from screening to baseline, and staff time required for each methodology. A total of 713 individuals signed consent and were screened; 640 met eligibility and were randomized to one of 3 assessment arms; and 581 completed baseline. Dropout, time from screening to baseline, and total staff time were highest among those assigned to internet-based computer Kiosk. However, efficiency measures were driven by nonrecurring start-up activities suggesting that differences may be mitigated over a long trial. Performance among Home-Based Assessment instruments collected through different

technologies will be compared with established outcomes over this 4-year study. Copyright © 2013 by Lippincott Williams & Wilkins.

Schiffmann, R., Ries, M., Blankenship, D., Nicholls, K., Mehta, A., Clarke, J. T. R., . . . Huertas, P.

(2013). Changes in plasma and urine globotriaosylceramide levels do not predict Fabry disease progression over 1 year of agalsidase alfa. *Genetics in Medicine*, 15(12), 983-989.

doi:10.1038/gim.2013.56

Purpose: Globotriaosylceramide concentrations were assessed as potential predictors of change from baseline after 12 months by estimated glomerular filtration rate and left-ventricular mass index using pooled data from three randomized, placebo-controlled agalsidase alfa trials and open-label extensions of patients with Fabry disease. **Methods:** Males (aged 18 years or older) with Fabry disease received agalsidase alfa (0.2 mg/kg every other week for 12 months). A backward-elimination approach evaluated potential predictors (baseline estimated glomerular filtration rate and left-ventricular mass index; age at first dose; baseline and change from baseline at 12 months of globotriaosylceramide (urine, plasma); urine protein excretion; and systolic and diastolic blood pressure). Subgroups included patients randomized to placebo or agalsidase alfa (double-blind phase), then to agalsidase alfa (open-label extensions; placebo→agalsidase alfa or agalsidase alfa→agalsidase alfa, respectively) and stage 2/3 chronic kidney disease patients. **Results:** Baseline estimated glomerular filtration rate, age at first dose, baseline urine globotriaosylceramide excretion, and baseline and change from baseline urine protein excretion significantly predicted change from baseline estimated glomerular filtration rate in the analysis population (N = 73; all P<0.05), although not in all subgroups. Change from baseline urine and plasma globotriaosylceramide (baseline and change from baseline) concentrations did not predict change from baseline estimated glomerular filtration rate. No predictors of left-ventricular mass index were significant. **Conclusion:** Changes in globotriaosylceramide concentrations do not appear to be useful biomarkers for prediction of Fabry disease-related changes in estimated glomerular filtration rate or left-ventricular mass index. © American College of Medical Genetics and Genomics.

Schousboe, J. T., Rosen, H. R., Vokes, T. J., Cauley, J. A., Cummings, S. R., Nevitt, M. C., . . . Ensrud, K. E. (2013). Prediction Models of Prevalent Radiographic Vertebral Fractures Among Older Men. *Journal of Clinical Densitometry*, doi:10.1016/j.jocd.2013.09.020

No studies have compared how well different prediction models discriminate older men who have a radiographic prevalent vertebral fracture (PVFx) from those who do not. We used area under receiver operating characteristic curves and a net reclassification index to compare how well regression-derived prediction models and nonregression prediction tools identify PVFx among men age ≥ 65 yr with femoral neck T-score of -1.0 or less enrolled in the Osteoporotic Fractures in Men Study. The area under receiver operating characteristic for a model with age, bone mineral density, and historical height loss (HHL) was 0.682 compared with 0.692 for a complex model with age, bone mineral density, HHL, prior non-spine fracture, body mass index, back pain, grip strength, smoking, and glucocorticoid use (p values for difference in 5 bootstrapped samples 0.14-0.92). This complex model, using a cutpoint prevalence of 5%, correctly reclassified only a net 5.7% (p = 0.13) of men as having or not having a PVFx compared with a simple criteria list (age ≥ 80 yr, HHL >4 cm, or glucocorticoid use). In conclusion, simple criteria identify older men with PVFx and regression-based models. Future research to identify additional risk factors that more accurately identify older men with PVFx is needed. © 2013 The International Society for Clinical Densitometry.

Scolaro, J. A., Voleti, P., Makani, A., Namdari, S., Mirza, A., & Mehta, S. (2013). Surgical fixation of extra-articular distal humerus fractures with a posterolateral plate through a triceps-reflecting technique. *Journal of Shoulder and Elbow Surgery / American Shoulder and Elbow Surgeons ...[Et Al.]*, doi:10.1016/j.jse.2013.09.020; 10.1016/j.jse.2013.09.020

BACKGROUND: Surgical management of extra-articular distal humerus fractures results in predictable fracture alignment. Open reduction and internal fixation also decrease the soft tissue complications and frequent follow-up required with functional bracing. A triceps-reflecting posterior approach provides excellent exposure to the humerus and minimizes trauma to the triceps. An anatomically precontoured plate on the posterolateral surface of the humerus provides stable fixation of these injuries and is placed directly through the interval developed by the triceps-reflecting approach. METHODS: We retrospectively reviewed the trauma databases at 2

level I academic trauma institutions during a 5-year period for all patients with an extra-articular distal humerus fracture treated with a triceps-reflecting approach and an anatomically precontoured posterolateral distal humerus plate. Patient and fracture characteristics were recorded, as were QuickDASH functional scores and visual analog scale scores for pain, function, and quality of life. RESULTS: Forty patients were eligible for our study. Average follow-up was 88 weeks. Thirty-eight (95%) patients went on to union. Seven (20%) patients required a secondary procedure. The average QuickDASH score was 17.5 (range, 2.6-56.8). The average visual analog scale scores were 1.9 (range, 0-7) for pain, 2.3 (range, 0-8) for function, and 1.6 (range, 0-5) for quality of life. Thirty-five (87.5%) patients reported satisfaction with the outcome of their surgery. DISCUSSION: Surgical fixation of extra-articular distal humerus fractures through a triceps-reflecting approach with an anatomically precontoured posterolateral distal humerus plate results in predictable osseous union and overall excellent functional results for patients with this injury.

Sehi, M., Goharian, I., Konduru, R., Tan, O., Srinivas, S., Satta, S. R., . . . Greenfield, D. S. (2013).

Retinal Blood Flow in Glaucomatous Eyes with Single-Hemifield Damage. *Ophthalmology*, doi:10.1016/j.ophtha.2013.10.022

Purpose: To examine the hypotheses that in glaucomatous eyes with single-hemifield damage, retinal blood flow (RBF) is significantly reduced in the retinal hemisphere corresponding with the abnormal visual hemifield and that there are significant associations among reduced retinal sensitivity (RS) in the abnormal hemifield, RBF, and structural measurements in the corresponding hemisphere. Design: Prospective, nonrandomized, case-control study.

Participants: Thirty eyes of 30 patients with glaucoma with visual field loss confined to a single hemifield and 27 eyes of 27 controls. Methods: Normal and glaucomatous eyes underwent spectral-domain optical coherence tomography (SD-OCT) and standard automated perimetry. Doppler SD-OCT with a double-circle scanning pattern was used to measure RBF. The RBF was derived from the recorded Doppler frequency shift and the measured angle between the beam and the vessel. Total and hemispheric RBF, retinal nerve fiber layer (RNFL), and ganglion cell complex (GCC) values were calculated. The RS values were converted to 1/Lambert. Analysis of variance and regression analyses were performed. Main Outcome Measures: Total and

hemispheric RS, RBF, RNFL, and GCC values. Results: The total RBF (34.6 ± 12.2 $\mu\text{l}/\text{minute}$) and venous cross-sectional area (0.039 ± 0.009 mm^2) were reduced ($P < 0.001$) in those with glaucoma compared with controls (46.5 ± 10.6 $\mu\text{l}/\text{minute}$; 0.052 ± 0.012 mm^2). Mean RBF was reduced in the abnormal hemisphere compared with the opposite hemisphere (15.3 ± 5.4 vs. 19.3 ± 8.4 $\mu\text{l}/\text{minute}$; $P = 0.004$). The RNFL and GCC were thinner in the corresponding abnormal hemisphere compared with the opposite hemisphere (87.0 ± 20.2 vs. 103.7 ± 20.6 μm , $P = 0.002$; 77.6 ± 12.1 vs. 83.6 ± 10.1 μm , $P = 0.04$). The RBF was correlated with RNFL ($r = 0.41$; $P = 0.02$) and GCC ($r = 0.43$; $P = 0.02$) but not the RS ($r = 0.31$; $P = 0.09$) in the abnormal hemisphere. The RBF (19.3 ± 8.4 $\mu\text{l}/\text{minute}$), RNFL (103.7 ± 20.6 μm), and GCC (83.6 ± 10.1 μm) were reduced ($P < 0.05$) in the hemisphere with apparently normal visual field in glaucomatous eyes compared with the mean hemispheric values of the normal eyes (23.2 ± 5.3 $\mu\text{l}/\text{minute}$, 124.8 ± 9.6 μm , and 96.1 ± 5.7 μm , respectively). Conclusions: In glaucomatous eyes with single-hemifield damage, the RBF is significantly reduced in the hemisphere associated with the abnormal hemifield. Reduced RBF is associated with thinner RNFL and GCC in the corresponding abnormal hemisphere. Reduced RBF and RNFL and GCC loss also are observed in the perimetrically normal hemisphere of glaucomatous eyes. Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. © 2013 American Academy of Ophthalmology.

Selby, J. V., Smith, D. H., Johnson, E. S., Raebel, M. A., Friedman, G. D., & McFarland, B. H. (2007). *Kaiser Permanente Medical Care Program* John Wiley & Sons, Ltd.
doi:10.1002/9780470059876.ch15

Sengle, G., Charbonneau, N. L., Ono, R. N., & Sakai, L. Y. (2009). *Connective Tissue Pathways That Regulate Growth Factors* John Wiley & Sons, Inc. doi:10.1002/9780470623992.ch5

Shafritz, D. A., Oertel, M., Dabeva, M. D., & Grompe, M. (2009). *Liver Repopulation by Cell Transplantation and the Role of Stem Cells* John Wiley & Sons, Ltd.
doi:10.1002/9780470747919.ch38

Shaw, J. S., Norlin, C., Gillespie, R. J., Weissman, M., & McGrath, J. (2013). The national improvement partnership network: State-based partnerships that improve primary care quality.

