References

Abraham, A. D., Neve, K. A., & Lattal, K. M. (2013). Dopamine and extinction: A convergence of theory with fear and reward circuitry. *Neurobiology of Learning and Memory,* doi:10.1016/j.nlm.2013.11.007; 10.1016/j.nlm.2013.11.007

Research on dopamine lies at the intersection of sophisticated theoretical and neurobiological approaches to learning and memory. Dopamine has been shown to be critical for many processes that drive learning and memory, including motivation, prediction error, incentive salience, memory consolidation, and response output. Theories of dopamine's function in these processes have, for the most part, been developed from behavioral approaches that examine learning mechanisms in reward-related tasks. A parallel and growing literature indicates that dopamine is involved in fear conditioning and extinction. These studies are consistent with long-standing ideas about appetitive-aversive interactions in learning theory and they speak to the general nature of cellular and molecular processes that underlie behavior. We review the behavioral and neurobiological literature showing a role for dopamine in fear conditioning and extinction. At a cellular level, we review dopamine signaling and receptor pharmacology, cellular and molecular events that follow dopamine receptor activation, and brain systems in which dopamine functions. At a behavioral level, we describe theories of learning and dopamine function that could describe the fundamental rules underlying how dopamine modulates different aspects of learning and memory processes.

Ahmann, A., Szeinbach, S. L., Gill, J., Traylor, L., & Garg, S. K. (2013). Comparing Patient Preferences and Healthcare Provider Recommendations with the Pen Versus Vial-and-Syringe Insulin Delivery in Patients with Type 2 Diabetes. *Diabetes Technology & Therapeutics,* doi:10.1089/dia.2013.0172

Abstract Objectives: This study aimed to examine healthcare provider (HCP) recommendations and patient preferences for the insulin pen versus vial-and-syringe in patients with type 2 diabetes mellitus (T2DM) and to assess clinical end points and safety outcomes. Subjects and Methods: Using a randomized, open-label, crossover design, in total, 405 insulin-naive adults with T2DM from 60 centers received basal insulin glargine in one of two device treatment sequences (2 weeks of pen followed by 2 weeks of vial-and-syringe, or vice versa). The primary

end point, patient device preference, was evaluated at Week 4 (end of the crossover period) using the Insulin Injection Preference Questionnaire. Patient preference and HCP recommendation were assessed with one global item and three subscale items (blood glucose control, reluctance to use insulin, and long-term insulin use) using a 5-point scale ranging from 1=not preferred or not recommended to 5=preferred or recommended. Patients were then re-randomized to either pen or vial-and-syringe for further observation (6, 10, and 30 weeks) to evaluate clinical end points (glycosylated hemoglobin [A1C] and fasting blood glucose levels) and safety outcomes (hypoglycemia and adverse events). Results: Patients reported a significant preference for pens over vial-and-syringe, and HCPs strongly recommended pens over vial-and-syringe (both P<0.001). Consistent response patterns were observed by HCPs and patients for the three subscale items. Fasting blood glucose, A1C levels, and the incidence of hypoglycemia were comparable in the two groups. Conclusions: Patients preferred pens over vial-and-syringe, with the pen device also recommended by HCPs, when initiating basal insulin treatment in insulin-naive patients with T2DM.

Alexiev, U., & Farrens, D. L. (2013). Fluorescence spectroscopy of rhodopsins: Insights and approaches. *Biochimica Et Biophysica Acta - Bioenergetics,* doi:10.1016/j.bbabio.2013.10.008 Fluorescence spectroscopy has become an established tool at the interface of biology, chemistry and physics because of its exquisite sensitivity and recent technical advancements. However, rhodopsin proteins present the fluorescence spectroscopist with a unique set of challenges and opportunities due to the presence of the light-sensitive retinal chromophore. This review briefly summarizes some approaches that have successfully met these challenges and the novel insights they have yielded about rhodopsin structure and function. We start with a brief overview of fluorescence fundamentals and experimental methodologies, followed by more specific discussions of technical challenges rhodopsin proteins present to fluorescence studies. Finally, we end by discussing some of the unique insights that have been gained specifically about visual rhodopsin and its interactions with affiliate proteins through the use of fluorescence spectroscopy. This article is part of a Special Issue entitled: Retinal Proteins - You can teach an old dog new tricks. © 2013.

Ang, D. C., Warrick, A. L., Shilling, A., Beadling, C., Corless, C. L., & Troxell, M. L. (2013). Frequent phosphatidylinositol-3-kinase mutations in proliferative breast lesions. *Modern Pathology : An Official Journal of the United States and Canadian Academy of Pathology, Inc,* doi:10.1038/modpathol.2013.197; 10.1038/modpathol.2013.197

The phosphatidylinositol-3-kinase pathway is one of the most commonly altered molecular pathways in invasive breast carcinoma, with phosphatidylinositol-3-kinase catalytic subunit (PIK3CA) mutations in 25% of invasive carcinomas. Ductal carcinoma in situ (DCIS), benign papillomas, and small numbers of columnar cell lesions harbor an analogous spectrum of PIK3CA and AKT1 mutations, yet there is little data on usual ductal hyperplasia and atypical ductal and lobular neoplasias. We screened 192 formalin-fixed paraffin-embedded breast lesions from 75 patients for point mutations using a multiplexed panel encompassing 643 point mutations across 53 genes, including 58 PIK3CA substitutions. PIK3CA point mutations were identified in 31/62 (50%) proliferative lesions (usual ductal hyperplasia and columnar cell change), 10/14 (71%) atypical hyperplasias (atypical ductal hyperplasia and flat epithelial atypia), 7/16 (44%) lobular neoplasias (atypical lobular hyperplasia and lobular carcinoma in situ), 10/21 (48%) DCIS, and 13/37 (35%) invasive carcinomas. In genotyping multiple lesions of different stage from the same patient/specimen, we found considerable heterogeneity; most notably, in 12 specimens the proliferative lesion was PIK3CA mutant but the concurrent carcinoma was wild type. In 11 additional specimens, proliferative epithelium and cancer contained different point mutations. The frequently discordant genotypes of usual ductal hyperplasia/columnar cell change and concurrent carcinoma support a role for PIK3CA-activating point mutations in breast epithelial proliferation, perhaps more so than transformation. Further, these data suggest that proliferative breast lesions are heterogeneous and may represent non-obligate precursors of invasive carcinoma.Modern Pathology advance online publication, 1 November 2013; doi:10.1038/modpathol.2013.197.

Apostolides, P. F., & Trussell, L. O. (2013). Regulation of interneuron excitability by gap junction coupling with principal cells. *Nature Neuroscience, 16*(12), 1764-1772. doi:10.1038/nn.3569; 10.1038/nn.3569

Electrical coupling of inhibitory interneurons can synchronize activity across multiple neurons,

thereby enhancing the reliability of inhibition onto principal cell targets. It is unclear whether downstream activity in principal cells controls the excitability of such inhibitory networks. Using paired patch-clamp recordings, we show that excitatory projection neurons (fusiform cells) and inhibitory stellate interneurons of the dorsal cochlear nucleus form an electrically coupled network through gap junctions containing connexin36 (Cxc36, also called Gjd2). Remarkably, stellate cells were more strongly coupled to fusiform cells than to other stellate cells. This heterologous coupling was functionally asymmetric, biasing electrical transmission from the principal cell to the interneuron. Optogenetically activated populations of fusiform cells reliably enhanced interneuron excitability and generated GABAergic inhibition onto the postsynaptic targets of stellate cells, whereas deep afterhyperpolarizations following fusiform cell spike trains potently inhibited stellate cells over several hundred milliseconds. Thus, the excitability of an interneuron network is bidirectionally controlled by distinct epochs of activity in principal cells.

Apte, V., Tam, L., Han, A., Zhu, M., Ashraf, M., Sahn, D. J., & Zhang, Z. (2013). Evaluation of circumferential and longitudinal strain in a rabbit fetal heart model using 4D echocardiography. *39th Annual Northeast Bioengineering Conference, NEBEC 2013,* Syracuse, NY. 23-24. doi:10.1109/NEBEC.2013.18

Strain determination in fetal hearts is essential but conventional methods do not provide opportunities for orthogonal strain analysis and require the use of EKG-gating. A new non-gated 4D echocardiography method was tested for accuracy in strain computation. Fifteen rabbit hearts were studied. Each heart was mounted in a water tank to facilitate ultrasound scanning, connected to a calibrated pump by a balloon sutured into the left ventricle (LV), and pumped at Stroke Volumes (SV) 1-5 ml and Stroke Rates (SR) 40 and 80 bpm. Three 0.7mm sonomicrometry crystals were secured in the myocardium to conduct longitudinal strain (LS) and circumferential strain (CS) measurements. At each SV and each SR, 4D images were obtained by an X6-1 probe interfaced with the Philips iU-22 ultrasound system while sonomicrometry displacement was recorded. This process was performed pre and post simulated myocardial infarction (MI). 4D images were analyzed offline for strain by a MATLAB-based program. 4D echocardiography- derived strain data correlated with sonomicrometry-derived strain at each SV (CS: R2; = 0.91, $p<0.05$; LS: R2; = 0.87, $p<0.05$). A decrease in strain post-MI was detected by

both echocardiography and sonomicrometry. Non-gated 4D echocardiography is an accurate method for strain determination of fetal hearts. © 2013 IEEE.

Ascher, E., Veith, F. J., Gloviczki, P., Calligaro, K. D., Darling III, R. C., Kent, K. C., . . . Ricotta, J. J. (2012). *Haimovici's Vascular Surgery: 6th Edition* Wiley-Blackwell. doi:10.1002/9781118481370
To improve the diagnosis and management of patients with vascular disease turn to the most authoritative and trusted reference for 36 years and counting .... The role of the vascular surgeon has evolved. Vascular surgeons now perform minimally invasive vascular procedures and provide comprehensive care in addition to open surgery. Haimovici's Vascular Surgery, now in its 6th edition, has been extensively updated to provide you with: Expert perspectives on how the vascular surgery field has evolved so you continue to stay on the leading edge of this dynamic field Concise and practical advice about what these changes and new areas of practice mean to you - the practitioner and trainee in the fields of vascular surgery, interventional cardiology and interventional radiology Fundamental principles and best practices to treat traditional and new modalities that are now part of the vascular surgeons purview What's new in this edition? Full-color photographs and illustrations Complete coverage of the latest diagnostic imaging modalities, including intravascular ultrasound and computed tomography Expanded information on the most effective minimally invasive treatment options, including those for diseases of the carotid artery, lower extremity and abdominal aorta Full coverage of non-surgical techniques that vascular surgeons may add to their repertoire. Time-saving feature exclusive to the 6th edition To help you identify actionable information quickly, each chapter now highlights the most relevant clinical information. Apply what you learn to your own practice immediately. © 2012 Blackwell Publishing Ltd.

Ash, J. S., Sittig, D. F., Seshadri, V., Dykstra, R. H., Carpenter, J. D., & Stavri, P. Z. (2004). Adding insight: A qualitative cross-site study of physician order entry. *Studies in Health Technology and Informatics, 107*, 1013-1017. doi:10.3233/978-1-60750-949-3-1013
The research questions, strategies, and results of a six-year qualitative study of computerized physician order entry implementation (CPOE) at successful sites are reviewed over time. The iterative nature of qualitative inquiry stimulates a consecutive stream of research foci which, with

each iteration, add further insight into the overarching research question. A multidisciplinary team of researchers studied CPOE implementation in four organizations using a multi-method approach to address the question 'what are the success factors for implementing CPOE?' Four major themes emerged after studying three sites; ten themes resulted from blending the first results with those from a fourth site; and twelve principles were generated when results of a qualitative analysis of consensus conference transcripts were combined with the field data. The study has produced detailed descriptions of factors related to CPOE success and insight into the implementation process. © 2004 IMIA. All rights reserved.

Aslan, J. E., & McCarty, O. J. (2013). Rac and Cdc42 team up for platelets. *Blood, 122*(18), 3096-3097. doi:10.1182/blood-2013-08-516906; 10.1182/blood-2013-08-516906

Aziz, M. (2013). *The Role of Videolaryngoscopy in Airway Management* doi:10.1016/j.aan.2013.08.009

Bailey, S. R., O'Malley, J. P., Gold, R., Heintzman, J., Likumahuwa, S., & Devoe, J. E. (2013). Diabetes care quality is highly correlated with patient panel characteristics. *Journal of the American Board of Family Medicine : JABFM, 26*(6), 669-679. doi:10.3122/jabfm.2013.06.130018; 10.3122/jabfm.2013.06.130018

Introduction: Health care reimbursement is increasingly based on quality. Little is known about how clinic-level patient characteristics affect quality, particularly in community health centers (CHCs). METHODS: Using data from electronic health records for 4019 diabetic patients from 23 primary care CHCs in the OCHIN practice-based research network, we calculated correlations between a clinic's patient panel characteristics and rates of delivery of diabetes preventive services in 2007. Using regression models, we estimated the proportion of variability in clinics' preventive services rates associated with the variability in the clinics' patient panel characteristics. We also explored whether clinics' performance rates were affected by how patient panel denominators were defined. RESULTS: Clinic rates of hemoglobin testing, influenza immunizations, and lipid screening were positively associated with the percentage of patients with continuous health insurance coverage and negatively associated with the percentage of uninsured patients. Microalbumin screening rates were positively associated with the percentage

of racial minorities in a clinic's panel. Associations remained consistent with different panel denominators. CONCLUSIONS: Clinic variability in delivery rates of preventive services correlates with differences in clinics' patient panel characteristics, particularly the percentage of patients with continuous insurance coverage. Quality scores that do not account for these differences could create disincentives to clinics providing diabetes care for vulnerable patients.

Balaji, S., Daga, A., Bradley, D. J., Etheridge, S. P., Law, I. H., Batra, A. S., . . . Shah, M. (2013). An international multicenter study comparing arrhythmia prevalence between the intracardiac lateral tunnel and the extracardiac conduit type of Fontan operations. *The Journal of Thoracic and Cardiovascular Surgery,* doi:10.1016/j.jtcvs.2013.08.070; 10.1016/j.jtcvs.2013.08.070 OBJECTIVE: The study objective was to determine whether the extracardiac conduit Fontan confers an arrhythmia advantage over the intracardiac lateral tunnel Fontan. METHODS: This multicenter study of 1271 patients compared bradyarrhythmia (defined as need for pacing) and tachyarrhythmia (defined as needing antiarrhythmic therapy) between 602 patients undergoing the intracardiac Fontan and 669 patients undergoing the extracardiac Fontan. The median age at the time of the Fontan procedure was 2.1 years (interquartile range, 1.6-3.2 years) for the intracardiac group and 3.0 years (interquartile range, 2.4-3.9) for the extracardiac group (P 30 days) bradyarrhythmia occurred in 105 patients (18%) in the intracardiac group and 63 patients (9%) in the extracardiac group (P 30 days) tachyarrhythmia occurred in 58 patients (10%) in the intracardiac group and 23 patients (3%) in the extracardiac group (P < .0001). By multivariate analysis factoring time since surgery, more patients in the extracardiac group had early bradycardia (odds ratio, 2.9; 95% confidence interval, 1.8-4.6), with no difference in early tachycardia, late bradycardia, or late tachycardia. CONCLUSIONS: Overall arrhythmia burden is similar between the 2 groups, but the extracardiac Fontan group had a higher incidence of early bradyarrhythmias. There was no difference in the incidence of late tachyarrhythmias over time between the 2 operations. Therefore, the type of Fontan performed should be based on factors other than an anticipated reduction in arrhythmia burden from the extracardiac conduit.

Banghart, M. R., Williams, J. T., Shah, R. C., Lavis, L. D., & Sabatini, B. L. (2013). Caged naloxone reveals opioid signaling deactivation kineticss. *Molecular Pharmacology, 84*(5), 687-695.

doi:10.1124/mol.113.088096

The spatiotemporal dynamics of opioid signaling in the brain remain poorly defined. Photoactivatable opioid ligands provide a means to quantitatively measure these dynamics and their underlying mechanisms in brain tissue. Although activation kinetics can be assessed using caged agonists, deactivation kinetics are obscured by slow clearance of agonist in tissue. To reveal deactivation kinetics of opioid signaling we developed a caged competitive antagonist that can be quickly photoreleased in sufficient concentrations to render agonist dissociation effectively irreversible. Carboxynitroveratrylnaloxone (CNV-NLX), a caged analog of the competitive opioid antagonist NLX, was readily synthesized from commercially available NLX in good yield and found to be devoid of antagonist activity at heterologously expressed opioid receptors. Photolysis in slices of rat locus coeruleus produced a rapid inhibition of the ionic currents evoked by multiple agonists of the μ-opioid receptor (MOR), but not of α-adrenergic receptors, which activate the same pool of ion channels. Using the high-affinity peptide agonist dermorphin, we established conditions under which light-driven deactivation rates are independent of agonist concentration and thus intrinsic to the agonist-receptor complex. Under these conditions, some MOR agonists yielded deactivation rates that are limited by G protein signaling, whereas others appeared limited by agonist dissociation. Therefore, the choice of agonist determines which feature of receptor signaling is unmasked by CNV-NLX photolysis. © 2013 by The American Society for Pharmacology and Experimental Therapeutics.

Banich, M. T., De La Vega, A., Andrews-Hanna, J. R., Mackiewicz Seghete, K., Du, Y., & Claus, E. D. (2013). Developmental trends and individual differences in brain systems involved in intertemporal choice during adolescence. *Psychology of Addictive Behaviors, 27*(2), 416-430. doi:10.1037/a0031991

This study used functional magnetic resonance imaging (fMRI) to examine the neural systems activated during an intertemporal choice task in a group of 14- to 19-year-old adolescents, as well as the relationship of such activation patterns to individual differences in the self-reported ability to engage in nonimmediate thinking (i.e., less impulsive and more future-oriented thoughts and action). With increasing age, there was greater differentiation between patterns of brain activity for immediate versus future choices across three distinct brain systems involved in

intertemporal choice - those involved in exerting control over behavior, attributing affective value to choices, and imagining future outcomes. Furthermore, a greater propensity toward self-reported nonimmediate thinking was associated with decreased activity in the systems involved in cognitive control, possibly suggesting that individuals with greater self-reported nonimmediate thinking need to rely less on cognitive control regions during conditions of intertemporal choice. These results highlight the role that both developmental age and individual differences play in influencing neural systems involved in intertemporal choice. Implications for understanding the onset of substance abuse disorders during adolescence are discussed.

Barile, J. P., Thompson, W. W., Zack, M. M., Krahn, G. L., Horner-Johnson, W., & Bowen, S. E. (2013). Multiple chronic medical conditions and health- related quality of life in older adults, 2004-2006. *Preventing Chronic Disease, 10*(9) doi:10.5888/pcd10.120282

Introduction: Understanding longitudinal relationships among multiple chronic conditions, limitations in activities of daily living, and health-related quality of life is important for identifying potential opportunities for health promotion and disease prevention among older adults. Methods: This study assessed longitudinal associations between multiple chronic conditions and limitations in activities of daily living on health-related quality of life among older adults (>65 years) from 2004 through 2006, using data from the Medicare Health Outcomes Survey (N = 27,334). Results: Using a longitudinal path model, we found the numbers of chronic conditions at baseline and 2-year follow-up were independently associated with more limitations in activities of daily living at 2-year follow-up. In addition, more limitations in activities of daily living at 2-year follow-up were associated with worse health-related quality of life during the follow-up time period. The association between multiple chronic conditions and indices of health-related quality of life was mediated by changes in limitations in activities of daily living. Conclusion: Both baseline and new multiple chronic conditions led to worse health in terms of activities of daily living and healthrelated quality of life and should be considered important outcomes to intervene on for improved long-term health. In addition, public health practitioners should consider addressing classes of multiple chronic conditions by using interventions designed to reduce the

emergence of multiple chronic conditions, such as physical activity, reductions in smoking rates, and improved and coordinated access to health care services.

Barrett, C. M., Troxell, M. L., Larsen, C. P., & Houghton, D. C. (2013). Membranous glomerulonephritis with crescents. *International Urology and Nephrology,* doi:10.1007/s11255-013-0593-x

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

Belknap, J. K., McWeeney, S., Reed, C., Burkhart-Kasch, S., McKinnon, C. S., Li, N., . . . Phillips, T. J. (2013). Genetic factors involved in risk for methamphetamine intake and sensitization. *Mammalian Genome : Official Journal of the International Mammalian Genome Society,* doi:10.1007/s00335-013-9484-9

Lines of mice were created by selective breeding for the purpose of identifying genetic

mechanisms that influence the magnitude of the selected trait and to explore genetic correlations for additional traits thought to be influenced by shared mechanisms. DNA samples from high and low methamphetamine-drinking (MADR) and high and low methamphetamine-sensitization lines were used for quantitative trait locus (QTL) mapping. Significant additive genetic correlations between the two traits indicated a common genetic influence, and a QTL on chromosome X was detected for both traits, suggesting one source of this commonality. For MADR mice, a QTL on chromosome 10 accounted for more than 50 % of the genetic variance in that trait. Microarray gene expression analyses were performed for three brain regions for methamphetamine-naive MADR line mice: nucleus accumbens, prefrontal cortex, and ventral midbrain. Many of the genes that were differentially expressed between the high and low MADR lines were shared in common across the three brain regions. A gene network highly enriched in transcription factor genes was identified as being relevant to genetically determined differences in methamphetamine intake. When the mu opioid receptor gene (Oprm1), located on chromosome 10 in the QTL region, was added to this top-ranked transcription factor network, it became a hub in the network. These data are consistent with previously published findings of opioid response and intake differences between the MADR lines and suggest that Oprm1, or a gene that impacts activity of the opioid system, plays a role in genetically determined differences in methamphetamine intake.

Bess, S., Line, B. G., Lafarge, V., Schwab, F., Shaffrey, C. I., Hart, R. A., . . . International Spine Study Group ISSG. (2013). Does Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) Use in Adult Spinal Deformity (ASD) Increase Complications and Are Complications Associated With Location of rhBMP-2 Use?: A Prospective, Multicenter Study of 279 Consecutive Patients. *Spine,* doi:10.1097/BRS.0000000000000104

Study Design. Multi-center, prospective analysis of consecutive ASD patients.Objective. Evaluate complications associated with rhBMP-2 use in ASDSummary of Background Data. Off-label rhBMP-2 use is common, however under-reporting of rhBMP-2 associated complications has been recently scrutinized.Methods. ASD patients consecutively enrolled into a prospective, multicenter database, were evaluated for type and timing of acute perioperative complications. Inclusion criteria: age >/= 18 years, ASD, spinal arthrodesis >4 levels, and >/=3 months follow-up. Patients divided into those receiving rhBMP-2 (BMP) or no rhBMP-2 (NOBMP). BMP divided into

location of use: posterior (PBMP), interbody (IBMP), and interbody + posterior spine (I+PBMP). Correlations between acute perioperative complications and rhBMP-2 use including total dose, dose/level and location of use were evaluated.Results. 279 patients (mean age 57 years, mean spinal levels fused 12.0, mean follow-up 28.8 months) met inclusion criteria. BMP (n = 172; average posterior dose = 2.5 mg/level, average interbody dose = 5 mg/level) had similar age, smoking history, previous spine surgery, total spinal levels fused, estimated blood loss, and duration of hospital stay as NOBMP (n = 107; p>0.05). BMP had greater Charlson Comorbidity Index (1.9 vs. 1.2), greater scoliosis (43 degrees vs. 38 degrees), longer operative time (488.2 vs. 414.6 minutes), more osteotomies/patient (4.0 vs. 1.6) and greater percentage of anteroposterior fusion (APSF; 20.9% vs. 8.4%) than NOBMP, respectively (p0.05). Multivariate analysis demonstrated small to non-existent correlations between rhBMP-2 use and complications.Conclusions. RhBMP-2 use and location of rhBMP-2 use in ASD surgery, at reported doses, does not increase acute major, neurological or wound complications. Research is needed for higher rhBMP-2 dosing and long-term follow-up.

Bethell, C. D., Read, D., Blumberg, S. J., & Newacheck, P. W. (2013). What is the Prevalence of Children with Special Health Care Needs? Toward an Understanding of Variations in Findings and Methods Across Three National Surveys. *Maternal and Child Health Journal, 17*(10), 2007-007-0281-5. doi:10.1007/s10995-007-0281-5; 10.1007/s10995-007-0281-5

Billings, C. (2013). Uses and limitations of electrophysiology with hearing aids. *Seminars in Hearing, 34*(4), 257-269. doi:10.1055/s-0033-1356638

There is currently a strong interest among both audiologists and hearing researchers to find a physiological measure that can be used as a marker of how amplified sounds are processed by the brain (i.e., hearing aid fitting) or how the brain changes with exposure to amplified sounds (i.e., hearing aid acclimatization). Currently, auditory evoked potentials are used, or proposed to be used, for both of these purposes to some degree. It is clear from the literature that some of these uses are potentially useful clinically and others are quite problematic. The current state of aided cortical auditory evoked potentials will be discussed relative to their application to hearing

aid fitting/verification and in understanding hearing aid acclimatization. Future areas of promise as well as current gaps in the literature will be addressed.

Bishop, C. V., Aazzerah, R. A., Quennoz, L. M., Hennebold, J. D., & Stouffer, R. L. (2013). Effects of steroid ablation and progestin replacement on the transcriptome of the primate corpus luteum during simulated early pregnancy. *Molecular Human Reproduction,* doi:10.1093/molehr/gat079 Previous microarray analyses indicated that a portion of the transcriptome in the macaque corpus luteum (CL) of the menstrual cycle was regulated indirectly by luteinizing hormone via the local actions of steroid hormones, notably progesterone (P). The current study was designed to investigate this concept in the CL of early pregnancy by analyzing chorionic gonadotrophin (CG)-regulated genes that are dependent versus independent of local steroid action. Exogenous human chorionic gonadotropin treatment simulating early pregnancy (SEP) began on Day 9 of the luteal phase in female rhesus monkeys with and without concurrent administration of the 3-beta-hydroxysteroid dehydrogenase inhibitor trilostane (TRL) with or without the synthetic progestin R5020. Compared with SEP treatment alone, TRL altered 50 mRNA transcripts on Day 10, rising to 95 on Day 15 (P /=2-fold change in gene expression). Steroid-sensitive genes were validated; notably effects of steroid ablation and P replacement varied by day. Expression of some genes previously identified as P-regulated in the macaque CL during the menstrual cycle were not significantly altered by steroid ablation and P replacement during CG exposure in SEP. These data indicate that the majority of CG-regulated luteal transcripts are differentially expressed independently of local steroid actions. However, the steroid-regulated genes in the macaque CL may be essential during early pregnancy, based on previous reports that TRL treatment initiates premature structural regression of the CL during SEP. These data reinforce the concept that the structure, function and regulation of the rescued CL in early pregnancy differs from the CL of the menstrual cycle in primates.

Botero, T. M., Sedgley, C. M., Paniagua, M. I., & Tobón, D. M. (2013). *Clinical Correlate: Regenerative Endodontics in an Immature Tooth with Pulpal Necrosis and Periapical Pathosis* John Wiley & Sons, Inc. doi:10.1002/9781118704868.ch25

Boudko, S. P., Ishikawa, Y., Nix, J., Chapman, M. S., & Peter Bachinger, H. (2013). Structure of human peptidyl-prolyl cis-trans isomerase FKBP22 containing two EF-hand motifs. *Protein Science : A Publication of the Protein Society,* doi:10.1002/pro.2391; 10.1002/pro.2391

The FK506-binding protein (FKBP) family consists of proteins with a variety of protein-protein interaction domains and versatile cellular functions. It is assumed that all members are peptidyl-prolyl cis-trans isomerases with the enzymatic function attributed to the FKBP domain. Six members of this family localize to the mammalian endoplasmic reticulum (ER). Four of them, FKBP22 (encoded by the FKBP14 gene), FKBP23 (FKBP7), FKBP60 (FKBP9), and FKBP65 (FKBP10), are unique among all FKBPs as they contain the EF-hand motifs. Little is known about the biological roles of these proteins, but emerging genetics studies are attracting great interest to the ER resident FKBPs, as mutations in genes encoding FKBP10 and FKBP14 were shown to cause a variety of matrix disorders. Although the structural organization of the FKBP-type domain as well as of the EF-hand motif has been known for a while, it is difficult to conclude how these structures are combined and how it affects the protein functionality. We have determined a unique 1.9 A resolution crystal structure for human FKBP22, which can serve as a prototype for other EF hand-containing FKBPs. The EF-hand motifs of two FKBP22 molecules form a dimeric complex with an elongated and predominantly hydrophobic cavity that can potentially be occupied by an aliphatic ligand. The FKBP-type domains are separated by a cleft and their putative active sites can catalyze isomerazation of two bonds within a polypeptide chain in extended conformation. These structural results are of prime interest for understanding biological functions of ER resident FKBPs containing EF-hand motifs.

Braga, J. C. T., Klaz, I., Scope, A., Gareau, D., Rajadhyaksha, M., & Marghoob, A. A. (2011). *Confocal Microscopy of Skin Cancers* John Wiley & Sons, Inc. doi:10.1002/9780470767061.ch5

Brambrink, A. M., Rock, P., & Kirsch, J. R. (2013). Pre-operative Management of the Patient with Chronic Disease. *The Medical Clinics of North America, 97*(6), xv-xvi. doi:10.1016/j.mcna.2013.08.002; 10.1016/j.mcna.2013.08.002

Bryan Bell, R., Markiewicz, M. R., & Gelesko, S. (2013). *Maxillofacial Trauma* John Wiley & Sons, Inc,. doi:10.1002/9781118704493.ch4

Burke, W., Matheny Antommaria, A. H., Bennett, R., Botkin, J., Clayton, E. W., Henderson, G. E., . . . Zimmern, R. (2013). Recommendations for returning genomic incidental findings? We need to talk! *Genetics in Medicine, 15*(11), 854-859. doi:10.1038/gim.2013.113

The American College of Medical Genetics and Genomics recently issued recommendations for reporting incidental findings from clinical whole-genome sequencing and whole-exome sequencing. The recommendations call for evaluating a specific set of genes as part of all whole-genome sequencing/whole-exome sequencing and reporting all pathogenic variants irrespective of patient age. The genes are associated with highly penetrant disorders for which treatment or prevention is available. The effort to generate a list of genes with actionable findings is commendable, but the recommendations raise several concerns. They constitute a call for opportunistic screening, through intentional effort to identify pathogenic variants in specified genes unrelated to the clinical concern that prompted testing. Yet for most of the genes, we lack evidence about the predictive value of testing, genotype penetrance, spectrum of phenotypes, and efficacy of interventions in unselected populations. Furthermore, the recommendations do not allow patients to decline the additional findings, a position inconsistent with established norms. Finally, the recommendation to return adult-onset disease findings when children are tested is inconsistent with current professional consensus, including other policy statements of the American College of Medical Genetics and Genomics. Instead of premature practice recommendations, we call for robust dialogue among stakeholders to define a pathway to normatively sound, evidence-based guidelines. © American College of Medical Genetics and Genomics.

Burrows, G. G., Maziarz, R. T., Hunady, K., Lehman, N., Raber, A., Deans, R. J., & Van't Hof, W. (2013). Human multipotent adult progenitor cells transcriptionally regulate fucosyltransferase VII. *Cytotherapy,* doi:10.1016/j.jcyt.2013.08.004; 10.1016/j.jcyt.2013.08.004

BACKGROUND AIMS: Targeted recruitment of leukocytes to sites of inflammation is a crucial event in normal host defense against pathogens, and attachment to and rolling on activated endothelial cells is a prerequisite first step for eventual leukocyte extravasation into sites of inflammation. These key events are mediated by interactions between glycosylated ligands expressed on leukocytes and selectins expressed on activated endothelium. Cell surface

expression of selectin ligands on leukocytes is regulated by the rate-limiting enzyme fucosyltransferase VII (Fut7), and in its absence extravasation of leukocytes is severely inhibited. Multipotent adult progenitor cells (MAPCs) are an adherent cell population isolated from adult bone marrow. Intravenous administration of MAPCs provided functional improvement in multiple pre-clinical models of injury or disease, but the mechanisms by which these outcomes were achieved remain poorly understood. METHODS: In vitro cell analysis studies including fluorescence-activated cell sorting, messenger RNA analysis, T-cell proliferation assays and endothelial cell binding assays were performed. RESULTS: The in vitro cell analysis studies characterized the ability of MAPCs to secrete factors that transcriptionally attenuate expression of Fut7 in T cells, blocking the terminal fucosylation event in the biosynthesis of selectin ligands and reducing T-cell binding to endothelial cells. CONCLUSIONS: This study presents the first example of a distinct regulatory mechanism involving transcriptional down-regulation of Fut7 by MAPCs that could modulate the trafficking behavior of T cells in vivo.

C Ang, D., Warrick, A. L., Shilling, A., Beadling, C., Corless, C. L., & Troxell, M. L. (2013). Frequent phosphatidylinositol-3-kinase mutations in proliferative breast lesions. *Modern Pathology,* doi:10.1038/modpathol.2013.197

The phosphatidylinositol-3-kinase pathway is one of the most commonly altered molecular pathways in invasive breast carcinoma, with phosphatidylinositol-3-kinase catalytic subunit (PIK3CA) mutations in 25% of invasive carcinomas. Ductal carcinoma in situ (DCIS), benign papillomas, and small numbers of columnar cell lesions harbor an analogous spectrum of PIK3CA and AKT1 mutations, yet there is little data on usual ductal hyperplasia and atypical ductal and lobular neoplasias. We screened 192 formalin-fixed paraffin-embedded breast lesions from 75 patients for point mutations using a multiplexed panel encompassing 643 point mutations across 53 genes, including 58 PIK3CA substitutions. PIK3CA point mutations were identified in 31/62 (50%) proliferative lesions (usual ductal hyperplasia and columnar cell change), 10/14 (71%) atypical hyperplasias (atypical ductal hyperplasia and flat epithelial atypia), 7/16 (44%) lobular neoplasias (atypical lobular hyperplasia and lobular carcinoma in situ), 10/21 (48%) DCIS, and 13/37 (35%) invasive carcinomas. In genotyping multiple lesions of different stage from the same patient/specimen, we found considerable heterogeneity; most notably, in 12 specimens the

proliferative lesion was PIK3CA mutant but the concurrent carcinoma was wild type. In 11 additional specimens, proliferative epithelium and cancer contained different point mutations. The frequently discordant genotypes of usual ductal hyperplasia/columnar cell change and concurrent carcinoma support a role for PIK3CA-activating point mutations in breast epithelial proliferation, perhaps more so than transformation. Further, these data suggest that proliferative breast lesions are heterogeneous and may represent non-obligate precursors of invasive carcinoma.Modern Pathology advance online publication, 1 November 2013; doi:10.1038/modpathol.2013.197.

Cameron, M., Mazumder, R., Murchison, C., & King, L. (2014). Mini Balance Evaluation Systems Test in people with multiple sclerosis: Reflects imbalance but may not predict falls. *Gait & Posture, 39*(1), 669. doi:10.1016/j.gaitpost.2013.08.009; 10.1016/j.gaitpost.2013.08.009

Cameron, M. H., Thielman, E., Mazumder, R., & Bourdette, D. (2013). Predicting falls in people with multiple sclerosis: fall history is as accurate as more complex measures. *Multiple Sclerosis International, 2013*, 496325. doi:10.1155/2013/496325; 10.1155/2013/496325 Background. Many people with MS fall, but the best method for identifying those at increased fall risk is not known. Objective. To compare how accurately fall history, questionnaires, and physical tests predict future falls and injurious falls in people with MS. Methods. 52 people with MS were asked if they had fallen in the past 2 months and the past year. Subjects were also assessed with the Activities-specific Balance Confidence, Falls Efficacy Scale-International, and Multiple Sclerosis Walking Scale-12 questionnaires, the Expanded Disability Status Scale, Timed 25-Foot Walk, and computerized dynamic posturography and recorded their falls daily for the following 6 months with calendars. The ability of baseline assessments to predict future falls was compared using receiver operator curves and logistic regression. Results. All tests individually provided similar fall prediction (area under the curve (AUC) 0.60-0.75). A fall in the past year was the best predictor of falls (AUC 0.75, sensitivity 0.89, specificity 0.56) or injurious falls (AUC 0.69, sensitivity 0.96, specificity 0.41) in the following 6 months. Conclusion. Simply asking people with MS if they have fallen in the past year predicts future falls and injurious falls as well as more complex, expensive, or time-consuming approaches.

Carney, P. A., Waller, E., Patrice Eiff, M., Saultz, J. W., Jones, S., Fogarty, C. T., . . . Green, L. (2013). Measuring family physician identity: The development of a new instrument. *Family Medicine, 45*(10), 708-718.

Objective: Our objective was to describe the development and psychometric assessment of an instrument designed to assess family medicine identity in residency training sites and compare responses from physician faculty and residents. Methods: We conducted 28 focus groups between 2007-2008, 14 with faculty and 14 with residents who were part of the Preparing Personal Physicians for Practice (P4) Project. The first 22 focus groups were exploratory, and the second six were confirmatory where we shared working variable statements scored using a 5-point Likert scale. We then administered the survey to 223 faculty and 147 residents who were part of the P4 Project, followed by a principal component (factor) analysis, retaining items that reflected domains with eigenvalues higher than 1.0. Results: A total of 223 family physician faculty and 147 residents completed the identity survey. The item analysis extraction loadings ranged from 0.36 to 0.70. Based on item grouping patterns, five domains were reflected in the data: Patient/Family Relationships, Patient Advocacy, Career Flexibility, Balancing the Breadth and Depth in Practice, and Comprehensive Nature of Patient Care. Compared to residents, faculty conveyed stronger agreement about being comfortable balancing the breadth and depth of medical knowledge needed in practice and using a variety of approaches to supplement their medical knowledge about patient care compared to residents (90.6% versus 68.7% for breadth and depth, 95.9% versus 88.3 for using a variety of approaches). Compared to faculty, residents agreed more strongly that the ability to choose many options in how to build their practice appeals to them compared to faculty (89.1% versus 82.9%). Conclusions: We successfully developed and tested a survey designed to measure family medicine identity in residencies, with five domains. Survey item responses were different between residents and faculty, which indicates the instrument may be sensitive to important changes over time.