Improvement partnerships (IPs) are a model for collaboration among public and private organizations that share interests in improving child health and the quality of health care delivered to children. Their partners typically include state public health and Medicaid agencies, the local chapter of the American Academy of Pediatrics, and an academic health care organization or children's hospital. Most IPs also engage other partners, including a variety of public, private, and professional organizations and individuals. IPs lead and support measurement-based, systems-focused quality improvement (QI) efforts that primarily target primary care practices that care for children. Their projects are most often conducted as learning collaboratives that involve a team from each of 8 to 15 participating practices over 9 to 12 months. The improvement teams typically include a clinician, office manager, clinical staff (nurses or medical assistants), and, for some projects, a parent; the IPs provide the staff and local infrastructure. The projects target clinical topics, chosen because of their importance to public health, local clinicians, and funding agencies, including asthma, attention-deficit/hyperactivity disorder, autism, developmental screening, obesity, mental health, medical home implementation, and several others. Over the past 13 years, 19 states have developed (and 5 are exploring developing) IPs. These organizations share similar aims and methods but differ substantially in leadership, structure, funding, and longevity. Their projects generally engage pediatric and family medicine practices ranging from solo private practices to community health centers to large corporate practices. The practices learn about the project topic and about QI, develop specific improvement strategies and aims that align with the project aims, perform iterative measures to evaluate and guide their improvements, and implement systems and processes to support and sustain those improvements. Since 2008, IPs have offered credit toward Part 4 of Maintenance of Certification for participants in some of their projects. To date, IPs have focused on achieving improvements in care delivery through individual projects. Rigorous measurement and evaluation of their efforts and impact will be essential to understanding, spreading, and sustaining state/regional child health care QI programs. We describe the origins, evolution to date, and hopes for the future of these partnerships and the National Improvement Partnership Network (NIPN), which was established to support existing and nurture new IPs. Copyright © 2013 by Academic Pediatric Association.

Sideras, S., McKenzie, G., Noone, J., Markle, D., Frazier, M., & Sullivan, M. (2013). Making simulation come alive: Standardized patients in undergraduate nursing education. *Nursing Education Perspectives, 34*(6), 421-425. doi:10.5480/1536-5026-34.6.421

Simon, T. D., Starmer, A. J., Conway, P. H., Landrigan, C. P., Shah, S. S., Shen, M. W., . . . Wilson, K. M. (2013). Quality improvement research in pediatric hospital medicine and the role of the Pediatric Research in Inpatient Settings (PRIS) network. *Academic Pediatrics, 13*(6 SUPPL.), S54-S60. doi:10.1016/j.acap.2013.04.006

Pediatric hospitalists care for many hospitalized children in community and academic settings, and they must partner with administrators, other inpatient care providers, and researchers to assure the reliable delivery of high-quality, safe, evidence-based, and cost-effective care within the complex inpatient setting. Paralleling the growth of the field of pediatric hospital medicine is the realization that innovations are needed to address some of the most common clinical questions. Some of the unique challenges facing pediatric hospitalists include the lack of evidence for treating common conditions, children with chronic complex conditions, compressed time frame for admissions, and the variety of settings in which hospitalists practice. Most pediatric hospitalists are engaged in some kind of quality improvement (QI) work as hospitals provide many opportunities for QI activity and innovation. There are multiple national efforts in the pediatric hospital medicine community to improve quality, including the Children's Hospital Association (CHA) collaboratives and the Value in Pediatrics Network (VIP). Pediatric hospitalists are also challenged by the differences between QI and QI research; understanding that while improving local care is important, to provide consistent quality care to children we must study single-center and multicenter QI efforts by designing, developing, and evaluating interventions in a rigorous manner, and examine how systems variations impact implementation. The Pediatric Research in Inpatient Setting (PRIS) network is a leader in QI research and has several ongoing projects. The Prioritization project and Pediatric Health Information System Plus (PHIS+) have used administrative data to study variations in care, and the IPE-PRIS Accelerating Safe Sign-outs (I-PASS) study highlights the potential for innovative QI research methods to improve care and clinical training. We address the importance, current state, accomplishments, and challenges of QI and QI research in pediatric hospital medicine; define the role of the PRIS Network in QI

research; describe an exemplary QI research project, the I-PASS Study; address challenges for funding, training and mentorship, and publication; and identify future directions for QI research in pediatric hospital medicine. Copyright © 2013 by Academic Pediatric Association.

Slack, J. R., & Woods, M. (2013). The effect of regioisomerism on the coordination chemistry and CEST properties of lanthanide(III) NB-DOTA-tetraamide chelates. *Journal of Biological Inorganic Chemistry*, , 1-17. doi:10.1007/s00775-013-1060-y

Chemical exchange saturation transfer (CEST) offers many advantages as a method of generating contrast in magnetic resonance images. However, many of the exogenous agents currently under investigation suffer from detection limits that are still somewhat short of what can be achieved with more traditional Gd³⁺ agents. To remedy this limitation we have undertaken an investigation of Ln³⁺ DOTA-tetraamide chelates (where DOTA is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) that have unusually rigid ligand structures: the nitrobenzyl derivatives of DOTA-tetraamides with (2-phenylethyl)amide substituents. In this report we examine the effect of incorporating hydrophobic amide substituents on water exchange and CEST. The ligand systems chosen afforded a total of three CEST-active isomeric square antiprismatic chelates; each of these chelates was found to have different water exchange and CEST characteristics. The position of a nitrobenzyl substituent on the macrocyclic ring strongly influenced the way in which the chelate and Ln³⁺ coordination cage distorted. These differential distortions were found to affect the rate of water proton exchange in the chelates. But, by far the greatest effect arose from altering the position of the hydrophobic amide substituent, which, when forced upwards around the water binding site, caused a substantial reduction in the rate of water proton exchange. Such slow water proton exchange afforded a chelate that was 4.5 times more effective as a CEST agent than its isomeric counterparts in dry acetonitrile and at low temperatures and very low presaturation powers. © 2013 SBIC.

Slater, M. S. (2006). *Minimally invasive saphenous vein harvesting for coronary artery bypass grafting*. Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8_39

Despite the steadily increasing use of arterial grafts, the greater saphenous vein remains the most commonly used conduit for coronary artery bypass grafting (CABG). Utilized sporadically in

the late 1950s and early 1960s, saphenous vein use for coronary artery bypass grafting increased exponentially in the 1970s and 1980s. Patency rates following coronary bypass grafting using saphenous vein have been reported to be 78%, 65%, and 57% at 1, 5, and 10 years respectively [1]. The saphenous vein has been proven versatile, has provided reliable results, and remains central to the conduct of surgical revascularization of the heart. Traditionally, the greater saphenous vein has been harvested via a continuous or near continuous incision on the medial aspect of the lower extremity [2]. This approach is attractive in several ways as it provides excellent exposure, is rapid, does not require specialized equipment, and can be carried out by team members with basic surgical skills such as physician's assistants and surgical trainees. Unfortunately, complications such as wound infections and seromas are frequently associated with the long incisions required for the open technique. Wound infection rates from 14% to 26% have been reported [3-5] and overall complication rates as high as 43% have been described [6]. Co-morbidities such as obesity, peripheral vascular disease, and diabetes are all associated with increased wound complication rates and are prevalent in this patient population. The high rate of complications associated with lower extremity vein harvest incisions is not unexpected given the debilitated, aging population of patients currently undergoing coronary artery bypass surgery. The highly varied rates of complications reported in studies of saphenous vein harvest may be explained by differing definitions of complications, duration and quality of follow-up, and variations in patient population and surgical technique. Because the majority of complications related to lower extremity harvest incisions develop after hospital discharge, studies without formal follow-up often underestimate wound complications. The high complication rate associated with saphenous vein harvest and the growing trend to less invasive surgical techniques has motivated cardiac surgical teams to explore ways of minimizing the morbidity associated with traditional saphenous vein harvest. Endoscopic vein harvest was reported by Lumsden in 1994 [7] and has slowly gained acceptance in the practice of cardiac surgery. This chapter will outline the techniques, benefits, and limitations of minimally invasive vein harvest techniques for use in coronary artery bypass surgery (Table 39.1). © Springer-Verlag Berlin Heidelberg 2006.

Slater, M. S. (2007). *Heart* Springer New York. doi:10.1007/978-0-387-69012-4_25

Seven days after undergoing a thoracotomy and repair of a cardiac laceration, a 22-year-old

patient develops tachycardia, substernal chest pain (worse on inspiration) and fatigue. He is afebrile and hemodynamically stable. On auscultation, a pericardial friction rub is discovered. Electrocardiography demonstrates ST segment elevation throughout the pericardium. Helical computed tomography scan shows no evidence of a pulmonary embolism. Chest x-ray reveals expanded bilateral lungs and a normal cardiac silhouette. Which of the following would be the most appropriate management approach? (A) Administration of a nonsteroidal antiinflammatory agent (B) Pericardiocentesis (C) Reexploration (D) Insertion of a pulmonary artery catheter (E) Cardiac catheterization © 2007 Springer-Verlag New York.

Slifka, M. K., Leung, D. Y., Hammarlund, E., Raue, H. P., Simpson, E. L., Tofte, S., . . . Hanifin, J. (2013). Transcutaneous yellow fever vaccination of subjects with or without atopic dermatitis. *The Journal of Allergy and Clinical Immunology*, doi:10.1016/j.jaci.2013.10.037; 10.1016/j.jaci.2013.10.037

BACKGROUND: Atopic dermatitis (AD) is a common inflammatory skin disease with a global prevalence ranging from 3% to 20%. Patients with AD have an increased risk for complications after viral infection (eg, herpes simplex virus), and vaccination of patients with AD with live vaccinia virus is contraindicated because of a heightened risk of eczema vaccinatum, a rare but potentially lethal complication associated with smallpox vaccination. **OBJECTIVE:** We sought to develop a better understanding of immunity to cutaneous viral infection in patients with AD. **METHODS:** In a double-blind randomized study we investigated the safety and immunogenicity of live attenuated yellow fever virus (YFV) vaccination of nonatopic subjects and patients with AD after standard subcutaneous inoculation or transcutaneous vaccination administered with a bifurcated needle. Viremia, neutralizing antibody, and antiviral T-cell responses were analyzed for up to 30 days after vaccination. **RESULTS:** YFV vaccination administered through either route was well tolerated. Subcutaneous vaccination resulted in higher seroconversion rates than transcutaneous vaccination but elicited similar antiviral antibody levels and T-cell responses in both the nonatopic and AD groups. After transcutaneous vaccination, both groups mounted similar neutralizing antibody responses, but patients with AD demonstrated lower antiviral T-cell responses by 30 days after vaccination. Among transcutaneously vaccinated subjects, a significant inverse correlation between baseline IgE levels and the magnitude of antiviral antibody

and CD4+ T-cell responses was observed. CONCLUSIONS: YFV vaccination of patients with AD through the transcutaneous route revealed that high baseline IgE levels provide a potential biomarker for predicting reduced virus-specific immune memory after transcutaneous infection with a live virus.

Smith, R., McIlwraith, W., Schweitzer, R., Kadler, K., Cook, J., Caterson, B., . . . Nixon, A. (2014).

Advances in the understanding of tendinopathies: A report on the Second Havemeyer Workshop on equine tendon disease. *Equine Veterinary Journal*, 46(1), 4-9. doi:10.1111/evj.12128

Smith, T. L., & Sautter, N. B. (2013). Is montelukast indicated for treatment of chronic rhinosinusitis with polyposis? *Laryngoscope*, doi:10.1002/lary.24477

Song, H. K., Tibayan, F. A., Kahl, E. A., Sera, V. A., Slater, M. S., Deloughery, T. G., & Scanlan, M. M.