Cefalu, W. T., Rosenstock, J., Henry, R. R., & Riddle, M. (2013). Signals and noise in drug safety analyses: The incretin therapy debate provides the rationale for revamping epidemiologic pharmacovigilance. *Diabetes Care, 36*(7), 1804-1806. doi:10.2337/dc13-0895

Chang, H., Borowsky, A., Spellman, P., & Parvin, B. (2013). Classification of tumor histology via morphometric context. *26th IEEE Conference on Computer Vision and Pattern Recognition, CVPR 2013,* Portland, OR. 2203-2210. doi:10.1109/CVPR.2013.286

Image-based classification of tissue histology, in terms of different components (e.g., normal signature, categories of aberrant signatures), provides a series of indices for tumor composition. Subsequently, aggregation of these indices in each whole slide image (WSI) from a large cohort can provide predictive models of clinical outcome. However, the performance of the existing techniques is hindered as a result of large technical and biological variations that are always present in a large cohort. In this paper, we propose two algorithms for classification of tissue histology based on robust representations of morphometric context, which are built upon nuclear level morphometric features at various locations and scales within the spatial pyramid matching (SPM) framework. These methods have been evaluated on two distinct datasets of different tumor types collected from The Cancer Genome Atlas (TCGA), and the experimental results indicate that our methods are (i) extensible to different tumor types, (ii) robust in the presence of wide technical and biological variations, (iii) invariant to different nuclear segmentation strategies, and (iv) scalable with varying training sample size. In addition, our experiments suggest that enforcing sparsity, during the construction of morphometric context, further improves the performance of the system.

Chang, H., Nayak, N., Spellman, P. T., & Parvin, B. (2013). *Characterization of tissue histopathology via predictive sparse decomposition and spatial pyramid matching* (Nagoya ed.) doi:10.1007/978-3-642-40763-5_12

Image-based classification of tissue histology, in terms of different components (e.g., subtypes of aberrant phenotypic signatures), provides a set of indices for tumor composition. Subsequently, integration of these indices in whole slide images (WSI), from a large cohort, can provide predictive models of the clinical outcome. However, the performance of the existing histology-based classification techniques is hindered as a result of large technical and biological variations that are always present in a large cohort. In this paper, we propose an algorithm for classification of tissue histology based on predictive sparse decomposition (PSD) and spatial pyramid matching (SPM), which utilize sparse tissue morphometric signatures at various locations and scales. The

method has been evaluated on two distinct datasets of different tumor types collected from The Cancer Genome Atlas (TCGA). The novelties of our approach are: (i) extensibility to different tumor types; (ii) robustness in the presence of wide technical and biological variations; and (iii) scalability with varying training sample size. © 2013 Springer-Verlag.

Chang, J. C., Hazelett, D. J., Stewart, J. A., & Morton, D. B. (2013). Motor neuron expression of the voltage-gated calcium channel cacophony restores locomotion defects in a Drosophila, TDP-43 loss of function model of ALS. *Brain Research,* doi:10.1016/j.brainres.2013.11.019; 10.1016/j.brainres.2013.11.019

Dysfunction of the RNA-binding protein, TDP-43, is strongly implicated as a causative event in many neurodegenerative diseases including amyotrophic lateral sclerosis (ALS). TDP-43 is normally found in the nucleus and pathological hallmarks of ALS include the presence of cytoplasmic protein aggregates containing TDP-43 and an associated loss of TDP-43 from the nucleus. Loss of nuclear TDP-43 likely contributes to neurodegeneration. Using Drosophila melanogaster to model TDP-43 loss of function, we show that reduced levels of the voltage-gated calcium channel, cacophony, mediate some of the physiological effects of TDP-43 loss. Null mutations in the Drosophila orthologue of TDP-43, named TBPH, resulted in defective larval locomotion and reduced levels of cacophony protein in whole animals and at the neuromuscular junction. Restoring the levels of cacophony in all neurons or selectively in motor neurons rescued these locomotion defects. Using TBPH immunoprecipitation, we showed that TBPH associates with cacophony transcript, indicating that it is likely to be a direct target for TBPH. Loss of TBPH leads to reduced levels of cacophony transcript, possibly due to increased degradation. In addition, TBPH also appears to regulate the inclusion of some alternatively spliced exons of cacophony. If similar effects of cacophony or related calcium channels are found in human ALS patients, these could be targets for the development of pharmacological therapies for ALS.

Chen, Q., Panksepp, J. B., & Lahvis, G. P. (2009). Empathy is moderated by genetic background in mice. *Plos One, 4*(2) doi:10.1371/journal.pone.0004387

Empathy, as originally defined, refers to an emotional experience that is shared among individuals. When discomfort or alarm is detected in another, a variety of behavioral responses

can follow, including greater levels of nurturing, consolation or increased vigilance towards a threat. Moreover, changes in systemic physiology often accompany the recognition of distressed states in others. Employing a mouse model of cue-conditioned fear, we asked whether exposure to conspecific distress influences how a mouse subsequently responds to environmental cues that predict this distress. We found that mice are responsive to environmental cues that predict social distress, that their heart rate changes when distress vocalizations are emitted from conspecifics, and that genetic background substantially influences the magnitude of these responses. Specifically, during a series of pre-exposure sessions, repeated experiences of object mice that were exposed to a tone-shock (CS-UCS) contingency resulted in heart rate deceleration in subjects from the gregarious C57BL/6J (B6) strain, but not in subjects from the less social BALB/cJ (BALB) strain. Following the pre-exposure sessions, subjects were individually presented with the CS-only for 5 consecutive trials followed by 5 consecutive pairings of the CS with the UCS. Pre-exposure to object distress increased the freezing responses of B6 mice, but not BALB mice, on both the CS-only and the CS-UCS trials. These physiological and behavioral responses of B6 mice to social distress parallel features of human empathy. Our paradigm thus has construct and face validity with contemporary views of empathy, and provides unequivocal evidence for a genetic contribution to the expression of empathic behavior. © 2009 Chen et al.

Cheng, X., Wilm, J., Seshamani, S., Fogtmann, M., Kroenke, C., & Studholme, C. (2013). Adapting parcellation schemes to study fetal brain connectivity in serial imaging studies. *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2013,* Osaka. 73-76. doi:10.1109/EMBC.2013.6609440

A crucial step in studying brain connectivity is the definition of the Regions Of Interest (ROI's) which are considered as nodes of a network graph. These ROI's identified in structural imaging reflect consistent functional regions in the anatomies being compared. However in serial studies of the developing fetal brain such functional and associated structural markers are not consistently present over time. In this study we adapt two non-atlas based parcellation schemes to study the development of connectivity networks of a fetal monkey brain using Diffusion Weighted Imaging techniques. Results demonstrate that the fetal brain network exhibits small-world characteristics and a pattern of increased cluster coefficients and decreased global

efficiency. These findings may provide a route to creating a new biomarker for healthy fetal brain development. © 2013 IEEE.

Cherian, S. V., Thampy, E., & Das, S. (2013). A rare "mimicker" of lung malignancy. *New Zealand Medical Journal, 126*(1385), 87-88.

Cheskes, S., Schmicker, R. H., Verbeek, P. R., Salcido, D. D., Brown, S. P., Brooks, S., . . . Christenson, J. (2013). The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation,* doi:10.1016/j.resuscitation.2013.10.014

Background: Previous research has demonstrated significant relationships between peri-shock pause and survival to discharge from out-of-hospital shockable cardiac arrest (OHCA). Objective: To determine the impact of peri-shock pause on survival from OHCA during the ROC PRIMED randomized controlled trial. Methods: We included patients in the ROC PRIMED trial who suffered OHCA between June 2007 and November 2009, presented with a shockable rhythm and had CPR process data for at least one shock. We used multivariable logistic regression to determine the association between peri-shock pause duration and survival to hospital discharge. Results: Among 2006 patients studied, the median (IQR) shock pause duration was: pre-shock pause 15 s (8, 22); post-shock pause 6 s (4, 9); and peri-shock pause 22.0 s (14, 31). After adjusting for Utstein predictors of survival as well as CPR quality measures, the odds of survival to hospital discharge were significantly higher for patients with pre-shock pause <10 s (OR: 1.52, 95% CI: 1.09, 2.11) and peri-shock pause <20 s (OR: 1.82, 95% CI: 1.17, 2.85) when compared to patients with pre-shock pause ≥20 s and peri-shock pause ≥40 s. Post-shock pause was not significantly associated with survival to hospital discharge. Results for neurologically intact survival (Modified Rankin Score ≤ 3) were similar to our primary outcome. Conclusions: In patients with cardiac arrest presenting in a shockable rhythm during the ROC PRIMED trial, shorter pre- and peri-shock pauses were significantly associated with higher odds of survival. Future cardiopulmonary education and technology should focus on minimizing all peri-shock pauses.

Chiba, N., & Fennerty, M. B. (2010). *Gastroesophageal Reflux Disease* Wiley-Blackwell. doi:10.1002/9781444314403.ch2

Chou, S., Boivin, G., Ives, J., & Elston, R. (2013). Phenotypic Evaluation of Previously Uncharacterized Cytomegalovirus DNA Polymerase Sequence Variants Detected in a Valganciclovir Treatment Trial. *The Journal of Infectious Diseases,* doi:10.1093/infdis/jit654
Background. In a large randomized trial comparing oral valganciclovir and intravenous ganciclovir for treatment of cytomegalovirus disease in solid organ transplantation, confirmed genotypic drug resistance was uncommon (20 sequence variants including the nonviable mutations and several resistance mutations.Conclusions. Newly phenotyped UL54 sequence variants did not significantly change the reported incidence of drug resistance in the clinical trial. Unrecognized sequence variants in diagnostic genotyping reports should be confirmed by additional testing in order to improve clinical decision making.

Cordo, P., Wolf, S., Lou, J. S., Bogey, R., Stevenson, M., Hayes, J., & Roth, E. (2013). Treatment of severe hand impairment following stroke by combining assisted movement, muscle vibration, and biofeedback. *Journal of Neurologic Physical Therapy : JNPT, 37*(4), 194-203. doi:10.1097/NPT.0000000000000023; 10.1097/NPT.0000000000000023
BACKGROUND AND PURPOSE: Few studies have addressed the rehabilitation of hand function in persons with severe impairment following stroke, and few therapeutic options are available for treatment. We investigated whether an intervention of robot-assisted movement and muscle vibration could reduce impairment and enable hand-opening to a greater extent when combined with torque biofeedback or electromyographic (EMG) biofeedback. METHODS: Forty-three participants with severe hand impairment due to chronic stroke (>/=1 year poststroke) were randomized to 1 of 2 treatment groups receiving assisted movement and muscle vibration combined with either torque or EMG biofeedback. Each participant received 30 sessions (30 minutes duration per session) directed at the impaired hand over 10 to 12 weeks. Outcomes were assessed using the Upper Extremity Fugl-Meyer Assessment (UE-FMA), Stroke Impact Scale, and Box-and-Block Test scores. RESULTS: Twenty-eight of 43 participants had no baseline finger extension; the remainder had an average of 23 +/- 26 mm extension in the most active

finger. Assisted movement and muscle vibration were associated with a significant increase in all outcome measures across both treatment groups, and for the UE-FMA and Stroke Impact Scale within treatment groups, with no significant difference between groups. Based on the Box-and-Block Test scores, the assisted movement and muscle vibration intervention did not restore functional hand-opening to participants with baseline UE-FMA scores less than 17/66, regardless of the form of biofeedback. DISCUSSION AND CONCLUSIONS: Assisted movement and muscle vibration, combined with either EMG or torque biofeedback, appears to reduce upper limb impairment, improve volitional activation of the hand muscles, and restore a modicum of hand function in some persons with severe hand impairment due to chronic stroke.Video Abstract available (see Video, Supplemental Digital Content 1, http://links.lww.com/JNPT/A64) for more insights from the authors.

Cowburn, S., Carlson, M. J., Lapidus, J. A., & DeVoe, J. E. (2013). The association between insurance status and cervical cancer screening in community health centers: Exploring the potential of electronic health records for population-level surveillance, 2008-2010. *Preventing Chronic Disease, 10*(10) doi:10.5888/pcd10.130034

Introduction Cervical cancer incidence and mortality rates in the United States have decreased 67% over the past 3 decades, a reduction mainly attributed to widespread use of the Papanicolaou (Pap) test for cervical cancer screening. In the general population, receipt of cervical cancer screening is positively associated with having health insurance. Less is known about the role insurance plays among women seeking care in community health centers, where screening services are available regardless of insurance status. The objective of our study was to assess the association between cervical cancer screening and insurance status in Oregon and California community health centers by using data from electronic health records. Methods We used bilevel log-binomial regression models to estimate prevalence ratios and 95% confidence intervals for receipt of a Pap test by insurance status, adjusted for patient-level demographic factors and a clinic-level random effect. Results Insurance status was a significant predictor of cervical cancer screening, but the effect varied by race/ethnicity and age. In our study uninsured non-Hispanic white women were less likely to receive a Pap test than were uninsured women of other races. Young, uninsured Hispanic women were more likely to receive a Pap test than were

young, fully insured Hispanic women, a finding not previously reported. Conclusion Electronic health records enable population-level surveillance in community health centers and can reveal factors influencing use of preventive services. Although community health centers provide cervical cancer screening regardless of insurance status, disparities persist in the association between insurance status and receipt of Pap tests. In our study, after adjusting for demographic factors, being continuously insured throughout the study period improved the likelihood of receiving a Pap test for many women.

Crabbe, J. C., Metten, P., Belknap, J. K., Spence, S. E., Cameron, A. J., Schlumbohm, J. P., . . . Phillips, T. J. (2013). Progress in a Replicated Selection for Elevated Blood Ethanol Concentrations in HDID Mice. *Genes, Brain, and Behavior,* doi:10.1111/gbb.12105; 10.1111/gbb.12105 Drinking in the Dark (DID) is a limited access ethanol drinking phenotype in mice. High Drinking in the Dark (HDID-1) mice have been bred for 27 selected generations (S27) for elevated blood ethanol concentrations (BECs) after a 4 hr period of access to 20% ethanol. A second replicate line (HDID-2) was started later from the same founder population and is currently in S20. An initial report of response to selection in HDID-1 was published after S11. This paper reports genetic and behavioral characteristics of both lines in comparison with the HS controls. Heritability is low in both replicates (h2 = 0.09) but the lines have shown 4-5 fold increases in BEC since S0; 80% of HDID-1 and 60% of HDID-2 mice reach BECs greater than 1.0 mg/ml. Several hours after a DID test, HDID mice show mild signs of withdrawal. Although not considered during selection, intake of ethanol (g/kg) during the DID test increased by approximately 80% in HDID-1 and 60% in HDID-2. Common genetic influences were more important than environmental influences in determining the similarity between BEC and intake for HDID mice. Analysis of the partitioning of intake showed that 60% of intake is concentrated in the last 2 hr of the 4 hr session. However, this has not changed during selection. Hourly BECs during the DID test reach peak levels after 3 or 4 hr of drinking. HDID mice do not differ from HS mice in their rate of elimination of an acute dose of alcohol.

Crawford, J. D., Wong, V. W., Deloughery, T. G., Mitchell, E. L., Liem, T. K., Landry, G. J., . . . Moneta, G. L. (2013). Paroxysmal Nocturnal Hemoglobinuria: A Red Clot Syndrome. *Annals of*

Vascular Surgery, doi:10.1016/j.avsg.2013.07.003; 10.1016/j.avsg.2013.07.003
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, nonmalignant disorder of hematopoietic stem cells characterized by hemolysis, diminished hematopoiesis, and thrombophilia. We describe a 65-year-old woman with known PNH and peripheral arterial disease who presented with critical limb ischemia and a nonhealing left foot ulcer. She underwent surgical bypass of a diffusely diseased left superficial femoral artery with autologous reversed saphenous vein graft. Her postoperative course was complicated by wound sepsis and PNH exacerbation with resultant graft thrombosis requiring an above-knee amputation. This case highlights several key concepts relevant to the management of vascular surgery patients with PNH: (1) their predisposition for arterial and venous thrombosis; (2) hypercoagulability despite standard anticoagulation regimens; (3) the role of eculizumab (a monoclonal antibody that inhibits complement activation used to treat PNH) in reducing thrombotic complications and hemolysis; and (4) complications associated with the immunosuppressive effects of eculizumab. We recommend careful monitoring of hemolysis and immunosuppression, aggressive anticoagulation, frequent graft surveillance, and early consultation with hematology.

Cunningham, A., Miranda-Saksena, M., Diefenbach, R., & Johnson, D. (2013). Letter in response to: Making the case: Married versus Separate models of alphaherpes virus anterograde transport in axons. *Reviews in Medical Virology, 23*(6), 414-418. doi:10.1002/rmv.1760

Curti, B. D., Kovacsovics-Bankowski, M., Morris, N., Walker, E., Chisholm, L., Floyd, K., . . . Weinberg, A. D. (2013). OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients. *Cancer Research,* doi:10.1158/0008-5472.CAN-12-4174
OX40 is a potent costimulatory receptor that can potentiate T-cell receptor signaling on the surface of T lymphocytes, leading to their activation by a specifically recognized antigen. In particular, OX40 engagement by ligands present on dendritic cells dramatically increases the proliferation, effector function, and survival of T cells. Preclinical studies have shown that OX40 agonists increase antitumor immunity and improve tumor-free survival. In this study, we performed a phase I clinical trial using a mouse monoclonal antibody (mAb) that agonizes human OX40 signaling in patients with advanced cancer. Patients treated with one course of the anti-

OX40 mAb showed an acceptable toxicity profile and regression of at least one metastatic lesion in 12 of 30 patients. Mechanistically, this treatment increased T and B cell responses to reporter antigen immunizations, led to preferential upregulation of OX40 on CD4+ FoxP3+ regulatory T cells in tumor-infiltrating lymphocytes, and increased the antitumor reactivity of T and B cells in patients with melanoma. Our findings clinically validate OX40 as a potent immune-stimulating target for treatment in patients with cancer, providing a generalizable tool to favorably influence the antitumor properties of circulating T cells, B cells, and intratumoral regulatory T cells. Cancer Res; 73(24); 1-10. (c)2013 AACR.

Davare, M. A., Saborowski, A., Eide, C. A., Tognon, C., Smith, R. L., Elferich, J., . . . Druker, B. J. (2013). Foretinib is a potent inhibitor of oncogenic ROS1 fusion proteins. *Proceedings of the National Academy of Sciences of the United States of America, 110*(48), 19519-19524. doi:10.1073/pnas.1319583110; 10.1073/pnas.1319583110

The rapidly growing recognition of the role of oncogenic ROS1 fusion proteins in the malignant transformation of multiple cancers, including lung adenocarcinoma, cholangiocarcinoma, and glioblastoma, is driving efforts to develop effective ROS1 inhibitors for use as molecularly targeted therapy. Using a multidisciplinary approach involving small molecule screening in combination with in vitro and in vivo tumor models, we show that foretinib (GSK1363089) is a more potent ROS1 inhibitor than crizotinib (PF-02341066), an ALK/ROS inhibitor currently in clinical evaluation for lung cancer patients harboring ROS1 rearrangements. Whereas crizotinib has demonstrated promising early results in patients with ROS1-rearranged non-small-cell lung carcinoma, recently emerging clinical evidence suggests that patients may develop crizotinib resistance due to acquired point mutations in the kinase domain of ROS1, thus necessitating identification of additional potent ROS1 inhibitors for therapeutic intervention. We confirm that the ROS1(G2032R) mutant, recently reported in clinical resistance to crizotinib, retains foretinib sensitivity at concentrations below safe, clinically achievable levels. Furthermore, we use an accelerated mutagenesis screen to preemptively identify mutations in the ROS1 kinase domain that confer resistance to crizotinib and demonstrate that these mutants also remain foretinib sensitive. Taken together, our data strongly suggest that foretinib is a highly effective ROS1

inhibitor, and further clinical investigation to evaluate its potential therapeutic benefit for patients with ROS1-driven malignancies is warranted.

Davis, L. (2012). *Placental Respiratory Gas Exchange* Wiley-Blackwell. doi:10.1002/9781118477076.ch3

Debarber, A. E., Luo, J., Star-Weinstock, M., Purkayastha, S., Geraghty, M. T., Chiang, J. P., . . . Steiner, R. D. (2013). A Blood Test for Cerebrotendinous Xanthomatosis with Potential for Disease Detection in Newborns. *Journal of Lipid Research,* doi:10.1194/jlr.P043273 Cerebrotendinous xanthomatosis (CTX) is a rare, difficult to diagnose genetic disorder of bile acid (BA) synthesis that can cause progressive neurological damage and premature death. Detection of CTX in the newborn period would be beneficial since an effective oral therapy for CTX is available to prevent disease progression. There is no suitable test to screen newborn dried bloodspots (DBS) for CTX. Blood screening for CTX is currently performed by GC-MS measurement of elevated 5alpha-cholestanol. We present here LC-ESI/MS/MS methodology utilizing keto derivatization with (O-(3-trimethylammonium-propyl) hydroxylamine) reagent to enable sensitive detection of ketosterol BA precursors that accumulate in CTX. The availability of isotopically enriched derivatization reagent allowed ready tagging of ketosterols to generate internal standards for isotope dilution quantification. Ketosterols were quantified and their utility as markers for CTX compared to 5alpha-cholestanol. 7alpha12alpha-Dihydroxy-4-cholesten-3-one provided the best discrimination between CTX and unaffected samples. In two CTX newborn DBS concentrations of this ketosterol (120-214 ng/ml) were around 10-fold higher than in unaffected newborn DBS (16.4+/-6.0 ng/ml), such that its quantification provides a test with potential to screen newborn DBS for CTX. Early detection and intervention through newborn screening would greatly benefit those affected with CTX, preventing morbidity and mortality.

Dehlinger, K., Tarnowski, K., House, J. L., Los, E., Hanavan, K., Bustamante, B., . . . Ward, W. K. (2013). Can trained dogs detect a hypoglycemic scent in patients with type 1 diabetes? *Diabetes Care, 36*(7), e98-e99. doi:10.2337/dc12-2342

Deininger, M. W., Kopecky, K. J., Radich, J. P., Kamel-Reid, S., Stock, W., Paietta, E., . . . Druker, B. J. (2013). Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: Results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. *British Journal of Haematology,* doi:10.1111/bjh.12618

Summary: The standard dose of imatinib for newly diagnosed patients with chronic phase chronic myeloid leukaemia (CP-CML) is 400 mg daily (IM400), but the optimal dose is unknown. This randomized phase II study compared the rates of molecular, haematological and cytogenetic response to IM400 vs. imatinib 400 mg twice daily (IM800) in 153 adult patients with CP-CML. Dose adjustments for toxicity were flexible to maximize retention on study. Molecular response (MR) at 12 months was deeper in the IM800 arm (4-log reduction of BCR-ABL1 mRNA: 25% vs. 10% of patients, P = 0·038; 3-log reduction: 53% vs. 35%, P = 0·049). During the first 12 months BCR-ABL1 levels in the IM800 arm were an average 2·9-fold lower than in the IM400 arm (P = 0·010). Complete haematological response was similar, but complete cytogenetic response was higher with IM800 (85% vs. 67%, P = 0·040). Grade 3-4 toxicities were more common for IM800 (58% vs. 31%, P = 0·0007), and were most commonly haematological. Few patients have relapsed, progressed or died, but both progression-free (P = 0·048) and relapse-free (P = 0·031) survival were superior for IM800. In newly diagnosed CP-CML patients, IM800 induced deeper MRs than IM400, with a trend for improved progression-free and overall survival, but was associated with more severe toxicity.

Derdeyn, C. P., Chimowitz, M. I., Lynn, M. J., Fiorella, D., Turan, T. N., Janis, L. S., . . . Cloft, H. J. (2013). Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *The Lancet,* doi:10.1016/S0140-6736(13)62038-3

Background: Early results of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis trial showed that, by 30 days, 33 (14·7%) of 224 patients in the stenting group and 13 (5·8%) of 227 patients in the medical group had died or had a stroke (percentages are product limit estimates), but provided insufficient data to establish whether stenting offered any longer-term benefit. Here we report the long-term outcome of patients in this trial. Methods: We randomly assigned (1:1, stratified by centre with randomly

permuted block sizes) 451 patients with recent transient ischaemic attack or stroke related to 70-99% stenosis of a major intracranial artery to aggressive medical management (antiplatelet therapy, intensive management of vascular risk factors, and a lifestyle-modification programme) or aggressive medical management plus stenting with the Wingspan stent. The primary endpoint was any of the following: stroke or death within 30 days after enrolment, ischaemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularisation procedure of the qualifying lesion during follow-up. Primary endpoint analysis of between-group differences with log-rank test was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT 00576693. Findings: During a median follow-up of 32·4 months, 34 (15%) of 227 patients in the medical group and 52 (23%) of 224 patients in the stenting group had a primary endpoint event. The cumulative probability of the primary endpoints was smaller in the medical group versus the percutaneous transluminal angioplasty and stenting (PTAS) group (p=0·0252). Beyond 30 days, 21 (10%) of 210 patients in the medical group and 19 (10%) of 191 patients in the stenting group had a primary endpoint. The absolute differences in the primary endpoint rates between the two groups were 7·1% at year 1 (95% CI 0·2 to 13·8%; p=0·0428), 6·5% at year 2 (-0·5 to 13·5%; p=0·07) and 9·0% at year 3 (1·5 to 16·5%; p=0·0193). The occurrence of the following adverse events was higher in the PTAS group than in the medical group: any stroke (59 [26%] of 224 patients vs 42 [19%] of 227 patients; p=0·0468) and major haemorrhage (29 [13%]of 224 patients vs 10 [4%] of 227 patients; p=0·0009). Interpretation: The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up. Our findings lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis. Funding: National Institute of Neurological Disorders and Stroke (NINDS) and others.

Dhindsa, D. S., Black, J. A., Koler, R. D., Rigas, D. A., Templeton, J. W., & Metcalfe, J. (1976). Respiratory characteristics of blood from Basenji dogs with classical erythrocyte pyruvate kinase deficiency. *Respiration Physiology, 26*(1), 65-75. doi:10.1016/0008-8749(76)90331-2

The oxygen affinities of blood from eight Basenji dogs homozygous for classical erythrocyte

pyruvate kinase deficiency and four dogs heterozygous for the defect were compared with blood from 14 Labrador retrievers and two normal Basenji dogs. The homozygous dogs showed significant anemia compared to heterozygous and normal dogs ($P < 0.01$). The average blood P50 value (at 38°C and plasma pH of 7.40) for both homozygous and heterozygous dogs was significantly higher ($P < 0.01$) than for normal dogs (33.6 ± 0.7 and 31.8 ± 0.7 vs 30.8 ± 0.6 mm Hg). The concentrations of 2,3 diphosphoglycerate (DPG) in the blood of both heterozygous and homozygous dogs were significantly higher than normal values. Four months after splenectomy P50 values declined to normal in four homozygous Basenji dogs without any change in the degree of anemia or blood 2,3 DPG concentrations. Iron kinetic studies showed a shorter plasma clearance time in a homozygous than in a normal dog with the heterozygote falling midway between. The red cell life span in the normal and heterozygous dogs was approximately 120 days. The 59Fe studies on the homozygous dog indicate markedly different survival characteristics which can be attributed to the existence of three populations of red cells differing in their life spans.

Dille, M. F., Ellingson, R. M., McMillan, G. P., & Konrad-Martin, D. (2013). ABR Obtained from Time-Efficient Train Stimuli for Cisplatin Ototoxicity Monitoring. *Journal of the American Academy of Audiology, 24*(9), 769-781. doi:10.3766/jaaa.24.9.2; 10.3766/jaaa.24.9.2

Background: Nonbehavioral methods for identifying cisplatin ototoxicity are important for testing patients with cancer who become too tired or sick to provide a reliable response. The auditory brainstem response (ABR) is a nonbehavioral test that is sensitive to ototoxicity but can be time consuming to implement over a range of frequencies and/or levels. To address this issue, trains of stimuli were developed that offer reliable ABR testing over a range of tone-burst frequencies and levels at a time savings of 77% relative to tone-burst stimuli presented individually. The clinical accuracy of this new method has yet to be determined on a clinical population. Purpose: This project was designed to determine the test performance of a time-effective ABR methodology aimed at identifying hearing shifts from cisplatin among veterans. A secondary goal was to determine whether improved test performance could be achieved by including our previously developed ototoxicity risk assessment model in the ABR prediction algorithm. Research Design: A set of discriminant functions were derived using logistic regression to model the risk for

cisplatin-induced hearing change. Independent variables were one of several ABR metrics alone and combined with an ototoxicity risk assessment model that includes pre-exposure hearing and cisplatin dose. Receiver operating characteristic curve analysis was used to evaluate the test performance of these discriminant functions. Study Sample: Twenty-two male veterans treated with cisplatin for various cancers provided data from a total of 71 monitoring appointments. Data Collection and Analysis: Data were collected prospectively from one ear of each participant as designated below. Hearing shift was determined for frequencies within an octave of each patient's high-frequency hearing limit, tested in 1/6th-octave steps. ABRs were monitored using a set of two intensity trains from the highest two multiple frequency tone-burst center frequencies (up to 11.3 kHz) that yielded a robust response at baseline. Each intensity train was presented at 65-105 dB peSPL in 10 dB steps. Scorable ABRs were generally limited to the highest two intensities; therefore, analyses concern those levels. Results: The ABR measurement failure was high, up to 52% for some frequencies and levels. Furthermore, the ABR was not frequently obtained at levels below 85 dB peSPL, consistent with previous studies that suggest a stimulus level of greater than 80 dB peSPL is required to obtain a reliable response to trained stimuli. Using multivariate metrics that included the dose-ototoxicity model, the most accurate scoring function was change in amplitude at lowest half-octave frequency obtained at 105 dB (change in wave V amplitude at frequency 2/105). However, absence of wave V at a monitor patient visit of the ABR response at levels 105 or 95 dB peSPL was deemed the preferred scoring function, because it had lower measurement failure and was within one standard error of the most accurate function. Conclusions: Because of the large number of responses that could not be measured at baseline, this technique as implemented holds limited value as an ototoxicity-monitoring method.

Dille, M. F., Jacobs, P. G., Gordon, S. Y., Helt, W. J., & McMillan, G. P. (2013). OtoID: New extended frequency, portable audiometer for ototoxicity monitoring. *Journal of Rehabilitation Research and Development, 50*(7), 997-1006. doi:10.1682/JRRD.2012.09.0176

Portability of equipment is an increasingly important component in the practice of audiology. We report on a new device, the OtoID, that supports evidence-based ototoxicity testing protocols, provides capability for hearing testing on the hospital treatment unit, and can automate patient self-testing. The purpose of this article is to report on the validation and verification of the OtoID

portable audiometer in 40 subjects both young and old, with and without hearing impairment. Subjects were evaluated by an audiologist using the manual hearing test program and then self-tested via an automated testing program. Testing was done in a sound booth and on a hospital treatment unit. Therefore, data were collected in four conditions (booth vs hospital unit and automated vs manual testing) and analyzed for testing bias, repeatability, and American Speech-Language-Hearing Association-significant ototoxicity false-positive rate. Repeatable hearing threshold results were obtained on all subjects who performed the test, regardless of hearing status or testing location.

Dilts, D. M. (2013). A "Three-Plus-One" Evaluation Model for Clinical Research Management. *Evaluation and the Health Professions, 36*(4), 464-477. doi:10.1177/0163278713499019

Clinical research management (CRM) is a critical resource for the management of clinical trials and it requires proper evaluation. This article advances a model of evaluation that has three local levels, plus one global level, for evaluating the value of CRM. The primary level for evaluation is that of the study or processes level. The managerial or aggregate level concerns management of the portfolio of trials under the control of the CRM office. The third, often overlooked level of evaluation, is the strategic level, whose goal is encapsulated in the phrase, "doing the right trials, while doing trials right." The global ("plus one") evaluation level concerns the need to evaluate the ever-increasing number of multi-institutional and multinational studies. As there are host of evaluation metrics, this article provides representative examples of metrics at each level and provides methods that can aid in the selecting appropriate metrics for an organization. © The Author(s) 2013.

Dodge, H. H., Zhu, J., Lee, C. W., Chang, C. C., & Ganguli, M. (2013). Cohort Effects in Age-Associated Cognitive Trajectories. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences,* doi:10.1093/gerona/glt181

BACKGROUND: The age-specific prevalence and incidence of dementia and cognitive impairment in the United States have either remained stable or even slightly declined during the 1980s-1990s. A suggested but untested reason for this improvement in cognitive function over time is higher educational attainment among more recent cohorts. METHODS: We used data from two

large prospective population-based epidemiological dementia studies conducted in two adjacent regions during the period 1987-2012. We examined whether (i) cohort effects could be observed in age-associated trajectories of cognitive functions and (ii) the observed cohort effects could be explained by educational attainment. Trajectories of neuropsychological tests tapping three domains (psychomotor speed, executive function, and language) were compared among cohorts born between 1902 and 1911, 1912 and 1921, 1922 and 1931, and 1932 and 1943. We examined Age x Cohort interactions in mixed-effects models with/without controlling for education effects. RESULTS: Cohort effects in age-associated trajectories were observed in all three domains, with consistent differences between the earliest born cohort and the most recent cohort. Executive functions showed the strongest and persistent differences between the most recent and other three cohorts. Education did not attenuate any of these associations. CONCLUSIONS: Cohort effects were observed in all examined cognitive domains and, surprisingly, remained significant after controlling for educational effects. Factors other than education are likely responsible for the cohort effects in cognitive decline.

Donaires, F., Vargas-Herrera, J., Cabezas, C., Ponce, J., & Hoffman, K. (2013). Information systems for dengue about Peru: Need for real-time monitoring and analysis. [Sistemas de información sobre dengue en el Perú: Necesidad de monitoreo y análisis en tiempo real] *Revista Peruana De Medicina De Experimental y Salud Publica, 30*(3), 528-529.

Duffy, R. M., Vansandt, A., & Sandler, A. B. (2012). *Primary Sarcomas of the Lung* John Wiley & Sons, Inc. doi:10.1002/9781118464557.ch21

Primary pulmonary sarcomas 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 upon immunohistochemical and cytogenetic analysis. Primary pulmonary sarcomas are typically very advanced at the time of diagnosis, with symptoms related to tumor invasion or postobstructive pneumonia commonly prompting evaluation. Some patients, however, are asymptomatic at the time of diagnosis, and primary pulmonary sarcoma is an incidental finding on an imaging study. The clinical symptoms and radiographic findings of primary pulmonary sarcoma are myriad and

can resemble many other disease entities, so primary pulmonary sarcoma needs to be entertained in the differential diagnosis during evaluation of other diseases. Complete surgical resection remains the only therapeutic approach for cure but due to advanced stage at diagnosis, many patients are not eligible for resection. Chemotherapy and radiation therapy are important for treatment but newer, more efficacious therapeutic agents are needed. © 2012 by John Wiley & Sons, Inc.

Dunst, C. M., & Swanstrom, L. L. (2012). *Surgical Treatment of Gastroesophageal Reflux Disease* Wiley-Blackwell. doi:10.1002/9781444346220.ch32

Earl, T. R., Saha, S., Lombe, M., Korthuis, P. T., Sharp, V., Cohn, J., . . . Beach, M. C. (2013). Race, relationships, and trust in providers among black patients with HIV/AIDS. *Social Work Research, 37*(3), 219-226. doi:10.1093/swr/svt017

A trustful patient-provider relationship is a strong predictor of positive outcomes, including treatment adherence and viral suppression, among patients with HIV/AIDS. Understanding the factors that inform this relationship is especially relevant for black patients, who bear a disproportionate burden of HIV morbidity and mortality and may face challenges associated with seeing providers of a racial and ethnic background that is different from their own. Using data collected through the Enhancing Communication and HIV Outcomes (ECHO) study, the authors examined patient and provider characteristics that may influence black patients' trust in their provider. ECHO data were collected from four ambulatory care sites in Baltimore, Detroit, New York, and Portland, Oregon (N = 435). Regression analysis results indicate that trust in health care institutions and cultural similarity between the patient and the provider are strongly associated with patients' trust in their provider. Lower perceived social status, being currently employed, and having an older provider were also related to greater patient-provider trust. These findings can inform interventions to improve trust and reduce disparities in HIV care and outcomes that stem from mistrust among black patients. © 2013 National Association of Social Workers.

Earp, M. A., Kelemen, L. E., Magliocco, A. M., Swenerton, K. D., Chenevix-Trench, G., Lu, Y., . . . Brooks-Wilson, A. (2013). Genome-wide association study of subtype-specific epithelial ovarian

cancer risk alleles using pooled DNA. *Human Genetics,* , 1-17. doi:10.1007/s00439-013-1383-3

Epithelial ovarian cancer (EOC) is a heterogeneous cancer with both genetic and environmental risk factors. Variants influencing the risk of developing the less-common EOC subtypes have not been fully investigated. We performed a genome-wide association study (GWAS) of EOC according to subtype by pooling genomic DNA from 545 cases and 398 controls of European descent, and testing for allelic associations. We evaluated for replication 188 variants from the GWAS [56 variants for mucinous, 55 for endometrioid and clear cell, 53 for low-malignant potential (LMP) serous, and 24 for invasive serous EOC], selected using pre-defined criteria. Genotypes from 13,188 cases and 23,164 controls of European descent were used to perform unconditional logistic regression under the log-additive genetic model; odds ratios (OR) and 95 % confidence intervals are reported. Nine variants tagging six loci were associated with subtype-specific EOC risk at $P < 0.05$, and had an OR that agreed in direction of effect with the GWAS results. Several of these variants are in or near genes with a biological rationale for conferring EOC risk, including ZFP36L1 and RAD51B for mucinous EOC (rs17106154, OR = 1.17, P = 0.029, n = 1,483 cases), GRB10 for endometrioid and clear cell EOC (rs2190503, P = 0.014, n = 2,903 cases), and C22orf26/BPIL2 for LMP serous EOC (rs9609538, OR = 0.86, P = 0.0043, n = 892 cases). In analyses that included the 75 GWAS samples, the association between rs9609538 (OR = 0.84, P = 0.0007) and LMP serous EOC risk remained statistically significant at $P < 0.0012$ adjusted for multiple testing. Replication in additional samples will be important to verify these results for the less-common EOC subtypes.

Eil, R., Diggs, B. S., Wang, S. J., Dolan, J. P., Hunter, J. G., & Thomas, C. R. (2013). Nomogram for predicting the benefit of neoadjuvant chemoradiotherapy for patients with esophageal cancer: A SEER-Medicare analysis. *Cancer,* doi:10.1002/cncr.28447; 10.1002/cncr.28447

BACKGROUND: The survival impact of neoadjuvant chemoradiotherapy (CRT) on esophageal cancer remains difficult to establish for specific patients. The aim of the current study was to create a Web-based prediction tool providing individualized survival projections based on tumor and treatment data. METHODS: Patients diagnosed with esophageal cancer between 1997 and 2005 were selected from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The covariates analyzed were sex, T and N classification, histology, total number of

lymph nodes examined, and treatment with esophagectomy or CRT followed by esophagectomy. After propensity score weighting, a log-logistic regression model for overall survival was selected based on the Akaike information criterion. RESULTS: A total of 824 patients with esophageal cancer who were treated with esophagectomy or trimodal therapy met the selection criteria. On multivariate analysis, age, sex, T and N classification, number of lymph nodes examined, treatment, and histology were found to be significantly associated with overall survival and were included in the regression analysis. Preoperative staging data and final surgical margin status were not available within the SEER-Medicare data set and therefore were not included. The model predicted that patients with T4 or lymph node disease benefitted from CRT. The internally validated concordance index was 0.72. CONCLUSIONS: The SEER-Medicare database of patients with esophageal cancer can be used to produce a survival prediction tool that: 1) serves as a counseling and decision aid to patients and 2) assists in risk modeling. Patients with T4 or lymph node disease appeared to benefit from CRT. This nomogram may underestimate the benefit of CRT due to its variable downstaging effect on pathologic stage. It is available at skynet.ohsu.edu/nomograms. Cancer 2013;. (c) 2013 American Cancer Society.