(2013). Safety and efficacy of prothrombin complex concentrates for the treatment of coagulopathy after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery*, doi:10.1016/j.jtcvs.2013.11.020; 10.1016/j.jtcvs.2013.11.020

OBJECTIVE: Coagulopathy is an important cause of bleeding after complex cardiac surgery. The conventional treatment for coagulopathy is transfusion, which is associated with adverse outcomes. We report our initial experience with the prothrombin complex concentrate FEIBA (factor VIII inhibitor bypassing activity) for the rescue treatment of coagulopathy and life-threatening bleeding after cardiac surgery. METHODS: Twenty-five patients who underwent cardiac surgery with coagulopathy and life-threatening bleeding refractory to conventional treatment received FEIBA as rescue therapy at our institution. This cohort represents approximately 2% of patients undergoing cardiac surgery in our university-based practice during the study. RESULTS: The patients were at high risk for postoperative coagulopathy with nearly all patients having at least 2 risk factors for this. Aortic root replacement (Bentall or valve-sparing procedure) and heart transplant with or without left ventricular assist device explant were the most common procedures. The mean FEIBA dose was 2154 units. The need for fresh frozen plasma and platelet transfusion decreased significantly after FEIBA administration ($P = .0001$ and $P < .0001$). The mean internationalized normalized ratio decreased from 1.58 to 1.13 ($P < .0001$). Clinical outcomes were excellent. No patient returned to the operating room for

reexploration. There was no hospital mortality and all patients were discharged home. One patient who had a central line and transvenous pacemaker developed an upper extremity deep vein thrombosis. CONCLUSIONS: Our initial experience with FEIBA administration for the rescue treatment of postoperative coagulopathy and life-threatening bleeding has been favorable. Further studies are indicated to confirm its efficacy and safety and determine specific clinical indications for its use in patients undergoing cardiac surgery.

Sonnenberg, A. (2009). *Cost-Effectiveness of Colonoscopy Screening* Wiley-Blackwell.

doi:10.1002/9781444316902.ch18

Soot, L., Weerasinghe, R., Wang, L., & Nelson, H. D. (2013). Rates and indications for surgical breast

biopsies in a community-based health system. *American Journal of Surgery*,

doi:10.1016/j.amjsurg.2013.07.046

Background: High rates of surgical breast biopsies in community hospitals have been reported but may misrepresent actual practice. Methods: Patient-level data from 5,757 women who underwent breast biopsies in a large integrated health system were evaluated to determine biopsy types, rates, indications, and diagnoses. Results: Between 2008 and 2010, 6,047 breast biopsies were performed on 5,757 women. Surgical biopsy was the initial diagnostic procedure in 16% (n = 942) of women overall and in 6% (72 of 1,236) of women with newly diagnosed invasive breast cancer. Invasive breast cancer was diagnosed in 72 women (8%) undergoing surgical biopsy compared with 1,164 (24%) undergoing core needle biopsy (P < .001, age adjusted). Main indications for surgical biopsies included symptomatic abnormalities, technical challenges, and patient choice. Conclusions: Surgical biopsy was the initial diagnostic procedure in 16% of women with breast abnormalities, comparable with rates at academic centers. Rates could be improved by more careful consideration of indications. © 2013 Elsevier Inc. All rights reserved.

Stacey, D., Kryworuchko, J., Belkora, J., Davison, B. J., Durand, M. -, Eden, K. B., . . . Street, R. L.

(2013). Coaching and guidance with patient decision aids: A review of theoretical and empirical evidence. *BMC Medical Informatics and Decision Making*, 13(SUPPL. 2) doi:10.1186/1472-6947-

13-S2-S11

Background: Coaching and guidance are structured approaches that can be used within or alongside patient decision aids (PtDAs) to facilitate the process of decision making. Coaching is provided by an individual, and guidance is embedded within the decision support materials. The purpose of this paper is to: a) present updated definitions of the concepts "coaching" and "guidance"; b) present an updated summary of current theoretical and empirical insights into the roles played by coaching/guidance in the context of PtDAs; and c) highlight emerging issues and research opportunities in this aspect of PtDA design. Methods. We identified literature published since 2003 on shared decision making theoretical frameworks inclusive of coaching or guidance. We also conducted a sub-analysis of randomized controlled trials included in the 2011 Cochrane Collaboration Review of PtDAs with search results updated to December 2010. The sub-analysis was conducted on the characteristics of coaching and/or guidance included in any trial of PtDAs and trials that allowed the impact of coaching and/or guidance with PtDA to be compared to another intervention or usual care. Results: Theoretical evidence continues to justify the use of coaching and/or guidance to better support patients in the process of thinking about a decision and in communicating their values/preferences with others. In 98 randomized controlled trials of PtDAs, 11 trials (11.2%) included coaching and 63 trials (64.3%) provided guidance. Compared to usual care, coaching provided alongside a PtDA improved knowledge and decreased mean costs. The impact on some other outcomes (e.g., participation in decision making, satisfaction, option chosen) was more variable, with some trials showing positive effects and other trials reporting no differences. For values-choice agreement, decisional conflict, adherence, and anxiety there were no differences between groups. None of these outcomes were worse when patients were exposed to decision coaching alongside a PtDA. No trials evaluated the effect of guidance provided within PtDAs. Conclusions: Theoretical evidence continues to justify the use of coaching and/or guidance to better support patients to participate in decision making. However, there are few randomized controlled trials that have compared the effectiveness of coaching used alongside PtDAs to PtDAs without coaching, and no trials have compared the PtDAs with guidance to those without guidance. © 2013 Stacey et al; licensee BioMed Central Ltd.

Starmer, A. J., Sectish, T. C., Simon, D. W., Keohane, C., McSweeney, M. E., Chung, E. Y., . . . Landrigan, C. P. (2013). Rates of medical errors and preventable adverse events among

hospitalized children following implementation of a resident handoff bundle. *JAMA : The Journal of the American Medical Association*, 310(21), 2262-2270. doi:10.1001/jama.2013.281961; 10.1001/jama.2013.281961

IMPORTANCE: Handoff miscommunications are a leading cause of medical errors. Studies comprehensively assessing handoff improvement programs are lacking. **OBJECTIVE:** To determine whether introduction of a multifaceted handoff program was associated with reduced rates of medical errors and preventable adverse events, fewer omissions of key data in written handoffs, improved verbal handoffs, and changes in resident-physician workflow. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective intervention study of 1255 patient admissions (642 before and 613 after the intervention) involving 84 resident physicians (42 before and 42 after the intervention) from July-September 2009 and November 2009-January 2010 on 2 inpatient units at Boston Children's Hospital. **INTERVENTIONS:** Resident handoff bundle, consisting of standardized communication and handoff training, a verbal mnemonic, and a new team handoff structure. On one unit, a computerized handoff tool linked to the electronic medical record was introduced. **MAIN OUTCOMES AND MEASURES:** The primary outcomes were the rates of medical errors and preventable adverse events measured by daily systematic surveillance. The secondary outcomes were omissions in the printed handoff document and resident time-motion activity. **RESULTS:** Medical errors decreased from 33.8 per 100 admissions (95% CI, 27.3-40.3) to 18.3 per 100 admissions (95% CI, 14.7-21.9; $P < .001$), and preventable adverse events decreased from 3.3 per 100 admissions (95% CI, 1.7-4.8) to 1.5 (95% CI, 0.51-2.4) per 100 admissions ($P = .04$) following the intervention. There were fewer omissions of key handoff elements on printed handoff documents, especially on the unit that received the computerized handoff tool (significant reductions of omissions in 11 of 14 categories with computerized tool; significant reductions in 2 of 14 categories without computerized tool). Physicians spent a greater percentage of time in a 24-hour period at the patient bedside after the intervention (8.3%; 95% CI 7.1%-9.8%) vs 10.6% (95% CI, 9.2%-12.2%; $P = .03$). The average duration of verbal handoffs per patient did not change. Verbal handoffs were more likely to occur in a quiet location (33.3%; 95% CI, 14.5%-52.2% vs 67.9%; 95% CI, 50.6%-85.2%; $P = .03$) and private location (50.0%; 95% CI, 30%-70% vs 85.7%; 95% CI, 72.8%-98.7%; $P = .007$) after the intervention. **CONCLUSIONS AND RELEVANCE:** Implementation of a handoff bundle was associated with a significant reduction

in medical errors and preventable adverse events among hospitalized children. Improvements in verbal and written handoff processes occurred, and resident workflow did not change adversely.

Stone, M. P., Huang, H., Cho, Y. .-, Kim, H. .-, Kozekov, I. D., Kozekova, A., . . . Lloyd, R. S. (2010).

Interstrand DNA Cross-Linking 1, N 2-Deoxyguanosine Adducts Derived from α,β -Unsaturated Aldehydes: Structure-Function Relationships Wiley-VCH Verlag GmbH & Co. KGaA.

doi:10.1002/9783527630110.ch9

Stouffer, R. L., Bishop, C. V., Bogan, R. L., Xu, F., & Hennebold, J. D. (2013). Endocrine and local control of the primate corpus luteum. *Reproductive Biology*, 13(4), 259-271.

doi:10.1016/j.repbio.2013.08.002; 10.1016/j.repbio.2013.08.002

The primate corpus luteum is a transient endocrine gland that differentiates from the ovulatory follicle midway through the ovarian (menstrual) cycle. Its formation and limited lifespan is critical for fertility, as luteal-derived progesterone is the essential steroid hormone required for embryo implantation and maintenance of intra-uterine pregnancy until the placenta develops. It is well-established that LH and the LH-like hormone, CG, are the vital luteotropic hormones during the menstrual cycle and early pregnancy, respectively. Recent advances, particularly through genome analyses and cellular studies, increased our understanding of various local factors and cellular processes associated with the development, maintenance and regression of the corpus luteum. These include paracrine or autocrine factors associated with angiogenesis (e.g., VEGF), and that mediate LH/CG actions (e.g., progesterone), or counteract luteotropic effects (i.e., local luteolysis; e.g., PGF2alpha). However, areas of mystery and controversy remain, particularly regarding the signals and events that initiate luteal regression in the non-fecund cycle. Novel approaches capable of gene "knockdown" or amplification", in vivo as well as in vitro, should identify novel or underappreciated gene products that are regulated by or modulate LH/CG actions to control the functional lifespan of the primate corpus luteum. Further advances in our understanding of luteal physiology will help to improve or control fertility for purposes ranging from preservation of endangered primate species to designing novel ovary-based contraceptives and treating ovarian disorders in women.