Elliot, D. L., & Goldberg, L. (2012). *Athletes Targeting Healthy Exercise and Nutrition Alternatives: Harm Reduction/Health Promotion Program for Female High School Athletes* John Wiley & Sons, Inc. doi:10.1002/9781118269848.ch7

Enomoto, T. M., Larson, D., & Martindale, R. G. (2013). Patients requiring perioperative nutritional support. *The Medical Clinics of North America, 97*(6), 1181-1200. doi:10.1016/j.mcna.2013.07.003; 10.1016/j.mcna.2013.07.003

One of the most important factors affecting outcome and recovery from surgical trauma is preoperative nutritional status. Research in perioperative nutritional support has suffered from a lack of consensus as to the definition of malnutrition, no recognition of which nutrients are important to surgical healing, and a paucity of well-designed studies. In the past decade, there has been some activity to address this situation, recognizing the importance of nutrition as a therapy before surgery, after surgery, and possibly even during surgery.

Fairchild, K. D., Schelonka, R. L., Kaufman, D. A., Carlo, W. A., Kattwinkel, J., Porcelli, P. J., . . . Moorman, J. R. (2013). Septicemia mortality reduction in neonates in a heart rate characteristics monitoring trial. *Pediatric Research, 74*(5), 570-575. doi:10.1038/pr.2013.136

Background:Abnormal heart rate characteristics (HRC) wax and wane in early stages of culture-positive, late-onset septicemia (LOS) in patients in the neonatal intensive care unit (NICU). Continuously monitoring an HRC index leads to a reduction in mortality among very low birth weight (VLBW) infants. We hypothesized that the reduction in mortality was due to a decrease in septicemia-associated mortality.Methods:This is a secondary analysis of clinical and HRC data from 2,989 VLBW infants enrolled in a randomized clinical trial of HRC monitoring in nine NICUs from 2004 to 2010.Results:LOS was diagnosed 974 times in 700 patients, and the incidence and distribution of organisms were similar in HRC display and nondisplay groups. Mortality within 30 d of LOS was lower in the HRC display as compared with the nondisplay group (11.8 vs. 19.6%; relative risk: 0.61; 95% confidence interval: 0.43, 0.87; $P < 0.01$), but mortality reduction was not statistically significant for patients without LOS. There were fewer large, abrupt increases in the HRC index in the days leading up to LOS diagnosis in infants whose HRC index was displayed.Conclusion:Continuous HRC monitoring is associated with a lower septicemia-associated mortality in VLBW infants, possibly due to diagnosis earlier in the course of illness. © 2013 International Pediatric Research Foundation, Inc.

Fay, J. F., & Farrens, D. L. (2013). The Membrane Proximal Region of the Cannabinoid Receptor CB1 N-Terminus Can Allosterically Modulate Ligand Affinity. *Biochemistry, 52*(46), 8286-8294. doi:10.1021/bi400842k; 10.1021/bi400842k

The human cannabinoid receptor, CB1, a G protein-coupled receptor (GPCR), contains a relatively long (approximately 110 a.a.) amino terminus, whose function is still not defined. Here we explore a potential role for the CB1 N-terminus in modulating ligand binding to the receptor. Although most of the CB1 N-terminus is not necessary for ligand binding, previous studies have found that mutations introduced into its conserved membrane proximal region (MPR) do impair the receptors ability to bind ligand. Moreover, within the highly conserved MPR (approximately residues 90-110) lie two cysteine residues that are invariant in all CB1 receptors. We find these two cysteines (C98 and C107) form a disulfide in heterologously expressed human CB1, and this

C98-C107 disulfide is much more accessible to reducing agents than the previously known disulfide in extracellular loop 2 (EL2). Interestingly, the presence of the C98-C107 disulfide modulates ligand binding to the receptor in a way that can be quantitatively analyzed by an allosteric model. The C98-C107 disulfide also alters the effects of allosteric ligands for CB1, Org 27569 and PSNCBAM-1. Together, these results provide new insights into how the N-terminal MPR and EL2 act together to influence the high-affinity orthosteric ligand binding site in CB1 and suggest that the CB1 N-terminal MPR may be an area through which allosteric modulators can act.

Fender, E., Tripuraneni, A., & Henrikson, C. A. (2013). Dual defibrillation for refractory ventricular fibrillation in a patient with a left ventricular assist device. *Journal of Heart and Lung Transplantation, 32*(11), 1144-1145. doi:10.1016/j.healun.2013.07.006

Figueiredo, N., Chora, A., Raquel, H., Pejanovic, N., Pereira, P., Hartleben, B., . . . Moita, L. F. (2013). Anthracyclines induce DNA damage response-mediated protection against severe sepsis. *Immunity, 39*(5), 874-884. doi:10.1016/j.immuni.2013.08.039

Severe sepsis remains a poorly understood systemic inflammatory condition with high mortality rates andlimited therapeutic options in addition to organ support measures. Here we show that the clinically approved group of anthracyclines acts therapeutically at a low dose regimen to confer robust protection against severe sepsis in mice. This salutary effect is strictly dependent on the activation of DNA damage response and autophagy pathways in the lung, as demonstrated by deletion of the ataxia telangiectasia mutated (Atm) or the autophagy-related protein 7 (Atg7) specifically in this organ. The protective effect of anthracyclines occurs irrespectively of pathogen burden, conferring disease tolerance to severe sepsis. These findings demonstrate that DNA damage responses, including the ATM and Fancony Anemia pathways, are important modulators of immune responses and might be exploited to confer protection to inflammation-driven conditions, including severe sepsis. © 2013 Elsevier Inc.

Fleseriu, M., Yedinak, C. G., Brzana, J., & Mccartney, S. (2013). *Pituitary Disorders - Specific Issues for Women* Wiley-Blackwell. doi:10.1002/9781118559406.ch18

Pituitary diseases in womenpresent unique challenges in both diagnosis and management.

Menstrual disorders are a hallmark of pituitary dysfunction; they may present as hypogonadism or infertility and warrant a full investigation of pituitary function. Understanding of anatomic and physiologic pituitary changes during pregnancy and intrapartum can guide evaluation and diagnosis for peripartum pituitary disorders. The evaluation and management of Cushing disease, acromegaly, prolactinomas, both intra- and postpartum, is different from that in a nonpregnant state or in men; management pearls are offered. New-onset visual symptoms or pituitary deficiencies proximal to pregnancy can signify a potentially fatal pituitary disorder such as lymphocytic hypophystis or Sheehan syndrome and demand early diagnosis and treatment. Psychosocial changes have been documented in a high number of women with pituitary diseases and could persist after treatment, requiring concomitant or ongoing identification and treatment.

Foster Jr., R. S., Hunter, J. G., Spivak, H., Smith, C. D., & Davis Jr., S. S. (2010). *Adrenal glands open adrenalectomy laparoscopic adrenalectomy* Springer Berlin Heidelberg. doi:10.1007/978-3-540-74177-0_17

The anterior transabdominal approach was once the standard operative procedure for almost all adrenal lesions. This chapter describes alternative approaches that may provide better exposure for specific types of tumors or permit excision of the adrenal tumor with decreased morbidity. In addition to the anterior abdominal approach, alternative surgical approaches that are discussed include, the posterior approach, posterolateral extraperitoneal approach, thoracoabdomi-nal approach, thoracolumbar approach, and minimally invasive approaches. One of us (R.S.F.) has found each of the open procedures useful for specific adrenal tumors and four of us (J.G.H., H.S., C.D.S., S.S.D.) have performed endoscopic adrenalectomies

Fowlery, A., Roarky, B., Orhan, U., Erdogmus, D., & Fried-Okeny, M. (2013). Improved inference and autotyping in EEG-based BCI typing systems. *15th International ACM SIGACCESS Conference on Computers and Accessibility, ASSETS 2013,* Bellevue, WA. doi:10.1145/2513383.2513453

The RSVP KeyboardTM is a brain-computer interface (BCI)-based typing system for people with severe physical disabilities, specifically those with locked-in syndrome (LIS). It uses signals from

an electroencephalogram (EEG) combined with information from an n-gram language model to select letters to be typed. One characteristic of the system as currently configured is that it does not keep track of past EEG observations, i.e., observations of user intent made while the user was in a different part of a typed message. We present a principled approach for taking all past observations into account, and show that this method results in a 20% increase in simulated typing speed under a variety of conditions on realistic stimuli. We also show that this method allows for a principled and improved estimate of the probability of the backspace symbol, by which mis-typed symbols are corrected. Finally, we demonstrate the utility of automatically typing likely letters in certain contexts, a technique that achieves increased typing speed under our new method, though not under the baseline approach.

Fried, L. F., Emanuele, N., Zhang, J. H., Brophy, M., Conner, T. A., Duckworth, W., . . . VA NEPHRON-D Investigators. (2013). Combined Angiotensin inhibition for the treatment of diabetic nephropathy. *The New England Journal of Medicine, 369*(20), 1892-1903. doi:10.1056/NEJMoa1303154; 10.1056/NEJMoa1303154

BACKGROUND: Combination therapy with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain. Methods We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m(2) of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo. The primary end point was the first occurrence of a change in the estimated GFR (a decline of >/= 30 ml per minute per 1.73 m(2) if the initial estimated GFR was >/= 60 ml per minute per 1.73 m(2) or a decline of >/= 50% if the initial estimated GFR was <60 ml per minute per 1.73 m(2)), end-stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury. Results The study was stopped early owing to safety concerns. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-

therapy group (hazard ratio with combination therapy, 0.88; 95% confidence interval [CI], 0.70 to 1.12; P=0.30). A trend toward a benefit from combination therapy with respect to the secondary end point (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; P=0.10) decreased with time (P=0.02 for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95% CI, 0.73 to 1.49; P=0.75) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; P<0.001) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, P<0.001). Conclusions Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.).

Gallagher, E. R., & Berg, J. (2013). *Clinical Correlate: Cleft Lip and Palate* John Wiley & Sons, Inc. doi:10.1002/9781118704868.ch2

Gattey, D., Zhu, A. Y., Stagner, A., Terry, M. A., & Jun, A. S. (2013). Fuchs Endothelial Corneal Dystrophy in Patients With Myotonic Dystrophy: A Case Series. *Cornea,* doi:10.1097/ICO.0000000000000018

PURPOSE:: The aim was to report 4 cases of Fuchs endothelial corneal dystrophy (FECD) in patients with an established diagnosis of myotonic dystrophy (DM) and suggest a mechanism for their association based on the known molecular genetics and potential pathophysiological parallels of DM and FECD. METHODS:: We reviewed all available medical records and pathology slides for the 4 reported cases from the Department of Ophthalmology at Oregon Health and Science University's Casey Eye Institute and Devers Eye Institute at the Legacy Good Samaritan Medical Center in Portland, OR. RESULTS:: Four patients were found to have DM and bilateral corneal guttae, consistent with the diagnosis of FECD. All the identified patients were female and were aged between 34 and 63, and 2 patients were related (mother and daughter). The corneal specimens from 2 of the 4 patients who had undergone a corneal transplant were pathologically confirmed to be consistent with the diagnosis of FECD. CONCLUSIONS:: To our knowledge, FECD has not been previously reported in association with DM. Because both diseases are somewhat

prevalent in the United States, it is possible that their coexistence is merely a coincidence in these patients. However, recent studies into the pathogenesis of each disease have shown more parallels between FECD and DM, suggesting the possibility of a noncoincidental association. Potential mutual pathogenic mechanisms may involve altered protein expression causing the deregulation of ion homeostasis, an unstable intronic trinucleotide repeat expansion, or activation of the unfolded protein response and oxidative stress pathways.

Gelesko, S., Markiewicz, M. R., & Bell, R. B. (2013). Responsible and prudent imaging in the diagnosis and management of facial fractures. *Oral and Maxillofacial Surgery Clinics of North America, 25*(4), 545-560. doi:10.1016/j.coms.2013.07.001; 10.1016/j.coms.2013.07.001

This article reviews the current standard of care in imaging considerations for the diagnosis and management of craniomaxillofacial trauma. Injury-specific imaging techniques and options for computer-aided surgery as related to craniomaxillofacial trauma are reviewed, including preoperative planning, intraoperative navigation, and intraoperative computed tomography. Specific imaging considerations by anatomic region include frontal sinus fractures, temporal bone fractures, midfacial fractures, mandible fractures, laryngotracheal injuries, and vascular injuries. Imaging considerations in the pediatric trauma patient are also discussed. Responsible postoperative imaging as it relates to facial trauma management and outcomes assessment is reviewed.

Gelow, J. M., Song, H. K., Weiss, J. B., Mudd, J. O., & Broberg, C. S. (2013). Organ allocation in adults with congenital heart disease listed for heart transplant: Impact of ventricular assist devices. *Journal of Heart and Lung Transplantation, 32*(11), 1059-1064. doi:10.1016/j.healun.2013.06.024

Background Adults with congenital heart disease (CHD) listed for heart transplantation are rarely supported by ventricular assist devices (VADs). This may be a disadvantage to their priority for organ allocation. We sought to determine the relationship between VAD implantation and successful transplantation among patients listed for heart transplant. Methods Adults with CHD patients (N = 1,250) were identified from the United Network for Organ Sharing (UNOS) database from 1985 to 2010 and compared to patients without congenital etiology for heart

failure (N = 59,606). VAD use at listing, listing status, status upgrades and reasons for upgrade prior to transplant were trended at 5-year intervals and appropriate statistical comparisons were made between groups. Results Since 1985, VAD use prior to transplant has increased significantly in patients without CHD, but not in CHD patients (17% vs 3% in 2006 to 2010, $p < 0.0001$). CHD patients were more likely to be listed as Status 2, compared to those without (66% vs 40%, $p < 0.001$ for 2006 to 2010), and less likely to be upgraded to Status 1 after listing (43% vs 55%, $p = 0.03$). Among those upgraded to Status 1, CHD patients were less likely to have a VAD at transplant than those without (3% vs 18%, $p = 0.005$). VAD use was more likely to result in death in CHD patients. Conclusions VAD use is less common in CHD patients than in patients without CHD, both at the time of listing and transplantation. Reduced VAD use appears to contribute to lower listing status and organ allocation. These differences have grown more disparate over time. Separate criteria for organ allocation for CHD patients may be justified.

Gillingham, M. B., Harding, C. O., Schoeller, D. A., Matern, D., & Purnell, J. Q. (2013). Altered body composition and energy expenditure but normal glucose tolerance among humans with a long-chain fatty acid oxidation disorder. *American Journal of Physiology - Endocrinology and Metabolism, 305*(10), E1299-E1308. doi:10.1152/ajpendo.00225.2013

The development of insulin resistance has been associated with impaired mitochondrial fatty acid oxidation (FAO), but the exact relationship between FAO capacity and glucose metabolism continues to be debated. To address this controversy, patients with long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) deficiency underwent an oral glucose tolerance test (OGTT) and measurement of energy expenditure, body composition, and plasma metabolites. Compared with controls, patients with LCHAD deficiency had a trend toward higher total body fat and extramyocellular lipid deposition but similar levels of intramyocelluar and intrahepatic lipids. Resting energy expenditure was similar between the groups, but respiratory quotient was higher and total energy expenditure was lower in LCHAD-deficient patients compared with controls. High-molecular-weight (HMW) adiponectin levels were lower and plasma long-chain acyl-carnitines were higher among LCHAD-deficient patients. Fasting and post-OGTT levels of glucose, insulin, and ghrelin, along with estimates of insulin sensitivity, were the same between the

groups. Despite decreased capacity for FAO, lower total energy expenditure and plasma HMW adiponectin, and increased plasma acylcarnitines, LCHAD-deficient patients exhibited normal glucose tolerance. These data suggest that inhibition of the FAO pathway in humans is not sufficient to induce insulin resistance. © 2013 the American Physiological Society.

Golden, S., & Shaw, T. (2013). Hand dermatitis: review of clinical features and treatment options. *Seminars in Cutaneous Medicine and Surgery, 32*(3), 147-157.
Hand dermatitis affects a significant portion of the population and can be caused by a variety of endogenous factors (ie, atopy) as well as occupational and environmental exposures. It is often a chronic problem with high costs to individuals, employers, and society. This review discusses subtypes of hand dermatitis based on their clinical features and pathogenesis. It also offers an approach to treatment.

Goldsmith, K. A., Kasehagen, L. J., Rosenberg, K. D., Sandoval, A. P., & Lapidus, J. A. (2013). Unintended childbearing and knowledge of emergency contraception in a population-based survey of postpartum women. *Maternal and Child Health Journal, 17*(10), 2008-007-0282-4. doi:10.1007/s10995-007-0282-4; 10.1007/s10995-007-0282-4

Gotlib, J., Maxson, J. E., George, T. I., & Tyner, J. W. (2013). The new genetics of chronic neutrophilic leukemia and atypical CML: Implications for diagnosis and treatment. *Blood, 122*(10), 1707-1711. doi:10.1182/blood-2013-05-500959
Although activation of tyrosine kinase pathways is a shared theme among myeloproliferative neoplasms, the pathogenetic basis of chronic neutrophilic leukemia (CNL) has remained elusive. Recently, we identified high-frequency oncogenic mutations in the granulocyte-colony stimulating factor receptor (CSF3R) in CNL and in some patients with atypical chronic myeloid leukemia. Inhibition of Janus kinase 2 or SRC kinase signaling downstream of mutated CSF3R is feasible and should be explored therapeutically. Herein, we discuss the potential impact of these findings for the classification and treatment of these disorders. © 2013 by The American Society of Hematology.

Grazier, K. L., Trochim, W. M., Dilts, D. M., & Kirk, R. (2013). Estimating Return on Investment in Translational Research: Methods and Protocols. *Evaluation and the Health Professions, 36*(4), 478-491. doi:10.1177/0163278713499587

Assessing the value of clinical and translational research funding on accelerating the translation of scientific knowledge is a fundamental issue faced by the National Institutes of Health (NIH) and its Clinical and Translational Awards (CTSAs). To address this issue, the authors propose a model for measuring the return on investment (ROI) of one key CTSA program, the clinical research unit (CRU). By estimating the economic and social inputs and outputs of this program, this model produces multiple levels of ROI: investigator, program, and institutional estimates. A methodology, or evaluation protocol, is proposed to assess the value of this CTSA function, with specific objectives, methods, descriptions of the data to be collected, and how data are to be filtered, analyzed, and evaluated. This article provides an approach CTSAs could use to assess the economic and social returns on NIH and institutional investments in these critical activities. © The Author(s) 2013.

Green, C. A., McCarty, D., Mertens, J., Lynch, F. L., Hilde, A., Firemark, A., . . . Anderson, B. M. (2013). "The chief of the service is very enthusiastic about it": A qualitative study of the adoption of buprenorphine for opioid addiction treatment. *Journal of Substance Abuse Treatment,* doi:10.1016/j.jsat.2013.09.002

Qualified physicians may prescribe buprenorphine to treat opioid dependence, but medication use remains controversial. We examined adoption of buprenorphine in two not-for-profit integrated health plans, over time, completing 101 semi-structured interviews with clinicians and clinician-administrators from primary and specialty care. Transcripts were reviewed, coded, and analyzed. A strong leader championing the new treatment was critical for adoption in both health plans. Once clinicians began using buprenorphine, patients' and other clinicians' experiences affected decisions more than did the champion. With experience, protocols developed to manage unsuccessful patients and changed to support maintenance rather than detoxification. Diffusion outside addiction and mental health settings was nonexistent; primary care clinicians cited scope-of-practice issues and referred patients to specialty care. With greater diffusion came questions about long-term use and safety. Recognizing how implementation processes develop may

suggest where, when, and how to best expend resources to increase adoption of such treatments.

Gustin, J. K., & Douglas, J. L. (2013). BST-2/tetherin: Viral tether, viral sensor or both? *Future Virology, 8*(11), 1053-1060. doi:10.2217/fvl.13.96

In the fields of virology and innate immunity, BST-2/tetherin is well known for its ability to block the egress of enveloped viruses from infected cells. This appears to be accomplished by 'tethering' virions to the cell surface, thereby limiting virion release. In the past year, several groups have discovered that BST-2/tetherin can activate NF-κB, a transcriptional activator that leads to the rapid expression of both proinflammatory cytokines and proteins involved in cell survival. While this new BST-2 function has been interpreted as a possible viral-sensing mechanism, there may also be broader implications for HIV gene regulation. This article reviews the evidence for BST-2-dependent NF-κB activation, and explores the significance of these exciting new results.

Gwinner, F. P., Bottino, M. A., Nogueira-Junior, L., & Bona, A. D. (2013). Effect of finish line on marginal fit of sintered gold copings. *Brazilian Dental Journal, 24*(4), 322-325. doi:10.1590/0103-6440201301575; 10.1590/0103-6440201301575

The aim of this study was to evaluate the vertical marginal gap of sintered gold copings and metal-ceramic crowns with different finish line preparations: a beveled round shoulder (BRS) and a beveled long chamfer (BLC), testing the null hypotheses that there are no differences in marginal gap regardless of finish line and phase of restoration (coping or crown). Stainless steel master models were fabricated to simulate tooth preparation for metal-ceramic crowns with different finish lines (BRS and BLC). Ten dies were obtained from each model. Preparations were coated with 2 layers of spacer to 1 mm from the margin. Sintercast gold copings were prepared, sintered and adjusted to the dies. The copings (n=10) were placed onto the master model and the marginal gap was measured in 24 equidistant points using optical microscopy (X230). An opaque and two body ceramic layers were subsequently applied to the copings and the same measuring procedure was performed for the crowns. The data were analyzed statistically using paired and unpaired Student's t-test (alpha=0.05). Mean marginal gap values (microm) for the

copings and crowns were, respectively: 113.6 and 117.1 for the BRS; and 58.2 and 74.3 for the BLC preparation. Significantly greater marginal gaps (p=0.0307) were found for restorations with BRS than with BLC finish line, which also showed statistically significant differences in the gap size between coping and crown (p=0.001). In conclusion, marginal gap is influenced by ceramic application on copings fabricated on BLC preparation, and greater marginal gaps were found for restorations with BRS finish line, rejecting the experimental null hypotheses.

Haack, T. B., Hogarth, P., Gregory, A., Prokisch, H., & Hayflick, S. J. (2013). *BPAN. The Only X-Linked Dominant NBIA Disorder* doi:10.1016/B978-0-12-410502-7.00005-3

Beta-propeller protein-associated neurodegeneration (BPAN) is the most recently identified subtype of neurodegeneration with brain iron accumulation (NBIA), being unique with respect to the underlying disease genetics, the associated clinical presentation, and the suggested pathomechanism. Mutations in X-chromosomal WDR45 arise de novo; however, the dominant pattern of inheritance is unusual for an X-linked disorder and additional mechanisms such as X-inactivation or somatic mosaicism are likely to contribute to the phenotype that is indistinguishable between males and females. The course of the disease is two-staged with developmental delay and intellectual disability in childhood and a second phase of rapid neurological deterioration characterized by parkinsonism and dementia occurring in adolescence or early adulthood. At this time, neuroimaging findings are characteristic and provide excellent diagnostic guidance. There is increasing evidence that human WDR45 deficiency impairs autophagy, thereby raising the possibility that this rare disorder will offer insights into more common neurodegenerative disorders such as Parkinson or Alzheimer disease. © 2013 Elsevier Inc.

Haberthur, K., Kraft, A., Arnold, N., Park, B., Meyer, C., Asquith, M., . . . Messaoudi, I. (2013). Genome-wide analysis of t cell responses during acute and latent simian varicella virus infections in rhesus macaques. *Journal of Virology, 87*(21), 11751-11761. doi:10.1128/JVI.01809-13

Varicella zoster virus (VZV) is the etiological agent of varicella (chickenpox) and herpes zoster (HZ [shingles]). Clinical observa- tions suggest that VZV-specific T cell immunity plays a more critical role than humoral immunity in the prevention of VZV reac- tivation and development of

herpes zoster. Although numerous studies have characterized T cell responses directed against se-lect VZV open reading frames (ORFs), a comprehensive analysis of the T cell response to the entire VZV genome has not yet been conducted. We have recently shown that intrabronchial inoculation of young rhesus macaques with simian varicella virus (SVV), a homolog of VZV, recapitulates the hallmarks of acute and latent VZV infection in humans. In this study, we character- ized the specificity of T cell responses during acute and latent SVV infection. Animals generated a robust and broad T cell re-sponse directed against both structural and nonstructural viral proteins during acute infection in bronchoalveolar lavage (BAL) fluid and peripheral blood. During latency, T cell responses were detected only in the BAL fluid and were lower and more re-stricted than those observed during acute infection. Interestingly, we identified a small set of ORFs that were immunogenic dur- ing both acute and latent infection in the BAL fluid. Given the close genome relatedness of SVV and VZV, our studies highlight immunogenic ORFs that may be further investigated as potential components of novel VZV vaccines that specifically boost T cell immunity.

Han, D., Zager, J. S., Shyr, Y., Chen, H., Berry, L. D., Iyengar, S., . . . Leong, S. P. (2013). Clinicopathologic Predictors of Sentinel Lymph Node Metastasis in Thin Melanoma. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,* doi:10.1200/JCO.2013.50.1114

PURPOSE: Indications for sentinel lymph node biopsy (SLNB) for thin melanoma are continually evolving. We present a large multi-institutional study to determine factors predictive of sentinel lymph node (SLN) metastasis in thin melanoma. PATIENTS AND METHODS: Retrospective review of the Sentinel Lymph Node Working Group database from 1994 to 2012 identified 1,250 patients who had an SLNB and thin melanomas (/= 0.75 mm, Clark level >/= IV, ulceration, and absence of regression differed significantly between positive and negative SLN groups (all P /= 0.75 mm (P = .03), Clark level >/= IV (P = .05), and ulceration (P = .01) significantly predicted SLN metastasis with 6.3%, 7.0%, and 11.6% of the patients with these respective characteristics having SLN disease. Melanomas /= 0.75 mm (P = .03), Clark level >/= IV (P = .05), and ulceration (P = .01) significantly predicted SLN metastasis with 6.3%, 7.0%, and 11.6% of the patients with these respective characteristics having SLN disease. Melanomas /= 0.75 mm, Clark

level >/= IV, and ulceration significantly predict SLN disease in thin melanoma. Most SLN metastases (86.2%) occur in melanomas >/= 0.75 mm, with 6.3% of these patients having SLN disease, whereas in melanomas /= 0.75 mm, Clark level >/= IV, and ulceration significantly predict SLN disease in thin melanoma. Most SLN metastases (86.2%) occur in melanomas >/= 0.75 mm, with 6.3% of these patients having SLN disease, whereas in melanomas /= 0.75 mm, but further study is needed to define indications for SLNB in melanomas < 0.75 mm.

Harriff, M. J., Burgdorf, S., Kurts, C., Wiertz, E. J., Lewinsohn, D. A., & Lewinsohn, D. M. (2013). TAP Mediates Import of Mycobacterium tuberculosis-Derived Peptides into Phagosomes and Facilitates Loading onto HLA-I. *PloS One, 8*(11), e79571. doi:10.1371/journal.pone.0079571; 10.1371/journal.pone.0079571

Processing and presentation of antigen on MHC-I class I molecules serves to present peptides derived from cytosolic proteins to CD8(+) T cells. Infection with bacteria that remain in phagosomal compartments, such as Mycobacterium tuberculosis (Mtb), provides a challenge to this immune recognition as bacterial proteins are segregated from the cytosol. Previously we identified the Mtb phagosome itself as an organelle capable of loading MHC Class I molecules with Mtb antigens. Here, we find that the TAP transporter, responsible for importing peptides into the ER for loading in Class I molecules, is both present and functional in Mtb phagosomes. Furthermore, we describe a novel peptide reagent, representing the N-terminal domain of the bovine herpes virus UL49.5 protein, which is capable of specifically inhibiting the lumenal face of TAP. Together, these results provide insight into the mechanism by which peptides from intra-phagosomal pathogens are loaded onto Class I molecules.

Hatch, B., Angier, H., Marino, M., Heintzman, J., Nelson, C., Gold, R., . . . Devoe, J. (2013). Using Electronic Health Records to Conduct Children's Health Insurance Surveillance. *Pediatrics,* doi:10.1542/peds.2013-1470

OBJECTIVE:Health insurance options are changing. Electronic health record (EHR) databases present new opportunities for providers to track the insurance coverage status of their patients. This study demonstrates the use of EHR data for this purpose.METHODS:Using EHR data from the OCHIN Network of community health centers, we conducted a retrospective cohort study of data

from children presenting to a community health center in 2010-2011 (N = 185 959). We described coverage patterns for children, used generalized estimating equation logistic regression to compare uninsured children with those with insurance, and assessed insurance status at subsequent visits.RESULTS:At their first visit during the study period, 21% of children had no insurance. Among children uninsured at a first visit, 30% were uninsured at all subsequent visits. In multivariable analyses (including gender, age, race, ethnicity, language, income, location, and type of clinic), we observed significant differences in the characteristics of children who were uninsured as compared with those with insurance coverage. For example, compared with white, non-Hispanic children, nonwhite and/or Hispanic children had lower odds of being uninsured than having Medicaid/Medicare (adjusted odds ratio, 0.73; 95% confidence interval: 0.71-0.75) but had higher odds of being uninsured than having commercial insurance (adjusted odds ratio, 1.50; 95% confidence interval: 1.44-1.56).CONCLUSIONS:Nearly one-third of children uninsured at their first visit remained uninsured at all subsequent visits, which suggests a need for clinics to conduct insurance surveillance and develop mechanisms to assist patients with obtaining coverage. EHRs can facilitate insurance surveillance and inform interventions aimed at helping patients obtain and retain coverage.

He, W. A., Berardi, E., Cardillo, V. M., Acharyya, S., Aulino, P., Thomas-Ahner, J., . . . Guttridge, D. C. (2013). NF-κB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. *Journal of Clinical Investigation, 123*(11), 4821-4835. doi:10.1172/JCI68523
Cachexia is a debilitating condition characterized by extreme skeletal muscle wasting that contributes significantly to morbidity and mortality. Efforts to elucidate the underlying mechanisms of muscle loss have predominantly focused on events intrinsic to the myofiber. In contrast, less regard has been given to potential contributory factors outside the fiber within the muscle microenvironment. In tumor-bearing mice and patients with pancreatic cancer, we found that cachexia was associated with a type of muscle damage resulting in activation of both satellite and nonsatellite muscle progenitor cells. These muscle progenitors committed to a myogenic program, but were inhibited from completing differentiation by an event linked with persistent expression of the self-renewing factor Pax7. Overexpression of Pax7 was sufficient to induce atrophy in normal muscle, while under tumor conditions, the reduction of Pax7 or

exogenous addition of its downstream target, MyoD, reversed wasting by restoring cell differentiation and fusion with injured fibers. Furthermore, Pax7 was induced by serum factors from cachectic mice and patients, in an NF-κB-dependent manner, both in vitro and in vivo. Together, these results suggest that Pax7 responds to NF-κB by impairing the regenerative capacity of myogenic cells in the muscle microenvironment to drive muscle wasting in cancer.

Henares, B., Kommineni, S., Chumsakul, O., Ogasawara, N., Ishikawa, S., & Nakano, M. M. (2013). The ResD response regulator, through functional interaction with NsrR and Fur, plays three distinct roles in Bacillus subtilis transcriptional control. *Journal of Bacteriology,* doi:10.1128/JB.01166-13

The ResD response regulator activates transcription of diverse genes in Bacillus subtilis in response to oxygen limitation. ResD regulon genes that are the most highly induced during nitrate respiration include the nitrite reductase operon (nasDEF) and the flavohemoglobin gene (hmp) whose products function in nitric oxide (NO) metabolism. Transcription of these genes is also under the negative control of the NO-sensitive NsrR repressor. Recent studies showed that the NsrR regulon contains genes with no apparent relevance to NO metabolism and that the ResD response regulator and NsrR coordinately regulate transcription. To determine whether these genes are direct targets of NsrR and ResD, we used Chromatin Affinity Precipitation coupled with tiling chip (ChAP-chip) and ChAP followed by qPCR (ChAP-qPCR) analyses. The study showed that ResD and NsrR directly control transcription of the ykuNOP operon in the Fur regulon. ResD functions as an activator at the nasD and hmp promoters, whereas it functions at the ykuN promoter as an anti-repressor of Fur and a co-repressor for NsrR. This mechanism likely participates in fine-tuning of transcript levels in response to different sources of stress such as, oxygen limitation, iron limitation, and exposure to NO.

Henriquez, O. A., Schlosser, R. J., Mace, J. C., Smith, T. L., & Soler, Z. M. (2013). Impact of synechiae after endoscopic sinus surgery on long-term outcomes in chronic rhinosinusitis. *Laryngoscope, 123*(11), 2615-2619. doi:10.1002/lary.24150

Objectives/Hypothesis Synechiae are one of the most common unwanted outcomes after endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS). However, there has been scant

investigation into the true significance of synechiae formation after ESS. The aim of this study was to evaluate the impact of synechiae formation on health-related quality of life (HRQoL) outcomes after ESS in patients with CRS. Study Design Prospective, multi-institutional cohort. Methods Rhinosinusitis Disability Index (RSDI) and Chronic Sinusitis Survey (CSS) scores were measured in adult patients before and after undergoing ESS for CRS. Differences in HRQoL were evaluated between those who developed sinonasal synechiae and those who did not, controlling for demographic factors, medical comorbidities, and measures of disease severity at baseline. Results A total of 286 patients underwent ESS, with 55 (19.2%) developing synechiae in the follow-up period. Patients developing synechiae reported significantly less improvement on the RSDI total scores (13.5 vs. 21.4, P = 0.008), RSDI physical subscores (5.3 vs. 8.3, P = 0.007), RSDI emotional subscores (2.9 vs. 5.8, P = 0.008), CSS total scores (14.5 vs. 21.2, P = 0.093), and CSS symptom subscores (19.9 vs 30.3, P = 0.069) compared to those who did not develop synechiae postoperatively. These differences persisted even after controlling for baseline differences in disease severity. Conclusions Synechiae of the sinonasal cavity commonly occurs following ESS, particularly in those undergoing revision surgeries. Although both groups improve, the degree of HRQoL improvement appears to be less in those who form postoperative synechiae after surgery compared to those who do not.

Hersh, W., Bhupatiraju, R. T., & Corley, S. (2004). Enhancing access to the bibliome: The TREC genomics track. *Studies in Health Technology and Informatics, 107*, 773-777. doi:10.3233/978-1-60750-949-3-773

The growing amount of scientific discovery in genomics and related biomedical disciplines has led to a corresponding increase in the amount of on-line data and information. A new challenge for biomedical researchers has been how to access and manage this ever-increasing quantity of information. The Text Retrieval Conference (TREC) has implemented a Genomics Track to create an experimental environmentfor research in the use of information retrieval systems in the genomics domain. In the first year of the track, an ad hoc document retrieval task and an information extraction task were carried out by 29 research groups. Future work will focus on

more complex data sources, searching tasks, and types of experiments. © 2004 IMIA. All rights reserved.

Hersh, W. R., Leen, T. K., Steve, P., & Malveau, S. (1998). Automatic prediction of trauma registry procedure codes from emergency room dictations. *9th World Congress on Medical Informatics, MedInfo 1998,* Seoul. *, 52* 665-669. doi:10.3233/978-1-60750-896-0-665
Current natural language processing techniques for recognition of concepts in the electronic medical record have been insufficient to allow their broad use for coding information automatically. We have undertaken a preliminary investigation into the use of machine learning methods to recognize procedure codes from emergency room dictations for a trauma registry. Our preliminary results indicate moderate success, and we believe future enhancements with additional learning techniques and selected natural language processing approaches will be fruitful. © 1998 IMIA. All rights reserved.

Hersh, W. R., & Valerius, J. D. (2013). A tale of two professions. *Journal of AHIMA / American Health Information Management Association, 84*(10), 38-41.

Hess, O., Khayat, M., Hwa, V., Heath, K. E., Teitler, A., Hritan, Y., . . . Tenenbaum-Rakover, Y. (2013). A novel mutation in IGFALS, c.380T>C (p.L127P), associated with short stature, delayed puberty, osteopenia and hyperinsulinaemia in two siblings: Insights into the roles of insulin growth factor-1 (IGF1). *Clinical Endocrinology, 79*(6), 838-844. doi:10.1111/cen.12200
Background The acid-labile subunit (ALS) protein is crucial for maintaining the circulating IGF/IGFBP system. Inactivating mutations of IGFALS result in IGF1 deficiency associated with growth retardation. Although the first IGFALS mutation in humans was described in 2004, only 16 mutations have been reported since. Moreover, the phenotype of affected patients as a consequence of ALS deficiency is still highly variable. We assessed whether children with idiopathic short stature (ISS) harbour mutations in IGFALS and characterized affected patients' phenotype. Design Sixty-five children with ISS were enrolled in the study. Serum ALS levels were measured by ELISA, and IGFALS was sequenced. Results A novel homozygous mutation in IGFALS, c.380T>C (p.L127P), was identified in two siblings of a consanguineous family. The proband, a 17·75-year-old male, was -1·9 SDS in height and -4·5 SDS in weight. Exaggerated

stimulated GH (38 ng/ml) and extremely low IGF1 and IGFBP3 (<25 and <500 ng/ml, respectively) indicated GH insensitivity. Both affected siblings had low or no ALS (43 and 0 mU/ml, respectively). They were also mildly small for gestational age, severely underweight and showed osteopenia, insulin insensitivity and delayed and slow puberty progression. Conclusions Acid-labile subunit deficiency due to IGFALS mutations is a rare cause of growth retardation in children. The unique combination of features presented by the two affected siblings emphasizes the important role of IGF1 in bone formation, insulin regulation and the pubertal process, in addition to its crucial effect on growth. Long-term follow-up is indicated since the clinical outcome with respect to osteoporosis, diabetes mellitus and fertility has not been recognized.

Hetts, S. W., Turk, A., English, J. D., Dowd, C. F., Mocco, J., Prestigiacomo, C., . . . on behalf of the Matrix and Platinum Science Trial Investigators. (2013). Stent-Assisted Coiling versus Coiling Alone in Unruptured Intracranial Aneurysms in the Matrix and Platinum Science Trial: Safety, Efficacy, and Mid-Term Outcomes. *AJNR.American Journal of Neuroradiology,* doi:10.3174/ajnr.A3755

BACKGROUND AND PURPOSE:Stent-assisted coiling may result in less aneurysm recanalization but more complications than coiling alone. We evaluated outcomes of coiling with and without stents in the multicenter Matrix and Platinum Science Trial.MATERIALS AND METHODS:All patients in the Matrix and Platinum Science Trial with unruptured intracranial aneurysms treated per protocol were included. Baseline patient and aneurysm characteristics, procedural details, neurologic outcomes, angiographic outcomes, and safety data were analyzed.RESULTS:Overall, 137 of 361 (38%) patients were treated with a stent. Stent-coiled aneurysms had wider necks (>/=4 mm in 62% with stents versus 33% without, P /=4 mm (OR, 4.5; P = .02) were the only independent predictors of ischemic stroke. Stent use was not an independent predictor of ischemic stroke at 2 years (OR, 1.1; P = .94). Stent use did not predict target aneurysm recurrence at 2 years, but aneurysm dome size >/=10 mm (OR, 9.94; P < .0001) did predict target aneurysm recurrence.CONCLUSIONS:Stent-coiling had similar outcomes as coiling despite stented aneurysms having more difficult morphology than coiled aneurysms. Increased ischemic

events in stent-coiled aneurysms were attributable to baseline risk factors and aneurysm morphology.

Hoang, P. D., Cameron, M. H., Gandevia, S. C., & Lord, S. R. (2013). Neuropsychological, Balance, and Mobility Risk Factors for Falls in People With Multiple Sclerosis: A Prospective Cohort Study. *Archives of Physical Medicine and Rehabilitation,* doi:10.1016/j.apmr.2013.09.017

Objectives: To determine whether impaired performance in a range of vision, proprioception, neuropsychological, balance, and mobility tests and pain and fatigue are associated with falls in people with multiple sclerosis (PwMS). Design: Prospective cohort study with 6-month follow-up. Setting: A multiple sclerosis (MS) physiotherapy clinic. Participants: Community-dwelling people (N=210; age range, 21-74y) with MS (Disease Steps 0-5). Interventions: Not applicable. Main Outcome Measures: Incidence of falls during 6 months' follow-up. Results: In the 6-month follow-up period, 83 participants (39.7%) experienced no falls, 57 (27.3%) fell once or twice, and 69 (33.0%) fell 3 or more times. Frequent falling (≥3) was associated with increased postural sway (eyes open and closed), poor leaning balance (as assessed with the coordinated stability task), slow choice stepping reaction time, reduced walking speed, reduced executive functioning (as assessed with the difference between Trail Making Test Part B and Trail Making Test Part A), reduced fine motor control (performance on the 9-Hole Peg Test [9-HPT]), and reported leg pain. Increased sway with the eyes closed, poor coordinated stability, and reduced performance in the 9-HPT were identified as variables that significantly and independently discriminated between frequent fallers and nonfrequent fallers (model $\chi 2$ 3=30.1, P<.001). The area under the receiver operating characteristic curve for this model was .712 (95% confidence interval, .638-.785). Conclusions: The study reveals important balance, coordination, and cognitive determinants of falls in PwMS. These should assist the development of effective strategies for prevention of falls in this high-risk group.

Hostetler, C. M., & Ryabinin, A. E. (2014). Social partners prevent alcohol relapse behavior in prairie voles. *Psychoneuroendocrinology, 39*, 152-157. doi:10.1016/j.psyneuen.2013.10.006; 10.1016/j.psyneuen.2013.10.006

There is robust evidence for a protective role of interpersonal factors such as social support on

alcohol relapse, but research on the mechanisms that social factors may be acting on to effectively protect individuals against relapse is lacking. Prairie voles are highly social, monogamous rodents that freely self-administer ethanol in high amounts, and are a useful model for understanding social influences on alcohol drinking. Here we investigated whether prairie voles can be used to model social influences on relapse using the alcohol deprivation effect, in which animals show a transient increase in ethanol drinking following deprivation. In Experiment I, subjects were housed alone during four weeks of 24-h access to 10% ethanol in a two-bottle choice test. Ethanol was then removed from the cage for 72h. Animals remained in isolation or were then housed with a familiar same-sex social partner, and ethanol access was resumed. Animals that remained isolated showed an increase in ethanol intake relative to pre-deprivation baseline, indicative of relapse-like behavior. However, animals that were socially housed did not show an increase in ethanol intake, and this was independent of whether the social partner also had access to ethanol. Experiment II replicated the alcohol deprivation effect in a separate cohort of isolated animals. These findings demonstrate that prairie voles display an alcohol deprivation effect and suggest a 'social buffering' effect of relapse-like behavior in the prairie vole. This behavioral paradigm provides a novel approach for investigating the behavioral and neurobiological underpinnings of social influences on alcohol relapse.

Huang, X., Meng, B., Iqbal, J., Ding, B. B., Perry, A. M., Cao, W., . . . Fu, K. (2013). Activation of the STAT3 Signaling Pathway Is Associated With Poor Survival in Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,* doi:10.1200/JCO.2013.52.8414

PURPOSE: We previously reported that constitutive STAT3 activation is a prominent feature of the activated B-cell subtype of diffuse large B-cell lymphomas (ABC-DLBCL). In this study, we investigated whether STAT3 activation can risk stratify patients with DLBCL. PATIENTS AND METHODS: By an immunohistochemical method, we investigated phosphotyrosine STAT3 (PY-STAT3) expression from 185 patients with DLBCL treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone). Cell line-based siRNA experiments were also performed to generate an 11-gene, PY-STAT3 activation signature, which was used to study a previously published cohort of 222 patients with DLBCL. The STAT3 activation status

determined by these two methods and by STAT3 mRNA levels were then correlated with survival. RESULTS: PY-STAT3 was detected in 37% of DLBCL and enriched in ABC-DLBCL cases (P = .03). PY-STAT3 positivity significantly correlated with poor overall survival (OS; P = .01) and event-free survival (EFS; P = .006). Similar observations were made for high levels of STAT3 mRNA. In multivariable analysis, PY-STAT3 status (P = .02), International Prognostic Index (P = .02), and BCL2 expression (P = .046) were independent prognosticators of OS in this cohort. Among the cell-of-origin subgroups, PY-STAT3 was associated with poor EFS among non-germinal center B-cell DLBCL cases only (P = .027). Similarly, the 11-gene STAT3 activation signature correlated with poor survival in the entire DLBCL cohort (OS, P < .001; EFS, P < .001) as well as the ABC-DLBCL subgroup (OS, P = .029; EFS, P = .025). CONCLUSION: STAT3 activation correlated with poor survival in patients with DLBCL treated with R-CHOP, especially those with tumors of the ABC-DLBCL subtype.

Huguet, N., Kaplan, M. S., & McFarland, B. H. (2013). The Effects of Misclassification Biases on Veteran Suicide Rate Estimates. *American Journal of Public Health,* doi:10.2105/AJPH.2013.301450

Objectives. We assessed the impact that possible veteran suicide misclassification biases (i.e., inaccuracy in ascertainment of veteran status on the death certificate and misclassification of suicide as other manner of death) have on veteran suicide rate estimates. Methods. We obtained suicide mortality data from the 2003-2010 National Violent Death Reporting System and the 2003-2010 Department of Defense Casualty Analysis System. We derived population estimates from the 2003-2010 American Community Survey and 2003-2010 Department of Veterans Affairs data. We computed veteran and nonveteran suicide rates. Results. The results showed that suicide rates were minimally affected by the adjustment for the misclassification of current military personnel suicides as veterans. Moreover, combining suicides and deaths by injury of undetermined intent did not alter the conclusions. Conclusions. The National Violent Death Reporting System is a valid surveillance system for veteran suicide. However, more than half of younger (< 25 years) male and female suicides, labeled as veterans, were likely to have been current military personnel at the time of their death and misclassified on the death certificate.

(Am J Public Health. Published online ahead of print November 14, 2013: e1-e5. doi:10.2105/AJPH.2013.301450).

Hundal, H. S., & Cigarroa, J. E. (2013). As the kidney goes, so goes the heart... *Catheterization and Cardiovascular Interventions, 82*(6), 886-887. doi:10.1002/ccd.25213

Iacovides, D. C., Johnson, A. B., Wang, N., Boddapati, S., Korkola, J., & Gray, J. W. (2013). Identification and quantification of AKT isoforms and phosphoforms in breast cancer using a novel nanofluidic immunoassay. *Molecular and Cellular Proteomics, 12*(11), 3210-3220. doi:10.1074/mcp.M112.023119

Breast cancer subtype-specific molecular variations can dramatically affect patient responses to existing therapies. It is thought that differentially phosphorylated protein isoforms might be a useful prognostic biomarker of drug response in the clinic. However, the accurate detection and quantitative analysis of cancer-related protein isoforms and phospho-isoforms in tumors are limited by current technologies. Using a novel, fully automated nanocapillary electrophoresis immunoassay (NanoProTM 1000) designed to separate protein molecules based on their isoelectric point, we developed a reliable and highly sensitive assay for the detection and quantitation of AKT isoforms and phosphoforms in breast cancer. This assay enabled the measurement of activated AKT1/2/3 in breast cancer cells using protein produced from as few as 56 cells. Importantly, we were able to assign an identity for the phosphorylated S473 phosphoform of AKT1, the major form of activated AKT involved in multiple cancers, including breast, and a current focus in clinical trials for targeted intervention. The ability of our AKT assay to detect and measure AKT phosphorylation from very low amounts of total protein will allow the accurate evaluation of patient response to drugs targeting activated PI3K-AKT using scarce clinical specimens. Moreover, the capacity of this assay to detect and measure all three AKT isoforms using one single pan-specific antibody enables the study of the multiple and variable roles that these isoforms play in AKT tumorigenesis. © 2013 by The American Society for Biochemistry and Molecular Biology, Inc.

Iliff, J. J., Wang, M., Zeppenfeld, D. M., Venkataraman, A., Plog, B. A., Liao, Y., . . . Nedergaard, M. (2013). Cerebral Arterial Pulsation Drives Paravascular CSF-Interstitial Fluid Exchange in the

Murine Brain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 33*(46), 18190-18199. doi:10.1523/JNEUROSCI.1592-13.2013; 10.1523/JNEUROSCI.1592-13.2013

CSF from the subarachnoid space moves rapidly into the brain along paravascular routes surrounding penetrating cerebral arteries, exchanging with brain interstitial fluid (ISF) and facilitating the clearance of interstitial solutes, such as amyloid beta, in a pathway that we have termed the "glymphatic" system. Prior reports have suggested that paravascular bulk flow of CSF or ISF may be driven by arterial pulsation. However, cerebral arterial pulsation could not be directly assessed. In the present study, we use in vivo two-photon microscopy in mice to visualize vascular wall pulsatility in penetrating intracortical arteries. We observed that unilateral ligation of the internal carotid artery significantly reduced arterial pulsatility by approximately 50%, while systemic administration of the adrenergic agonist dobutamine increased pulsatility of penetrating arteries by approximately 60%. When paravascular CSF-ISF exchange was evaluated in real time using in vivo two-photon and ex vivo fluorescence imaging, we observed that internal carotid artery ligation slowed the rate of paravascular CSF-ISF exchange, while dobutamine increased the rate of paravascular CSF-ISF exchange. These findings demonstrate that cerebral arterial pulsatility is a key driver of paravascular CSF influx into and through the brain parenchyma, and suggest that changes in arterial pulsatility may contribute to accumulation and deposition of toxic solutes, including amyloid beta, in the aging brain.

Ishikawa, Y., & Bächinger, H. P. (2013). An additional function of the rough endoplasmic reticulum protein complex prolyl 3-hydroxylase 1·cartilage-associated protein·Cyclophilin B: The CXXXC motif reveals disulfide isomerase activity in vitro. *Journal of Biological Chemistry, 288*(44), 31437-31446. doi:10.1074/jbc.M113.498063

Collagen biosynthesis occurs in the rough endoplasmic reticulum, and many molecular chaperones and folding enzymes are involved in this process. The folding mechanism of type I procollagen has been well characterized, and protein disulfide isomerase (PDI) has been suggested as a key player in the formation of the correct disulfide bonds in the noncollagenous carboxyl-terminal and amino-terminal propeptides. Prolyl 3-hydroxylase 1 (P3H1) forms a hetero-trimeric complex with cartilage-associated protein and cyclophilin B (CypB). This complex is a

multifunctional complex acting as a prolyl 3-hydroxylase, a peptidyl prolyl cis-trans isomerase, and a molecular chaperone. Two major domains are predicted from the primary sequence of P3H1: an amino-terminal domain and a carboxyl-terminal domain corresponding to the 2-oxoglutarate- and iron-dependent dioxygenase domains similar to the α-subunit of prolyl 4-hydroxylase and lysyl hydroxylases. The amino-terminal domain contains four CXXXC sequence repeats. The primary sequence of cartilage-associated protein is homologous to the amino-terminal domain of P3H1 and also contains four CXXXC sequence repeats. However, the function of the CXXXC sequence repeats is not known. Several publications have reported that short peptides containing a CXC or a CXXC sequence show oxido-reductase activity similar to PDI in vitro. We hypothesize that CXXXC motifs have oxido-reductase activity similar to the CXXC motif in PDI. We have tested the enzyme activities on model substrates in vitro using a GCRALCG peptide and the P3H1 complex. Our results suggest that this complex could function as a disulfide isomerase in the rough endoplasmic reticulum.

Jack, A. R., Norris, P. L., & Storrs, F. J. (2013). Allergic contact dermatitis to plant extracts in cosmetics. *Seminars in Cutaneous Medicine and Surgery, 32*(3), 140-146.

Topically applied cosmetics and medicaments containing botanical extracts are commonly used. Despite popular beliefs of their benignancy, some botanicals have been implicated in causing allergic contact dermatitis in susceptible patients. The offending allergen may be the botanical extract itself or another ingredient such as a fragrance, preservative, dye, or sunscreen found in the product. Specific botanicals implicated in causing cosmetic contact dermatitis include Compositae family plants, tea tree oil, peppermint, lavender, lichens, henna, and others.

Jensen, S. M., Paustain, C. C., & Fox, B. A. (2014). In Rosenblatt J.D., Barber G.N., Podack E.R. and Ochoa A.(Eds.), *Employing T Cell Homeostasis as an Antitumor Strategy* doi:10.1007/978-1-4614-8809-5_6

In the arena of cancer treatments, chemotherapeutic agents and radiotherapy were originally designed to kill rapidly dividing cancer cells and deletion of lymphoid cells was simply considered collateral damage. The last few decades have witnessed a growing appreciation for immunologic

control of tumor burdens, and consequently, numerous strategies designed to harness the immune system to combat cancers have been developed. While on the surface the combination of immune-depleting chemo/radiotherapies and immunotherapies may seem counterintuitive, the fact that the immune system has mechanisms in place for compensatory expansion after depletion, an effect called homeostasis-driven T cell expansion, has been exploited in both preclinical models as well as clinical therapies. This chapter examines both. © Springer Science+Business Media New York 2014.

Jimison, H. B., Klein, K. A., & Marcoe, J. L. (2013). A socialization intervention in remote health coaching for older adults in the home. *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2013,* Osaka. 7025-7028. doi:10.1109/EMBC.2013.6611175

Previous studies have shown that social ties enhance both physical and mental health, and that social isolation has been linked to increased cognitive decline. As part of our cognitive training platform, we created a socialization intervention to address these issues. The intervention is designed to improve social contact time of older adults with remote family members and friends using a variety of technologies, including Web cameras, Skype software, email and phone. We used usability testing, surveys, interviews and system usage monitoring to develop design guidance for socialization protocols that were appropriate for older adults living independently in their homes. Our early results with this intervention show increased number of social contacts, total communication time (we measure email, phone, and Skype usage) and significant participant satisfaction with the intervention. © 2013 IEEE.

Kair, L. R., Jaffe, A. C., & Phillipi, C. A. (2013). In healthy term infants, does restriction from pacifiers in the first two to four weeks of life increase breastfeeding duration? *Paediatrics and Child Health (Canada), 18*(9), 473-474.

Kanemaki, N., Fukiage, C., Ichikawa, Y., Shearer, T. R., & Azuma, M. (2013). Serum antibodies against βH-crystallins in the American Cocker Spaniel. *Veterinary Ophthalmology,* doi:10.1111/vop.12113

Objective: To detect antibodies for lens βH-crystallins in the serum from the American Cocker

Spaniel (ACS) presenting with and without cataracts and with and without uveitis. Animal Studied: Seventy-three American Cocker Spaniels and six normal Beagles. Procedures: Sera were collected from 73 ACSs, including those with normal lenses and those with cataracts, or uveitis. Fractionated, normal Beagle lens βH-crystallins were separated by one- or two-dimensional electrophoresis. The separated lens βH-crystallins were used on immunoblots as sentinel substrates against which the ACS sera were tested for the presence of antibodies against βH-crystallins. Results: Sera from approximately two-thirds of study animals contained antibodies to some βH-crystallin polypeptides, but reactivity varied among patients. Contrary to some hypotheses, serum antibodies to groups of βH-crystallins did not relate to the stages of cataract. However, detailed analysis by two-dimensional immunoblotting and mass spectrometry showed that three spots originating from βA1-crystallin were detected only in sera from cataract patients. Conclusion: Serum antibodies to βA1-crystallin may be associated with the development of cataract. © 2013 The Authors Veterinary Ophthalmology published by Wiley Periodicals, Inc.

Kaplan, M. S., Huguet, N., Feeny, D., McFarland, B. H., Caetano, R., Bernier, J., . . . Ross, N. A. (2013). The association between alcohol use and long-term care placement among older Canadians: A 14-year population-based study. *Addictive Behaviors,* 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.

Karamlou, T., Welke, K. F., McMullan, D. M., Cohen, G. A., Gelow, J., Tibayan, F. A., . . . Song, H. K. (2013). Combined heart-kidney transplant improves post-transplant survival compared with isolated heart transplant in recipients with reduced glomerular filtration rate: Analysis of 593 combined heart-kidney transplants from the United Network Organ Sharing Database. *Journal of Thoracic and Cardiovascular Surgery,* doi:10.1016/j.jtcvs.2013.09.017

Objective: Criteria for simultaneous heart-kidney transplant (HKTx) recipients are unclear. We characterized the evolution of combined HKTx in the United States over time compared with isolated heart transplantation (HTx) and determined factors maximizing post-transplant survival. We focused on whether a threshold estimated glomerular filtration rate (eGFR) could be identified that justified combined transplantation. Methods: A supplemented United Network Organ Sharing Dataset identified HTx and HKTx recipients from 2000 to 2010. eGFR was calculated for HTx and recipients were grouped into eGFR quintiles. Time-related mortality was compared among recipients, with multivariable factors sought using Cox proportional hazard regression models. Results: We identified 26,183 HTx recipients, of whom 593 were HKTx recipients. HTx increased modestly over time (3.6%), whereas prevalence of HKTx increased dramatically (147%). Risk-unadjusted survival was similar among HTx recipients (8.4 ± 0.04 years) and HKTx recipients (7.7 ± 0.2 years) ($P = .76$). Isolated HTx recipients in the lowest eGFR quintile had decreased survival ($P < .001$), but those in the third eGFR quintile had superior survival, suggesting a benefit in this subgroup. HTx recipients in the lowest eGFR quintile (eGFR less than mean 37 mL/minute) had worse survival than combined HKTx recipients (7.1 ± 0.07 vs 7.7 ± 0.2; $P < .001$). Multivariable factors for increased mortality among HTx recipients included lower eGFR, higher recent panel reactive antibody score, older age, African American race, diabetes, longer ischemic time, and certain diagnoses. Conclusions: Performance of combined HKTx is increasing out of proportion to isolated HTx. eGFR is an important determinant of improved HTx

survival. Combined HKTx recovers post-transplant survival in patients with eGFR <37 mL/minute and can be recommended in this subgroup. © 2013 The American Association for Thoracic Surgery.

Kaufman, K. R., Kelly, M. J., & Roselli, C. E. (2013). Rapid effects of 17β-estradiol on male copulatory behaviors are not elicited by the novel membrane active estrogenic compound STX. *Behavioral Neuroscience, 127*(4), 598-605. doi:10.1037/a0032950

Estrogens have been shown to rapidly promote male copulatory behaviors with a time-course that suggests rapid signaling events are involved. The present study tested the hypothesis that estrogen acts through a novel Gq protein-coupled membrane estrogen receptor (ER). Thus, either estradiol (E2), STX (a diphenylacrylamide compound that selectively activates a membrane ER pathway), or vehicle were administered acutely to castrated male rats that bore subcutaneous (sc) dihydrotestosterone implants to maintain genital sensitivity. Appetitive (level changes, genital investigation) and consummatory (mounts, intromissions, ejaculations) components of male sexual behavior were measured in a bilevel testing apparatus. Testing showed that E2 treatment promoted olfactory and mounting behaviors, but had no effect on motivation as measured by anticipatory level changes. STX treatment showed no effect on either component of male sexual behavior. These results support previous results that showed that E2 can rapidly affect male sexual behaviors but fail to support a role for the specific membrane-initiated pathway activated by STX. © 2013 American Psychological Association.

Kazmierczak, C. (2013). The quality of point-of-care testing: Something positive and something negative too. *Klinichescheskaya Laboratornaya Diagnostika,* (7), 19-20.

Kim, S. -., Lee, B., Kim, D. -., Kim, J., Lee, S., Lee, S. -., & Lee, J. W. (2013). Control of energy balance by hypothalamic gene circuitry involving two nuclear receptors, neuron-derived orphan receptor 1 and glucocorticoid receptor. *Molecular and Cellular Biology, 33*(19), 3826-3834. doi:10.1128/MCB.00385_13

Nuclear receptors (NRs) regulate diverse physiological processes, including the central nervous system control of energy balance. However, the molecular mechanisms for the central actions of NRs in energy balance remain relatively poorly defined. Here we report a hypothalamic gene

network involving two NRs, neuron-derived orphan receptor 1 (NOR1) and glucocorticoid receptor (GR), which directs the regulated expression of orexigenic neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) in response to peripheral signals. Our results suggest that the anorexigenic signal leptin induces NOR1 expression likely via the transcription factor cyclicAMPresponse element-binding protein (CREB), while the orexigenic signal glucocorticoid mobilizesGRto inhibit NOR1 expression by antagonizing the action of CREB. Also, NOR1 suppresses glucocorticoid-dependent expression of AgRP and NPY. Consistently, relative to wild-type mice, NOR1-null mice showed significantly higher levels of AgRP and NPY and were less responsive to leptin in decreasing the expression of AgRP and NPY. These results identify mutual antagonism between NOR1 andGR to be a key rheostat for peripheral metabolic signals to centrally control energy balance.

Kim, S. O., Dozier, B. L., Kerry, J. A., & Duffy, D. M. (2013). EP3 receptor isoforms are differentially expressed in subpopulations of primate granulosa cells and couple to unique G-proteins. *Reproduction, 146*(6), 625-635. doi:10.1530/REP-13-0274

Prostaglandin E2 (PGE2) produced within the ovarian follicle is necessary for ovulation. PGE2 is recognized by four distinct G-proteincoupled receptors. Among them, PTGER3 (also known as EP3) is unique in that mRNA splicing generates multiple isoforms. Each isoform has a distinct amino acid composition in the C-terminal region, which is involved in G-protein coupling. To determine whether monkey EP3 isoforms couple to different G-proteins, each EP3 isoform was expressed in Chinese hamster ovary cells, and intracellular signals were examined after stimulation with the EP3 agonist sulprostone. Stimulation of EP3 isoform 5 (EP3-5) reduced cAMP in a pertussis toxin (PTX)-sensitive manner, indicating involvement of Gai. Stimulation of EP3-9 increased cAMP, which was reduced by the general G-protein inhibitor GDP-β-S, and also increased intracellular calcium, which was reduced by PTX and GDP-β-S. So, EP3-9 likely couples to both Gαs and a PTX-sensitive G-protein to regulate intracellular signals. Stimulation of EP3-14 increased cAMP, which was further increased by PTX, so EP3-14 likely regulates cAMP via multiple G-proteins. Granulosa cell expression of all EP3 isoforms increased in response to an ovulatory dose of human chorionic gonadotropin. Two EP3 isoforms were differentially expressed in functional subpopulations of granulosa cells. EP3-5 was low in granulosa cells at the follicle apex

while EP3-9 was high in cumulus granulosa cells. Differential expression of EP3 isoforms may yield different intracellular responses to PGE2 in granulosa cell subpopulations, contributing to the different roles played by granulosa cell subpopulations in the process of ovulation. © 2013 Society for Reproduction and Fertility.

King, L. A., Horak, F. B., Mancini, M., Pierce, D., Priest, K. C., Chesnutt, J., . . . Chapman, J. C. (2013). Instrumenting the Balance Error Scoring System for use with patients reporting persistent balance problems after mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation,* doi:10.1016/j.apmr.2013.10.015; 10.1016/j.apmr.2013.10.015

OBJECTIVE: To determine whether alterations to the Balance Error Scoring System (BESS), such as modified conditions and/or instrumentation, would improve the ability to correctly classify TBI status in patients with mild TBI with persistent self-reported balance complaints. Design: A cross-sectional study. SETTING: An outpatient clinic in the Department of Rehabilitation Services at Oregon Health & Sciences University (OHSU). SUBJECTS: Thirteen subjects (age 16.3 +/-2) with a recent history of concussion (mTBI group) and 13 demographically matched control subjects (age 16.7 +/-2) (control group). INTERVENTION: Not applicable. MAIN OUTCOME MEASURES: Outcome measures included the BESS, Modified BESS (Mod. BESS), Instrumented BESS (Instr. BESS), and Instrumented Modified BESS (Instr. Mod. BESS). All subjects were tested on the non-instrumented BESS and Mod. BESS, scored by visual observation of instability in six and three stance conditions, respectively. Instrumentation of these 2 tests utilized one inertial sensor (APDM-3D), with an accelerometer and gyroscope to quantify bi-directional body sway. RESULTS: Scores from the BESS and the Mod. BESS tests were similar between groups. However, results from the instrumented measures using the inertial sensorb were significantly different between groups. The Instr. Mod. BESS had superior diagnostic classification and the largest Area Under the Curve (AUC) when compared to the other balance measures. CONCLUSIONS: A concussion may disrupt the sensory processing required for optimal postural control, measured by sway during quiet stance. These results suggest that the use of portable inertial sensorsb may be useful in the move towards more objective and sensitive measures of balance control post-concussion but more work is needed to increase sensitivity.

Klein, E., & Bourdette, D. (2013). Postmarketing adverse drug reactions: A duty to report? *Neurology.Clinical Practice, 3*(4), 288-294. doi:10.1212/CPJ.0b013e3182a1b9f0

Physicians play an important role in recognizing and reporting suspected adverse drug reactions (ADRs) to the Food and Drug Administration (FDA). Physicians can report suspected ADRs directly to the FDA via its MedWatch program, by contacting the manufacturer of the drug, and by publishing case reports. While this takes time, physicians have an ethical obligation to participate in recognizing and reporting ADR.

Klein, E., & Karlawish, J. (2013). Ethical issues in the neurology of aging and cognitive decline. *Handbook of Clinical Neurology, 118*, 233-242. doi:10.1016/B978-0-444-53501-6.00020-2; 10.1016/B978-0-444-53501-6.00020-2

Caring for persons with Alzheimer's disease presents neurologists with ethical challenges. Some of these, such as end-of-life care or research participation, are well known and have significant overlap with challenges in other areas of medicine or other neurologic diseases, such as cancer or traumatic brain injury, while others, such as the rise of biomarker-based diagnostics, are more novel and reflect the impact of developments in the science and clinical care of Alzheimer's disease. A thoughtful and systematic approach to these challenges, from the preclinical to the late symptomatic stage of this disease, is required and will help clinicians be better advocates and stewards of their patients. This chapter addresses a number of the most pressing ethical problems facing patients, caregivers, and clinicians during this disease, including early and presymptomatic testing, assessment of decision-making capacity for treatment or research participation, restriction of driving, remote monitoring, assisted suicide, and treatment of disruptive behaviors.

Klein, E. P. (2013). Patient Health Incentives: Ethical Challenges and Frameworks. *International Journal of Behavioral Medicine,* doi:10.1007/s12529-013-9373-3

BACKGROUND: Patient incentives for encouraging healthy behavior raise a number of ethical concerns: Do they target the vulnerable? Do they involve psychological manipulation? Do they undermine intrinsic motivation? PURPOSE: To the purpose of this paper is to provide an overview of ethical challenges raised by patient incentives and incentive programs and develop a

systematic approach to understanding and analyzing these ethical challenges. METHOD: Ethical considerations raised by patient incentives can be broadly grouped into two kinds: medical ("patient-oriented") and public health ("constituent-oriented") concerns. Ethical frameworks suitable to these kinds of concerns are explored. RESULTS: Two ethical frameworks are applied to the challenges raised by patient incentives: (1) Incentives are assessed in terms of personal and social responsibility for health; and (2) incentives are assessed as elements of normatively structured clinical relationships (e.g., the traditional patient-clinician relationship). CONCLUSION: A better understanding of ethical concerns and the resources available within the personal responsibility and clinical encounter frameworks suggest complementary guidance may be available for approaching many of the ethical issues raised by patient incentives.

Kornblith, L. Z., Kutcher, M. E., Callcut, R. A., Redick, B. J., Hu, C. K., Cogbill, T. H., . . . Western Trauma Association Study Group. (2013). Mechanical ventilation weaning and extubation after spinal cord injury: A Western Trauma Association multicenter study. *The Journal of Trauma and Acute Care Surgery, 75*(6), 1060-1070. doi:10.1097/TA.0b013e3182a74a5b; 10.1097/TA.0b013e3182a74a5b

BACKGROUND: Respiratory failure after acute spinal cord injury (SCI) is well recognized, but data defining which patients need long-term ventilator support and criteria for weaning and extubation are lacking. We hypothesized that many patients with SCI, even those with cervical SCI, can be successfully managed without long-term mechanical ventilation and its associated morbidity. METHODS: Under the auspices of the Western Trauma Association Multi-Center Trials Group, a retrospective study of patients with SCI at 14 major trauma centers was conducted. Comprehensive injury, demographic, and outcome data on patients with acute SCI were compiled. The primary outcome variable was the need for mechanical ventilation at discharge. Secondary outcomes included the use of tracheostomy and development of acute lung injury and ventilator-associated pneumonia. RESULTS: A total of 360 patients had SCI requiring mechanical ventilation. Sixteen patients were excluded for death within the first 2 days of hospitalization. Of the 344 patients included, 222 (64.5%) had cervical SCI. Notably, 62.6% of the patients with cervical SCI were ventilator free by discharge. One hundred forty-nine patients (43.3%) underwent tracheostomy, and 53.7% of them were successfully weaned from the ventilator,

compared with an 85.6% success rate among those with no tracheostomy ($p < 0.05$). Patients who underwent tracheostomy had significantly higher rates of ventilator-associated pneumonia (61.1% vs. 20.5%, $p < 0.05$) and acute lung injury (12.8% vs. 3.6%, $p < 0.05$) and fewer ventilator-free days (1 vs. 24 $p < 0.05$). When controlled for injury severity, thoracic injury, and respiratory comorbidities, tracheostomy after cervical SCI was an independent predictor of ventilator dependence with an associated 14-fold higher likelihood of prolonged mechanical ventilation (odds ratio, 14.1; 95% confidence interval, 2.78-71.67; $p < 0.05$). CONCLUSION: While many patients with SCI require short-term mechanical ventilation, the majority can be successfully weaned before discharge. In patients with SCI, tracheostomy is associated with major morbidity, and its use, especially among patients with cervical SCI, deserves further study. LEVEL OF EVIDENCE: Prognostic study, level III.

Krol, A. L. (2011). *Angiolymphoid Hyperplasia with Eosinophilia* Wiley-Blackwell. doi:10.1002/9781444345384.ch98

Kurian, M. A., & Hayflick, S. J. (2013). *Pantothenate Kinase-Associated Neurodegeneration (PKAN) and PLA2G6-Associated Neurodegeneration (PLAN). Review of Two Major Neurodegeneration with Brain Iron Accumulation (NBIA) Phenotypes* doi:10.1016/B978-0-12-410502-7.00003-X Neurodegeneration with brain iron accumulation (NBIA) comprises a heterogeneous group of disorders characterized by the presence of radiologically discernible high brain iron, particularly within the basal ganglia. A number of childhood NBIA syndromes are described, of which two of the major subtypes are pantothenate kinase-associated neurodegeneration (PKAN) and PLA2G6-associated neurodegeneration (PLAN). PKAN and PLAN are autosomal recessive NBIA disorders due to mutations in PANK2 and PLA2G6, respectively. Presentation is usually in childhood, with features of neurological regression and motor dysfunction. In both PKAN and PLAN, a number of classical and atypical phenotypes are reported. In this chapter, we describe the clinical, radiological, and genetic features of these two disorders and also discuss the pathophysiological mechanisms postulated to play a role in disease pathogenesis. © 2013 Elsevier Inc.

Kurosawa, H., Ikeyama, T., Achuff, P., Perkel, M., Watson, C., Monachino, A., . . . Nishisaki, A. (2013). A Randomized, Controlled Trial of In Situ Pediatric Advanced Life Support Recertification

("Pediatric Advanced Life Support Reconstructed") Compared With Standard Pediatric Advanced Life Support Recertification for ICU Frontline Providers. *Critical Care Medicine,* doi:10.1097/CCM.0000000000000024

OBJECTIVE:: Recent evidence shows poor retention of Pediatric Advanced Life Support provider skills. Frequent refresher training and in situ simulation are promising interventions. We developed a "Pediatric Advanced Life Support-reconstructed" recertification course by deconstructing the training into six 30-minute in situ simulation scenario sessions delivered over 6 months. We hypothesized that in situ Pediatric Advanced Life Support-reconstructed implementation is feasible and as effective as standard Pediatric Advanced Life Support recertification. DESIGN:: A prospective randomized, single-blinded trial. SETTING:: Single-center, large, tertiary PICU in a university-affiliated children's hospital. SUBJECTS:: Nurses and respiratory therapists in PICU. INTERVENTIONS:: Simulation-based modular Pediatric Advanced Life Support recertification training. MEASUREMENTS AND MAIN RESULTS:: Simulation-based pre- and postassessment sessions were conducted to evaluate participants' performance. Video-recorded sessions were rated by trained raters blinded to allocation. The primary outcome was skill performance measured by a validated Clinical Performance Tool, and secondary outcome was behavioral performance measured by a Behavioral Assessment Tool. A mixed-effect model was used to account for baseline differences. Forty participants were prospectively randomized to Pediatric Advanced Life Support reconstructed versus standard Pediatric Advanced Life Support with no significant difference in demographics. Clinical Performance Tool score was similar at baseline in both groups and improved after Pediatric Advanced Life Support reconstructed (pre, 16.3 +/- 4.1 vs post, 22.4 +/- 3.9; $p < 0.001$), but not after standard Pediatric Advanced Life Support (pre, 14.3 +/- 4.7 vs post, 14.9 +/- 4.4; $p = 0.59$). Improvement of Clinical Performance Tool was significantly higher in Pediatric Advanced Life Support reconstructed compared with standard Pediatric Advanced Life Support ($p = 0.006$). Behavioral Assessment Tool improved in both groups: Pediatric Advanced Life Support reconstructed (pre, 33.3 +/- 4.5 vs post, 35.9 +/- 5.0; $p = 0.008$) and standard Pediatric Advanced Life Support (pre, 30.5 +/- 4.7 vs post, 33.6 +/- 4.9; $p = 0.02$), with no significant difference of improvement between both groups ($p = 0.49$). CONCLUSIONS:: For PICU-based nurses and respiratory therapists, simulation-based "Pediatric Advanced Life Support-reconstructed" in situ training is feasible and more effective

than standard Pediatric Advanced Life Support recertification training for skill performance. Both Pediatric Advanced Life Support recertification training courses improved behavioral performance.

Kusano, A. S., Thomas Jr., C. R., Bonner, J. A., DeWeese, T. L., Formenti, S. C., Hahn, S. M., . . . Mittal, B. B. (2013). Burnout in United States Academic Chairs of Radiation Oncology Programs. *International Journal of Radiation Oncology, Biology, Physics,* doi:10.1016/j.ijrobp.2013.09.027 Purpose: The aims of this study were to determine the self-reported prevalence of burnout in chairs of academic radiation oncology departments, to identify factors contributing to burnout, and to compare the prevalence of burnout with that seen in other academic chair groups. Methods and Materials: An anonymous online survey was administered to the membership of the Society of Chairs of Academic Radiation Oncology Programs (SCAROP). Burnout was measured with the Maslach Burnout Inventory-Human Services Survey (MBI-HSS). Results: Questionnaires were returned from 66 of 87 chairs (76% response rate). Seventy-nine percent of respondents reported satisfaction with their current positions. Common major stressors were budget deficits and human resource issues. One-quarter of chairs reported that it was at least moderately likely that they would step down in the next 1 to 2 years; these individuals demonstrated significantly higher emotional exhaustion. Twenty-five percent of respondents met the MBI-HSS criteria for low burnout, 75% for moderate burnout, and none for high burnout. Group MBI-HSS subscale scores demonstrated a pattern of moderate emotional exhaustion, low depersonalization, and moderate personal accomplishment, comparing favorably with other specialties. Conclusions: This is the first study of burnout in radiation oncology chairs with a high response rate and using a validated psychometric tool. Radiation oncology chairs share similar major stressors to other chair groups, but they demonstrate relatively high job satisfaction and lower burnout. Emotional exhaustion may contribute to the anticipated turnover in coming years. Further efforts addressing individual and institutional factors associated with burnout may improve the relationship with work of chairs and other department members.

Kyser, K. L., Lu, X., Santillan, D., Santillan, M., Caughey, A. B., Wilson, M. C., & Cram, P. (2013). Forceps Delivery Volumes in Teaching and Nonteaching Hospitals: Are Volumes Sufficient for Physicians to Acquire and Maintain Competence? *Academic Medicine : Journal of the Association*

of American Medical Colleges, doi:10.1097/ACM.0000000000000048

PURPOSE: The decline in the use of forceps in operative deliveries over the last two decades raises questions about teaching hospitals' ability to provide trainees with adequate experience in the use of forceps. The authors examined (1) the number of operative deliveries performed in teaching and nonteaching hospitals, and (2) whether teaching hospitals performed a sufficient number of forceps deliveries for physicians to acquire and maintain competence. METHOD: The authors used State Inpatient Data from nine states to identify all women hospitalized for childbirth in 2008. They divided hospitals into three categories: major teaching, minor teaching, and nonteaching. They calculated delivery volumes (total operative, cesarean, vacuum, forceps, two or more methods) for each hospital and compared data across hospital categories. RESULTS: The sample included 1,344,305 childbirths in 835 hospitals. The mean cesarean volumes for major teaching, minor teaching, and nonteaching hospitals were 969.8, 757.8, and 406.9. The mean vacuum volumes were 301.0, 304.2, and 190.4, and the mean forceps volumes were 25.2, 15.3, and 8.9. In 2008, 31 hospitals (3.7% of all hospitals) performed no vacuum extractions, and 320 (38.3%) performed no forceps deliveries. In 2008, 13 (23%) major teaching and 44 (44%) minor teaching hospitals performed five or fewer forceps deliveries. CONCLUSIONS: Low forceps delivery volumes may preclude many trainees from acquiring adequate experience and proficiency. These findings highlighted broader challenges, faced by many specialties, in ensuring that trainees and practicing physicians acquire and maintain competence in infrequently performed, highly technical procedures.