Streu, R., Hansen, J., Abrahamse, P., & Alderman, A. K. (2013). Professional Burnout Among US

Plastic Surgeons: Results of a National Survey. *Annals of Plastic Surgery*,

doi:10.1097/SAP.0000000000000056

PURPOSE: Little is known about professional burnout among plastic surgeons. Our purpose is to describe its prevalence among a large national sample of plastic surgeons and identify contributing factors. METHODS: A mailed, self-administered survey was sent to 708 plastic surgeons who were randomly sampled from the American Society of Plastic Surgeons national membership (71% response rate). The dependent variable was professional burnout, measured by 3 subscales from the validated Maslach Burnout Inventory-Human Services Survey. "High" scores in either the emotional exhaustion or depersonalization subscale categories predict professional burnout. The independent variables included surgeon sociodemographic and professional characteristics. chi was used for the bivariate analyses. RESULTS: Nearly one third (29%) of surgeons scored high in subscale categories predictive of professional burnout. Factors associated with high emotional exhaustion scores included surgeon age, 40-50 years ($P = 0.03$); fair/poor physician health ($P = 0.03$); 60 work hours per week ($P = 0.03$); primarily reconstructive practice ($P < 0.01$); private practice ($P = 0.01$); and group practice ($P = 0.02$). Factors associated with high depersonalization scores included fair/poor physician health ($P = 0.01$); ER call ($P < 0.01$); private practice ($P = 0.01$); and group practice ($P = 0.02$). CONCLUSIONS: Nearly one third of plastic surgeons have signs of professional burnout. Middle-aged surgeons and those in poor health are most at risk; along with those who have a reconstructive rather than cosmetic practice, long work hours, ER call responsibility, a nonacademic setting, and group as compared to solo practice. These data have important implications for future workforce shortages and health care quality.

Stussman, B. J., Bethell, C. D., Gray, C., & Nahin, R. L. (2013). Development of the adult and child

complementary medicine questionnaires fielded on the National Health Interview Survey. *BMC*

Complementary and Alternative Medicine, 13 doi:10.1186/1472-6882-13-328

The 2002, 2007, and 2012 complementary medicine questionnaires fielded on the National Health Interview Survey provide the most comprehensive data on complementary medicine available for the United States. They filled the void for large-scale, nationally representative, publicly available

datasets on the out-of-pocket costs, prevalence, and reasons for use of complementary medicine in the U.S. Despite their wide use, this is the first article describing the multi-faceted and largely qualitative processes undertaken to develop the surveys. We hope this in-depth description enables policy makers and researchers to better judge the content validity and utility of the questionnaires and their resultant publications. © 2013 Stussman et al.; licensee BioMed Central Ltd.

Sullivan, E. L., Nousen, E. K., & Chamlou, K. A. (2014). *Maternal high fat diet consumption during the perinatal period programs offspring behavior* doi:10.1016/j.physbeh.2012.07.014

The environment that a developing offspring experiences during the perinatal period is markedly influenced by maternal health and diet composition. Evidence from both epidemiological studies and animal models indicates that maternal diet and metabolic status play a critical role in programming the neural circuitry that regulates behavior, resulting in long-term consequences for offspring behavior. Maternal diet and metabolic state influence the behavior of offspring directly by impacting the intrauterine environment and indirectly by modulating maternal behavior. The mechanisms by which maternal diet and metabolic profile shape the perinatal environment remain largely unknown, but recent research has found that increases in inflammatory cytokines, nutrients (glucose and fatty acids), and hormones (insulin and leptin) affect the environment of the developing offspring. Offspring exposed to maternal obesity and high fat diet consumption during development are more susceptible to developing mental health and behavioral disorders such as anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders. Recent evidence suggests that this increased risk for behavioral disorders is driven by modifications in the development of neural pathways involved in behavioral regulation. In particular, research indicates that the development of the serotonergic system is impacted by exposure to maternal obesity and high fat diet consumption, and this disruption may underlie many of the behavioral disturbances observed in these offspring. Given the high rates of obesity and high fat diet consumption in pregnant women, it is vital to examine the influence that maternal nutrition and metabolic profile have on the developing offspring. © 2012 Elsevier Inc.

Swanson, N., Smith, C. C., Kaur, M., & Goldenberg, G. (2013). Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Two phase 3 multicenter, randomized, double-blind, placebo-controlled studies. *Journal of Drugs in Dermatology*, 12(11), 1278-1282.

Background: Imiquimod 3.75% and 2.5% creams were studied for the treatment of actinic keratosis (AK) of the full face or balding scalp, to determine comparable efficacy and tolerability to imiquimod 5% cream. Methods: In two identical multicenter, randomized, double-blind, placebo controlled studies. Adult subjects with 5 to 20 visible lesions, or palpable AKs in an area that exceeded 25cm² on either the face or balding scalp were randomized to imiquimod 3.75%, 2.5% or vehicle cream (1:1:1) applied once daily for two 2-week treatment cycles, with a 2-week, no-treatment interval between cycles. Efficacy was assessed 8 weeks posttreatment (End of Study Visit [EOS]). Primary efficacy was rate of complete clearance of AK lesions. Secondary efficacy endpoints were rate of partial clearance at EOS (> 75% reduction in number of AK lesions compared to baseline) and median percent decrease from baseline lesion count. Safety assessments included visual assessment of local skin reactions (LSRs), number and duration of study treatment rest periods required due to intolerant LSRs, adverse events (AEs) and clinical laboratory tests. Results: Overall 479 patients were randomized to imiquimod 3.75%, 2.5%, or vehicle. Complete clearance rates were 35.6%, 30.6%, and 6.3% respectively (both P<.001 versus vehicle). The difference in complete clearance rates (imiquimod minus vehicle) was 29.3% and 24.3%, respectively. Partial clearance rates were 59.4%, 48.1 %, and 22.6% respectively (both P<.001 versus vehicle). Median % reductions in AK lesions were 81.8%, 71.8%, and 25.0% respectively (-<.001 versus vehicle). All primary and secondary efficacy end- points were greater in Study 1. Photodamage in the treatment area was 'much improved' with imiquimod 3.75%. Both active creams were well tolerated with few treatment-related discontinuations. Conclusions: In two well-controlled Phase 3 studies, both imiquimod 3.75% and 2.5% creams were more effective than vehicle and well tolerated when administered daily as a 2-week on/off/on regimen to treat AK. Reduction in AK lesions was comparable to that reported with imiquimod 5% with fewer local AEs. Copyright © 2013.

Swanstrom, L. L., & Goers, T. A. (2011). *Lengthening gastroplasty for managing GERD and giant paraesophageal hernia* Springer London. doi:10.1007/978-1-84996-492-0_33

Hiatal hernias result from a multifactorial combination of the failure of diaphragmatic integrity, degeneration of the phrenoesophageal suspensory ligament, and the normal pressure differential between the thorax and abdomen; some combination of these factors results in the cephalad migration of the gastroesophageal junction (GEJ) and the anatomic shortening of the esophagus. These changes are often combined with some degree of gastroesophageal reflux (GER). GER can lead to chronic esophageal irritation and damage, with resulting thickening of the mucosal layers, sometimes development of intestinal type columnar epithelium, and progressive fibrosis and damage of the muscularis mucosa. In especially severe and chronic cases there can even be transmural changes in the mediastinum with hypervascularity and thickening of the normally pliable areolar tissues. These factors can lead to loss of the usual elasticity of the esophagus as well as causing it to be more fixed within the mediastinum. When this process is combined with hiatal herniation (or perhaps even partially causing such migration?) it can lead to not only anatomic shortening of the esophagus but also non-reversible shortening of the esophagus, which can make it impossible to replace the GEJ into the abdominal during anti-reflux surgery or paraesophageal hernia (PEH) repair. © Springer-Verlag London Limited 2011.

Terakedis, B. E., Anker, C. J., Leachman, S. A., Andtbacka, R. H., Bowen, G. M., Sause, W. T., . . .

Shrieve, D. C. (2013). Patterns of failure and predictors of outcome in cutaneous malignant melanoma of the scalp. *Journal of the American Academy of Dermatology*, doi:10.1016/j.jaad.2013.10.028; 10.1016/j.jaad.2013.10.028

BACKGROUND: Patients with melanoma of the scalp may have higher failure rates than melanoma of other body sites. OBJECTIVE: We sought to characterize survival and patterns of failure for patients with scalp melanoma. METHODS: Between 1998 and 2010, 250 nonmetastatic patients underwent wide local excision of a primary scalp melanoma. Kaplan-Meier analyses were performed to evaluate overall survival, scalp control, regional neck control, distant metastases-free survival, and disease-free survival. RESULTS: Five-year overall survival was 86%, 57%, and 45% for stages I, II, and III, respectively, and 5-year scalp control rates were 92%, 75%, and 63%, respectively. Five-year distant metastases-free survival for these stages were 92%, 65%, and 45%, respectively. Of the 74 patients who recurred, the site of first recurrence included distant disease in 47%, although 31% recurred in the scalp alone. LIMITATIONS: This is a

retrospective review. CONCLUSION: Distant metastases-free survival and overall survival for stage II and III patients with scalp melanoma are poor, and stage III patients experience relatively high rates of scalp failure suggesting that these patients may benefit from additional adjuvant systemic and local therapy. Further research is needed to characterize the environmental, microenvironmental, and genetic causes of the increased aggressiveness of scalp melanoma and to identify more effective treatment and surveillance methods.

The Parkinson Study Group SURE-PD Investigators, Schwarzschild, M. A., Ascherio, A., Beal, M. F., Cudkovicz, M. E., Curhan, G. C., . . . Eaton, K. (2013). Inosine to Increase Serum and Cerebrospinal Fluid Urate in Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurology*, doi:10.1001/jamaneurol.2013.5528; 10.1001/jamaneurol.2013.5528

IMPORTANCE Convergent biological, epidemiological, and clinical data identified urate elevation as a candidate strategy for slowing disability progression in Parkinson disease (PD). OBJECTIVE To determine the safety, tolerability, and urate-elevating capability of the urate precursor inosine in early PD and to assess its suitability and potential design features for a disease-modification trial. DESIGN, SETTING, AND PARTICIPANTS The Safety of Urate Elevation in PD (SURE-PD) study, a randomized, double-blind, placebo-controlled, dose-ranging trial of inosine, enrolled participants from 2009 to 2011 and followed them for up to 25 months at outpatient visits to 17 credentialed clinical study sites of the Parkinson Study Group across the United States. Seventy-five consenting adults (mean age, 62 years; 55% women) with early PD not yet requiring symptomatic treatment and a serum urate concentration less than 6 mg/dL (the approximate population median) were enrolled. INTERVENTIONS Participants were randomized to 1 of 3 treatment arms: placebo or inosine titrated to produce mild (6.1-7.0 mg/dL) or moderate (7.1-8.0 mg/dL) serum urate elevation using 500-mg capsules taken orally up to 2 capsules 3 times per day. They were followed for up to 24 months (median, 18 months) while receiving the study drug plus 1 washout month. MAIN OUTCOMES AND MEASURES The prespecified primary outcomes were absence of unacceptable serious adverse events (safety), continued treatment without adverse event requiring dose reduction (tolerability), and elevation of urate assessed serially in serum and once (at 3 months) in cerebrospinal fluid. RESULTS Serious adverse events (17), including infrequent cardiovascular events, occurred at the same or lower rates in the

inosine groups relative to placebo. No participant developed gout and 3 receiving inosine developed symptomatic urolithiasis. Treatment was tolerated by 95% of participants at 6 months, and no participant withdrew because of an adverse event. Serum urate rose by 2.3 and 3.0 mg/dL in the 2 inosine groups ($P < .001$ for each) vs placebo, and cerebrospinal fluid urate level was greater in both inosine groups ($P = .006$ and $<.001$, respectively). Secondary analyses demonstrated nonfutility of inosine treatment for slowing disability. **CONCLUSIONS AND RELEVANCE** Inosine was generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. The findings support advancing to more definitive development of inosine as a potential disease-modifying therapy for PD. **TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00833690.