Lane, N. E., Parimi, N., Corr, M., Yao, W., Cauley, J. A., Nielson, C. M., . . . Orwoll, E. (2013). Association of serum fibroblast growth factor 23 (FGF23) and incident fractures in older men: The Osteoporotic Fractures in Men (MrOS) study. *Journal of Bone and Mineral Research, 28*(11), 2325-2332. doi:10.1002/jbmr.1985

Normal mineral metabolism is critical for skeletal integrity, and recently serum fibroblast growth factor 23 (FGF23) levels were found to be directly related to overall fracture risk in elderly Swedish men. To confirm this association, we performed a prospective case-cohort study to understand the relation of FGF23 and fracture risk in older white men enrolled in the Osteoporotic Fractures in Men (MrOS) study. In the cohort of 5994 men attending the baseline MrOS

examination, we evaluated a subgroup of 387 men with incident nonvertebral fracture including 73 hip fractures and a sample of 1385 men randomly selected from the cohort with baseline mineral and calcium hormone measurements. FGF23 was measured in baseline serum samples by ELISA (Millipore, Billerica, MA, USA). Modified Cox proportional hazards models that account for case-cohort study design were used to estimate the relative hazards (RH) of fracture in men across quartiles of FGF23. Subjects were also stratified by renal function, and RH per strata was estimated in men with the highest quartile of FGF23 compared with quartiles 3, 2, and 1. Overall, there was no difference in risk of nonspine or hip fracture by baseline FGF23. However, associations differed by strata of eGFRCrCy. Among men with eGFRCrCys 60 mL/min/1.73 m2 (304/1370 fractures) the RH was 0.91 (95% CI 0.66-1.25) after adjustment for age, clinic site, body mass index, race, total hip bone mineral density, vitamin D, parathyroid hormone, alcohol use, physical activity, fracture history, and serum phosphorus. Serum FGF23 levels are not associated with incident fractures in elderly men overall. However, higher levels of serum FGF23 are associated with fracture risk in those with poor renal function.

Lee, C. G., Schwartz, A. V., Yaffe, K., Hillier, T. A., Leblanc, E. S., Cawthon, P. M., & Study of Osteoporotic Fractures Research Group. (2013). Changes in physical performance in older women according to presence and treatment of diabetes mellitus. *Journal of the American Geriatrics Society, 61*(11), 1872-1878. doi:10.1111/jgs.12502; 10.1111/jgs.12502

OBJECTIVES: To determine whether older women with diabetes mellitus have a greater longitudinal decline in physical performance than those without and whether any decline differs according to insulin sensitizer use. DESIGN: Prospective cohort study. SETTING: Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela, Pennsylvania. PARTICIPANTS: Community-dwelling women (mean age 78.5 +/- 3.6) enrolled in the Study of Osteoporotic Fractures in 1997-98 and restudied 4.9 +/- 0.6 years later (N = 2,864). MEASUREMENTS: Women were categorized as having no diabetes mellitus (n = 2,680) or having diabetes mellitus (n = 184). A prescription medication inventory was used to determine use of insulin sensitizers (metformin and thiazolidinedione). The outcomes were longitudinal changes in physical performance measures, including grip strength, usual walk speed, and rapid walk speed.

RESULTS: Estimates from fully adjusted models showed that women with diabetes mellitus had greater declines in usual walk speed (-0.16 m/s, 95% confidence interval (CI) = -0.19 to -0.14) and rapid walk speed (-0.21 m/s, 95% CI = -0.24 to -0.17) than those without (usual walk speed -0.11 m/s, 95% CI = -0.12 to -0.11, P < .001; rapid walk speed -0.15 m/s, 95% CI = -0.16 to -0.14; P = .005). Women with diabetes mellitus taking insulin sensitizers had less decline in usual walk speed than those not taking insulin sensitizers (P < .001). Declines in grip strength did not differ significantly by diabetes mellitus status or insulin sensitizer use. CONCLUSION: Older women with diabetes mellitus have a greater decline in walk speed, but not grip strength, than older women without diabetes mellitus. Clinical studies in older adults to determine whether diabetes mellitus treatments such as insulin sensitizers can prevent loss in walk speed and mobility are needed.

Lee, J. T., Kingdom, T. T., Smith, T. L., Setzen, M., Brown, S., & Batra, P. S. (2013). Practice patterns in endoscopic skull base surgery: Survey of the American Rhinologic Society. *International Forum of Allergy and Rhinology,* doi:10.1002/alr.21248

Background: The introduction of advanced endoscopic techniques has facilitated significant growth in the field of endoscopic skull base surgery (SBS). The purpose of this study is to evaluate the impact of endoscopic SBS on the clinical practice patterns of the American Rhinologic Society (ARS) membership. Methods: A 23-item survey vetted by the ARS Board of Directors was electronically disseminated to the ARS membership from February 5, 2013, to March 31, 2013. The target group encompassed 982 ARS members. Results: A total of 152 physicians (15.5%) completed the survey. Open and endoscopic skull base procedures were performed by 41% and 94% of the respondents, respectively. During a typical year, the number of endoscopic skull base cases ranged from 0 to 20 in 56%, 21 to 50 in 26%, 51 to 100 in 9%, and >100 in 8%. Endoscopic cerebrospinal fluid (CSF) leak repair (96%) and transsphenoidal pituitary surgery (81%) were the most commonly performed procedures, followed by transcribriform (68.4%), transplanum (54.4%), and transclival (49.6%) approaches. Overall, 69.6% used endoscopy for resections of malignant sinus/skull base lesions. Considerable variation in Current Procedural Terminology (CPT) coding philosophy was observed, with open skull base (32%), unlisted endoscopic (29%), sinus surgery (24%), and unlisted neurosurgical

(15%) codes employed by surgeons. Only 29% of physicians reported adequate reimbursement in ≥75% of cases. Eighty-five percent of respondents supported creation of dedicated endoscopic SBS codes. Conclusion: This study illustrates the widespread integration of endoscopic SBS procedures into rhinologic clinical practice among survey respondents. However, current variability in coding strategies and inadequate reimbursement may warrant development of specific guidelines to standardize coding and billing processes in the future.

Li, F., Harmer, P., Stock, R., Fitzgerald, K., Stevens, J., Gladieux, M., . . . Voit, J. (2013). Implementing an Evidence-Based Fall Prevention Program in an Outpatient Clinical Setting. *Journal of the American Geriatrics Society,* doi:10.1111/jgs.12509

Objectives: To investigate the dissemination potential of a Tai Ji Quan-based program, previously shown to be efficacious for reducing risk of falls in older adults, through outpatient clinical settings. Design: A single-group pre/post design in which participants attended a twice-weekly Tai Ji Quan training program for 24 weeks. Setting: Communities in Lane County, Oregon. Participants: Independently living individuals (N = 379) aged 65 and older. Measurements: Using the Reach, Effectiveness, Adoption, Implementation and Maintenance framework, the primary outcome was the proportion of participating healthcare providers who made referrals. Secondary outcomes were the proportion of referred individuals agreeing to participate and enrolling in the program, and measures of program implementation, maintenance, and effectiveness (on measures of falls, balance, gait, physical performance, and balance efficacy). Results: Of the 252 providers invited to participate, 157 made referrals (62% adoption rate). Of 564 individuals referred, 379 (67% reach) enrolled in the program, which was successfully implemented in senior and community centers with good fidelity, 283 completed the program (75% retention), and 212 of these attended 75% or more of the 48 sessions. Participants reported a reduction in falls, with an incidence rate of 0.13 falls per person-month, and showed significant improvement from baseline in all outcome measures. A 3-month postintervention follow-up indicated encouraging levels of program maintenance among providers, participants, and community centers. Conclusion: Healthcare providers successfully implemented a protocol to refer individuals at risk of falling to a Tai Ji Quan-based program. The evidence-based program appears readily scalable

and exportable, with potential for substantial clinical and public health effect. © 2013, The American Geriatrics Society.

Lieberman, D. (2013). Colon Polyp Surveillance Clinical Decision Tool. *Gastroenterology,* doi:10.1053/j.gastro.2013.11.029; 10.1053/j.gastro.2013.11.029

Lighthall, J. G., & Wang, T. D. (2013). Complications of forehead lift. *Facial Plastic Surgery Clinics of North America, 21*(4), 619-624. doi:10.1016/j.fsc.2013.07.006; 10.1016/j.fsc.2013.07.006
Complications and prevention of complications in brow lift are presented. A discussion of anatomic features of the brow introduces the article in keeping with the focus that a thorough understanding of the anatomy, patient variations, and potential complications is requisite for surgeons performing forehead rejuvenation. The varying approaches to brow lift are discussed. Complications reviewed are bleeding, nerve injury, scarring, alopecia, brow asymmetry, and brow elevation overcorrection or undercorrection.

Logan, J. R., McCashland, T., & Lieberman, D. A. (2004). Evaluation of reliability in the use of endoscopic terminology. *Studies in Health Technology and Informatics, 107*, 396-400. doi:10.3233/978-1-60750-949-3-396
Variability in the reporting of gastrointestinal endoscopic findings may affect the validity of analyses of data collected from clinical reports of those findings. In this project, images of 10 endoscopic findings were collected from the data repository of the Clinical Outcomes Research Initiative (CORI), all of which had been described by the reporting endoscopist. These images were presented to 52 experienced endoscopists recruited from the clinical affiliates of CORI who were asked to assign each a term from the Minimal Standard Terminology for Digestive Endoscopy. Proportion of agreement with the endoscopist varied by finding from 84.3% to 51.0% (overall 67.6% with 95% CI 63.4-71.8%). Proportion of agreement among the subjects varied by finding from 76.3% to 38.5%. (overall 55.6% with 95% CI 52.4-58.8%). Possible reasons for this lack of agreement are discussed. © 2004 IMIA. All rights reserved.

Lopez, A. M., & Hendrickson, R. G. (2014). Toxin-induced hepatic injury. *Emergency Medicine Clinics of North America, 32*(1), 103-125. doi:10.1016/j.emc.2013.09.005; 10.1016/j.emc.2013.09.005

Toxins such as pharmaceuticals, herbals, foods, and supplements may lead to hepatic damage. This damage may range from nonspecific symptoms in the setting of liver test abnormalities to acute hepatic failure. The majority of severe cases of toxin-induced hepatic injury are caused by acetaminophen and ethanol. The most important step in the patient evaluation is to gather an extensive history that includes toxin exposure and exclude common causes of liver dysfunction. Patients whose hepatic dysfunction progresses to acute liver failure may benefit from transfer to a transplant service for further management. Currently, the mainstay in management for most exposures is discontinuing the offending agent. This manuscript will review the incidence, pathophysiology, diagnosis and management of the different forms of toxin-induced hepatic injury and exam in-depth the most common hepatic toxins.

Lovci, M. T., Ghanem, D., Marr, H., Arnold, J., Gee, S., Parra, M., . . . Yeo, G. W. (2013). Rbfox proteins regulate alternative mRNA splicing through evolutionarily conserved RNA bridges. *Nature Structural and Molecular Biology,* doi:10.1038/nsmb.2699

Alternative splicing (AS) enables programmed diversity of gene expression across tissues and development. We show here that binding in distal intronic regions (>500 nucleotides (nt) from any exon) by Rbfox splicing factors important in development is extensive and is an active mode of splicing regulation. Similarly to exon-proximal sites, distal sites contain evolutionarily conserved GCATG sequences and are associated with AS activation and repression upon modulation of Rbfox abundance in human and mouse experimental systems. As a proof of principle, we validated the activity of two specific Rbfox enhancers in KIF21A and ENAH distal introns and showed that a conserved long-range RNA-RNA base-pairing interaction (an RNA bridge) is necessary for Rbfox-mediated exon inclusion in the ENAH gene. Thus we demonstrate a previously unknown RNA-mediated mechanism for AS control by distally bound RNA-binding proteins.

Luoh, S. W., Ramsey, B., Park, B., & Keenan, E. (2013). Quantitative Progesterone Receptor Expression and Efficacy of Anti-estrogen Therapy in Breast Cancer. *The Breast Journal,* doi:10.1111/tbj.12200; 10.1111/tbj.12200

The central role of estrogen receptor (ER) presence in predicting which breast cancer patients are

likely to benefit from anti-estrogen therapies is well-established, but the added benefit of progesterone receptor (PR) and in particular low levels of PR is less well understood. The objective of this study was to determine the quantitative relationship between borderline levels of PR and subsequent benefit from anti-estrogen therapy. We examined data from 447 patients, age 50 or older. ER and PR levels were quantitated by conventional ligand binding assay and Scatchard plot analysis or by enzyme-linked immunoassay. Comparison of clinical outcome in relation with ER and PR status was calculated using Kaplan-Meier actuarial survival analysis and the log-rank test. Subpopulation treatment effect pattern plot (STEPP) analysis was used to explore the interaction between treatment effects and ER or PR levels for the 409 patients with ER values greater than 0. For anti-estrogen treated patients, when the ER and PR positivity cut-off was set at 1.0 fmole/mg protein, there was a statistically significant advantage for patients with ER+PR+ over ER+ PR- tumors for both breast cancer-free interval (BCFI) and overall survival (OS). STEPP analysis found no overall interaction between treatment outcome (5 year survival probability) and levels of hormone receptor. However, patients with borderline PR levels did not appear to benefit from anti-estrogen therapy. PR levels above borderline in addition to the presence of ER predicts an increased probability of benefit from anti-estrogen therapy in breast cancer patients.

Marino, M., Li, Y., Rueschman, M. N., Winkelman, J. W., Ellenbogen, J. M., Solet, J. M., . . . Buxton, O. M. (2013). Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep, 36*(11), 1747-1755. doi:10.5665/sleep.3142; 10.5665/sleep.3142 OBJECTIVES: We validated actigraphy for detecting sleep and wakefulness versus polysomnography (PSG). DESIGN: Actigraphy and polysomnography were simultaneously collected during sleep laboratory admissions. All studies involved 8.5 h time in bed, except for sleep restriction studies. Epochs (30-sec; n = 232,849) were characterized for sensitivity (actigraphy = sleep when PSG = sleep), specificity (actigraphy = wake when PSG = wake), and accuracy (total proportion correct); the amount of wakefulness after sleep onset (WASO) was also assessed. A generalized estimating equation (GEE) model included age, gender, insomnia diagnosis, and daytime/nighttime sleep timing factors. SETTING: Controlled sleep laboratory conditions. PARTICIPANTS: Young and older adults, healthy or chronic primary insomniac (PI)

patients, and daytime sleep of 23 night-workers (n = 77, age 35.0 +/- 12.5, 30F, mean nights = 3.2). INTERVENTIONS: N/A. MEASUREMENTS AND RESULTS: Overall, sensitivity (0.965) and accuracy (0.863) were high, whereas specificity (0.329) was low; each was only slightly modified by gender, insomnia, day/night sleep timing (magnitude of change 30 min/night. CONCLUSIONS: This validation quantifies strengths and weaknesses of actigraphy as a tool measuring sleep in clinical and population studies. Overall, the participant-specific accuracy is relatively high, and for most participants, above 80%. We validate this finding across multiple nights and a variety of adults across much of the young to midlife years, in both men and women, in those with and without insomnia, and in 77 participants. We conclude that actigraphy is overall a useful and valid means for estimating total sleep time and wakefulness after sleep onset in field and workplace studies, with some limitations in specificity. CITATION: Marino M; Li Y; Rueschman MN; Winkelman JW; Ellenbogen JM; Solet JM; Dulin H; Berkman LF; Buxton OM. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. SLEEP 2013;36(11):1747-1755.

Marks, K. P. (2013). My concerns about the aap clinical report on "motor delays: Early identification and evaluation. *Pediatrics, 132*(5), e1449-e1450. doi:10.1542/peds.2013-2720A

Martin, B. I., Franklin, G. M., Deyo, R. A., Wickizer, T. M., Lurie, J. D., & Mirza, S. K. (2013). How do coverage policies influence practice patterns, safety, and cost of initial lumbar fusion surgery? A population-based comparison of workers' compensation systems. *Spine Journal,* doi:10.1016/j.spinee.2013.08.018

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

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

Martinez, A. E., & Siegel, D. (2011). *Kindler Syndrome* Wiley-Blackwell.

doi:10.1002/9781444345384.ch119

Kindler syndrome is a rare autosomal recessive genodermatosis characterized by acral blisters in the neonatal period, followed by trauma-induced blister formation in early childhood, photosensitivity, generalized progressive poikiloderma, diffuse cutaneous atrophy and mucosal inflammation. The gene responsible for Kindler's syndrome is located on chromosome 20p.12.3. The skin fragility in Kindler's syndrome is a result of the loss of expression of an actin-

cytoskeleton-associated protein named fermitin family homologue 1 (previously termed KIND-1). © 2011 Blackwell Publishing Ltd.

Matsumura, Y., Sakai, J., & Skach, W. R. (2013). Endoplasmic reticulum protein quality control is determined by cooperative interactions between Hsp/c70 protein and the CHIP E3 ligase. *Journal of Biological Chemistry, 288*(43), 31069-31079. doi:10.1074/jbc.M113.479345
Background: The CHIP E3 ligase regulates Hsp70 pro-degradation activities. Results: The P269A CHIP U-box mutation induces CHIP oligomerization and modulates nucleotide- and substrate-dependent interactions between the TPR domain and Hsp70 C terminus. Conclusion: The U-box domain plays a key role in CHIP recruitment to Hsp70-client complexes, possibly by controlling oligomerization. Significance: Hsp70-CHIP substrate triage is governed by complex allosteric interactions between multiple domains in both proteins. © 2013 by The American Society for Biochemistry and Molecular Biology, Inc. Published in the U.S.A.

Matthews, M., Nigg, J. T., & Fair, D. A. (2013). Attention Deficit Hyperactivity Disorder. *Current Topics in Behavioral Neurosciences,* doi:10.1007/7854_2013_249
Over the last two decades, there have been numerous technical and methodological advances available to clinicians and researchers to better understand attention deficit hyperactivity disorder (ADHD) and its etiology. Despite the growing body of literature investigating the disorder's pathophysiology, ADHD remains a complex psychiatric disorder to characterize. This chapter will briefly review the literature on ADHD, with a focus on its history, the current genetic insights, neurophysiologic theories, and the use of neuroimaging to further understand the etiology. We address some of the major concerns that remain unclear about ADHD, including subtype instability, heterogeneity, and the underlying neural correlates that define the disorder. We highlight that the field of ADHD is rapidly evolving; the descriptions provided here will hopefully provide a sturdy foundation for which to build and improve our understanding of the disorder.

Mayer, D. K., & Reiner, A. (2013). On leadership from the bedside to the boardroom. *Clinical Journal of Oncology Nursing, 17*(4), 353-354. doi:10.1188/13.CJON.353-354

McCartney, S., Weltin, M., & Burchiel, K. J. (2013). Use of an Artificial Neural Network for Diagnosis of Facial Pain Syndromes: An Update. *Stereotactic and Functional Neurosurgery, 92*(1), 44-52. doi:10.1159/000353188

Background: Based on a classification scheme for facial pain syndromes and a binomial (yes/no) facial pain questionnaire, we previously reported on the ability of an artificial neural network (ANN) to recognize and correctly diagnose patients with different facial pain syndromes. Objectives: We now report on an updated questionnaire, the development of a secure web-based neural network application and details of ANNs trained to diagnose patients with different facial pain syndromes. Methods: Online facial pain questionnaire responses collected from 607 facial pain patients (395 female, 65%, ratio F/M 1.86/1) over 5 years and 7 months were used for ANN training. Results: Sensitivity and specificity of the currently running ANN for trigeminal neuralgia type 1 and trigeminal neuralgia type 2 are 92.4 and 62.5% and 87.8 and 96.4%, respectively. Sensitivity and specificity are 86.7 and 95.2% for trigeminal neuropathic pain, 0 and 100% for trigeminal deafferentation pain and 100% for symptomatic trigeminal neuralgia and postherpetic neuralgia. Sensitivity is 50% for nervus intermedius neuralgia (NIN) and 0% for atypical facial pain (AFP), glossopharyngeal neuralgia (GPN) and temporomandibular joint disorder (TMJ). Specificity for AFP, NIN and TMJ is 99% and for GPN, 100%. Conclusions: We demonstrate the utilization of question-based historical self-assessment responses used as inputs to design an ANN for the purpose of diagnosing facial pain syndromes (outputs) with high accuracy. (c) 2013 S. Karger AG, Basel.

McCully, B. H., Hasan, W., Streiff, C. T., Houle, J. C., Woodward, W. R., Giraud, G. D., . . . Habecker, B. A. (2013). Sympathetic cardiac hyperinnervation and atrial autonomic imbalance in diet-induced obesity promote cardiac arrhythmias. *American Journal of Physiology - Heart and Circulatory Physiology, 305*(10), H1530-H1537. doi:10.1152/ajpheart.00196.2013

Obesity increases the risk of arrhythmias and sudden cardiac death, but the mechanisms are unknown. This study tested the hypothesis that obesity-induced cardiac sympathetic outgrowth and hyperinnervation promotes the development of arrhythmic events. Male Sprague-Dawley rats (250-275 g), fed a high-fat diet (33% kcal/fat), diverged into obesity-resistant (OR) and obesity-prone (OP) groups and were compared with rats fed normal chow (13% kcal/fat; CON). In vitro

experiments showed that both OR and OP rats exhibited hyperinnervation of the heart and high sympathetic outgrowth compared with CON rats, even though OR rats are not obese. Despite the hyperinnervation and outgrowth, we showed that, in vivo, OR rats were less susceptible to arrhythmic events after an intravenous epinephrine challenge compared with OP rats. On examining total and stimulus-evoked neurotransmitter levels in an ex vivo system, we demonstrate that atrial acetylcholine content and release were attenuated in OP compared with OR and CON groups. OP rats also expressed elevated atrial norepinephrine content, while norepinephrine release was suppressed. These findings suggest that the consumption of a high-fat diet, even in the absence of overt obesity, stimulates sympathetic outgrowth and hyperinnervation of the heart. However, normalized cardiac parasympathetic nervous system control may protect the heart from arrhythmic events.

McCully, S. P., Fabricant, L. J., Kunio, N. R., Groat, T. L., Watson, K. M., Differding, J. A., . . . Schreiber, M. A. (2013). The International Normalized Ratio overestimates coagulopathy in stable trauma and surgical patients. *The Journal of Trauma and Acute Care Surgery, 75*(6), 947-953. doi:10.1097/TA.0b013e3182a9676c; 10.1097/TA.0b013e3182a9676c

BACKGROUND: The international normalized ratio (INR) was developed to assess adequacy of Coumadin dosing. Its use has been generalized to guide fresh frozen plasma (FFP) therapy in stable patients. Thrombelastography (TEG) is a whole-blood assay measuring the viscoelastic properties of the clot in near real time. This study hypothesized that INR does not reflect coagulopathy and should not be used to guide FFP therapy in stable trauma and surgical patients. METHODS: Prospective observational data were collected from stable trauma and surgical patients (n = 106) who received FFP transfusions. Pretransfusion and posttransfusion blood samples were obtained to assess complete blood count, standard coagulation parameters (INR, partial thromboplastin time, fibrinogen and D-dimer), soluble clotting factors (II, V, VII, VIII, IX, X, XI, XII, proteins C and S) and TEG. Data were analyzed using a Mann-Whitney U-test. Significance was defined as $p < 0.05$. RESULTS: A total of 262 U of FFP were transfused, with 78% of 106 patients receiving two or more units. Despite a reduction in INR, median TEG values remained within normal limits, while clotting factor levels retained adequate function to produce

normal clotting before and following FFP transfusion. CONCLUSION: The use of FFP in this population did not affect coagulation status in a clinically relevant manner based on TEG values and coagulation factor function. INR is not a predictor of coagulopathy and should not be used to guide coagulation factor replacement in stable trauma and surgical patients. LEVEL OF EVIDENCE: Diagnostic study, level III.

Mcdonald, J. W. D., Burroughs, A. K., Feagan, B. G., & Fennerty, M. B. (2010). Introduction. *Evidence-Based Gastroenterology and Hepatology: Third Edition,* , 1-15. doi:10.1002/9781444314403.ch1

McElvany, M., Benninger, B., Smith, S., Mirza, A., Marshall, L., & Friess, D. (2013). Are distal femoral traction pins intra-articular? A cadaveric study. *Journal of Orthopaedic Trauma, 27*(11), e250-e253. doi:10.1097/BOT.0b013e318291005c

OBJECTIVES:: To examine the frequency of intra-articular placement of distal femoral traction pins and their proximity to the superficial femoral artery (SFA). METHODS:: Wires were placed in the distal femurs of 28 cadaveric knees at the adductor tubercle (ADT), the superior pole of the patella (SPP), and 2 cm proximal to SPP (SPP+2). A lateral fluoroscopic image was obtained after injection of radiopaque contrast to assess for joint penetration. Dissection was performed to confirm or refute fluoroscopic findings. The distance from each wire to the SFA was measured. RESULTS:: The percentage of intra-articular placement was higher (29%) at the ADT than the SPP+2 (0%) level. The mean (SD) distances from the ADT, SPP, and SPP+2 to the SFA were 7.4 (±1.8) cm, 5.7 (±1.7) cm, and 3.8 (±1.7) cm, respectively (P 0.7 cm proximal to the ADT may lower the risk of intra-articular placement. No difference was detected between fluoroscopic arthrography and gross dissection. Copyright © 2013 by Lippincott Williams & Wilkins.

McHugh, A., Bierzychudek, P., Greever, C., Marzulla, T., Van Buskirk, R., & Binford, G. (2013). A molecular phylogenetic analysis of Speyeria and its implications for the management of the threatened Speyeria zerenehippolyta. *Journal of Insect Conservation,* , 1-17. doi:10.1007/s10841-013-9605-5

The genetic structure of lineages can provide important information for delineating "evolutionarily significant units" (ESUs) for conservation, and for planning actions to protect and restore taxa

threatened with extinction. Speyeria zerenehippolyta, the Oregon silverspot butterfly, is a U.S.A. federally threatened subspecies that is the focus of considerable conservation effort, but whose evolutionary relationships with other Speyeria taxa are not well-understood. We conducted a genetic analysis of nine Speyeria species and 25 subspecies from western U.S.A., using both mitochondrial and nuclear markers. Our goal was to determine whether such data supported (a) S. z.hippolyta's designation as an ESU, and (b) the current morphologically-based taxonomy of Speyeria spp. Our data for S. z.hippolyta were equivocal; while nuclear markers resolved all these individuals into a single clade, mtDNA data suggested the existence of two clades. Aside from S. cybele, which was consistently supported as monophyletic, our data provided little support for most of the species currently recognized for western U.S. Speyeria, including S. zerene, and even less for the many subspecies designations. These genetic findings stand in contrast to the morphological differences recognized by experts, and suggest a relatively recent origin for many of these taxa. Two of 66 individuals screened for Wolbachia infection tested positive for this symbiont. Our results provide no persuasive evidence that S. z.hippolyta should lose its status as an ESU, but they have important implications for ongoing management actions such as population augmentation.

Messaoudi, I., Asquith, M., Engelmann, F., Park, B., Brown, M., Rau, A., . . . Grant, K. A. (2013). Moderate alcohol consumption enhances vaccine-induced responses in rhesus macaques. *Vaccine,* doi:10.1016/j.vaccine.2013.10.076; 10.1016/j.vaccine.2013.10.076

We have recently shown that chronic alcohol consumption in a rhesus macaque model of ethanol self-administration significantly modulates the serum cytokine profile. In this study, we extended these observations by investigating the impact of chronic ethanol exposure on the immune response to Modified Vaccinia Ankara (MVA). All animals were vaccinated with MVA before ethanol exposure to ethanol and then again after 7 months of 22h/day of "open-access" drinking of 4% (w/v) ethanol. Our results indicate that animals whose blood ethanol concentration (BEC) chronically exceeded 80mg/dl had lower CD4 and CD8 T cell proliferation as well as IgG responses following MVA booster than control animals. In contrast, relatively moderate drinkers whose BEC remained below 80mg/ml exhibited more robust MVA-specific IgG and CD8 T cell responses than controls. To begin to uncover mechanisms underlying the differences in MVA-

specific responses between the three groups, we analyzed plasma cytokine levels and microRNA expression in peripheral blood mononuclear cells following MVA booster. Our findings suggest that moderate ethanol consumption results in higher levels of antiviral cytokines and an expression profile of microRNAs linked to CD8 T cell differentiation. In summary, moderate alcohol consumption enhances recall vaccine responses, whereas chronic alcohol intoxication suppresses this response.

Metsch, L. R., Feaster, D. J., Gooden, L., Schackman, B. R., Matheson, T., Das, M., . . . Colfax, G. N. (2013). Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: The AWARE randomized clinical trial. *JAMA - Journal of the American Medical Association, 310*(16), 1701-1710. doi:10.1001/jama.2013.280034

IMPORTANCE: To increase human immunodeficiency virus (HIV) testing rates, many institutions and jurisdictions have revised policies to make the testing process rapid, simple, and routine. A major issue for testing scale-up efforts is the effectiveness of HIV risk-reduction counseling, which has historically been an integral part of the HIV testing process. OBJECTIVE: To assess the effect of brief patient-centered risk-reduction counseling at the time of a rapid HIV test on the subsequent acquisition of sexually transmitted infections (STIs). DESIGN, SETTING, AND PARTICIPANTS: From April to December 2010, Project AWARE randomized 5012 patients from 9 sexually transmitted disease (STD) clinics in the United States to receive either brief patient-centered HIV risk-reduction counseling with a rapid HIV test or the rapid HIV test with information only. Participants were assessed for multiple STIs at both baseline and 6-month follow-up. INTERVENTIONS: Participants randomized to counseling received individual patient-centered risk-reduction counseling based on an evidence-based model. The core elements included a focus on the patient's specific HIV/STI risk behavior and negotiation of realistic and achievable risk-reduction steps. All participants received a rapid HIV test. MAIN OUTCOMES AND MEASURES: The prespecified outcome was a composite end point of cumulative incidence of any of the measured STIs over 6 months. All participants were tested for Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum (syphilis), herpes simplex virus 2, and HIV. Women were also tested for Trichomonas vaginalis. RESULTS: There was no significant difference in 6-month composite STI incidence by study group (adjusted risk ratio, 1.12; 95% CI, 0.94-1.33).

There were 250 of 2039 incident cases (12.3%) in the counseling group and 226 of 2032 (11.1%) in the information-only group. CONCLUSION AND RELEVANCE: Risk-reduction counseling in conjunction with a rapid HIV test did not significantly affect STI acquisition among STD clinic patients, suggesting no added benefit from brief patient-centered risk-reduction counseling. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01154296.

Mhawech-Fauceglia, P., Wang, D., Samrao, D., Kim, G., Lawrenson, K., Meneses, T., . . . Pejovic, T. (2013). Clinical Implications of Marker Expression of Carcinoma-Associated Fibroblasts (CAFs) in Patients with Epithelial Ovarian Carcinoma After Treatment with Neoadjuvant Chemotherapy. *Cancer Microenvironment,* , 1-7. doi:10.1007/s12307-013-0140-4

Cancer-associated fibroblasts (CAFs) play an important role in tumor initiation and progression. The aim of this study is to explore the role of 2 CAF markers, fibroblast activated protein (FAP) and α-smooth muscle actin (αSMA), in patients with epithelial ovarian cancer (EOC) post-neoadjuvant chemotherapy. Sixty-six patients with the diagnosis of EOC treated with debulking surgery after neoadjuvant therapy were retrieved from the archives. Immunohistochemistry for FAP and αSMA antibodies were performed on paraffin-embedded tissue. Fisher's exact test was performed to test the association between FAP and αSMA expression and disease status. Kaplan-Meier method with log-rank test was used to check the survival difference between different FAP tumor/stroma expressions. FAP stromapos. expression was strongly associated with higher recurrences rate [OR: 15.95; 95 % CI: 1.521-835.206; p = 0.0072]. Cases with combined FAP stromapos and FAP tumorneg had higher death rate [OR: 4.845; 95 % CI: 1.53-16.61; p = 0.0046] and higher recurrence rate [OR: 5.12; 95 % CI: 0.91-54.42; p = 0.0487] compared to all the others. Cases with combined FAP stromaneg and FAP tumorneg were more likely to have lower recurrence rates [OR: 0.086; 95 % CI: 0.001-0.997; p = 0.0248]. αSMA was expressed by tumor-associated stroma in 95 % of cases and by tumor cells in 9 % of cases. No statistical power was found for αSMA and disease status. Our data indicate that FAP plays an important role in predicting tumor aggressiveness in patients with EOC post-neoadjuvant therapy, and its frequent expression in this malignancy implicates that FAP targeted therapy could be a very attractive strategy.

Millard, S. P., Lutz, F., Li, G., Galasko, D. R., Farlow, M. R., Quinn, J. F., . . . Bekris, L. M. (2014). *Association of cerebrospinal fluid Aβ42 with A2M gene in cognitively normal subjects* doi:10.1016/j.neurobiolaging.2013.07.027

Low cerebrospinal fluid (CSF) Aβ42 levels correlate with increased brain Aβ deposition in Alzheimer's disease (AD), which suggests a disruption in the degradation and clearance of Aβ from the brain. In addition, APOE ε4 carriers have lower CSF Aβ42 levels than non-carriers. The hypothesis of this investigation was that CSF Aβ42 levels would correlate with regulatory region variation in genes that are biologically associated with degradation or clearance of Aβ from the brain. CSF Aβ42 levels were tested for associations with Aβ degradation and clearance genes and APOE ε4. Twenty-four SNPs located within the 5' and 3' regions of 12 genes were analyzed. The study sample consisted of 99 AD patients and 168 cognitively normal control subjects. CSF Aβ42 levels were associated with APOE ε4 status in controls but not in AD patients; A2M regulatory region SNPs were also associated with CSF Aβ42 levels in controls butnot in AD patients, even after adjusting for APOE ε4. These results suggest that genetic variation within the A2M gene influences CSF Aβ42 levels. © 2014 Elsevier Inc.

Moneta, G. L. (2012). *Arterial and Venous Duplex Scanning* Wiley-Blackwell. doi:10.1002/9781118481370.ch1

Moneta, G. L., & Landry, G. J. (2012). *Vasospastic Disease of the Upper Extremity: Primary Raynaud's Syndrome* Wiley-Blackwell. doi:10.1002/9781118481370.ch75

Mooney, M., McWeeney, S., Canderan, G., & Sékaly, R. -. (2013). A systems framework for vaccine design. *Current Opinion in Immunology,* doi:10.1016/j.coi.2013.09.014

Numerous challenges have been identified in vaccine development, including variable efficacy as a function of population demographics and a lack of characterization and mechanistic understanding of immune correlates of protection able to guide delivery and dosing. There is tremendous opportunity in recent technological and computational advances to elucidate systems level understanding of pathogen-host interactions and correlates of immunity. A systems biology approach to vaccinology provides a new paradigm for rational vaccine design in a 'precision medicine' context. © 2013.

Morgan, S. R., Chang, A. M., Alqatari, M., & Pines, J. M. (2013). Non-emergency department interventions to reduce ED utilization: A systematic review. *Academic Emergency Medicine, 20*(10), 969-985. doi:10.1111/acem.12219

Objectives Recent health policy changes have focused efforts on reducing emergency department (ED) visits as a way to reduce costs and improve quality of care. This was a systematic review of interventions based outside the ED aimed at reducing ED use. Methods This study was designed as a systematic review. We reviewed the literature on interventions in five categories: patient education, creation of additional non-ED capacity, managed care, prehospital diversion, and patient financial incentives. Studies written in English, with interventions administered outside of the ED, and a comparison group where ED use was an outcome, were included. Two independent reviewers screened search results using MEDLINE, Cochrane, OAIster, or Scopus. The following data were abstracted from included studies: type of intervention, study design, population, details of intervention, effect on ED use, effect on non-ED health care use, and other health and financial outcomes. Quality of individual articles was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines. Results Of 39 included studies, 34 were observational and five were randomized controlled trials. Two of five studies on patient education found reductions in ED use ranging from 21% to 80%. Out of 10 studies of additional non-ED capacity, four showed decreases of 9% to 54%, and one a 21% increase. Both studies on prehospital diversion found reductions of 3% to 7%. Of 12 studies on managed care, 10 had decreases ranging from 1% to 46%. Nine out of 10 studies on patient financial incentives found decreases of 3% to 50%, and one a 34% increase. Nineteen studies reported effect on non-ED use with mixed results. Seventeen studies included data on health outcomes, but 13 of these only included data on hospitalizations rather than morbidity and mortality. Seven studies included data on cost outcomes. According to the GRADE guidelines, all studies had at least some risk of bias, with four moderate quality, one low quality, and 34 very low quality studies. Conclusions Many studies have explored interventions based outside the ED to reduce ED use in various populations, with mixed evidence. Approximately two-thirds identified here showed reductions in ED use. The interventions with the greatest number of studies showing reductions in ED use include patient financial incentives and managed care, while the greatest magnitude of reductions

were found in patient education. These findings have implications for insurers and policymakers seeking to reduce ED use. © 2013 by the Society for Academic Emergency Medicine.

Muench, J. (2013). Meta-analysis. *Family Medicine, 45*(10), 738.

Nakaishi, L., Moss, H., Weinstein, M., Perrin, N., Rose, L., Anger, W. K., . . . Glass, N. (2013). Exploring workplace violence among home care workers in a consumer-driven Home Health Care Program. *Workplace Health and Safety, 61*(10), 441-450. doi:10.3928/21650799-20130916-17 Nominal research has examined sexual harassment and workplace violence against home care workers within consumer- driven home care models such as those offered in Oregon. This study examined home care workers' experiences of violence while providing care to consumer employers, the patients who hire and manage home care workers. Focus groups and interviews were conducted in Oregon with 83 home care workers, 99 Oregon Department of Human Services (DHS) employees, and 11 consumer employers. Home care workers reported incidents of workplace physical violence (44%), psychological abuse (65%), sexual harassment (41%), and sexual violence (14%). Further, three themes were identified that may increase the risk of workplace violence: (1) real and perceived barriers to reporting violence; (2) tolerance of violence; and (3) limited training to prevent violence. To ensure worker safety while maintaining quality care, safety policies and training for consumer employers, state DHS employees, and home care workers must be developed. Workplace Health Saf 2013;61(10):441-450. © American Association of Occupational Health Nurses, Inc.

Nakajima, E., Hammond, K. B., Shearer, T. R., & Azuma, M. (2013). Activation of the mitochondrial caspase pathway and subsequent calpain activation in monkey RPE cells cultured under zinc depletion. *Eye (London, England),* doi:10.1038/eye.2013.239; 10.1038/eye.2013.239 PurposeDecreased zinc levels in the macula are reported in patients with age-related macular degeneration, and the zinc chelator N,N,N',N'-tetrakis (2- pyridylmethyl) ethylenediamine) (TPEN) causes death of human retinal pigment epithelial (RPE) cells. The purpose of the present study was to investigate signal transduction pathways during cell death initiated by TPEN, using monkey RPE cells.MethodsRPE cells were cultured with TPEN. Activation of calpains and caspases, and proteolysis of their substrates were detected by immunoblotting. Incubation of calpain

inhibitor SNJ-1945 or caspase inhibitor z-VAD-fmk was used to confirm activation of specific proteases.ResultsTPEN caused a time-dependent decrease in viable RPE cells. Cell death was accompanied by activation of calpain-1, caspase-9, and caspase-3. SNJ-1945 inhibited calpain activation and slightly inhibited caspase-9 activation. z-VAD-fmk inhibited caspases and calpain-1 activation. TPEN did not activate caspase-12.ConclusionsRelative zinc deficiency in RPE cells causes activation of cytosolic calpain and mitochondrial caspase pathways without ER stress.Eye advance online publication, 8 November 2013; doi:10.1038/eye.2013.239.

Nakayasu, E. S., Tempel, R., Cambronne, X. A., Petyuk, V. A., Jones, M. B., Gritsenko, M. A., . . . Heffron, F. (2013). Comparative phosphoproteomics reveals components of host cell invasion and post-transcriptional regulation during francisella infection. *Molecular and Cellular Proteomics, 12*(11), 3297-3309. doi:10.1074/mcp.M113.029850

Francisella tularensis is a facultative intracellular bacterium that causes the deadly disease tularemia. Most evidence suggests that Francisella is not well recognized by the innate immune system that normally leads to cytokine expression and cell death. In previous work, we identified new bacterial factors that were hyper-cytotoxic to macrophages. Four of the identified hyper-cytotoxic strains (lpcC, manB, manC, and kdtA) had an impaired lipopolysaccharide (LPS) synthesis and produced an exposed lipid A lacking the O-antigen. These mutants were not only hyper-cytotoxic but also were phagocytosed at much higher rates compared with the wild type parent strain. To elucidate the cellular signaling underlying this enhanced phagocytosis and cell death, we performed a large-scale comparative phosphoproteomic analysis of cells infected with wild-type and delta-lpcC F. novicida. Our data suggest that not only actin but also intermediate filaments and microtubules are important for F. novicida entry into the host cells. In addition, we observed differential phosphorylation of tristetraprolin, a key component of the mRNA-degrading machinery that controls the expression of a variety of genes including many cytokines. Infection with the delta-lpcC mutant induced the hyper- phosphorylation and inhibition of tristetraprolin, leading to the production of cytokines such as IL-1beta and TNF-alpha that may kill the host cells by triggering apoptosis. Together, our data provide new insights for Francisella invasion and a post-transcriptional mechanism that prevents the expression of host immune response factors

that control infection by this pathogen. © 2013 by The American Society for Biochemistry and Molecular Biology, Inc.

Nan, X., Collisson, E. A., Lewis, S., Huang, J., Tamgüney, T. M., Liphardt, J. T., . . . Chu, S. (2013). Single-molecule superresolution imaging allows quantitative analysis of RAF multimer formation and signaling. *Proceedings of the National Academy of Sciences of the United States of America, 110*(46), 18519-18524. doi:10.1073/pnas.1318188110

The RAF serine/threonine kinases regulate cell growth through the MAPK pathway, and are targeted by small-molecule RAF inhibitors (RAFis) in human cancer. It is now apparent that protein multimers play an important role in RAF activation and tumor response to RAFis. However, the exact stoichiometry and cellular location of these multimers remain unclear because of the lack of technologies to visualize them. In the present work, we demonstrate that photoactivated localization microscopy (PALM), in combination with quantitative spatial analysis, provides sufficient resolution to directly visualize protein multimers in cells. Quantitative PALM imaging showed that CRAF exists predominantly as cytoplasmic monomers under resting conditions but forms dimers as well as trimers and tetramers at the cell membrane in the presence of active RAS. In contrast, N-terminal truncated CRAF (CatC) lacking autoinhibitory domains forms constitutive dimers and occasional tetramers in the cytoplasm, whereas a CatC mutant with a disrupted CRAF-CRAF dimer interface does not. Finally, artificially forcing CRAF to the membrane by fusion to a RAS CAAX motif induces multimer formation but activates RAF/MAPK only if the dimer interface is intact. Together, these quantitative results directly confirm the existence of RAF dimers and potentially higher-order multimers and their involvement in cell signaling, and showed that RAF multimer formation can result from multiple mechanisms and is a critical but not suf ficient step for RAF activation.

Nation, D. A., Edland, S. D., Bondi, M. W., Salmon, D. P., Delano-Wood, L., Peskind, E. R., . . . Galasko, D. R. (2013). Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults. *Neurology,* doi:10.1212/01.wnl.0000436935.47657.78

OBJECTIVE: The current study examined the association between pulse pressure (PP) and CSF-based biomarkers for Alzheimer disease, including beta-amyloid 1-42 (Abeta1-42) and

phosphorylated tau (P-tau) protein, in cognitively normal older adults. METHODS: One hundred seventy-seven cognitively normal, stroke-free older adult participants (aged 55-100 years) underwent blood pressure assessment for determination of PP (systolic - diastolic blood pressure) and lumbar puncture for measurement of CSF Abeta1-42 and P-tau. Pearson correlations and multiple linear regression, controlling for age, sex, APOE genotype, and body mass index, evaluated the relationship between PP and Alzheimer disease biomarkers. RESULTS: PP elevation was associated with increased P-tau ($r = 0.23$, $p = 0.002$), reduced Abeta1-42 ($r = -0.19$, $p = 0.01$), and increased P-tau to Abeta1-42 ratio ($r = 0.27$, $p < 0.001$). After controlling for covariates, PP remained associated with P-tau (beta = 0.18, $p = 0.0196$) and P-tau to Abeta1-42 ratio (beta = 0.0016, $p < 0.001$) but was no longer associated with Abeta1-42 (beta = -0.1, $p = 0.35$). Post hoc multivariate analyses indicated that increased PP was associated with all biomarkers in younger participants (aged 55-70 years) (Abeta1-42: $p = 0.050$; P-tau: $p = 0.003$; P-tau to Abeta ratio: $p = 0.0007$) but not older participants (aged 70-100 years). CONCLUSIONS: PP elevation is associated with increased CSF P-tau and decreased Abeta1-42 in cognitively normal older adults, suggesting that pulsatile hemodynamics may be related to amyloidosis and tau-related neurodegeneration. The relationship between PP and CSF biomarkers is age-dependent and observed only in participants in the fifth and sixth decades of life.

Nelson, H. D. (2013). *Breast Cancer Screening* John Wiley & Sons, Inc. doi:10.1002/9781118312513.ch10

Nezhat, F. R., Pejovic, T., Finger, T. N., & Khalil, S. S. (2013). Role of minimally invasive surgery in ovarian cancer. *Journal of Minimally Invasive Gynecology, 20*(6), 754-765. doi:10.1016/j.jmig.2013.04.027

The standard treatment of ovarian cancer includes upfront surgery with intent to accurately diagnose and stage the disease and to perform maximal cytoreduction, followed by chemotherapy in most cases. Surgical staging of ovarian cancer traditionally has included exploratory laparotomy with peritoneal washings, hysterectomy, salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies, and possible pelvic and para-aortic lymphadenectomy. In the early 1990s, pioneers in laparoscopic surgery used minimally invasive

techniques to treat gynecologic cancers, including laparoscopic staging of early ovarian cancer and primary and secondary cytoreduction in advanced and recurrent disease in selected cases. Since then, the role of minimally invasive surgery in gynecologic oncology has been continually expanding, and today advanced laparoscopic and robotic-assisted laparoscopic techniques are used to evaluate and treat cervical and endometrial cancer. However, the important question about the place of the minimally invasive approach in surgical treatment of ovarian cancer remains to be evaluated and answered. Overall, the potential role of minimally invasive surgery in treatment of ovarian cancer is as follows: i) laparoscopic evaluation, diagnosis, and staging of apparent early ovarian cancer; ii) laparoscopic assessment of feasibility of upfront surgical cytoreduction to no visible disease; iii) laparoscopic debulking of advanced ovarian cancer; iv) laparoscopic reassessment in patients with complete remission after primary treatment; and v) laparoscopic assessment and cytoreduction of recurrent disease. The accurate diagnosis of suspect adnexal masses, the safety and feasibility of this surgical approach in early ovarian cancer, the promise of laparoscopy as the most accurate tool for triaging patients with advanced disease for surgery vs upfront chemotherapy or neoadjuvant chemotherapy, and its potential in treatment of advanced cancer have been documented and therefore should be incorporated in the surgical methods of every gynecologic oncology unit and in the training programs in gynecologic oncology.

Ng, J. K., Fraunfelder, F. W., & Winthrop, K. L. (2013). Review and Update on the Epidemiology, Clinical Presentation, Diagnosis, and Treatment of Fungal Keratitis. *Current Fungal Infection Reports,* , 1-8. doi:10.1007/s12281-013-0163-9

Fungal keratitis is a leading cause of ocular morbidity worldwide. Globally, there has been a steady increase in the prevalence of fungal keratitis, yet the management of disease continues to be a challenge. This review will focus on the epidemiology of fungal keratitis on a global scale, as well as a review of the literature on the risk factors associated with the increasing trend of infection including ocular trauma, climate, contact lens use, ocular surgery, ocular surface disease, and systemic diseases. This review will also briefly cover the clinical presentation, diagnosis, and treatment of fungal infections.

Nguyen, B. T., Shih, G., & Turok, D. K. (2013). Putting the man in contraceptive mandate. *Contraception,* doi:10.1016/j.contraception.2013.10.001; 10.1016/j.contraception.2013.10.001

Nguyen, M. V., Felice, C. A., Du, F., Covey, M. V., Robinson, J. K., Mandel, G., & Ballas, N. (2013). Oligodendrocyte lineage cells contribute unique features to rett syndrome neuropathology. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 33*(48), 18764-18774. doi:10.1523/JNEUROSCI.2657-13.2013; 10.1523/JNEUROSCI.2657-13.2013

Mutations in the methyl-CpG binding protein 2 gene, Mecp2, affect primarily the brain and lead to a wide range of neuropsychiatric disorders, most commonly Rett syndrome (RTT). Although the neuropathology of RTT is well understood, the cellular and molecular mechanism(s), which lead to the disease initiation and progression, has yet to be elucidated. RTT was initially attributed only to neuronal dysfunction, but our recent studies and those of others show that RTT is not exclusively neuronal but rather also involves interactions between neurons and glia. Importantly, studies have shown that MeCP2-restored astrocytes and microglia are able to attenuate the disease progression in otherwise MeCP2-null mice. Here we show that another type of glia, oligodendrocytes, and their progenitors are also involved in manifestation of specific RTT symptoms. Mice that lost MeCP2 specifically in the oligodendrocyte lineage cells, although overall normal, were more active and developed severe hindlimb clasping phenotypes. Inversely, restoration of MeCP2 in oligodendrocyte lineage cells, in otherwise MeCP2-null mice, although only mildly prolonging their lifespan, significantly improved the locomotor deficits and hindlimb clasping phenotype, both in male and female mice, and fully restored the body weight in male mice. Finally, we found that the level of some myelin-related proteins was impaired in the MeCP2-null mice. Expression of MeCP2 in oligodendrocytes of these mice only partially restored their expression, suggesting that there is a non-cell-autonomous effect by other cell types in the brains on the expression of myelin-related proteins in oligodendrocytes.

Noonan, W., Dismuke, A. D., & Turker, M. S. (2013). Epigenetic patents: A stressful environment for an emerging science. *Biotechnology Law Report, 32*(5), 302-312. doi:10.1089/blr.2013.9868

Norris, S. L. (2013). A piece of my mind. My best work. *JAMA : The Journal of the American Medical Association, 310*(17), 1801-1802. doi:10.1001/jama.2013.280213; 10.1001/jama.2013.280213

Nutt, J., Siderowf, A., Guttman, M., Schmidt, P., Zamudio, J., Wu, S., . . . The National Parkinson Foundation Quality Improvement Initiative Investigators. (2013). Mobility, mood and site of care impact health related quality of life in Parkinson's disease. *Parkinsonism & Related Disorders,* doi:10.1016/j.parkreldis.2013.10.004; 10.1016/j.parkreldis.2013.10.004

OBJECTIVE: Examine the correlates of Health Related Quality of Life (HRQL) in a large cohort of Parkinson's disease (PD) patients from National Parkinson Foundation (NPF) Centers of Excellence (COEs). BACKGROUND: Improving outcomes for PD will depend upon uncovering disease features impacting HRQL to identify targets for intervention and variables for risk-adjustment models. Differences in HRQL outcomes between COEs could uncover modifiable aspects of care delivery. METHODS: This cross-sectional study examined the relative contribution of demographic, social, clinical and treatment features potentially related to HRQL, as measured by the PDQ-39, in 4601 consecutive subjects from 18 COEs. Stepwise linear regression was utilized to identify correlates of HRQL. RESULTS: The variability in the PDQ-39 summary index score correlated with H&Y stage (R2 = 22%), Timed up and Go (TUG) (17%), disease duration (11%), comorbidities (8%), cognitive status (8%), antidepressant use (6%) and center at which a patient received care (5%). Stepwise regression reordered the importance of the variables, with the H&Y first and TUG and the center becoming equal and the second most important variables determining the PDQ-39 total score. All independent variables together accounted for 44% of the variability in HRQL. CONCLUSIONS: We confirmed many but not all HRQL associations found in smaller studies. A novel observation was that the site of care was an important contributor to HRQL, suggesting that comparison of outcomes and processes among centers may identify best practices.

Öhrvik, H., Nose, Y., Wood, L. K., Kim, B. -., Gleber, S. -., Ralle, M., & Thiele, D. J. (2013). Ctr2 regulates biogenesis of a cleaved form of mammalian Ctr1 metal transporter lacking the copper- And cisplatin-binding ecto-domain. *Proceedings of the National Academy of Sciences of the United States of America, 110*(46), E4279-E4288. doi:10.1073/pnas.1311749110

Copper is an essential catalytic cofactor for enzymatic activities that drive a range of metabolic biochemistry including mitochondrial electron transport, iron mobilization, and peptide hormone maturation. Copper dysregulation is associated with fatal infantile disease, liver, and cardiac

dysfunction, neuropathy, and anemia. Here we report that mammals regulate systemic copper acquisition and intracellular mobilization via cleavage of the copper-binding ecto-domain of the copper transporter 1 (Ctr1). Although full-length Ctr1 is critical to drive efficient copper import across the plasma membrane, cleavage of the ecto-domain is required for Ctr1 to mobilize endosomal copper stores. The biogenesis of the truncated form of Ctr1 requires the structurally related, previously enigmatic copper transporter 2 (Ctr2). Ctr2-/- mice are defective in accumulation of truncated Ctr1 and exhibit increased tissue copper levels, and X-ray fluorescence microscopy demonstrates that copper accumulates as intracellular foci. These studies identify a key regulatory mechanism for mammalian copper transport through Ctr2-dependent accumulation of a Ctr1 variant lacking the copper-and cisplatin-binding ecto-domain.

Ojeda, S. R., & Lomniczi, A. (2013). Puberty in 2013: Unravelling the mystery of puberty. *Nature Reviews.Endocrinology,* doi:10.1038/nrendo.2013.233; 10.1038/nrendo.2013.233

Olds, D., Donelan-Mccall, N., O'brien, R., Macmillan, H., Jack, S., Jenkins, T., . . . Beeber, L. (2013). Improving the nurse-family partnership in community practice. *Pediatrics, 132*(SUPPL.2), S110-S117. doi:10.1542/peds.2013-1021I

BACKGROUND: Evidence-based preventive interventions are rarely final products. They have reached a stage of development that warrant public investment but require additional research and development to strengthen their effects. The Nurse-Family Partnership (NFP), a program of nurse home visiting, is grounded in findings from replicated randomized controlled trials. OBJECTIVE: Evidence-based programs require replication in accordance with the models tested in the original randomized controlled trials in order to achieve impacts comparable to those found in those trials, and yet they must be changed in order to improve their impacts, given that interventions require continuous improvement. This article provides a framework and illustrations of work our team members have developed to address this tension. METHODS: Because the NFP is delivered in communities outside of research contexts, we used quantitative and qualitative research to identify challenges with the NFP program model and its implementation, as well as promising approaches for addressing them. RESULTS: We describe a framework used to address these issues and illustrate its use in improving nurses' skills in retaining participants, reducing

closely spaced subsequent pregnancies, responding to intimate partner violence, observing and promoting caregivers' care of their children, addressing parents' mental health problems, classifying families' risks and strengths as a guide for program implementation, and collaborating with indigenous health organizations to adapt and evaluate the program for their populations. We identify common challenges encountered in conducting research in practice settings and translating findings from these studies into ongoing program implementation. CONCLUSIONS: The conduct of research focused on quality improvement, model improvement, and implementation in NFP practice settings is challenging, but feasible, and holds promise for improving the impact of the NFP. Pediatrics 2013;132:S110-S117. © 2013 by the American Academy of Pediatrics.

Olive, V., Sabio, E., Bennett, M. J., De Jong, C. S., Biton, A., McGann, J. C., . . . He, L. (2013). A component of the mir-17-92 polycistronic oncomir promotes oncogene-dependent apoptosis. *Elife, 2013*(2) doi:10.7554/eLife.00822.001

mir-17-92, a potent polycistronic oncomir, encodes six mature miRNAs with complex modes of interactions. In the Eμ-myc Burkitt's lymphoma model, mir-17-92 exhibits potent oncogenic activity by repressing c-Myc-induced apoptosis, primarily through its miR-19 components. Surprisingly, mir-17-92 also encodes the miR-92 component that negatively regulates its oncogenic cooperation with c-Myc. This miR-92 effect is, at least in part, mediated by its direct repression of Fbw7, which promotes the proteosomal degradation of c-Myc. Thus, overexpressing miR-92 leads to aberrant c-Myc increase, imposing a strong coupling between excessive proliferation and p53-dependent apoptosis. Interestingly, miR-92 antagonizes the oncogenic miR-19 miRNAs; and such functional interaction coordinates proliferation and apoptosis during c-Myc-induced oncogenesis. This miR-19:miR-92 antagonism is disrupted in B-lymphoma cells that favor a greater increase of miR-19 over miR-92. Altogether, we suggest a new paradigm whereby the unique gene structure of a polycistronic oncomir confers an intricate balance between oncogene and tumor suppressor crosstalk. © Olive et al.

Olsen, E. A., & Brambrink, A. M. (2013). Anesthesia for the young child undergoing ambulatory procedures: current concerns regarding harm to the developing brain. *Current Opinion in*

Anaesthesiology, 26(6), 677-684. doi:10.1097/ACO.0000000000000016; 10.1097/ACO.0000000000000016

PURPOSE OF REVIEW: Sedation and anesthesia are often necessary for children at any age, and are frequently provided in ambulatory settings. Concerns have mounted, based on both laboratory studies including various mammalian species and retrospective human clinical studies, that the very drugs that induce sedation and anesthesia may trigger an injury in the developing brain, resulting in long-lasting neurobehavioral consequences. RECENT FINDINGS: New retrospective studies further augment these concerns. Specifically, recent studies support that a single anesthesia exposure before age 3 may increase the risk for long-term disabilities in language acquisition and abstract reasoning, and that exposure to two or more anesthetics before age 2 nearly doubles the risk for an attention-deficit hyperactivity disorder diagnosis by age 19. However, methodological limitations preclude final conclusions or change in practice based on these reports, as retrospective studies cannot prove causation. Ongoing prospective clinical studies such as 'General Anesthesia and Apoptosis Study', 'Pediatric Anesthesia NeuroDevelopment Assessment', and 'Mayo Safety in Kids' trials will offer more answers in the future. Meanwhile, laboratory experiments continue to describe differential morphologic injury to individual structures in the neuropil, and have identified mitochondrial dysfunction and neuroinflammation as potential links in the injury process. Additionally, concepts for protection against anesthesia-induced neurotoxicity continue to be tested in the laboratory. SUMMARY: Results from ongoing prospective clinical trials and translational research will help clarify whether anesthesia-associated neurotoxicity affects the developing human brain, including whether it causes long-term disability, and may further identify the injury mechanisms and potential strategies for protection. Currently, the available evidence does not support a change in practice.

Orfanakis, A., & Deloughery, T. (2013). Patients with disorders of thrombosis and hemostasis. *The Medical Clinics of North America, 97*(6), 1161-1180. doi:10.1016/j.mcna.2013.07.004; 10.1016/j.mcna.2013.07.004

Surgery, by definition, is a challenge to the hemostatic system. In addition, a surgical procedure may provoke inappropriate venous or arterial thrombosis, such as is suggested historically by Virchow's Triad. For these reasons, proper functioning of the hematologic system is integral in a

successful and safe perioperative period. Patients with a disorder of either coagulation or hemostasis, therefore, present an exciting challenge to the preoperative physician. Diagnosis of a hematologic disorder may be more or less occult. A proper bleeding and clotting history can serve to elucidate such a disorder and is therefore paramount to the preoperative workup. For those patients with a previously diagnosed disorder of the hematologic system, appropriate laboratory investigation and a concise therapeutic plan for the day of surgery can help to minimize risks in the perioperative period.

Palucka, K., Coussens, L. M., & O'Shaughnessy, J. (2013). Dendritic cells, inflammation, and breast cancer. *Cancer Journal (Sudbury, Mass.), 19*(6), 511-516. doi:10.1097/PPO.0000000000000007; 10.1097/PPO.0000000000000007

Solid tumors are well known for their genomic heterogeneity. Although some aspects of this derive from so-called driver mutations, it is now clear that tumor cells possess a seemingly limitless capacity to evade cell death pathway activation, maintain essential survival programming, and initiate resistance networks that block efficacy of cytotoxic and targeted therapy. Given this amazing survival capability, how then to design approaches for effective eradication of malignant cells? Also present within all solid tumors is a diverse assemblage of genomically stable immune cell types. Whereas some of these possess documented activities that foster tumor progression, others possess inherent activities that when favored lead to rapid tumor cell elimination. This review focuses on aspects of dendritic cell biology in solid tumors, especially breast cancers, which point to dendritic cells as a tractable tool to exploit for immune-based therapies.

Patel, S., Lalwani, K., Koh, J., Wu, L., & Fu, R. (2013). Temporal variation of the leak pressure of uncuffed endotracheal tubes following pediatric intubation: an observational study. *Journal of Anesthesia,* , 1-6. doi:10.1007/s00540-013-1728-z

Purpose: Uncuffed endotracheal tubes are still preferred over cuffed tubes in certain situations in pediatric anesthesia. Inaccurately sized uncuffed endotracheal tubes may lead to inadequate ventilation or tracheal mucosal damage during anesthesia. Endotracheal tube size in children is usually assessed by measuring the audible leak pressure; if the fit of the tube and the leak

pressure decrease significantly with time, reintubation during surgery as a result of inability to ventilate effectively may be challenging, and could lead to patient morbidity. There is no evidence to indicate whether leak pressure increases or decreases with time following endotracheal intubation with uncuffed tubes in children. Methods: We measured leak pressure for 30 min following tracheal intubation in 46 ASA I children age 0-7 years after excluding factors known to modify leak pressure. Results: The largest mean change in leak pressure occurred between time points 0 and 15 min, an increase of 3.5 cmH2O. Endotracheal tube size and type of procedure were associated with the leak pressure. In the final linear mixed model, there were no statistically significant variations in leak pressure over time (P = 0.129) in this group of children. Conclusions: We did not identify a consistent change in leak pressure within 30 min following tracheal intubation with uncuffed endotracheal tubes in this group of children.

Perrine, J. A., & Logan, J. R. (2004). Developing an interaction-centered evaluation tool for distance education. *Studies in Health Technology and Informatics, 107*, 916-920. doi:10.3233/978-1-60750-949-3-916

Web-based distance instruction is growing in popularity. As more courses and programs go online, instructional methods and technologies are changing to meet new demands. These courses and instructional methods need be evaluated to determine their quality and to aid in their development. An instrument that measures the quality of student interaction within courses could play a useful role in this evaluation. The objective of this project was to produce an interaction-centered evaluation tool for distance education. We developed items for the evaluation tool based on a review of the literature and interviews with distance education faculty. We then conducted a measurement study to determine the instrument's validity and reliability. Fifty-five students in seven medical informatics courses participated in this study. Questionnaire items were included or rejected based on their fit with underlying theoretical constructs. In conclusion, the Web-based evaluation tool developed in this project measures student perception of quality of course interactions with demonstrated validity and reliability.

Pham, T. D., Le, D. T. P., Xu, J., Nguyen, D. T., Martindale, R. G., & Deveney, C. W. (2014). Personalized identification of abdominal wall hernia meshes on computed tomography. *Computer Methods and Programs in Biomedicine, 113*(1), 153-161. doi:10.1016/j.cmpb.2013.09.019

An abdominal wall hernia is a protrusion of the intestine through an opening or area of weakness in the abdominal wall. Correct pre-operative identification of abdominal wall hernia meshes could help surgeons adjust the surgical plan to meet the expected difficulty and morbidity of operating through or removing the previous mesh. First, we present herein for the first time the application of image analysis for automated identification of hernia meshes. Second, we discuss the novel development of a new entropy-based image texture feature using geostatistics and indicator kriging. Third, we seek to enhance the hernia mesh identification by combining the new texture feature with the gray-level co-occurrence matrix feature of the image. The two features can characterize complementary information of anatomic details of the abdominal hernia wall and its mesh on computed tomography. Experimental results have demonstrated the effectiveness of the proposed study. The new computational tool has potential for personalized mesh identification which can assist surgeons in the diagnosis and repair of complex abdominal wall hernias. © 2013 Elsevier Ireland Ltd.

Phelps, R., Nickel, R., Eisert, D., & Stein, M. T. (2013). Parental Influence on a Child's Autistic Traits. *Journal of Developmental and Behavioral Pediatrics : JDBP, 34*(9), 730-732. doi:10.1097/DBP.0000000000000004; 10.1097/DBP.0000000000000004

CASE: Robbie is a 4-year-old boy whose parents are concerned about his speech, social skills, and repetitive behaviors. He has poor articulation; at time, he is difficult to understand. On the other hand, he has a fair vocabulary, and he has good intent to communicate. He is generally able to communicate his needs and wants. He likes to tell his parents about his day.When he begins the day at preschool, Robbie initially stands by himself and watches. He slowly warms up and eventually participates in activities. He engages in parallel play or follows other children. He knows names of children at preschool, and he is well liked. He is affectionate with his parents.When Robbie is excited, he wiggles his fingers, flaps his arms, and grimaces. He can be quite rigid; for example, he gets very distressed when his mother sets his cup down on his right side instead of his left. However, in general, Robbie has a sunny personality. He likes to watch

children's television shows. He pretends plays with action figures. Robbie is an only child who lives with both parents. His mother works full-time, and his father is in home with Robbie during the day.When examined in the office, Robbie had a bright affect, good eye contact, and social referencing. He demonstrated good communicative intent, but poor articulation and some jargoning. He frequently wiggled his fingers and flapped his hands with excitement. Robbie had a borderline score on the Autism Diagnostic Observation Schedule.During the visit, the pediatrician noted that Robbie's father was rather quiet and rarely responded to questions. When he did respond, he had a monotone quality to his voice. He maintained either a flat or nervous affect throughout the visit. He made limited eye contact, and occasionally he stared excessively.

Picker, L. J., & Deeks, S. G. (2013). HIV: Antibodies advance the search for a cure. *Nature, 503*(7475), 207-208. doi:10.1038/nature12703; 10.1038/nature12703

Piepkorn, M. W., Barnhill, R. L., Elder, D. E., Knezevich, S. R., Carney, P. A., Reisch, L. M., & Elmore, J. G. (2013). The MPATH-Dx reporting schema for melanocytic proliferations and melanoma. *Journal of the American Academy of Dermatology,* doi:10.1016/j.jaad.2013.07.027
Background: The histologic diagnosis of melanoma and nevi can be subject to discordance and errors, potentially leading to inappropriate treatment and harm. Diagnostic terminology is not standardized, creating confusion for providers and patients and challenges for investigators. Objective: We sought to describe the development of a pathology reporting form for more precise research on melanoma and a diagnostic-treatment mapping tool for improved patient care and consistency in treatment. Methods: Three dermatopathologists independently reviewed melanocytic lesions randomly selected from a dermatopathology database. Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) reporting schema evolved from iterative case review and form revision. Results: Differences in diagnostic thresholds, interpretation, and nomenclature contributed to development of the MPATH-Dx histology reporting form, which groups lesions by similarities in histogenesis and degrees of atypia. Because preliminary results indicate greater agreement regarding suggested treatments than for specific diagnoses, the diverse terminologies of the MPATH-Dx histology reporting form were stratified by commonalities of treatments in the MPATH-Dx diagnostic-treatment mapping

scheme. Limitations: Without transformative advances in diagnostic paradigms, the interpretation of melanocytic lesions frequently remains subjective. Conclusions: The MPATH-Dx diagnostic-treatment mapping scheme could diminish confusion for those receiving reports by categorizing diverse nomenclature into a hierarchy stratified by suggested management interventions.

Pissani, F., Malherbe, D. C., Schuman, J. T., Robins, H., Park, B. S., Krebs, S. J., . . . Haigwood, N. L. (2013). Improvement of antibody responses by HIV envelope DNA and protein co-immunization. *Vaccine,* doi:10.1016/j.vaccine.2013.11.022; 10.1016/j.vaccine.2013.11.022

BACKGROUND: Developing HIV envelope (Env) vaccine components that elicit durable and protective antibody responses is an urgent priority, given the results from the RV144 trial. Optimization of both the immunogens and vaccination strategies will be needed to generate potent, durable antibodies. Due to the diversity of HIV, an effective Env-based vaccine will most likely require an extensive coverage of antigenic variants. A vaccine co-delivering Env immunogens as DNA and protein components could provide such coverage. Here, we examine a DNA and protein co-immunization strategy by characterizing the antibody responses and evaluating the relative contribution of each vaccine component. METHOD: We co-immunized rabbits with representative subtype A or B HIV gp160 plasmid DNA plus Env gp140 trimeric glycoprotein and compared the responses to those obtained with either glycoprotein alone or glycoprotein in combination with empty vector. RESULTS: DNA and glycoprotein co-immunization was superior to immunization with glycoprotein alone by enhancing antibody kinetics, magnitude, avidity, and neutralizing potency. Importantly, the empty DNA vector did not contribute to these responses. Humoral responses elicited by mismatched DNA and protein components were comparable or higher than the responses produced by the matched vaccines. CONCLUSION: Our data show that co-delivering DNA and protein can augment antibodies to Env. The rate and magnitude of immune responses suggest that this approach has the potential to streamline vaccine regimens by inducing higher antibody responses using fewer vaccinations, an advantage for a successful HIV vaccine design.

Pitre, T. M. (2009). Palliative sedation at the end of life uses and abuses. *Linacre Quarterly, 76*(4), 390-407. doi:10.1179/002436309803889034

Palliative sedation is becoming more widely used in complex end-of-life scenarios. Its use is clearly a significant advance in good medical care in some settings but without the clear ethical guidelines of our Catholic moral tradition its use can lead to euthanasia. The current literature on palliative sedation is reviewed from both the secular and Catholic ethical perspectives. Case scenarios are used to illustrate both perspectives. Particular emphasis is placed on using sound ethical principles in the consideration of using palliative sedation at the end of life. Trends in the use of palliative sedation are reviewed. © 2009 by the Catholic Medical Association. All rights reserved.

Quintanilla-Dieck, L., & Gross, N. D. (2012). *Injury of the Major Vessels* John Wiley & Sons, Ltd. doi:10.1002/9781118444832.ch18

Injury to the great vessels is a feared complication of any surgery involving the neck since it can lead to devastating consequences. It is imperative for the head and neck endocrine surgeon to have a thorough knowledge of the anatomy of the great vessels of the neck, including their anomalous pathways. The scenarios in which the great vessels of the neck are injured can be observed by even the most experienced surgeons. Therefore, it is essential that every surgeon operating in the neck understands techniques for prevention of injury, and is prepared with a management algorithm for both intraoperative and postoperative haemorrhage. © 2013 John Wiley & Sons, Ltd.

Raslan, A. M., & Burchiel, K. J. (2013). Diffuse low-grade gliomas: Response. *Journal of Neurosurgery, 119*(5), 1353-1354. doi:10.3171/2013.6.JNS131153

Reiss, L. A. J., Turner, C. W., Karsten, S. A., & Gantz, B. J. (2014). Plasticity in human pitch perception induced by tonotopically mismatched electro-acoustic stimulation. *Neuroscience, 256*, 43-52. doi:10.1016/j.neuroscience.2013.10.024

Under normal conditions, the acoustic pitch percept of a pure tone is determined mainly by the tonotopic place of the stimulation along the cochlea. Unlike acoustic stimulation, electric stimulation of a cochlear implant (CI) allows for the direct manipulation of the place of

stimulation in human subjects. CI sound processors analyze the range of frequencies needed for speech perception and allocate portions of this range to the small number of electrodes distributed in the cochlea. Because the allocation is assigned independently of the original resonant frequency of the basilar membrane associated with the location of each electrode, CI users who have access to residual hearing in either or both ears often have tonotopic mismatches between the acoustic and electric stimulation. Here we demonstrate plasticity of place pitch representations of up to three octaves in Hybrid CI users after experience with combined electro-acoustic stimulation. The pitch percept evoked by single CI electrodes, measured relative to acoustic tones presented to the non-implanted ear, changed over time in directions that reduced the electro-acoustic pitch mismatch introduced by the CI programming. This trend was particularly apparent when the allocations of stimulus frequencies to electrodes were changed over time, with pitch changes even reversing direction in some subjects. These findings show that pitch plasticity can occur more rapidly and on a greater scale in the mature auditory system than previously thought possible. Overall, the results suggest that the adult auditory system can impose perceptual order on disordered arrays of inputs. © 2013 IBRO.

Richardson, D. K., Fromme, E., Zive, D., Fu, R., & Newgard, C. D. (2013). Concordance of Out-of-Hospital and Emergency Department Cardiac Arrest Resuscitation With Documented End-of-Life Choices in Oregon. *Annals of Emergency Medicine,* doi:10.1016/j.annemergmed.2013.09.004; 10.1016/j.annemergmed.2013.09.004

STUDY OBJECTIVE: Resuscitation measures should be guided by previous patient choices about end-of-life care, when they exist; however, documentation of these choices can be unclear or difficult to access. We evaluate the concordance of a statewide registry of actionable resuscitation orders unique to Oregon with out-of-hospital and emergency department (ED) care provided for patients found by emergency medical services (EMS) in out-of-hospital cardiac arrest. METHODS: This was a retrospective cohort study of patients found by EMS providers in out-of-hospital cardiac arrest in 5 counties in 2010. We used probabilistic linkage to match patients found in out-of-hospital cardiac arrest with previously signed documentation of end-of-life decisions in the Oregon Physician Orders for Life-Sustaining Treatment (POLST) registry. We evaluated resuscitation interventions in the field and ED. RESULTS: There were 1,577 patients found in out-

of-hospital cardiac arrest, of whom 82 had a previously signed POLST form. Patients with POLST do-not-resuscitate orders for whom EMS was called had resuscitation withheld or ceased before hospital admission in 94% of cases (95% confidence interval [CI] 83% to 99%). Compared with patients with no POLST or known do-not-resuscitate orders, more patients with attempt resuscitation POLST orders had field resuscitation attempted (84% versus 60%; difference 25%; 95% CI 12% to 37%) and were admitted to hospitals (38% versus 17%; difference 20%; 95% CI 3% to 37%), with no documented misinterpretations of the form once CPR was initiated. CONCLUSION: In this sample of patients in out-of-hospital cardiac arrest, out-of-hospital and ED care was generally concordant with previously documented end-of-life orders in the setting of critical illness. Further research is needed to compare the effectiveness of Oregon's POLST system to other methods of end-of-life order documentation.

Rohlman, D. S., Parish, M., Elliot, D. L., Montgomery, D., & Hanson, G. (2013). Characterizing the Needs of a Young Working Population: Making the Case for Total Worker Health in an Emerging Workforce. *Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine,* doi:10.1097/JOM.0000000000000039 OBJECTIVE:: Young workers are at increased risk for occupational injuries. Many lack appropriate skills to avoid workplace hazards. In addition, existing safety programs neither address total worker health principles nor align with the relatively high technological expectations of young workers. This article aimed to identify the content and process for an on-line total worker health training for young workers. METHODS:: During the summer of 2012, an on-line survey (n = 187) assessed young workers' behavior, knowledge, and attitudes on total worker health topics and on-line training delivery methods. RESULTS:: Forty-five percent of the workers indicated this was their first job; new workers demonstrated lower safety knowledge scores than returning workers. In addition, results demonstrated that workers would benefit from health behavior interventions delivered through technology-based means. CONCLUSIONS:: Findings characterize the work-related needs for this population and demonstrate the utility of using on-line training.