Thompson, M., Vodicka, T. A., Blair, P. S., Buckley, D. I., Heneghan, C., & Hay, A. D. (2013). Duration of symptoms of respiratory tract infections in children: Systematic review. *BMJ (Online)*, *347* doi:10.1136/bmj.f7027

Objective: To determine the expected duration of symptoms of common respiratory tract infections in children in primary and emergency care. **Design:** Systematic review of existing literature to determine durations of symptoms of earache, sore throat, cough (including acute cough, bronchiolitis, and croup), and common cold in children. **Data sources:** PubMed, DARE, and CINAHL (all to July 2012). **Eligibility criteria for selecting studies** Randomised controlled trials or observational studies of children with acute respiratory tract infections in primary care or emergency settings in high income countries who received either a control treatment or a placebo or over-the-counter treatment. **Study quality** was assessed with the Cochrane risk of bias framework for randomised controlled trials, and the critical appraisal skills programme framework for observational studies. **Main outcome measures:** Individual study data and, when possible, pooled daily mean proportions and 95% confidence intervals for symptom duration. Symptom duration (in days) at which each symptom had resolved in 50% and 90% of children. **Results:** Of 22 182 identified references, 23 trials and 25 observational studies met inclusion criteria. Study populations varied in age and duration of symptoms before study onset. In 90% of children, earache was resolved by seven to eight days, sore throat between two and seven days, croup by two days, bronchiolitis by 21 days, acute cough by 25 days, common cold by 15 days, and non-

specific respiratory tract infections symptoms by 16 days. Conclusions: The durations of earache and common colds are considerably longer than current guidance given to parents in the United Kingdom and the United States; for other symptoms such as sore throat, acute cough, bronchiolitis, and croup the current guidance is consistent with our findings. Updating current guidelines with new evidence will help support parents and clinicians in evidence based decision making for children with respiratory tract infections.

Tipps, M. E., Raybuck, J. D., & Lattal, K. M. (2013). Substance abuse, memory, and post-traumatic stress disorder. *Neurobiology of Learning and Memory*, doi:10.1016/j.nlm.2013.12.002; 10.1016/j.nlm.2013.12.002

A large body of literature demonstrates the effects of abused substances on memory. These effects differ depending on the drug, the pattern of delivery (acute or chronic), and the drug state at the time of learning or assessment. Substance use disorders involving these drugs are often comorbid with anxiety disorders, such as post-traumatic stress disorder (PTSD). When the cognitive effects of these drugs are considered in the context of the treatment of these disorders, it becomes clear that these drugs may play a deleterious role in the development, maintenance, and treatment of PTSD. In this review, we examine the literature evaluating the cognitive effects of three commonly abused drugs: nicotine, cocaine, and alcohol. These three drugs operate through both common and distinct neurobiological mechanisms and alter learning and memory in multiple ways. We consider how the cognitive and affective effects of these drugs interact with the acquisition, consolidation, and extinction of learned fear, and we discuss the potential impediments that substance abuse creates for the treatment of PTSD.

Torniai, C., Essaid, S., Barnes, C., Conlon, M., Williams, S., Hajagos, J. G., . . . Haendel, M. (2013).

From EHRs to Linked Data: representing and mining encounter data for clinical expertise evaluation. *AMIA Summits on Translational Science Proceedings AMIA Summit on Translational Science, 2013*, 165.

Translational science, today, involves multidisciplinary teams of scientists rather than single scientists. Teams facilitate biologically meaningful and clinically consequential breakthroughs.

There are a myriad of sources of data about investigators, physicians, research resources, clinical

encounters, and expertise to promote team interaction; however, much of this information is not connected and is left siloed. Large amounts of data have been published as Linked Data (LD), but there still remains a significant gap in the representation and connection of research resources and clinical expertise data. The CTSAconnect project addresses the problem of fragmentation and incompatible coding of information by creating a Semantic Framework that facilitates the production and consumption of LD about biomedical research resources, clinical activities, as well as investigator and physician expertise.

Turco, R. (2008). *Criminal profile construction and investigative procedures: Study of the Westley Dodd serial sexual murders* Humana Press. doi:10.1007/978-1-60327-049-6_14

This chapter deals with the development and construction of a criminal profile. The integration of a psychological profile with an ongoing investigation is discussed in the context of a multiple child serial murder investigation. The importance of teamwork involving various members of a homicide task force and the independent skills they bring to an investigation is emphasized. Psychodynamic factors are reviewed on a theoretical basis, but emphasis is placed on practical investigative techniques and factual information. The material integrates forensic science, psychological issues, and detective work. The purpose is to provide an adjunct to an overall homicide investigation. © 2008 Humana Press.

Turner, A. P., Chapko, M. K., Yanez, D., Leipertz, S. L., Sloan, A. P., Whitham, R. H., & Haselkorn, J. K. (2013). Access to multiple sclerosis specialty care. *PM and R*, 5(12), 1044-1050. doi:10.1016/j.pmrj.2013.07.009

Background: Health care providers recommend an annual visit to a multiple sclerosis specialty care provider. Objective: To examine potential barriers to the implementation of this recommendation in the Veterans Health Administration. Design: Observational cohort study. Setting: Veterans Health Administration. Participants: Participants were drawn from the Veterans Affairs Multiple Sclerosis National Data Repository and were included if they had an outpatient visit in 2007 and were alive in 2008 (N= 14,723). Main Outcome Measurements: Specialty care visit, receipt of medical services. Results: A total of 9643 (65.5%) participants had a specialty care visit in 2007. Veterans who were service connected, had greater medical comorbidity, and

who lived in urban settings were more likely to have received a specialty care visit. Veterans who were older and had to travel greater distances to a center were less likely to have a specialty care visit. Conclusions: Access to care in rural areas and areas at a greater distance from a major medical center represent notable barriers to rehabilitation and other multiple sclerosis-related care. © 2013 American Academy of Physical Medicine and Rehabilitation.

Turner, E. H. (2013). How to access and process FDA drug approval packages for use in research. *BMJ (Online)*, 347 doi:10.1136/bmj.f5992

Tuz, K., Bachmann-Gagescu, R., O'Day, D. R., Hua, K., Isabella, C. R., Phelps, I. G., . . . Ferland, R. J. (2013). Mutations in CSPP1 Cause Primary Cilia Abnormalities and Joubert Syndrome with or without Jeune Asphyxiating Thoracic Dystrophy. *American Journal of Human Genetics*, doi:10.1016/j.ajhg.2013.11.019; 10.1016/j.ajhg.2013.11.019

Joubert syndrome (JBTS) is a recessive ciliopathy in which a subset of affected individuals also have the skeletal dysplasia Jeune asphyxiating thoracic dystrophy (JATD). Here, we have identified biallelic truncating CSPP1 (centrosome and spindle pole associated protein 1) mutations in 19 JBTS-affected individuals, four of whom also have features of JATD. CSPP1 mutations explain approximately 5% of JBTS in our cohort, and despite truncating mutations in all affected individuals, the range of phenotypic severity is broad. Morpholino knockdown of *cspp1* in zebrafish caused phenotypes reported in other zebrafish models of JBTS (curved body shape, pronephric cysts, and cerebellar abnormalities) and reduced ciliary localization of Arl13b, further supporting loss of CSPP1 function as a cause of JBTS. Fibroblasts from affected individuals with CSPP1 mutations showed reduced numbers of primary cilia and/or short primary cilia, as well as reduced axonemal localization of ciliary proteins ARL13B and adenyl cyclase III. In summary, CSPP1 mutations are a major cause of the Joubert-Jeune phenotype in humans; however, the mechanism by which these mutations lead to both JBTS and JATD remains unknown.

Ulloa-Aguirre, A., Zariñán, T., Dias, J. A., & Conn, P. M. (2014). Mutations in G protein-coupled receptors that impact receptor trafficking and reproductive function. *Molecular and Cellular Endocrinology*, 382(1), 411-423. doi:10.1016/j.mce.2013.06.024

G protein coupled receptors (GPCRs) are a large superfamily of integral cell surface plasma

membrane proteins that play key roles in transducing extracellular signals, including sensory stimuli, hormones, neurotransmitters, or paracrine factors into the intracellular environment through the activation of one or more heterotrimeric G proteins. Structural alterations provoked by mutations or variations in the genes coding for GPCRs may lead to misfolding, altered plasma membrane expression of the receptor protein and frequently to disease. A number of GPCRs regulate reproductive function at different levels; these receptors include the gonadotropin-releasing hormone receptor (GnRHR) and the gonadotropin receptors (follicle-stimulating hormone receptor and luteinizing hormone receptor), which regulate the function of the pituitary-gonadal axis. Loss-of-function mutations in these receptors may lead to hypogonadotropic or hypergonadotropic hypogonadism, which encompass a broad spectrum of clinical phenotypes. In this review we describe mutations that provoke misfolding and failure of these receptors to traffick from the endoplasmic reticulum to the plasma membrane. We also discuss some aspects related to the therapeutic potential of some target-specific drugs that selectively bind to and rescue function of misfolded mutant GnRHR and gonadotropin receptors, and that represent potentially valuable strategies to treat diseases caused by inactivating mutations of these receptors. © 2013 Elsevier Ireland Ltd.

Vainstein, V., Eide, C. A., O'Hare, T., Shukron, O., & Druker, B. J. (2013). Integrating in vitro sensitivity and dose-response slope is predictive of clinical response to ABL kinase inhibitors in chronic myeloid leukemia. *Blood*, 122(19), 3331-3334. doi:10.1182/blood-2012-08-452409

BCR-ABL mutations result in clinical resistance to ABL tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML). Although in vitro 50% inhibitory concentration (IC50) values for specific mutations have been suggested to guide TKI choice in the clinic, the quantitative relationship between IC50 and clinical response has never been demonstrated. We used Hill's equation for in vitro response of Ba/F3 cells transduced with various BCR-ABL mutants to determine IC50 and the slope of the dose-response curve. We found that slope variability between mutants tracked with in vitro TKI resistance, provides particular additional interpretive value in cases where in vitro IC50 and clinical response are disparate. Moreover, unlike IC50 alone, higher inhibitory potential at peak concentration (IPP), which integrates IC50, slope, and peak concentration (Cmax), correlated with improved complete cytogenetic response (CCyR) rates in CML patients

treated with dasatinib. Our findings suggest a metric integrating in vitro and clinical data may provide an improved tool for BCR-ABL mutation-guided TKI selection. © 2013 by The American Society of Hematology.