Ron-Tal Fisher, O., Gralnek, I. M., Eisen, G. M., Williams, J. L., & Holub, J. L. (2013). Endoscopic hemostasis is rarely used for hematochezia: a population-based study from the Clinical Outcomes

Research Initiative National Endoscopic Database. *Gastrointestinal Endoscopy,* doi:10.1016/j.gie.2013.09.004

Background: Data on the use of endoscopic hemostasis performed during colonoscopy for hematochezia are primarily derived from expert opinion and case series from tertiary care settings. Objectives: To characterize patients with hematochezia who underwent in-patient colonoscopy and compare those who did and did not receive endoscopic hemostasis. Design: Retrospective analysis. Setting: Clinical Outcomes Research Initiative National Endoscopic Database, 2002 to 2008. Patients: Adults with hematochezia. Interventions: None. Main Outcome Measurements: Demographics, comorbidities, practice setting, adverse events, and colonoscopy procedural characteristics and findings. Results: We identified 3151 persons who underwent in-patient colonoscopy for hematochezia. Endoscopic hemostasis was performed in 144 patients (4.6%). Of those who received endoscopic hemostasis, the majority were male (60.3%), white (83.3%), and older (mean age 70.9 ± 12.3 years); had a low-risk American Society of Anesthesiologists classification (53.9%); and underwent colonoscopy in a community setting (67.4%). The hemostasis-receiving cohort was significantly more likely to be white (83.3% vs 71.0%, P = .02), have more comorbidities (classes 3 and 4, 46.2% vs 36.0%, P = .04), and have the cecum reached (95.8% vs 87.7%, P = .003). Those receiving hemostasis were significantly more likely to have an endoscopic diagnosis of arteriovenous malformations (32.6% vs 2.6%, P = .0001) or a solitary ulcer (8.3% vs 2.1%, P < .0001). Limitations: Retrospective database analysis. Conclusions: Less than 5% of persons presenting with hematochezia and undergoing inpatient colonoscopy received endoscopic hemostasis. These findings differ from published tertiary care setting data. These data provide new insights into in-patient colonoscopy performed primarily in a community practice setting for patients with hematochezia. © 2013 American Society for Gastrointestinal Endoscopy.

Ross, D. A. (2013). Shaving. *Journal of Neurosurgery, 119*(5), 1350-1351. doi:10.3171/2013.4.JNS13797

Rowland, M., Peterson-Besse, J., Dobbertin, K., Walsh, E. S., & Horner-Johnson, W. (2013). Health outcome disparities among subgroups of people with disabilities: A scoping review. *Disability and*

Health Journal, doi:10.1016/j.dhjo.2013.09.003

Background: A growing body of research has found that people with disabilities experience lower health status and an excess burden of disease relative to the general US population. However, the population of people with disabilities is quite diverse. Thus, it is important to understand health differences between subgroups of people with disabilities in order to most effectively target interventions to address disparities. An initial step in this process is reviewing and synthesizing available research addressing these subgroup differences. Objectives: To conduct a scoping review of literature to describe recent research activity that has examined health outcome disparities within populations of people with disabilities. Methods: We searched for relevant articles in MEDLINE, PsycINFO, and CINAHL databases. Three staff independently reviewed abstracts according to inclusion criteria. Two authors then independently extracted data from each included article. Results: For many of the health outcomes of interest, there was no published literature in relation to key disparity factors (e.g. race, income) within the population of people with disabilities. The health outcomes most frequently examined were diabetes and heart disease. The most frequently examined disparity factors were the type of disabling condition and gender. Conclusions: There are significant gaps in available research. Building a body of research that identifies disparities and potentially vulnerable subgroups may improve understanding of the causes of disparities and contribute to efforts to improve quality of life and health outcomes for individuals with disabilities.

Rozner, M. A., & Schulman, P. M. (2013). Dual chamber pacing mode without an atrial lead can produce R-on-T pacing and ventricular fibrillation. *Israel Medical Association Journal, 15*(10), 656-658.

Ruza, I., Mirfakhraee, S., Orwoll, E., & Gruntmanis, U. (2013). Clinical experience with intravenous zoledronic acid in the treatment of male osteoporosis: Evidence and opinions. *Therapeutic Advances in Musculoskeletal Disease, 5*(4), 182-198. doi:10.1177/1759720X13485829

Osteoporosis frequently remains underrecognized and undertreated in men. Most osteoporosis-related fractures could be prevented if men at risk would be diagnosed, treated, and remained compliant with therapy. Bisphosphonates, the mainstay of osteoporosis treatment, are potent

antiresorptive agents that inhibit osteoclast activity, suppress in vivo markers of bone turnover, increase bone mineral density, decrease fractures, and likely improve survival in men with osteoporosis. The focus of the article is on intravenous zoledronic acid, which may be a preferable alternative to oral bisphosphonate therapy in patients with cognitive dysfunction, the inability to sit upright, polypharmacy, significant gastrointestinal pathology or suspected medication noncompliance. Zoledronic acid is approved in the United States (US) and European Union (EU) as an annual 5 mg intravenous infusion to treat osteoporosis in men. The zoledronic acid 4 mg intravenous dose has been studied in the prevention of bone loss associated with androgen deprivation therapy. This article reviews the evidence for zoledronic acid, currently the most potent bisphosphonate available for clinical use, and its therapeutic effects in the treatment of men with osteoporosis. © The Author(s), 2013.

Saag, K. G., Winthrop, K., & Curtis, J. R. (2013). Tumor necrosis factor, tuberculosis, testing, and treatment: Teeing up the questions. *Arthritis Care and Research, 65*(11), 1719-1721. doi:10.1002/acr.22061

Saber, W., Cutler, C. S., Nakamura, R., Zhang, M. -., Atallah, E., Rizzo, J. D., . . . Horowitz, M. M. (2013). Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). *Blood, 122*(11), 1974-1982. doi:10.1182/blood-2013-04-496778

Allogeneic hematopoietic cell transplantation (HCT) from human leukocyte antigen (HLA) matched related donor (MRD) and matched unrelated donors (MUD) produces similar survival for patients with acute myelogenous leukemia.Whether these results can be extended to patientswithmyelodysplastic syndromes (MDS) is unknown. Therefore, analysis of post-HCT outcomes for MDS was performed. Outcomes of 701 adult MDS patients who underwent HCT between 2002 and 2006 were analyzed (MRD [n 5 176], 8 of 8 HLA-A, -B, -C, -DRB1 allele matchedMUD [n 5 413], 7 of 8 MUD [n 5 112]). Median agewas 53 years (range, 22-78 years). In multivariate analyses, MRD HCT recipients had similar disease free survival (DFS) and survival rates compared with 8 of 8 MUD HCT recipients (relative risk [RR] 1.13 [95% confidence interval (CI) 0.91-1.42] and 1.24 [95% CI 0.98-1.56], respectively), and both MRD and 8 of 8MUD had

superior DFS(RR1.47 [95%CI 1.10-1.96] and 1.29 [95%CI 1.00-1.66], respectively) and survival (RR 1.62 [95% CI 1.21-2.17] and 1.30 [95% CI 1.01-1.68], respectively) compared with 7 of 8 MUDHCT recipients. In patients with MDS, MRD remains the best stem cell source followed by 8 of 8 MUD. Transplantation from 7 of 8 MUD is associated with significantly poorer outcomes. © 2013 by The American Society of Hematology.

Sachdev, P. S., Lipnicki, D. M., Kochan, N. A., Crawford, J. D., Rockwood, K., Xiao, S., . . . Santabárbara, J. (2013). COSMIC (Cohort Studies of Memory in an International Consortium): An international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. *BMC Neurology, 13* doi:10.1186/1471-2377-13-165

Background: A large number of longitudinal studies of population-based ageing cohorts are in progress internationally, but the insights from these studies into the risk and protective factors for cognitive ageing and conditions like mild cognitive impairment and dementia have been inconsistent. Some of the problems confounding this research can be reduced by harmonising and pooling data across studies. COSMIC (Cohort Studies of Memory in an International Consortium) aims to harmonise data from international cohort studies of cognitive ageing, in order to better understand the determinants of cognitive ageing and neurocognitive disorders.Methods/Design: Longitudinal studies of cognitive ageing and dementia with at least 500 individuals aged 60 years or over are eligible and invited to be members of COSMIC. There are currently 17 member studies, from regions that include Asia, Australia, Europe, and North America. A Research Steering Committee has been established, two meetings of study leaders held, and a website developed. The initial attempts at harmonising key variables like neuropsychological test scores are in progress.Discussion: The challenges of international consortia like COSMIC include efficient communication among members, extended use of resources, and data harmonisation. Successful harmonisation will facilitate projects investigating rates of cognitive decline, risk and protective factors for mild cognitive impairment, and biomarkers of mild cognitive impairment and dementia. Extended implications of COSMIC could include standardised ways of collecting and reporting data, and a rich cognitive ageing database being made available to other researchers. COSMIC could potentially transform our

understanding of the epidemiology of cognitive ageing, and have a world-wide impact on promoting successful ageing. © 2013 Sachdev et al.; licensee BioMed Central Ltd.

Sahoo, M. K., Lefterova, M. I., Yamamoto, F., Waggoner, J. J., Chou, S., Holmes, S. P., . . . Pinsky, B. A. (2013). Detection of cytomegalovirus drug resistance mutations by next-Generation sequencing. *Journal of Clinical Microbiology, 51*(11), 3700-3710. doi:10.1128/JCM.01605-13 Antiviral therapy for cytomegalovirus (CMV) plays an important role in the clinical management of solid organ and hematopoietic stem cell transplant recipients.However, CMV antiviral therapy can be complicated by drug resistance associated with mutations in the phosphotransferase UL97 and the DNA polymerase UL54.We have developed an amplicon-based high-throughput sequencing strategy for detecting CMV drug resistance mutations in clinical plasma specimens using a microfluidics PCR platform for multiplexed library preparation and a benchtop next-generation sequencing instrument.Plasmid clones of the UL97 and UL54 genes were used to demonstrate the low overall empirical error rate of the assay (0.189%) and to develop a statistical algorithm for identifying authentic low-abundance variants.The ability of the assay to detect resistance mutations was tested with mixes of wild-type and mutant plasmids, as well as clinical CMV isolates and plasma samples that were known to contain mutations that confer resistance.Finally, 48 clinical plasma specimens with a range of viral loads (394 to 2,191,011 copies/ml plasma) were sequenced using multiplexing of up to 24 specimens per run.This led to the identification of seven resistance mutations, three of which were present in20% of the sequenced population.Thus, this assay offers more sensitive detection of minor variants and a higher multiplexing capacity than current methods for the genotypic detection of CMV drug resistance mutations © 2013, American Society for Microbiology.All Rights Reserved.

Salama-Hanna, J., & Chen, G. (2013). Patients with chronic pain. *The Medical Clinics of North America, 97*(6), 1201-1215. doi:10.1016/j.mcna.2013.07.005; 10.1016/j.mcna.2013.07.005 Preoperative evaluation of patients with chronic pain is important because it may lead to multidisciplinary preoperative treatment of patients' pain and a multimodal analgesia plan for effective pain control. Preoperative multidisciplinary management of chronic pain and comorbid conditions, such as depression, anxiety, deconditioning, and opioid tolerance, can improve patient

satisfaction and surgical recovery. Multimodal analgesia using pharmacologic and nonpharmacologic strategies shifts the burden of analgesia away from simply increasing opioid dosing. In more complicated chronic pain patients, multidisciplinary treatment, including pain psychology, physical therapy, judicious medication management, and minimally invasive interventions by pain specialists, can improve patients' satisfaction and surgical outcome.

Sally, M., & Malinoski, D. (2013). Current Research on Organ Donor Management in the Intensive Care Unit and Operating Room. *Anesthesiology Clinics,* doi:10.1016/j.anclin.2013.08.004
A shortage of organs is available for transplantation, with 116,000 patients on the Organ Procurement and Transplantation Network/United Network for Organ Sharing wait list. Because the demand for organs outweighs the supply, considerable care must be taken to maximize the number of organs transplanted per donor and optimize the quality of recovered organs. Studies designed to determine optimal donor management therapies are limited, and this research has many challenges. Although evidenced-based guidelines for managing potential organ donors do not exist, research in this area is increasing. This article reviews the existing literature and highlights recent trials that can guide management.

Sandborn, W. J., Feagan, B. G., Marano, C., Zhang, H., Strauss, R., Johanns, J., . . . Rutgeerts, P. (2013). Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis. *Gastroenterology,* doi:10.1053/j.gastro.2013.05.048
Background & Aims: Little is known about the efficacy of golimumab, a fully human monoclonal antibody to tumor necrosis factor (TNF) -α, for treatment of ulcerative colitis (UC). We evaluated subcutaneous golimumab induction therapy in TNF-α antagonist-naïve patients with moderate-to-severe UC despite conventional treatment. Methods: We integrated double-blind phase 2 dose-finding and phase 3 dose-confirmation trials in a study of 1064 adults with UC (Mayo score: 6-12; endoscopic subscore ≥2; 774 patients in phase 3). Patients were randomly assigned to groups given golimumab doses of 100 mg and then 50 mg (phase 2 only), 200 mg and then 100 mg, or 400 mg and then 200 mg, 2 weeks apart. The phase 3 primary end point was week-6 clinical response. Secondary end points included week-6 clinical remission, mucosal healing, and Inflammatory Bowel Disease Questionnaire (IBDQ) score change. Results: In phase 2, median

changes from baseline in the Mayo score were -1.0, -3.0, -2.0, and -3.0, in the groups given placebo, 100 mg/50 mg, 200/100 mg, and 400/200 mg golimumab, respectively. In phase 3, rates of clinical response at week 6 were 51.0% and 54.9% among patients given 200 mg/100 mg and 400 mg/200 mg golimumab, respectively, vs 30.3% among those given placebo (both, P ≤ .0001). Rates of clinical remission and mucosal healing and mean changes in IBDQ scores were significantly greater in both golimumab groups vs the placebo group (P ≤ .0014, all comparisons). Rates of serious adverse events were 6.1% and 3.0%, and rates of serious infection were 1.8% and 0.5%, in the placebo and golimumab groups, respectively. One patient in the 400 mg/200 mg group died as a result of surgical complications of an ischiorectal abscess. Conclusions: Treatment with subcutaneous golimumab induces clinical response, remission, and mucosal healing, and increases quality of life in larger percentages of patients with active UC than placebo. ClinicalTrials.gov Number: NCT00487539. © 2013 AGA Institute.

Saultz, J. (2013). Interdisciplinary family medicine. *Family Medicine, 45*(10), 739-740.

Scheers, C., Andre, J., Thompson, C., Rebuffat, E., Harag, S., & Kolivras, A. (2013). Refractory trichophyton rubrum infection in lamellar ichthyosis. *Pediatric Dermatology, 30*(6), e200-e203. doi:10.1111/pde.12160

A 10-month-old boy with congenital lamellar ichthyosis presented with a chronic Trichophyton rubrum infection. There was no history of atopy or immunosuppression, and examination revealed high total immunoglobulin E (IgE) with a positive specific IgE for T. rubrum. Multiple treatments with fluconazole were necessary to control the infection. T. rubrum is present worldwide and is responsible for the vast majority of chronic dermatophytosis. Lamellar ichthyosis is a risk factor for chronic dermatophytosis because of excessive keratin and the barrier defect. A delayed-type hypersensitivity reaction to T. rubrum is associated with cure, whereas immediate hypersensitivity and IgE are not protective and may lead to chronic infection. Atopy and the Th2 profile therefore seem to be associated with chronic dermatophytosis. The association between ichthyosis and atopy is well documented. T. rubrum also has an interesting ability to evade immunity, which helps explain the chronic infection. Finally, in ichthyosis, it is likely that fluconazole has difficulty penetrating the acanthotic stratum corneum, which explains

treatment failure. We report this case to alert clinicians to the possible association between lamellar ichthyosis and chronic dermatophytosis and to report the difficulties of management. © 2013 Wiley Periodicals, Inc.

Schulman, P. M., Rozner, M. A., Sera, V., & Stecker, E. C. (2013). Patients with pacemaker or implantable cardioverter-defibrillator. *The Medical Clinics of North America, 97*(6), 1051-1075. doi:10.1016/j.mcna.2013.05.004; 10.1016/j.mcna.2013.05.004

The preparation of patients with a cardiac implantable electronic device (CIED) for the perioperative period necessitates familiarity with recommendations from the American Society of Anesthesiologists and Heart Rhythm Society. Even clinicians who are not CIED experts should understand the indications for implantation, as well as the basic functions, operations, and limitations of these devices. Before any scheduled procedure, proper CIED function should be verified and a specific CIED prescription obtained. Acquiring the requisite knowledge base and developing the systems to competently manage the CIED patient ensures safe and efficient perioperative care.

Sheridan, D. C., Spiro, D. M., & Meckler, G. D. (2013). Pediatric Migraine: Abortive Management in the Emergency Department. *Headache,* doi:10.1111/head.12253

Studies suggest that headache accounts for approximately 1% of pediatric emergency department (ED) visits. ED physicians must distinguish between primary headaches, such as a tension or migraine, and secondary headaches caused by systemic disease including neoplasm, infection, or intracranial hemorrhage. A recent study found that 40% of children presenting to the ED with headache were diagnosed with a primary headache, and 75% of these were migraine. Once the diagnosis of migraine has been made, the ED physician is faced with the challenge of determining appropriate abortive treatment. This review summarizes the most recent literature on pediatric migraine with an emphasis on diagnosis and abortive treatment in the ED. © 2013 American Headache Society.

Shindo, M. (2012). *The Parathyroid Glands in Thyroid Surgery* John Wiley & Sons, Ltd. doi:10.1002/9781118444832.ch15

Transient hypocalcaemia is the most common complication of total thyroidectomy. In the hands

of experienced surgeons, the risk of permanent hypocalcaemia is very low. Understanding the anatomy and technique of preservation of these glands is critical to reducing the risk of hypocalcaemia. Hypocalcaemia is what generally prolongs a patient's hospital stay. In recent years, the trend has been to predict who is at risk of developing hypocalcaemia and empirically treat with calcium and vitamin D in order to facilitate early safe discharge following total thyroidectomy. © 2013 John Wiley & Sons, Ltd.

Shipley, S. M., Frederick, M. C., Filley, C. M., & Kluger, B. M. (2013). Potential for misdiagnosis in community-acquired PET scans for dementia. *Neurology.Clinical Practice, 3*(4), 305-312. doi:10.1212/CPJ.0b013e318296f2df

We reviewed records of patients seen in a tertiary Neurobehavior Clinic to identify those who had community-acquired PET scans as part of their dementia diagnostic evaluation with the goal of assessing factors influencing diagnostic accuracy. We compared outside radiologist PET diagnoses to our consensus clinical diagnosis and collected data regarding clinical variables, ordering reasons, and specialties of interpreting and ordering physicians. Among 1,580 total patients seen in our clinic, 46 met our inclusion criteria. There was disagreement between outside diagnosis based on PET and our consensus diagnosis in 65% (n = 30) of patients. Community-acquired PET scans may have lower diagnostic value in dementia evaluation than suggested by prior research and may be associated with significant risks including misdiagnosis with an incurable neurodegenerative disease.

Silk, A. D., Zasadil, L. M., Holland, A. J., Vitre, B., Cleveland, D. W., & Weaver, B. A. (2013). Chromosome missegregation rate predicts whether aneuploidy will promote or suppress tumors. *Proceedings of the National Academy of Sciences of the United States of America, 110*(44), E4134-E4141. doi:10.1073/pnas.1317042110

Aneuploidy, a chromosome content other than a multiple of the haploid number, is a common feature of cancer cells. Whole chromosomal aneuploidy accompanying ongoing chromosomal instability in mice resulting fromreduced levels of the centromere-linkedmotor protein CENP-E has been reported to increase the incidence of spleen and lung tumors, but to suppress tumors in three other contexts. Exacerbating chromosome missegregation in CENP-E+ mice by reducing

levels of another mitotic checkpoint component, Mad2, is now shown to result in elevated cell death and decreased tumor formation compared with reduction of either protein alone. Furthermore, we determine that the additional contexts in which increased whole-chromosome missegregation resulting from reduced CENP-E suppresses tumor formation have a preexisting, elevated basal level of chromosome missegregation that is exacerbated by reduction of CENP-E. Tumors arising from primary causes that do not generate chromosomal instability, including loss of the INK4a tumor suppressor and microsatellite instability from reduction of the DNA mismatch repair protein MLH1, are unaffected by CENP-E-dependent chromosome missegregation. These findings support a model in which low rates of chromosome missegregation can promote tumorigenesis, whereas missegregation of high numbers of chromosomes leads to cell death and tumor suppression.

Siragusa, D. A., Cardella, J. F., Hieb, R. A., Kaufman, J. A., Kim, H. S., Nikolic, B., . . . Wallace, M. J. (2013). Requirements for training in interventional radiology. *Journal of Vascular and Interventional Radiology, 24*(11), 1609-1612. doi:10.1016/j.jvir.2013.08.002

Smith, A. W., Ronnekleiv, O. K., & Kelly, M. J. (2013). Gq-mER signaling has opposite effects on hypothalamic orexigenic and anorexigenic neurons. *Steroids,* doi:10.1016/j.steroids.2013.11.007; 10.1016/j.steroids.2013.11.007

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

Smolen, J. S., Landewé, R., Breedveld, F. C., Buch, M., Burmester, G., Dougados, M., . . . van der Heijde, D. (2013). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Annals of the Rheumatic Diseases,* doi:10.1136/annrheumdis-2013-204573

In this article, the 2010 European League against Rheumatism (EULAR) recommendations for the

management of rheumatoid arthritis (RA) with synthetic and biological disease-modifying antirheumatic drugs (sDMARDs and bDMARDs, respectively) have been updated. The 2013 update has been developed by an international task force, which based its decisions mostly on evidence from three systematic literature reviews (one each on sDMARDs, including glucocorticoids, bDMARDs and safety aspects of DMARD therapy); treatment strategies were also covered by the searches. The evidence presented was discussed and summarised by the experts in the course of a consensus finding and voting process. Levels of evidence and grades of recommendations were derived and levels of agreement (strengths of recommendations) were determined. Fourteen recommendations were developed (instead of 15 in 2010). Some of the 2010 recommendations were deleted, and others were amended or split. The recommendations cover general aspects, such as attainment of remission or low disease activity using a treat-to-target approach, and the need for shared decision-making between rheumatologists and patients. The more specific items relate to starting DMARD therapy using a conventional sDMARD (csDMARD) strategy in combination with glucocorticoids, followed by the addition of a bDMARD or another csDMARD strategy (after stratification by presence or absence of adverse risk factors) if the treatment target is not reached within 6 months (or improvement not seen at 3 months). Tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars), abatacept, tocilizumab and, under certain circumstances, rituximab are essentially considered to have similar efficacy and safety. If the first bDMARD strategy fails, any other bDMARD may be used. The recommendations also address tofacitinib as a targeted sDMARD (tsDMARD), which is recommended, where licensed, after use of at least one bDMARD. Biosimilars are also addressed. These recommendations are intended to inform rheumatologists, patients, national rheumatology societies and other stakeholders about EULAR's most recent consensus on the management of RA with sDMARDs, glucocorticoids and bDMARDs. They are based on evidence and expert opinion and intended to improve outcome in patients with RA.

Solomon, D. N., & Hansen, L. (2013). Living through the end: The phenomenon of dying at home. *Palliative & Supportive Care,* , 1-10. doi:10.1017/S1478951513000898

Objectives: To explore the unique lived experiences of one patient who died at home and her

family members, and to interpret how dying at home influenced patterns of bereavement for this patient's family. Methods: Benner's (1985) interpretive phenomenological approach was employed to get at the embedded nature of the social phenomenon of dying at home, uncovering what may be taken for granted by participants - in this case, during and after the patient's home hospice course. The participants were a 78-year-old female diagnosed with amyotrophic lateral sclerosis six months prior to death, her husband, and three of her four children. In line with the patient's wish to die at home, she voluntarily forewent food and drink when she no longer wished to watch her body deteriorate and felt that her life had run its course. She informed her family of this plan, and all were supportive. For data collection, separate single in-depth interviews were conducted with the deceased three months prior to death, and after death with three of her four children and her spouse of 60 years. For data analysis, the interview transcripts were coded for paradigm cases, exemplars, and themes. Results: The paradigm case, "The Meaning of Being at Home," revealed that for study participants, remaining home with hospice provided a richly familiar, quiet, and safe environment for being together over time and focusing on relationships. Exemplars included "Driving Her Own Course" and "Not Being a Burden." Salient themes encompassed patient and family characteristics, support, emotions, the value of time, and aspects of the healthcare team. Significance of results: End-of-life care providers need to hold a patient-centered, family-focused view to facilitate patient and family wishes to remain home to die. Investigation into family relationships, from the perspectives of both patient and family members, longitudinally, may enrich understanding and ability and help patients to die at home.

Sonnenberg, A. (2014). Birth-cohort patterns in Crohn's disease and ulcerative colitis. *European Journal of Gastroenterology & Hepatology, 26*(1), 19-25. doi:10.1097/01.meg.0000435547.11908.97; 10.1097/01.meg.0000435547.11908.97

AIM: To test the long-term time trends of mortality from inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), for the presence of birth-cohort phenomena. METHODS: We analyzed mortality data from the national statistical offices of Canada, England and Wales, Italy, the Netherlands, Switzerland, and the USA for the past 60-80 years. Age-specific rates of death were plotted against the period of death, as period-age contours, and against the period of birth, as cohort-age contours. RESULTS: In all six countries

alike, the general time trends of IBD have been shaped by an underlying birth-cohort pattern. This pattern was also observed in the data of CD and UC analyzed separately. UC mortality increased in all generations born during the 19th century. It peaked among generations born shortly before the turn of the century and then decreased in all subsequent generations born throughout the 20th century. Compared with UC, the birth-cohort pattern of CD was delayed by 30-50 years. CONCLUSION: In addition to one risk factor responsible for the general occurrence of IBD and possibly UC alone, there exists at least one additional risk factor responsible for CD. Exposure to both separate risk factors must occur during early life.

Sonnenberg, A., & Byrd-Clark, D. D. (2013). U.S. Hospitalizations for Colorectal Cancer 1970-2010. *Digestive Diseases and Sciences,* , 1-5. doi:10.1007/s10620-013-2921-5
Background and Aims: The occurrence of colorectal cancer has been declining in the United States. The aim of the present study was to confirm such time trends using hospitalization data for colorectal cancer from the past four decades. Methods: U.S. hospital utilization data were available for individual years from 1970 to 2010 through the National Hospital Discharge Survey. Colon and rectum cancer were analyzed separately stratified by their ICD-9CM codes. Hospitalizations during consecutive 5-year periods were expressed as annual rates per 100,000 living U.S. population. Results: After an initial rise between 1970 and 1985, U.S. hospitalizations for colorectal cancer have declined ever since. Similar trends were found in men and women, and for colon and rectum cancer analyzed separately. The rise and fall of both cancer types were statistically significant ($p < 0.001$). The decline was most pronounced in the 65 years and older age group. Conclusions: Hospitalizations for colorectal cancer have declined in the United States since the mid-1980s. The onset of this decline preceded the widespread use of screening for colorectal cancer. Other mechanisms besides screening may have contributed to this observed decline. © 2013 Springer Science+Business Media New York (Outside the USA).

Soulellis, C. A., Bradette, M., Chiba, N., Fennerty, M. B., & Fallone, C. A. (2010). *Barrett's Esophagus* Wiley-Blackwell. doi:10.1002/9781444314403.ch3

Spackman, K. A. (1998). Integrating sources for a clinical reference terminology: Experience linking snomed to loinc and drug vocabularies. *9th World Congress on Medical Informatics, MedInfo*

1998, Seoul. *, 52* 600-603. doi:10.3233/978-1-60750-896-0-600

Achieving the promise of higher quality, lower cost and more available health care through electronic medical records requires the support of a comprehensive clinical reference terminology. In a previous paper we described SNOMED RT (reference terminology), and the data structures and logic syntax that support the transformation of the SNOMED III nomenclature into the SNOMED RT reference terminology. In this paper, we describe an approach to linking SNOMED RT to existing nomenclatures in the area of laboratory test names (LOINC™) and therapeutic drugs (Multum's MediSource™ Drug Lexicon), in order to achieve an integrated whole that solves the problem of a clinical reference terminology.

Stecker, E. C., & Schroeder, S. A. (2013). Adding Value to Relative-Value Units. *The New England Journal of Medicine,* doi:10.1056/NEJMp1310583

Relative-value units (RVUs) were developed in 1988 as a method of accounting for physicians' work effort and hospital or clinic expenses. Because RVUs provided a uniform, formulaic metric for myriad clinical services, they quickly became the prevailing method for setting fee-for-service payments for Medicare and private insurance. However, the dominance of the fee-for-service model has created strong structural impediments to physicians' participation in value-focused health care.1 The success of new models of care will require not only changes in the way that health systems are organized and paid but also vigorous engagement by generalists and specialists, yet RVU formulas for . . .

Stock, R., Mahoney, E., & Carney, P. A. (2013). Measuring team development in clinical care settings. *Family Medicine, 45*(10), 691-700.

Background And Objectives: Our objective was to describe the psychometric properties of a measure of team development that can be used to assess and guide team functioning in health care settings. Methods: The Team Development Measure (TDM) is a 31-item questionnaire constructed using the Rasch rating scale measurement model. We conducted an Mplus exploratory factor analysis using data collected from 1,194 individuals representing 120 different teams. Team size ranged from three to 39 members from rural and urban inpatient and ambulatory health care settings. Here we characterize the domains of teamness, while taking into

account the development of teams over time. Results: The TDM was found to have good psychometric properties with little measurement error and a Rasch person reliability of 0.95. Overall Cronbach's alpha was 0.97. An Mplus exploratory factor analysis combined with the stochastic nature of the Rasch model suggests a developmental sequence in building teams consisting of four sub-domains with the following mean item difficulty scores: cohesion=40.5, standard deviation (SD)=2.68, communication= 49.3 (SD=2.78), roles and goals=52.7 (SD=2.74), and team primacy=53.3 (SD=1.06). This pattern suggests cohesiveness is an initial element for team development, followed by communication, roles and goals clarity, and team primacy. Conclusions: We developed and tested a measure of team development that has strong psychometric properties. This tool could be used to study how team functioning affects clinical outcomes and as a quality improvement tool to improve team function.

Stump, M. R., Gong, Q., & Zhou, Z. (2013). LQT2 nonsense mutations generate trafficking defective NH2-terminally truncated channels by the reinitiation of translation. *American Journal of Physiology - Heart and Circulatory Physiology, 305*(9), H1397-H1404. doi:10.1152/ajpheart.00304.2013

The human ether-a-go-go-related gene (hERG) encodes a voltage-activated K+ channel that contributes to the repolarization of the cardiac action potential. Long QT syndrome type 2 (LQT2) is an autosomal dominant disorder caused by mutations in hERG, and patients with LQT2 are susceptible to severe ventricular arrhythmias. We have previously shown that nonsense and frameshift LQT2 mutations caused a decrease in mutant mRNA by the nonsense-mediated mRNA decay (NMD) pathway. The Q81X nonsense mutation was recently found to be resistant to NMD. Translation of Q81X is reinitiated at Met124, resulting in the generation of NH2-terminally truncated hERG channels with altered gating properties. In the present study, we identified two additional NMD-resistant LQT2 nonsense mutations, C39X and C44X, in which translation is reinitiated at Met60. Deletion of the first 59 residues of the channel truncated nearly one-third of the highly structured Per-Arnt-Sim domain and resulted in the generation of trafficking-defective proteins and a complete loss of hERG current. Partial deletion of the Per-Arnt-Sim domain also resulted in the accelerated degradation of the mutant channel proteins. The coexpression of mutant and wild-type channels did not significantly disrupt the function and trafficking properties

of wild-type hERG. Our present findings indicate that translation reinitiation may generate traffickingdefective as well as dysfunctional channels in patients with LQT2 premature termination codon mutations that occur early in the coding sequence. © 2013 the American Physiological Society.

Sukumar, M. (2013). Invited commentary. *The Annals of Thoracic Surgery, 96*(5), 1819. doi:10.1016/j.athoracsur.2013.07.021; 10.1016/j.athoracsur.2013.07.021

Sun, B. C., McCreath, H., Liang, L. J., Bohan, S., Baugh, C., Ragsdale, L., . . . Mangione, C. M. (2013). Randomized Clinical Trial of an Emergency Department Observation Syncope Protocol Versus Routine Inpatient Admission. *Annals of Emergency Medicine,* doi:10.1016/j.annemergmed.2013.10.029; 10.1016/j.annemergmed.2013.10.029
STUDY OBJECTIVE: Older adults are frequently hospitalized from the emergency department (ED) after an episode of unexplained syncope. Current admission patterns are costly, with little evidence of benefit. We hypothesize that an ED observation syncope protocol will reduce resource use without adversely affecting patient-oriented outcomes. METHODS: This randomized trial at 5 EDs compared an ED observation syncope protocol to inpatient admission for intermediate-risk adults (>/=50 years) presenting with syncope or near syncope. Primary outcomes included inpatient admission rate and length of stay. Secondary outcomes included 30-day and 6-month serious outcomes after hospital discharge, index and 30-day hospital costs, 30-day quality-of-life scores, and 30-day patient satisfaction. RESULTS: Study staff randomized 124 patients. Observation resulted in a lower inpatient admission rate (15% versus 92%; 95% confidence interval [CI] difference -88% to -66%) and shorter hospital length of stay (29 versus 47 hours; 95% CI difference -28 to -8). Serious outcome rates after hospital discharge were similar for observation versus admission at 30 days (3% versus 0%; 95% CI difference -1% to 8%) and 6 months (8% versus 10%; 95% CI difference -13% to 9%). Index hospital costs in the observation group were $629 (95% CI difference -$1,376 to -$56) lower than in the admission group. There were no differences in 30-day quality-of-life scores or in patient satisfaction. CONCLUSION: An ED observation syncope protocol reduced the primary outcomes of admission rate and hospital length of stay. Analyses of secondary outcomes suggest reduction in index

hospital costs, with no difference in safety events, quality of life, or patient satisfaction. Our findings suggest that an ED observation syncope protocol can be replicated and safely reduce resource use.

Tardif, S. D., Coleman, K., Hobbs, T. R., & Lutz, C. (2013). IACUC Review of nonhuman primate research. *ILAR Journal, 54*(2), 234-245. doi:10.1093/ilar/ilt040

This article will detail some of the issues that must be considered as institutional animal care and use committees (IACUCs) review the use of nonhuman primates (NHPs) in research. As large, intelligent, social, long-lived, and nondomesticated animals, monkeys are amongst the most challenging species used in biomedical research and the duties of the IACUC in relation to reviewing research use of these species can also be challenging. Issues of specific concern for review of NHP research protocols that are discussed in this article include scientific justification, reuse, social housing requirements, amelioration of distress, surgical procedures, and humane endpoints. Clear institutional policies and procedures as regards NHP in these areas are critical, and the discussion of these issues presented here can serve as a basis for the informed establishment of such policies and procedures.

Tedford, R. J., Mudd, J. O., Girgis, R. E., Mathai, S. C., Zaiman, A. L., Housten-Harris, T., . . . Kass, D. A. (2013). Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. *Circulation: Heart Failure, 6*(5), 953-963. doi:10.1161/CIRCHEARTFAILURE.112.000008

Background-Systemic sclerosis-associated pulmonary artery hypertension (SScPAH) has a worse prognosis compared with idiopathic pulmonary arterial hypertension (IPAH), with a median survival of 3 years after diagnosis often caused by right ventricular (RV) failure. We tested whether SScPAH or systemic sclerosis-related pulmonary hypertension with interstitial lung disease imposes a greater pulmonary vascular load than IPAH and leads to worse RV contractile function. Methods and Results-We analyzed pulmonary artery pressures and mean flow in 282 patients with pulmonary hypertension (166 SScPAH, 49 systemic sclerosis-related pulmonary hypertension with interstitial lung disease, and 67 IPAH). An inverse relation between pulmonary

resistance and compliance was similar for all 3 groups, with a near constant resistance×compliance product. RV pressure-volume loops were measured in a subset, IPAH (n=5) and SScPAH (n=7), as well as SSc without PH (n=7) to derive contractile indexes (end-systolic elastance [Ees] and preload recruitable stroke work [Msw]), measures of RV load (arterial elastance [Ea]), and RV pulmonary artery coupling (Ees/Ea). RV afterload was similar in SScPAH and IPAH (pulmonary vascular resistance=7.0±4.5 versus 7.9±4.3 Wood units; Ea=0.9±0.4 versus 1.2±0.5 mm Hg/mL; pulmonary arterial compliance=2.4±1.5 versus 1.7±1.1 mL/mm Hg; P>0.3 for each). Although SScPAH did not have greater vascular stiffening compared with IPAH, RV contractility was more depressed (Ees=0. 8±0.3 versus 2.3±1.1, P<0.01; Msw=21±11 versus 45±16, P=0.01), with differential RV-PA uncoupling (Ees/E a=1.0±0.5 versus 2.1±1.0; P=0.03). This ratio was higher in SSc without PH (Ees/Ea=2.3±1.2; P=0.02 versus SScPAH). Conclusions-RV dysfunction is worse in SScPAH compared with IPAH at similar afterload, and may be because of intrinsic systolic function rather than enhanced pulmonary vascular resistive and pulsatile loading.

Teoh, A. Y. B., Ng, E. K. W., Chock, A., Swanstrom, L., Varadarajulu, S., & Chiu, P. W. Y. (2013). Asian-Chinese patient perceptions of natural orifice transluminal endoscopic surgery cholecystectomy. *Digestive Endoscopy,* doi:10.1111/den.12192

Background and Aim: Patient and physician perceptions of natural orifice transluminal endoscopic surgery (NOTES) have been reported for the Western population. However, whether Asian-Chinese patients share the same perspectives as compared to the Western population is unknown. Methods: This was a cross-sectional survey carried out in the surgical outpatient's clinic at the Prince of Wales Hospital between June and September 2011. Patients were provided with an information leaflet and asked to complete a questionnaire regarding their perceptions of and preferences for NOTES cholecystectomy. Female patients attending the clinic were given an additional questionnaire regarding attitudes towards transvaginal surgery. Results: Two hundred patients were recruited to complete the questionnaire(s) and the male to female ratio was 1:1. One hundred and fourteen patients (57%) preferred to undergo NOTES cholecystectomy for cosmetic reasons (P=0.009). Oral and anal routes were both acceptable for NOTES accesses in males andfemales. Forty-one percent of the female patients would consider transvaginal NOTES.

Of these patients, significantly more patients indicated that the reason for choosing transvaginal NOTES was to minimize the risk of hernia (P=0.016) and to reduce pain associated with the procedure (P=0.017). The risk of complications (84.5%) and the cost of the procedure (58%) were considered the most important aspects when choosing a surgical approach by Asian-Chinese patients. Conclusions: Asian-Chinese preferred NOTES mainly for cosmetic reasons. However, the transvaginal route was less acceptable to females. Significant differences in patient perception on NOTES were observed between Asian-Chinese and Western patients. © 2013 Japan Gastroenterological Endoscopy Society.

Tian, X., Hersh, W., Logan, J., & Bennett, R. (2004). A database for Chinese outpatients with rheumatic diseases. *Studies in Health Technology and Informatics, 107*, 256-259. doi:10.3233/978-1-60750-949-3-256

Although several databases have been developed in rheumatology aimed at profiling the morbidity pattern of rheumatic diseases, or to capture the detailed clinical and outcome information of patients with a specific rheumatic disease, there is no database in China, as yet, for capturing visit-related health information of all outpatients with rheumatic diseases. In this project, a relational database was developed for the rheumatic outpatient clinic of Peking Union Medical College Hospital (PUMCH). The primary goal of this database is to collect and organize visitrelated information of outpatients with rheumatic diseases to meet information needs of clinical research, health care continuity and teaching of rheumatic diseases. The implementation of this database can improve health services, medical records management and clinical research of outpatients with rheumatic disease at PUMCH. © 2004 IMIA. All rights reserved.