Vajtai, Z., Korngold, E., Hooper, J. E., Sheppard, B. C., Foster, B. R., & Coakley, F. V. (2014).

Suprarenal retroperitoneal liposarcoma with intracaval tumor thrombus: An imaging mimic of adrenocortical carcinoma. *Clinical Imaging*, 38(1), 75-77. doi:10.1016/j.clinimag.2013.08.016

We report a 57-year-old previously healthy man who presented with dull right upper quadrant pain, weight loss, fatigue, and night sweats. Computed tomography demonstrated a large, heterogeneously enhancing, soft tissue mass with no macroscopic fat above the right kidney with tumor thrombus extending into the inferior vena cava and right atrium. Positron Emission Tomography scanning demonstrated intense Fluorodeoxyglucose avidity in the primary tumor and tumor thrombus. The presumptive radiological diagnosis was adrenocortical carcinoma, but surgical pathology revealed a dedifferentiated liposarcoma. We conclude that suprarenal retroperitoneal liposarcoma should be included in the differential diagnosis for an apparent adrenal mass with venous invasion. © 2014 Elsevier Inc.

Van Der Heijde, D., Fleischmann, R., Wollenhaupt, J., Deodhar, A., Kielar, D., Woltering, F., . . .

Mease, P. J. (2014). Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: Results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Annals of the Rheumatic Diseases*, 73(1), 233-237. doi:10.1136/annrheumdis-2013-203697

Objectives To report the effect of different imputation methodologies on the assessment of radiographic progression in clinical trials. Methods The 216-week RAPID-psoriatic arthritis (PsA) (NCT01087788) trial of certolizumab pegol (CZP) in patients with active PsA was double-blind and placebocontrolled until week 24. A primary end point was change from baseline in modified Total Sharp Score(s) (mTSS). Prespecified imputation methodology in patients with fewer than two analysable mTSS used minimum observed baseline score for missing baseline values and maximum observed week 24 score for missing week 24 values. Post hoc analyses used alternative methods of imputation in patients with fewer than two analysable mTSS. mTSS non-

progressors were defined as patients with ≤ 0 (predefined) or ≤ 0.5 (post hoc) change in mTSS from baseline to week 24. Baseline mTSS and C-reactive protein levels as predictors of radiographic progression were investigated. Results 409 patients were randomised. Baseline demographics were similar between groups. Prespecified imputation analysis inappropriately overestimated radiographic progression (least squares mean placebo, 28.9; CZP, 18.3; $p \geq 0.05$). Multiple post hoc analyses demonstrated that CZP inhibited radiographic progression compared with placebo, particularly in patients with high baseline mTSS and C-reactive protein levels. mTSS non-progression rate was higher in CZP than placebo groups in all analyses. Conclusions Inappropriate prespecified imputation methodology resulted in an unrealistic assessment of progression in all arms. Methodologies for imputing missing radiographic data can greatly affect assessment and reporting of mTSS progression.

Van Son, J. A. M., Smedts, F. M. M., Yang, C. -, & He, G. -. (2006). *Histology and comparison of arterial grafts used for coronary surgery* Springer Berlin Heidelberg. doi:10.1007/3-540-30084-8_1

Expanded use of the internal mammary artery for myocardial revascularization is based on the accumulating data of superior late patency of the internal mammary artery compared with venous conduits [1-9]. The primary consideration that has led to the gradual transition of use of the internal mammary artery as the conduit of choice is its relative freedom from atherosclerosis with follow-up of up to 20 years. Since during the last decade the frequency of coronary revascularization procedures has increased considerably in patients with diseased or absent greater and lesser saphenous veins, alternatives to this arterial conduit have been sought. The right gastroepiploic artery and the inferior epigastric artery have been advocated and used selectively or when traditional conduits are unsuitable or unavailable [10-24]. Although the radial artery has been used in the past as a conduit in myocardial revascularization and has been abandoned because of its high failure rate [25-28], there has been a recent resurgence of its use [29]. During the last 8 years we have performed histologic research on the internal mammary artery, the right gastroepiploic artery, the inferior epigastric artery, and the radial artery and in this chapter we will summarize our findings. © Springer-Verlag Berlin Heidelberg 2006.

Vilar, L., Fleseriu, M., Naves, L. A., Albuquerque, J. L., Gadelha, P. S., dos Santos Faria, M., . . .

Montenegro, R. M. (2013). Can we predict long-term remission after somatostatin analog withdrawal in patients with acromegaly? Results from a multicenter prospective trial. *Endocrine*, 1-8. doi:10.1007/s12020-013-0094-9

Somatostatin analogs (SSAs) represent the mainstay of therapy in acromegaly. One of the potential disadvantages is the expected need to maintain therapy indefinitely in previously non-irradiated patients. The aim of this multicenter prospective open trial was to evaluate the likelihood of successful discontinuation of SSA therapy in well-controlled acromegalic patients who fulfilled very strict criteria: two or more years of treatment with the long-acting SSA octreotide LAR (OCT-LAR), a stable dose and injections interval every 4 weeks or longer for the previous year, GH levels <2.5 ng/ml and normal IGF-1 levels for age, a tumor remnant <10 mm, no history of radiotherapy, and no use of cabergoline or pegvisomant over the previous 6 months. Disease recurrence was defined as an increase of IGF-1 to levels above 1.2-fold the upper limit of normal (ULN). Out of 220 patients, 20 patients (12 women and 8 men; mean age, 48.1 ± 10.3 years; age range, 27-64) treated for 2.74 ± 0.64 years (range, 2.0-4.4) were included in this prospective study and OCT-LAR therapy was stopped. Four patients (20 %) remained without clinical and biochemical/neuroradiological evidence of disease recurrence after 12-18 months of follow-up. Sixteen patients (80 %) relapsed biochemically within 9 months after drug withdrawal and restarted OCT-LAR at the same previous dose. Compared to recurring subjects, non-recurring patients had significantly lower mean IGF-1 (\times ULN) levels but there were some overlapping values in both groups. No other characteristic could be identified as a predictor of successful OCT-LAR discontinuation. Our findings demonstrated that OCT-LAR withdrawal, though rare, is possible in well-selected acromegalic patients treated for at least 2 years and considered optimally controlled in hormonal and neuroradiological terms. © 2013 Springer Science+Business Media New York.

Wald, D. A., & Choo, E. K. (2009). *Providing Feedback in the Emergency Department* Wiley-Blackwell.

doi:10.1002/9781444303636.ch6

Wappner, R. S., & Gibson, K. M. (2006). *Disorders of leucine metabolism* Springer Berlin Heidelberg.
doi:10.1007/3-540-28962-3_8

Warden, B. A., Freels, J. P., Furuno, J. P., & Mackay, J. (2014). Pharmacy-managed program for providing education and discharge instructions for patients with heart failure. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists*, 71(2), 134-139. doi:10.2146/ajhp130103; 10.2146/ajhp130103

PURPOSE: The impact of a pharmacy-managed program for providing education and discharge instructions for patients with heart failure (HF) was evaluated. METHODS: A before-and-after quasiexperimental design was used to quantify the effect of a pharmacist-managed HF medication education and discharge instruction program on the incidence of 30-day readmission rates and adherence to targeted Joint Commission core measures for HF (the provision of discharge instructions and the prescribing of an angiotensin-converting-enzyme inhibitor [ACEI]/angiotensin II receptor blocker [ARB] at discharge or documentation of the reason if therapy was not prescribed). Adult patients admitted to Oregon Health and Science University's cardiology unit with systolic HF exacerbation as their primary diagnosis between December 2010 and March 2011 were included. Throughout patients' hospitalization, the pharmacist collaborated with the multidisciplinary team to make treatment and monitoring recommendations; provided discharge medication reconciliation, discharge medication recommendations, and discharge instructions; answered patient-specific questions; and gave the patient a complete discharge medication list. RESULTS: The study enrolled 35 patients and compared results against a historical control group of 115 patients. The frequency of discharge counseling increased significantly ($p = 0.007$), as did the rate of ACEI/ARB prescribing at discharge ($p = 0.02$). Both 30-day all-cause and HF-related readmissions were reduced compared with baseline ($p = 0.02$ and $p = 0.11$, respectively). CONCLUSION: Pharmacist involvement in medication reconciliation and discharge counseling for HF patients was associated with a significant increase in adherence with the Joint Commission's core measures, a significant reduction in 30-day all-cause readmissions, and a positive effect on patient satisfaction.

Waterman, B. R., Cameron, K. L., Hsiao, M., Langston, J. R., Clark, N. J., & Owens, B. D. (2013).

Trends in the diagnosis of SLAP lesions in the US military. *Knee Surgery, Sports Traumatology, Arthroscopy*, , 1-7. doi:10.1007/s00167-013-2798-z

Purpose: Shoulder pathology, particularly SLAP (superior labrum anterior-posterior) lesions, is prevalent in overhead athletes and physically active individuals. The aim of this study is to quantify the burden of SLAP lesions in the military and establish risk factors for diagnosis.

Methods: A retrospective analysis of all service members diagnosed with a SLAP lesion (International Classification of Disease, Ninth Revision code 840.70) in the Defense Medical Epidemiological Database between 2002 and 2009 was performed. Available epidemiological risk factors including age, sex, race, military rank, and branch of service were evaluated using multivariate Poisson regression analysis, and cumulative and subgroup incidence rates were calculated. Results: During the study period, approximately 23,632 SLAP lesions were diagnosed among a population at risk of 11,082,738, resulting in an adjusted incidence rate of 2.13 per 1,000 person-years. The adjusted annual incidence rate for SLAP lesions increased from 0.31 cases per 1,000 person-years in 2002 to 1.88 cases per 1,000 person-years in 2009, with an average annual increase of 21.2 % (95 % CI 20.7 %, 22.0 %, $p < 0.0001$) during the study period. Age, sex, race, branch of military service, and military rank were independent risk factors associated with the incidence rate of SLAP lesion ($p < 0.01$). Male service members were over twofold more likely (IRR, 2.12; 95 % CI 2.01, 2.23) to sustain a SLAP lesion when compared with females. Increasing age category was associated with a statistically significant increase in the incidence rate for SLAP lesions in the present study ($p < 0.001$). After controlling for the other variables, those individuals of white race, enlisted ranks, or Marine Corps service experienced the highest incidence rates for SLAP. Conclusion: This is the first study to establish the epidemiology of SLAP lesions within an active military cohort in the American population. Sex, age, race, military rank, and branch of military service were all independently associated with the incidence rate of SLAP lesions in this physically active population at high risk for shoulder injury. Level of evidence: II. © 2013 Springer-Verlag Berlin Heidelberg (outside the USA).

Watnick, S., & Crowley, S. T. (2013). ESRD Care Within the US Department of Veterans Affairs: A Forward-Looking Program With an Illuminating Past. *American Journal of Kidney Diseases : The*

Official Journal of the National Kidney Foundation, doi:10.1053/j.ajkd.2013.10.046;

10.1053/j.ajkd.2013.10.046

The first governmental agency to provide maintenance hemodialysis to patients with end-stage renal disease (ESRD) was the Veterans Administration (VA; now the US Department of Veterans Affairs). Many historical VA policies and programs set the stage for the later care of both veteran and civilian patients with ESRD. More recent VA initiatives that target restructuring of care models based on quality management, system-wide payment policies to promote cost-effective dialysis, and innovation grants aim to improve contemporary care. The VA currently supports an expanded and diversified nationwide treatment program for patients with ESRD using an integrated patient-centered care paradigm. This narrative review of ESRD care by the VA explores not only the medical advances, but also the historical, socioeconomic, ethical, and political forces related to the care of veterans with ESRD.

Wax, M. K. (2013). The role of the implantable doppler probe in free flap surgery. *The Laryngoscope*, doi:10.1002/lary.24569; 10.1002/lary.24569

Background: Free tissue transfer has success rates greater than 95%. Approximately 10% will require re-exploration for vascular compromise. Return to the operating room within 48 hours yields the highest rate of successful salvage. Our aim was to determine whether an implantable Doppler used for intra/post operative monitoring would 1) alter the pattern of detecting flap failure and 2) alter the overall incidence of flap survival. Study Design: Prospective analysis. Methods: Generic and study specific data was collected. Note was made at the end of the case if revision of the vascular anastomosis was performed. Data was collected as to flap outcomes in the postoperative period. Results: 1236 free tissues transfers from 2001 through 2011 were analyzed. 94 were outside the head and neck or the Doppler was not used/inadvertently discontinued. 1142 flaps make up the study cohort. 134 (11.7 %) intra -operative flow problems were detected, all successfully revised. Of these 15 (11%) required post operative revision, 5(33%) were successfully salvaged, with an overall survival 93%. 1,008 flaps did not require intra-operative revision, 62 required re-exploration (6.1%), 38 (61%) were salvaged. The overall survival was 97.6 %. There were 8 false positive (no intervention), and 10 false negatives. Sensitivity was 87% with specificity 99%. Conclusion: Intra operative Doppler's increase the

detection of immediate/incipient vascular problems. Patients requiring revision in the operating room require revision more often in the post operative period ($p=.03$), and are less likely to have successful salvage and have a lower flap survival rate. ($p=.05$).

Webber, B. C., & Woods, M. (2014). *The confluence of structure and dynamics in lanthanide(iii) chelates: How dynamics help define structure in solution* doi:10.1039/c3dt52143e

Coordination exchange processes tend to dominate the solution state behaviour of lanthanide chelates and generally prohibit the study of small conformational changes. In this article we take advantage of coordinatively rigid Eu^{3+} chelates to examine the small conformational changes that occur in these chelates as water dissociatively exchanges in and out of the inner coordination sphere. The results show that the time-averaged conformation of the chelate alters as the water exchange rate increases. This conformational change reflects a change in the hydration state ($q/r\text{LnH}$ 6) of the chelate. The hydration state has recently come to be expressed as two separate parameters q and $r\text{LnH}$. However, these two parameters simultaneously describe the same structural considerations which in solution are indistinguishable and intrinsically related to, and dependent upon, the dissociative water exchange rate. This realization leads to the broader understanding that a solution state structure can only be appreciated with reference to the dynamics of the system. © 2014 The Royal Society of Chemistry.

Weddle, M. (2014). Rock paper scissors. *Patient Education and Counseling*, 94(1), 138-139.
doi:10.1016/j.pec.2013.09.011

Wei, E., Jia, Y., Tan, O., Potsaid, B., Liu, J. J., Choi, W., . . . Huang, D. (2013). Parafoveal Retinal Vascular Response to Pattern Visual Stimulation Assessed with OCT Angiography. *PLoS One*, 8(12), e81343. doi:10.1371/journal.pone.0081343; 10.1371/journal.pone.0081343

We used optical coherence tomography (OCT) angiography with a high-speed swept-source OCT system to investigate retinal blood flow changes induced by visual stimulation with a reversing checkerboard pattern. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to quantify blood flow as measured with parafoveal flow index (PFI), which is proportional to the density of blood vessels and the velocity of blood flow in the parafoveal region of the macula. PFI measurements were taken in 15 second intervals during a 4 minute period

consisting of 1 minute of baseline, 2 minutes with an 8 Hz reversing checkerboard pattern stimulation, and 1 minute without stimulation. PFI measurements increased $6.1 \pm 4.7\%$ ($p = .001$) during the first minute of stimulation, with the most significant increase in PFI occurring 30 seconds into stimulation ($p < 0.001$). These results suggest that pattern stimulation induces a change to retinal blood flow that can be reliably measured with OCT angiography.

Wen, H., Hubbard, J. M., Rakela, B., Linhoff, M. W., Mandel, G., & Brehm, P. (2013). Synchronous and asynchronous modes of synaptic transmission utilize different calcium sources. *Elife*, 2(0), e01206. doi:10.7554/eLife.01206; 10.7554/eLife.01206

Asynchronous transmission plays a prominent role at certain synapses but lacks the mechanistic insights of its synchronous counterpart. The current view posits that triggering of asynchronous release during repetitive stimulation involves expansion of the same calcium domains underlying synchronous transmission. In this study, live imaging and paired patch clamp recording at the zebrafish neuromuscular synapse reveal contributions by spatially distinct calcium sources. Synchronous release is tied to calcium entry into synaptic boutons via P/Q type calcium channels, whereas asynchronous release is boosted by a propagating intracellular calcium source initiated at off-synaptic locations in the axon and axonal branch points. This secondary calcium source fully accounts for the persistence following termination of the stimulus and sensitivity to slow calcium buffers reported for asynchronous release. The neuromuscular junction and CNS neurons share these features, raising the possibility that secondary calcium sources are common among synapses with prominent asynchronous release. DOI: <http://dx.doi.org/10.7554/eLife.01206.001>.

Whiteford, M. H. (2009). *Indications* Springer New York. doi:10.1007/978-0-387-76397-2-1

Wiener, R. S., & Slatore, C. G. (2013). Framing discussions about CT scan screening for lung cancer so that patients see the whole picture. *Chest*, 144(6), 1749-1750. doi:10.1378/chest.13-1521

Wildi, S., Thompson, S. K., Hunter, J. G., & Weber, M. (2007). *Laparoscopic Treatment for Diseases of the Gallbladder and Biliary Tree* Blackwell Publishing Ltd. doi:10.1002/9780470986981.ch9

Wilson, A. C., Moss, A., Palermo, T. M., & Fales, J. L. (2013). Parent Pain and Catastrophizing are Associated With Pain, Somatic Symptoms, and Pain-related Disability Among Early Adolescents. *Journal of Pediatric Psychology*, doi:10.1093/jpepsy/jst094

OBJECTIVE: To examine associations between parental history of pain and catastrophizing and their adolescent's pain, somatic symptoms, catastrophizing, and disability. **METHODS:** Participants included 178 youths aged 11-14 years recruited through public schools. Adolescents completed measures assessing pain characteristics, somatic symptoms, and pain catastrophizing. Parents reported on their own pain, and catastrophizing about their adolescent's pain. **RESULTS:** About one quarter of the adolescents and two thirds of parents reported having pain. Parent pain was associated with adolescent pain, somatic symptoms, and pain catastrophizing. Parent catastrophizing was a significant predictor of adolescent somatic symptoms and pain-related disability, beyond the contribution of parent pain. Adolescent catastrophizing mediated the association between parent catastrophizing and adolescent pain-related disability. **CONCLUSIONS:** Parent history of pain and pain-related cognitions may contribute to adolescent risk for chronic pain.

Winters-Stone, K. M., Lyons, K. S., Bennett, J. A., & Beer, T. M. (2013). Patterns and predictors of symptom incongruence in older couples coping with prostate cancer. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, doi:10.1007/s00520-013-2092-0

PURPOSE: Prostate cancer survivors (PCSs) may experience persistent symptoms following treatment. If PCSs and spouses differ in their perceptions of symptoms, that incongruence may cause mismanagement of symptoms and reduced relationship quality. The purpose of this study was to examine symptom incongruence and identify the PCS and spouse characteristics associated with symptom incongruence in older couples coping with prostate cancer. **METHODS:** Participants in the study were older PCSs (>60 years) and their spouses (N = 59 couples). Symptom incongruence was determined by comparing patient and spouse independent ratings of the severity of his cancer-related symptoms. Predictor variables included PCS age, time since diagnosis, PCS comorbidity, PCS and spouse depressive symptoms, and spouse caregiving strain. **RESULTS:** PCS and spouse ratings of his symptom severity and the amount of incongruence over

his symptoms varied significantly across couples. Overall, couples rated a moderate level of PCS symptom severity, but PCSs and their spouses significantly differed in their perceptions of PCS symptom severity with spouses rating severity higher ($t = -2.66$, $df = 51$, $p < 0.01$). PCS younger age and high spouse caregiver strain accounted for 29 % of incongruence in perceptions of PCS symptom severity. CONCLUSIONS: This study is among the first to show that PCSs and spouses may perceive cancer-related persistent symptoms differently. Among this older sample, younger PCS age and spouse caregiver strain were associated with incongruence in symptoms perceptions in couples. These and other factors may inform future interventions aimed at preserving relationship quality in older couples who have experienced prostate cancer.

Wolinsky, F. D., Malmstrom, T. K., Miller, J. P., Andresen, E. M., Schootman, M., & Miller, D. K.

(2013). Association between childhood school segregation and changes in adult sense of control in the african american health cohort. *Journals of Gerontology - Series B Psychological Sciences and Social Sciences*, 68(6), 956-962. doi:10.1093/geronb/gbt089

Objective. Cross-sectional associations between childhood school segregation and adult sense of control and physical performance have been established in the African American Health (AAH) cohort. Here we extend that work by estimating the association between childhood school segregation and 2-year changes in adult sense of control. Method. Complete data on 541 older AAH men and women were used to estimate the association between childhood school segregation and changes in the sense of control. Exposure to segregation was self-reported in 2004, and the sense of control was measured in 2008 and 2010 using Blom rank transformations of Mirowsky and Ross' 8-item scale. Declining subjective income and experiencing major life stressors between 2008 and 2010, as well as traditional covariates (demographic factors, socioeconomic status, self-rated health, racial attitudes and beliefs, and religiosity) were included for statistical adjustment. Multiple linear regression analysis with propensity score reweighting was used. Results. Receiving the majority of one's primary and secondary education in segregated schools had a significant net positive association ($d = 0.179$; $p = .029$) with 2-year changes in adult sense of control. Conclusion. AAH participants receiving the majority of their primary and secondary educations in segregated schools appeared to have been protected, in

part, from age-related declines in the sense of control. © The Author 2013. Published by Oxford University Press on behalf of The Gerontological Society of America. All rights reserved.

Wurdeman, S. R., Huisinga, J. M., Filipi, M., & Stergiou, N. (2013). Multiple sclerosis alters the mechanical work performed on the body's center of mass during gait. *Journal of Applied Biomechanics*, 29(4), 435-442.

Patients with multiple sclerosis (MS) have less-coordinated movements of the center of mass resulting in greater mechanical work. The purpose of this study was to quantify the work performed on the body's center of mass by patients with MS. It was hypothesized that patients with MS would perform greater negative work during initial double support and less positive work in terminal double support. Results revealed that patients with MS perform less negative work in single support and early terminal double support and less positive work in the terminal double support period. However, summed over the entire stance phase, patients with MS and healthy controls performed similar amounts of positive and negative work on the body's center of mass. The altered work throughout different periods in the stance phase may be indicative of a failure to capitalize on passive elastic energy mechanisms and increased reliance upon more active work generation to sustain gait. © 2013 Human Kinetics, Inc.

Yedinak, C., Brzana, J., & Fleseriu, M. (2013). Monitoring Patient Improvement Parameters following Pasireotide Treatment in Cushing's Disease. *Case Reports in Endocrinology*, 2013, 735489. doi:10.1155/2013/735489; 10.1155/2013/735489

Cushing's disease (CD) is a disorder in which chronic excess adrenocorticotrophic hormone production is associated with multiple comorbidities and diminished quality of life. Postsurgical monitoring is important, and newer therapies are available for the management of surgical failure or disease recurrence. In this clinical case, we illustrate the importance of the nursing role in long-term management of CD, particularly as nurses may be the first point of contact for patients with CD. Alertness to disease signs and symptoms is crucial for timely diagnosis and improved outcomes. Successful therapy for CD requires careful monitoring of hormonal control, metabolic parameters, and therapy complications. Ongoing management requires lifelong monitoring of metabolic parameters, of side effects of treatment, and of signs of disease recurrence.

Appropriate referrals may be required to facilitate overall outcomes and patient wellbeing. This patient was enrolled in a Phase III trial that was registered in the USA with clinicaltrials.gov.

Yee, L. M., Cheng, Y. W., Inturrisi, M., & Caughey, A. B. (2013). Gestational weight loss and perinatal outcomes in overweight and obese women subsequent to diagnosis of gestational diabetes mellitus. *Obesity, 21*(12), E770-E774. doi:10.1002/oby.20490

Objective To investigate whether gestational weight loss (GWL) after the diagnosis of gestational diabetes mellitus (GDM) in overweight and obese women is associated with improved perinatal outcomes. Obesity and GDM are risk factors for adverse perinatal outcomes, but few studies have investigated weight loss during pregnancy in women with these comorbidities. **Design and Methods** Retrospective cohort study of 26,205 overweight and obese gestational diabetic women enrolled in the California Diabetes and Pregnancy Program. Women with GWL during program enrollment were compared to those with weight gain. Perinatal outcomes were assessed using chi-square test and multivariable logistic regression analysis. **Results** About 5.2% of women experienced GWL. GWL was associated with decreased odds of macrosomia (aOR 0.63, 95% CI 0.52-0.77), NICU admission (aOR 0.51, 95% CI 0.27-0.95), and cesarean delivery (aOR 0.81, 95% CI 0.68-0.97). Odds of SGA status (aOR 1.69, 95% CI 1.32-2.17) and preterm delivery <34 weeks (aOR 1.71, 95% CI 1.23-2.37) were increased. **Conclusions** In overweight and obese women with GDM, third trimester weight loss is associated with some improved maternal and neonatal outcomes, although this effect is lessened by increased odds of SGA status and preterm delivery. Further research on weight loss and interventions to improve adherence to weight guidelines in this population is recommended. Copyright © 2013 The Obesity Society.

Zerbe, K. (2013). Personal meaning and eating disorder treatment: Comment on Warren et al. *Psychotherapy, 50*(4), 573-575. doi:10.1037/a0031493

Clinicians who treat eating disorders are reported by Warren, Schafer, Crowley, and Olivardia (2013, pp. 553-564) to have significant levels of burnout, with significant observed relationships to important factors such as experience in the field and recent patient mortality. The levels of burnout among those who persist in treating patients with eating disorders, however, were lower than expected, and clinicians with a personal history of eating disorders reported finding higher

levels of meaning in their work. This comment explores the possibility that many eating disorder clinicians find satisfaction and meaning in this work for reasons that may not be immediately obvious. Additionally, it considers the possibility that some of the personal meaning derived from clinicians who report themselves "recovered" may be due to residual, unrecognized, or unreported emotional struggle surrounding eating and exercise that lends additional personal significance to this work. © 2013 American Psychological Association.

Zhai, F., Zhang, R., Zhang, T., Steyger, P. S., & Dai, C. -. (2013). Preclinical and clinical studies of unrelieved aural fullness following intratympanic gentamicin injection in patients with intractable Ménière's disease. *Audiology and Neurotology*, *18*(5), 297-306. doi:10.1159/000351805

Objective: To clarify whether gentamicin affects vestibular dark cells in guinea pigs and relieves patients of aural fullness with intractable Ménière's disease following intratympanic administration. Materials and Methods: Purified gentamicin-Texas Red (GTTR) was injected intratympanically in guinea pigs that were sacrificed at 1, 3, 7, 14 and 28 days. GTTR uptake was examined in hair cells, and transitional cells and dark cells in vestibular end-organs were examined. Specific attention was paid to its distribution in dark cells under confocal microscopy, and the ultrastructure of dark cells using electron microscopy, following intratympanic injection. Results: Dark cells in the semicircular canals showed weak GTTR uptake at 1, 3, 7, 14 and 28 days after intratympanic injection, with no significant differences at various time points after injection. However, the adjacent transitional cells demonstrated intense GTTR uptake that was retained for at least 28 days. Ultrastructural studies demonstrated negligible characteristics associated with apoptosis or necrosis in these dark cells. The tight junctions between dark cells showed no signs of disruption at 7 or 28 days after injection. Conclusion: Intratympanic gentamicin has little direct impact on vestibular dark cells. Clinical Application: A modified low-dose titration intratympanic approach was used in 29 patients with intractable vertigo and the clinical outcomes were followed. Aural fullness following intratympanic gentamicin injection was not relieved based on our subjective scales, demonstrated by no statistically significant difference between preinjection (4.16 ± 3.08) and postinjection (3.58 ± 2.93 ; $p > 0.05$) aural fullness scores. Vertigo control was achieved in 88% of patients, with hearing deterioration identified in 16% of patients. Intratympanic gentamicin administration might not lead to relief of aural

fullness in patients with intractable vertigo, although it can achieve a high vertigo control rate with some cochleotoxicity. © 2013 S. Karger AG, Basel.

Zhang, C., Tonsfeldt, K. J., Qiu, J., Bosch, M. A., Kobayashi, K., Steiner, R. A., . . . Rønnekleiv, O. K. (2013). Molecular mechanisms that drive estradiol-dependent burst firing of Kiss1 neurons in the rostral periventricular preoptic area. *American Journal of Physiology - Endocrinology and Metabolism*, 305(11), E1384-E1397. doi:10.1152/ajpendo.00406.2013

Kisspeptin (Kiss1) neurons in the rostral periventricular area of the third ventricle (RP3V) provide excitatory drive to gonadotropin-releasing hormone (GnRH) neurons to control fertility. Using whole cell patch clamp recording and single-cell (sc)RT-PCR techniques targeting Kiss1-CreGFP or tyrosine hydroxylase (TH)-EGFP neurons, we characterized the biophysical properties of these neurons and identified the critical intrinsic properties required for burst firing in 17 β -estradiol (E2)-treated, ovariectomized female mice. One-fourth of the RP3V Kiss1 neurons exhibited spontaneous burst firing. RP3V Kiss1 neurons expressed a hyperpolarization-activated h-current (I_h) and a T-type calcium current (I_T), which supported hyperpolarization-induced rebound burst firing. Under voltage clamp conditions, all Kiss1 neurons expressed a kinetically fast I_h that was augmented 3.4-fold by high (LH surge-producing)-E2 treatment. scPCR analysis of Kiss1 neurons revealed abundant expression of the HCN1 channel transcripts. Kiss1 neurons also expressed a Ni²⁺- and TTA-P2-sensitive I_T that was augmented sixfold with high-E2 treatment. CaV3.1 mRNA was also highly expressed in these cells. Current clamp analysis revealed that rebound burst firing was induced in RP3V Kiss1 neurons in high-E2-treated animals, and the majority of Kiss1 neurons had a hyperpolarization threshold of -84.7 mV, which corresponded to the V_{1/2} for I_T de-inactivation. Finally, Kiss1 neurons in the RP3V were hyperpolarized by μ - and κ -opioid and GABAB receptor agonists, suggesting that these pathways also contribute to rebound burst firing. Therefore, Kiss1 neurons in the RP3V express the critical channels and receptors that permit E2-dependent rebound burst firing and provide the biophysical substrate that drives the preovulatory surge of GnRH. © 2013 the American Physiological Society.

Zhang, H., Fan, Y., Ge, N., Wang, X., Sun, W., Mao, R., . . . Yang, J. (2014). Amplification and over-expression of MAP3K3 gene in human breast cancer promotes formation and survival of breast

cancer cells. *Journal of Pathology*, 232(1), 75-86. doi:10.1002/path.4283

Gene amplifications in the 17q chromosomal region are observed frequently in breast cancers. An integrative bioinformatics analysis of this region nominated the MAP3K3 gene as a potential therapeutic target in breast cancer. This gene encodes mitogen-activated protein kinase kinase kinase 3 (MAP3K3/MEKK3), which has not yet been reported to be associated with cancer-causing genetic aberrations. We found that MAP3K3 was amplified in approximately 8-20% of breast cancers. Knockdown of MAP3K3 expression significantly inhibited cell proliferation and colony formation in MAP3K3-amplified breast cancer cell lines MCF-7 and MDA-MB-361 but not in MAP3K3 non-amplified breast cancer cells. Knockdown of MAP3K3 expression in MAP3K3-amplified breast cancer cells sensitized breast cancer cells to apoptotic induction by TNF α and TRAIL, as well as doxorubicin, VP-16 and fluorouracil, three commonly used chemotherapeutic drugs for treating breast cancer. In addition, ectopic expression of MAP3K3, in collaboration with Ras, induced colony formation in both primary mouse embryonic fibroblasts and immortalized human breast epithelial cells (MCF-10A). Combined, these results suggest that MAP3K3 contributes to breast carcinogenesis and may endow resistance of breast cancer cells to cytotoxic chemotherapy. Therefore, MAP3K3 may be a valuable therapeutic target in patients with MAP3K3-amplified breast cancers, and blocking MAP3K3 kinase activity with a small molecule inhibitor may sensitize MAP3K3-amplified breast cancer cells to chemotherapy. Copyright © 2013 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

Zierler, B. K., & Moneta, G. L. (2008). *Venous Testing in the Vascular Laboratory* Society for Vascular Medicine and Biology. doi:10.1002/9780470692356.ch8