Travaline, J. M., Burke, G. F., Isajiw, G., White, R. S., Pitre, T., Rybak, L. P., . . . Brehany, J. F. (2009). Response to the consortium of jesuit bioethics programs statement "undue burden?" the Catholic Medical Association. *Linacre Quarterly, 76*(3), 296-303. doi:10.1179/002436309803889179

Vandlac, A. A., Cowan, N. G., Chen, Y., Anderson, R. E., Conlin, M. J., La Rochelle, J. C., . . . Koppie, T. M. (2013). Timing, incidence, and risk factors of venous thromboembolism in patients undergoing radical cystectomy for malignancy: A case for extended duration pharmacologic

prophylaxis. *The Journal of Urology,* doi:10.1016/j.juro.2013.10.096; 10.1016/j.juro.2013.10.096

PURPOSE:: Patients undergoing radical cystectomy for bladder cancer are at high risk for development of venous thromboembolism. Recent data has demonstrated the risk of VTE often extends beyond hospital discharge in non-urologic surgical populations. The timing of VTE occurrence in radical cystectomy patients over a 30 day post-operative period has not been assessed. We evaluated the timing, incidence, and risk factors of VTE for patients undergoing RC for malignancy. MATERIALS AND METHODS:: This is a descriptive observational retrospective study. Data from 1,307 patients who underwent RC for malignancy from 2005-2011 were collected using the American College of Surgeons National Surgical Quality Improvement Program database. VTE occurrences were evaluated by postoperative day and whether they occurred while inpatient or after discharge. Univariate and multivariable Cox regression and logistic regression models were used to evaluate risk factors associated with VTE. RESULTS:: Seventy-eight of 1307 patients (6%) was diagnosed with VTE. The mean time to VTE diagnosis was 15.2 days post-operatively. Fifty-five percent of all VTE events were diagnosed after patient discharge. The 30 day mortality rate from VTE was 6.4%. Risk factors for development of VTE on multivariable analysis were age (p=0.024), operative time (p=0.004), and sepsis or septic shock (p=0.0001). CONCLUSIONS:: More than half of all VTEs (55%) in patients undergoing RC for malignancy occurred following patient discharge and the mean time to VTE diagnosis was 15.2 days postoperatively. It is reasonable to consider extended duration pharmacologic prophylaxis (4 weeks) in this high risk surgical population.

Varlamov, O., Chu, M. P., McGee, W. K., Cameron, J. L., O'Rourke, R. W., Meyer, K. A., . . . Roberts Jr., C. T. (2013). Ovarian cycle-specific regulation of adipose tissue lipid storage by testosterone in female nonhuman primates. *Endocrinology, 154*(11), 4126-4135. doi:10.1210/en.2013-1428

Previous studies in rodents and humans suggest that hyperandrogenemia causes white adipose tissue (WAT) dysfunction in females, although the underlying mechanisms are poorly understood. In light of the differences in the length of the ovarian cycle between humans and rodents, we used a nonhuman primate model to elucidate the effects of chronic hyperandrogenemia on WAT function in vivo. Female rhesus macaques implanted with testosterone capsules developed insulin

resistance and altered leptin secretion on a high-fat, Western-style diet. In control visceral WAT, lipolysis and hormone-sensitive lipase expression were upregulated during the luteal phase compared with the early follicular (menses) phase of the ovarian cycle. Hyperandrogenemia attenuated elevated lipolysis and hormone-sensitive lipase activity in visceral WAT during the luteal phase but not during menses. Under control conditions, insulin-stimulated Akt and Erk activation and fatty acid uptake in WAT were not significantly affected by the ovarian cycle. In contrast, testosterone treatment preferentially increased fatty acid uptake and insulin signaling at menses. The fatty acid synthase and glucose transporter-4 genes were upregulated by testosterone during the luteal phase. In summary, this study reveals ovarian stage-specific fluctuations in adipocyte lipolysis and suggests that male sex hormones increase and female sex hormones decrease lipid storage in female WAT.

Varley, C. D., Deodhar, A. A., Ehst, B. D., Bakke, A., Blauvelt, A., Vega, R., . . . Winthrop, K. L. (2013). Persistence of Staphylococcus aureus colonization among individuals with immune-mediated inflammatory diseases treated with TNF-alpha inhibitor therapy. *Rheumatology (Oxford, England),* doi:10.1093/rheumatology/ket351

Objective. We investigated the relationship between Staphylococcus aureus colonization and the use of immunosuppressive therapies in patients with immune-mediated inflammatory diseases (IMIDs).Methods. We prospectively enrolled IMID patients from the rheumatology and dermatology departments of Oregon Health & Science University. At enrolment, we surveyed patients for S. aureus infection risk factors and those using immune-modulating therapies, and evaluated their colonization status with bilateral nares and inguinal fold cultures. Patients were asked to follow up 6-12 months later for reassessment of colonization status by repeat culture. S. aureus isolates were tested for the presence of methicillin resistance by PCR.Results. We enrolled a total of 548 IMID patients. At enrolment, 219 (40.0%) patients were colonized with S. aureus, of which 27 (12.3%) were methicillin-resistant S. aureus (MRSA). Baseline colonization rates were similar between TNF-alpha inhibitor users and non-users (40.5% and 39.4%, P = 0.79), but were significantly higher for psoriasis patients compared with those with RA (43.5% and 31.8%, P = 0.02). A total of 384 patients were available for follow-up. Patients who were colonized at enrolment were more likely to be colonized at follow-up if they were treated with TNF-alpha

inhibitors during the study as compared to patients without TNF-alpha inhibitor exposure [odds ratio (OR) = 2.2 (95% CI 1.1, 4.2), P = 0.02].Conclusion. Patients with psoriasis are more likely to be colonized with S. aureus than patients with RA. Patients who are colonized with S. aureus are more likely to remain colonized if exposed to TNF-alpha inhibitors.

Ventres, W. (2013). Electronic Health Records: Upsides, Downsides, and Inside-Outsides on the Way Toward Their Use in Clinical Practice. *Teaching and Learning in Medicine, 25*(4), 366-368. doi:10.1080/10401334.2013.827982

Background: The author reviews his personal history learning to use Electronic Health Records (EHRs) and examination room computers. He asks key questions that pertain to the use of EHRs in practice and discusses the current state of knowledge regarding EHRs and doctor-patient communication. Summary: He notes that-regardless of the ubiquity of computers in our society and the recognition that they are a part of current medical practice-one cannot just plop down a computer in the examination room, click "on," and anticipate that communication between doctors and patients will flow smoothly. Conclusions: He recommends the accompanying article by Duke, Frankel, and Reis (see p. 358 in this issue) as an excellent step-by-step guide for framing how to teach the basics of EHR use in clinical practice. © 2013 Copyright Taylor and Francis Group, LLC.

Vetto, J. T. (2013). Short and Sweet: a Short Course on Concise Medical Writing. *Journal of Cancer Education : The Official Journal of the American Association for Cancer Education,* doi:10.1007/s13187-013-0584-8

Vinson, A., Prongay, K., & Ferguson, B. (2013). The value of extended pedigrees for next-generation analysis of complex disease in the rhesus macaque. *ILAR Journal, 54*(2), 91-105. doi:10.1093/ilar/ilt041

Complex diseases (e.g., cardiovascular disease and type 2 diabetes, among many others) pose the biggest threat to human health worldwide and are among the most challenging to investigate. Susceptibility to complex disease may be caused by multiple genetic variants (GVs) and their interaction, by environmental factors, and by interaction between GVs and environment, and large study cohorts with substantial analytical power are typically required to elucidate these

individual contributions. Here, we discuss the advantages of both power and feasibility afforded by the use of extended pedigrees of rhesus macaques (Macaca mulatta) for genetic studies of complex human disease based on next-generation sequence data. We present these advantages in the context of previous research conducted in rhesus macaques for several representative complex diseases. We also describe a single, multigeneration pedigree of Indian-origin rhesus macaques and a sample biobank we have developed for genetic analysis of complex disease, including power of this pedigree to detect causal GVs using either genetic linkage or association methods in a variance decomposition approach. Finally, we summarize findings of significant heritability for a number of quantitative traits that demonstrate that genetic contributions to risk factors for complex disease can be detected and measured in this pedigree. We conclude that the development and application of an extended pedigree to analysis of complex disease traits in the rhesus macaque have shown promising early success and that genome-wide genetic and higher order -omics studies in this pedigree are likely to yield useful insights into the architecture of complex human disease.

Vose, L. R., Vinukonda, G., Jo, S., Miry, O., Diamond, D., Korumilli, R., . . . Ballabh, P. (2013). Treatment with thyroxine restores myelination and clinical recovery after intraventricular hemorrhage. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 33*(44), 17232-17246. doi:10.1523/JNEUROSCI.2713-13.2013; 10.1523/JNEUROSCI.2713-13.2013

Intraventricular hemorrhage (IVH) remains a major cause of white matter injury in preterm infants with no viable therapeutic strategy to restore myelination. Maturation of oligodendrocytes and myelination is influenced by thyroid hormone (TH) signaling, which is mediated by TH receptor alpha (TRalpha) and TRbeta. In the brain, cellular levels of TH are regulated by deiodinases, with deiodinase-2 mediating TH activation and deiodinase-3 TH inactivation. Therefore, we hypothesized that IVH would decrease TH signaling via changes in the expression of deiodinases and/or TRs, and normalization of TH signaling would enhance maturation of oligodendrocytes and myelination in preterm infants with IVH. These hypotheses were tested using both autopsy materials from human preterm infants and a rabbit model of IVH. We found

that deiodinase-2 levels were reduced, whereas deiodinase-3 levels were increased in brain samples of both humans and rabbits with IVH compared with controls without IVH. TRalpha expression was also increased in human infants with IVH. Importantly, treatment with TH accelerated the proliferation and maturation of oligodendrocytes, increased transcription of Olig2 and Sox10 genes, augmented myelination, and restored neurological function in pups with IVH. Consistent with these findings, the density of myelinating oligodendrocytes was almost doubled in TH-treated human preterm infants compared with controls. Thus, in infants with IVH the combined elevation in deiodinase-3 and reduction in deiodinase-2 decreases TH signaling that can be worsened by an increase in unliganded TRalpha. Given that TH promotes neurological recovery in IVH, TH treatment might improve the neurodevelopmental outcome of preterm infants with IVH.

Walsh, E. S., Peterson, J. J., & Judkins, D. Z. (2013). Searching for disability in electronic databases of published literature. *Disability and Health Journal,* doi:10.1016/j.dhjo.2013.10.005

Background: As researchers in disability and health conduct systematic reviews with greater frequency, the definition of disability used in these reviews gains importance. Translating a comprehensive conceptual definition of "disability" into an operational definition that utilizes electronic databases in the health sciences is a difficult step necessary for performing systematic literature reviews in the field. Consistency of definition across studies will help build a body of evidence that is comparable and amenable to synthesis. Objective: To illustrate a process for operationalizing the World Health Organization's International Classification of Disability, Functioning, and Health concept of disability for MEDLINE, PsycINFO, and CINAHL databases. Methods: We created an electronic search strategy in conjunction with a reference librarian and an expert panel. Quality control steps included comparison of search results to results of a search for a specific disabling condition and to articles nominated by the expert panel. Results: The complete search strategy is presented. Results of the quality control steps indicated that our strategy was sufficiently sensitive and specific. Conclusions: Our search strategy will be valuable to researchers conducting literature reviews on broad populations with disabilities.

Wang, R. K., & Subhash, H. M. (2012). *Optical Microangiography: Theory and Application* Wiley-VCH Verlag GmbH & Co. KGaA. doi:10.1002/9783527651238.ch10

Warshaw, E. M., Raju, S. I., Mathias, C. G., Dekoven, J. G., Belsito, D. V., Maibach, H. I., . . . Storrs, F. J. (2013). Concomitant patch test reactions to mercapto mix and mercaptobenzothiazole: retrospective analysis from the north american contact dermatitis group, 1994-2008. *Dermatitis : Contact, Atopic, Occupational, Drug, 24*(6), 321-327. doi:10.1097/DER.0b013e3182a8c1ab; 10.1097/DER.0b013e3182a8c1ab

BACKGROUND: Mercaptobenzothiazole (MBT) and mercapto compounds are primarily used in rubber products. OBJECTIVE: This study aimed to examine concomitant-positive rates of MBT (1% pet) and the 4-part mercapto mix (MM) (1% pet). DESIGN: This is a retrospective cross-sectional data from the North American Contact Dermatitis Group. RESULTS: A total of 30,880 patients were patch tested to MM and MBT. There were 333 positive reactions to MM and 427 positive reactions to MBT. Ninety-eight patients were positive to MM alone, 192 to MBT alone, and 235 reacted to both. Forty-five percent (192/427) of MBT reactions would have been missed by only testing to MM, and 29% (98/333) of MM reactions would have been missed by testing to MBT alone. Most of these "missed" reactions, however, were doubtful (+/-) or mild (+) (MBT, 65%; MM, 78%), whereas most reactions in patients who reacted to both were moderate (++) and/or strong (+++) (52.3%). Gloves were the most common source. CONCLUSIONS: Mercaptobenzothiazole is the preferential screening allergen for mercapto compounds because of the following: (1) greater proportion of missed reactions with MM; (2) greater proportion of doubtful/mild reactions in the missed group for MM; and (3) in the group positive to both, the low rate (2%) of moderate/strong reactions to MM and doubtful/mild reactions to MBT as compared with the converse (21%). Mercapto mix may be useful in an auxiliary rubber series.

Wasson, N. J., Varley, C. D., Schwab, P., Fu, R., & Winthrop, K. L. (2013). " Serious skin & soft tissue infections in rheumatoid arthritis patients taking anti-tumor necrosis factor alpha drugs: A nested case-control study". *BMC Infectious Diseases, 13*(1) doi:10.1186/1471-2334-13-533

Background: Anti-tumor necrosis factor alpha (anti-TNF) drugs are very effective for the treatment of rheumatoid arthritis but may increase the risk of serious bacterial infections. We

assessed the association between the risk of serious skin and soft tissue infections (SSSTI) and the use of these agents in rheumatoid arthritis patients (RA).Methods: We conducted a nested case-control study among rheumatoid arthritis patients in the Veterans Integrated Service Network 20 from 2000-2008. We identified rheumatoid arthritis patients with SSSTI, matched them to three sets of RA controls and used conditional logistic regression to compare the risk of SSSTI between patients treated and those not treated with an anti-TNF drug, after adjusting for known confounders and important covariates. Limited by the design, we could not assess (absolute) risk but only relative risk in terms of association.Results: Among the 97 cases and 291 controls, 90 percent were male, 62 percent white, with a mean age of 63 years. Twenty percent received anti-TNF drugs during the study period. Thirty-nine percent of cases and 15 percent of controls died, (OR 3.5, 95% CI: 2.033, 6.11, p <0.01). Diabetes mellitus (37%), kidney disease (16%) and a history of skin infections (27%) were common among cases. Based on conditional logistic regression, anti-TNF use was not significantly associated with skin and soft tissue infections (OR 1.1, 95% CI: 0.61-2.03, p = 0.92). However, patients with diabetes mellitus (OR 2.5, 95% CI: 1.53-4.13, p = 0.01) or a prior history of skin infection (OR 5.7, 95% CI: 2.87-11.43, p <0.01) were more likely to have skin and soft tissue infections.Conclusion: Use of anti-TNF therapy among RA patients was not associated with an increased risk of SSSTI, but patients with diabetes mellitus and those with a history of prior skin infection were significantly more likely to have SSSTI and mortality was higher among cases than controls in this veteran cohort.

Webb, T., Valvano, T., Nugent, M., & Melzer-Lange, M. (2013). Child abuse pediatric consults in the pediatric emergency department improve adherence to hospital guidelines. *Wisconsin Medical Journal, 112*(5), 206-211.

Background: Little data describes the role of child abuse pediatricians in consultation for physical abuse patients the pediatric emergency department. Objectives: To compare adherence in the emergency department to hospital physical abuse guidelines and need to return for testing between 2 groups: those receiving a child abuse consultation in the pediatric emergency department vs those who received standard emergency department care with subsequent child abuse review. Methods: We reviewed 471 records of visits to the pediatric emergency

department for physical abuse. Data collected included demographics, studies performed, whether patients need to return after child abuse review, child abuse subpoenas, child abuse testimony in court. Results: Patients who received a child abuse consult in the emergency department or inpatient were more likely to be younger and to have more severe injuries. In cases where a consult was obtained, there was 100% adherence to emergency department clinical guidelines vs 66% when no consult was obtained. In addition, in cases that did not receive a child abuse consult, 8% had to return to the hospital for labs or radiographs after their emergency department visit. Conclusions: Child abuse consultation in the pediatric emergency department improves compliance with clinical guidelines and decreases the likelihood that patients will need to return for further testing.

Wehner, A. P., Hall, A. S., Weller, R. E., Lepel, E. A., & Schirmer, R. E. (1985). Do particles translocate from the vagina to the oviducts and beyond? *Food and Chemical Toxicology, 23*(3), 367-372. doi:10.1016/0278-6915(85)90070-5

To investigate whether particles deposited in the vagina translocate to the oviducts, 0.3 ml of a 4% bone black suspension was deposited in the posterior vaginal fornix of each of five cynomolgus monkeys (Macaca fascicularis) during their mid-menstrual cycle. Simultaneously, each animal received 10 units of oxytocin by intramuscular injection. The oviducts of three animals were removed 1 hr after administration of the bone black, while those of the remaining two animals were removed 72 hr after dosing. The removed oviducts were flushed with Hank's solution and then with collagenase solution. The solutions were collected in clear vials and filtered. The filters were examined for bone black particles by light microscopy, as were filters through which solution blanks (negative controls) had been passed. Particles resembling bone black were found on all filters. There were no appreciable differences in the numbers or shape of these particles between the solution-blank filters and the oviduct-flush filters. The particles on both the solution-blank filters and on the oviduct-flush filters probably originated from environmental contamination by ubiquitous carbon particles. While these results suggested that no translocation took place, translocation could not be ruled out with certainty in the absence of quantitative analyses. A more definitive pilot study was then conducted with two dosed monkeys and one control, using talc labelled by neutron activation to circumvent the problem of

environmental contamination. γ-Ray analysis of tissue and peritoneal lavage samples for the radionuclides 46Sc, 59Fe and 60Co indicated that no measurable quantities (i.e. > 0.5 μg) of talc translocated from the deposition site in the vagina to the uterine cavity and beyond.

Weymann, K. B., Wood, L. J., Zhu, X., & Marks, D. L. (2013). A role for orexin in cytotoxic chemotherapy-induced fatigue. *Brain, Behavior, and Immunity,* doi:10.1016/j.bbi.2013.11.003; 10.1016/j.bbi.2013.11.003

Fatigue is the most common symptom related to cytotoxic chemotherapeutic treatment of cancer. Peripheral inflammation associated with cytotoxic chemotherapy is likely a causal factor of fatigue. The neural mechanisms by which cytotoxic chemotherapy associated inflammation induces fatigue behavior are not known. This lack of knowledge hinders development of interventions to reduce or prevent this disabling symptom. Infection induced fatigue/lethargy in rodents is mediated by suppression of hypothalamic orexin activity. Orexin is critical for maintaining wakefulness and motivated behavior. Though there are differences between infection and cytotoxic chemotherapy in some symptoms, both induce peripheral inflammation and fatigue. Based on these similarities we hypothesized that cytotoxic chemotherapy induces fatigue by disrupting orexin neuron activity. We found that a single dose of a cytotoxic chemotherapy cocktail (cyclophosphamide, adriamycin, 5-fluorouracil - CAF) induced fatigue/lethargy in mice and rats as evidenced by a significant decline in voluntary locomotor activity measured by telemetry. CAF induced inflammatory gene expression - IL-1R1 ($p<0.001$), IL-6 ($p<0.01$), TNFalpha ($p<0.01$), and MCP-1 ($p<0.05$) - in the rodent hypothalamus 6-24h after treatment during maximum fatigue/lethargy. CAF decreased orexin neuron activity as reflected by decreased nuclear cFos localization in orexin neurons 24h after treatment ($p<0.05$) and by decreased orexin-A in cerebrospinal fluid 16h after treatment ($p<0.001$). Most importantly, we found that central administration of1mug orexin-A restored activity in CAF-treated rats ($p<0.05$). These results demonstrate that cytotoxic chemotherapy induces hypothalamic inflammation and that suppression of hypothalamic orexin neuron activity has a causal role in cytotoxic chemotherapy-induced fatigue in rodents.

Whittaker, M. M., & Whittaker, J. W. (2014). Expression and purification of recombinant Saccharomyces cerevisiae mitochondrial carrier protein YGR257Cp (Mtm1p). *Protein Expression and Purification, 93*, 77-86. doi:10.1016/j.pep.2013.10.014; 10.1016/j.pep.2013.10.014

The Saccharomyces cerevisiae mitochondrial carrier YGR257Cp (Mtm1p) is an integral membrane protein that plays an essential role in mitochondrial iron homeostasis and respiratory functions, but its carrier substrate has not previously been identified. Large amounts of pure protein are required for biochemical characterization, including substrate screening. Functional complementation of a Saccharomyces knockout by expression of TwinStrep tagged YGR257Cp demonstrates that an affinity tag does not interfere with protein function, but the expression level is very low. Heterologous expression in Pichia pastoris improves the yield but the product is heterogeneous. Expression has been screened in several Escherichia coli hosts, optimizing yield by modifying induction conditions and supplementing with rare tRNAs to overcome codon bias in the eukaryotic gene. Detection of an additional N-terminal truncation product in E. coli reveals the presence of a secondary intracistronic translation initiation site, which can be eliminated by silent mutagenesis of an alternative (Leu) initiation codon, resulting in production of a single, full-length polypeptide (approximately 30% of the total protein) as insoluble inclusion bodies. Purified inclusion bodies were successfully refolded and affinity purified, yielding approximately 40mg of pure, soluble product per liter of culture. Refolded YGR257Cp binds pyridoxal 5'-phosphate tightly (KD<1muM), supporting a new hypothesis that the mitochondrial carrier YGR237Cp and its homologs function as high affinity PLP transporters in mitochondria, providing the first evidence for this essential transport function in eukaryotes.

Witt, L. B., Olsen, D., & Ablah, E. (2013). Motivating Factors for Small and Midsized Businesses to Implement Worksite Health Promotion. *Health Promotion Practice, 14*(6), 876-884. doi:10.1177/1524839912472504

Objective. This study explores the decision-making process, including motivating factors, for small and midsized businesses in the Midwest to implement health promotion initiatives. Method. This a replication of a study conducted in the Pacific Northwest. Semistructured qualitative interviews were conducted with key informants from 12 Midwestern metropolitan employers with fewer than 1,000 employees. Informants were interviewed regarding their companies' policies

and practices around workplace health promotion programming adoption and valuation. Results. Workplace health promotion adoption at these small and midsized businesses was motivated by three goals: to lower health care costs, to address human relations objectives, and to improve productivity. Low upfront cost was the most frequently considered criterion in choosing which workplace health promotion program to offer. Barriers to implementation included lack of employee buy-in, prohibitive costs, and personnel or time constraints. Aids to implementation included employee buy-in and affordability. Conclusions. This study suggests that cost considerations predominate in the workplace health promotion decision-making process at small to midsized businesses. Furthermore, employee buy-in cannot be underestimated as a factor in successful program implementation or longevity. Employees, along with executives and human resources management, must be appropriately targeted by health promotion practitioners in workplace health promotion efforts.

Wolters, K. L., Ang, D., Warrick, A., Beadling, C., Corless, C. L., & Troxell, M. L. (2013). Frequent PIK3CA Mutations in Radial Scars. *Diagnostic Molecular Pathology : The American Journal of Surgical Pathology, Part B, 22*(4), 210-214. doi:10.1097/PDM.0b013e318288b346; 10.1097/PDM.0b013e318288b346

Radial scars are breast lesions of uncertain pathogenesis that are associated with a 2-fold increased risk of breast cancer compared with that in controls. Activating point mutations in PIK3CA are found in 25% to 30% of invasive breast cancers; however, they have not previously been investigated in radial scars. We sought to evaluate radial scars for known activating point mutations commonly seen in invasive breast cancer. Sixteen surgical cases containing 22 radial scars were identified from pathology archives. Lesional tissue was macrodissected from unstained paraffin sections; genomic DNA was then extracted and screened for a panel of known hotspot mutations using polymerase chain reaction and mass spectroscopy analysis. Of the 22 radial scars, 14 (63.6%) had PIK3CA mutations (10 with H1047R mutations, 2 G1049R mutations, 1 E542K, 1 E545K). The remaining 8 lesions were wild type for all of the screened genes. Of the radial scars without epithelial atypia, 9/16 (56.3%) had PIK3CA mutations; furthermore, 5/6 (83.3%) radial scars with atypia had mutations detected. In this study, the frequency of PIK3CA mutations was notably higher than the 25% to 30% mutation frequency of invasive breast

cancer. This finding raises interesting questions as to the role of PIK3CA mutations in breast cancer development. Additional larger studies are indicated to confirm and extend these observations in understanding the pathogenesis of radial scars and their relationship to breast cancer.

Woods, T. R., Cohen, D. M., Islam, M. N., Kratochvil, F. J., Stewart, J. C. B., Reeder, S. L., & Bhattacharyya, I. (2013). Intraoral Basal Cell Carcinoma, a Rare Neoplasm: Report of Three New Cases with Literature Review. *Head and Neck Pathology,* , 1-10. doi:10.1007/s12105-013-0505-5 Intraoral basal cell carcinoma (IOBCC) is an extremely rare entity that bears close microscopic resemblance to and is often confused with the peripheral ameloblastoma (PA). Basal cell carcinomas are thought to arise from pluripotential basal cells present within surface epithelium and adnexal structures, so theoretically they can arise within the oral cavity. Many of the early cases reported as IOBCC actually represent PA. Most of the well documented cases arise from the gingiva. The histologic features of basal cell carcinoma that help separate it from a PA include: tumor arising from surface epithelium, scattered mitotic figures and apoptotic cells, presence of mucoid ground substance and tumor infiltrating widely throughout the connective tissue and often exhibiting a prominent retraction artifact. Clinically IOBCC resemble carcinomas, compared to the benign and innocuous appearance of the PA and typically presents as surface ulcerations varying from rodent ulcer to an ulcerated erythroplakia appearance. This contrasts with the classic "bump on the gum" appearance of PAs with usually intact surface and appearing as small discrete, sessile, exophytic lesions. Importantly, the proliferative basaloid epithelium demonstrates positive immunoreactivity for the anti-epithelial antibody, Ber-EP4, a cell surface glycoprotein. The IOBCC has the potential for local recurrence and aggressive behavior and should be treated with wide surgical excision and close clinical follow up. We present 3 rare cases of IOBCC and discuss the salient histologic, immunohistochemical and clinical features.

Yedinak, C. G., & Fleseriu, M. (2013). Self-perception of cognitive function among patients with active acromegaly, controlled acromegaly, and non-functional pituitary adenoma: a pilot study. *Endocrine,* doi:10.1007/s12020-013-0106-9

Pituitary adenomas (PAs) represent 15 % of all brain tumors. One-sixth of these are reported to cause acromegaly via excess growth hormone secretion. These tumors have been associated with multiple comorbidities, including neuropsychiatric and cognitive dysfunction. We aimed to assess patient perception of cognitive deficits and the relationship of cognitive changes to active acromegaly (AA) versus controlled acromegaly (CA) versus non-functional PAs (NFPA). A modified FACT-Cog survey was used, which focused on the prevalence and severity of perceived dysfunction in five areas of cognitive function: ability to learn, concentration/distractibility, mental agility, memory and recall, and verbal recall. Patient perception of current health and health change over the previous 12 months was also assessed. The overall perceived prevalence and severity of cognitive dysfunction were the highest among NFPA groups, particularly in the areas of mental agility, verbal recall, and memory/recall. Patients with AA reported greater prevalence and severity of dysfunction with respect to concentration/distractibility and ability to learn. Patients with AA reported the best overall current health, though patients with CA reported the greatest improvement in health over the previous year. These findings may indicate that PAs can affect cognitive function regardless of whether excess growth hormone is present. Acromegaly and NFPA patients perceive specific areas of cognitive dysfunction that may require further evaluation and treatment. Further research may be useful regarding patient quality of life, patient functionality during normal daily activities, and perceived dysfunction despite biological disease control.

Yeh, S., & Rosenbaum, J. T. (2012). *Ophthalmic Risks and Complications Associated with the Treatment of Systemic Vasculitis* Wiley-Blackwell. doi:10.1002/9781118355244.ch45

A number of medications used to treat autoimmune systemic vasculitis may lead to ophthalmic complications. Long-term corticosteroid use may lead to cataract, glaucoma or, rarely, central serous chorioretinopathy. Corticosteroid-sparing immunosuppressive medications, particularly cyclophosphamide and/or the biologic agents, may lead to opportunistic eye infections including CMV retinitis, progressive outer retinal necrosis and fungal chorioretinitis due to fungemia. Other medications such as hydroxychloroquine and chloroquine may result in a distinct maculopathy, which may lead to central and paracentral visual loss and loss of color vision. Other medications

including rifabutin, which causes uveitis, and bisphosphonates, which may lead to uveitis and scleritis, are also discussed in this chapter. © 2012 Blackwell Publishing Ltd.

Zaidat, O. O., Castonguay, A. C., Fitzsimmons, B. -., Woodward, B. K., Wang, Z., Killer-Oberpfalzer, M., . . . Gress, D. R. (2013). Design of the vitesse intracranial stent study for ischemic therapy (VISSIT) trial in symptomatic intracranial stenosis. *Journal of Stroke and Cerebrovascular Diseases, 22*(7), 1131-1139. doi:10.1016/j.jstrokecerebrovasdis.2012.10.021
Background: Patients with high-grade symptomatic intracranial stenosis (≥70%) have an increased risk of recurrent stroke despite medical treatment with antiplatelet or anticoagulant therapy. Intracranial stenting has been proposed as a viable treatment option for this high-risk patient population; however, evaluation of this therapy in randomized multicenter trials is needed. In this article, we present the design and methods of the Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) trial for symptomatic intracranial stenosis. Methods: The VISSIT trial is a randomized control study designed to evaluate the safety, probable benefit, and effectiveness of the PHAROS Vitesse neurovascular balloon-expandable stent system plus medical therapy versus medical therapy alone in patients with cerebral or retinal ischemia due to neurovascular stenosis (≥70%) for preventing the primary composite end point: stroke in the same territory (distal to the target lesion) as the presenting event within 12 months of randomization or hard transient ischemic attack in the same territory (distal to the target lesion) as the presenting event from day 2 through month 12 postrandomization. Results: Enrollment began in February 2009 and was halted in January 2012 with 112 subjects enrolled into the study. Clinical follow-up will continue for the planned period of 12 months postrandomization. Conclusions: The VISSIT trial may provide valuable insight into the use of balloon-expandable intracranial stent as a treatment option for high-risk patients. Lessons learned from this trial may better guide future clinical trial design on best patient selection, stenting techniques, and periprocedural management. © 2013 by National Stroke Association.

Zhang, W., Cheng, J., Vagnerova, K., Ivashkova, Y., Young, J., Cornea, A., . . . Brambrink, A. M. (2013). Effects of Androgens on Early Post-ischemic Neurogenesis in Mice. *Translational Stroke Research,* , 1-11. doi:10.1007/s12975-013-0298-6

Although androgens are reported to affect stroke outcomes by altering ischemic tissue damage, their effect on post-injury repair is unknown. Since neurogenesis has recently been recognized as contributing to stroke outcomes, we investigated the role of androgens on stroke-induced neurogenesis. Adult male mice were subjected to transient middle cerebral artery occlusion (MCAO) and neurogenesis was examined 1 week later by quantifying BrdU/doublecortin-positive and BrdU/NeuN-positive neurons in brain germinal regions as well as the injured striatum. To elucidate the role of endogenous androgens, post-MCAO neurogenesis was examined in gonadally intact males, intact males implanted with the androgen receptor antagonist flutamide, and surgically castrated males. Surgical castration or pharmacologic androgen receptor blockade had no effects on post-ischemic neurogenesis, except that continuous androgen receptor blockade unexpectedly suppressed maturation of newborn neurons (BrdU/NeuN-positive cells) in the dentate gyrus. Post-MCAO neurogenesis was also examined in surgically castrated mice treated with continuous release implants containing testosterone or dihydrotestosterone (DHT). Testosterone and DHT robustly inhibited post-ischemic neurogenesis in the dentate gyrus, and the more potent androgen DHT virtually abolished the presence of immature newborn neurons (BrdU/doublecortin-positive cells) in the injured striatum. Our data suggest that endogenous androgens do not alter post-stroke neurogenesis quantitatively, but the presence of supra-physiological androgen stimulation profoundly suppresses early neurogenesis in germinal brain areas and reduces cellular repair in injured tissue after cerebral ischemia. These results advance the understanding of the role that androgens play in stroke outcomes.

Zhang, Z., Liu, Q., Leskov, K. S., Wu, X., Duan, J., Zhang, G. L., . . . Rosenbaum, J. T. (2013). Roscovitine Suppresses CD4+ T Cells and T Cell-Mediated Experimental Uveitis. *PloS One, 8*(11), e81154. doi:10.1371/journal.pone.0081154; 10.1371/journal.pone.0081154

BACKGROUND: T cells are essential for the development of uveitis and other autoimmune diseases. After initial activation, CD4+ lymphocytes express the co-stimulatory molecule OX40 that plays an important role in T cell proliferation. Cyclin dependent kinase 2 (CdK2) plays a pivotal role in the cell cycle transition from G1 to S phase. In addition, recent research has implicated CdK2 in T cell activation. Thus, we sought to test the immunosuppressive effect of

roscovitine, a potent CdK2 inhibitor, on CD4+ T cell activation, proliferation, and function. DESIGN AND METHODS: Mouse CD4+ T cells were activated by anti-CD3 and anti-CD28 antibodies. The expression of OX40, CD44, and CdK2 were analyzed by flow cytometry. In addition, cell cycle progression and apoptosis of control and roscovitine-treated T lymphocytes were measured by BrdU incorporation and annexin V assay, respectively. Furthermore, the immunoregulatory effect of roscovitine was evaluated in both ovalbumin-induced uveitis and experimental autoimmune uveitis (EAU) models. RESULTS: In this study, we found that T cell activation induced OX40 expression. Cell cycle analysis showed that more CD4+OX40+ cells entered S phase than OX40- T cells. Concurrently, CD4+OX40+ cells had a higher level of CdK2 expression. Roscovitine treatment blocked activated CD4+ cells from entering S phase. In addition, roscovitine not only reduced the viability of CD4+ lymphocytes but also suppressed T cell activation and cytokine production. Finally, roscovitine significantly attenuated the severity of T cell-dependent, OX40-enhanced uveitis. CONCLUSION: These results implicate CdK2 in OX40-augmented T cell response and expansion. Furthermore, this study suggests that roscovitine is a novel, promising, therapeutic agent for treating T cell-mediated diseases such as uveitis.

Zheng, J. -., Arnett, D. K., Lee, Y. -., Shen, J., Parnell, L. D., Smith, C. E., . . . Lai, C. -. (2013). Genome-Wide Contribution of Genotype by Environment Interaction to Variation of Diabetes-Related Traits. *Plos One, 8*(10) doi:10.1371/journal.pone.0077442

While genome-wide association studies (GWAS) and candidate gene approaches have identified many genetic variants that contribute to disease risk as main effects, the impact of genotype by environment (GxE) interactions remains rather under-surveyed. To explore the importance of GxE interactions for diabetes-related traits, a tool for Genome-wide Complex Trait Analysis (GCTA) was used to examine GxE variance contribution of 15 macronutrients and lifestyle to the total phenotypic variance of diabetes-related traits at the genome-wide level in a European American population. GCTA identified two key environmental factors making significant contributions to the GxE variance for diabetes-related traits: carbohydrate for fasting insulin (25.1% of total variance, P-nominal = 0.032) and homeostasis model assessment of insulin resistance (HOMA-IR) (24.2% of total variance, P-nominal = 0.035), n-6 polyunsaturated fatty acid (PUFA) for HOMA-β-cell-function (39.0% of total variance, P-nominal = 0.005). To

demonstrate and support the results from GCTA, a GxE GWAS was conducted with each of the significant dietary factors and a control E factor (dietary protein), which contributed a non-significant GxE variance. We observed that GxE GWAS for the environmental factor contributing a significant GxE variance yielded more significant SNPs than the control factor. For each trait, we selected all significant SNPs produced from GxE GWAS, and conducted anew the GCTA to estimate the variance they contributed. We noted the variance contributed by these SNPs is higher than that of the control. In conclusion, we utilized a novel method that demonstrates the importance of genome-wide GxE interactions in explaining the variance of diabetes-related traits.

Zick, S. M., Zwickey, H., Wood, L., Foerster, B., Khabir, T., Wright, B., . . . Harris, R. E. (2013). Preliminary differences in peripheral immune markers and brain metabolites between fatigued and non-fatigued breast cancer survivors: a pilot study. *Brain Imaging and Behavior,* , 1-11. doi:10.1007/s11682-013-9270-z

Persistent cancer-related fatigue (PCRF) is one of the most troubling side-effects of breast cancer (BC) treatment. One explanatory model for PCRF is sickness behavior, which is a set of adaptive responses including sleepiness and depressed mood in reaction to an inflammatory trigger. Prior research has investigated differences in inflammatory cytokines between fatigued and non-fatigued BC survivors, but no study has examined differences in brain metabolites. Differences in inflammatory markers, and brain metabolites using proton magnetic resonance spectroscopy were evaluated within 16 fatigued and 13 non-fatigued BC survivors. Fatigued BC survivors had significantly higher ratios of two markers derived from brain metabolites; namely (a) creatine, normalized to total creatine (creatine + phosphocreatine (Cr/tCr)) ratio (P = 0.03) and (b) glutamate + glutamine (Glx) to N-acetyl-aspartate (NAA) ratio (P = 0.01) in the posterior insula compared to non-fatigued breast cancer survivor. Further, serum IL-6 was increased in fatigued women compared to non-fatigued women (P = 0.03), Using receiver operator curves (ROC) we determined that the posterior insula Glx/NAA ratio was the best predictor of fatigue with an overall area under the receiver operating characteristic curve (AUROC) of 79 %, with a sensitivity of 81 % and a specificity of 69 %. However, posterior insula Glx/NAA, Cr/tCr and serum IL-6 were not significantly correlated with one another implying the possibility of independent biological mechanisms for PCRF rather than an interrelated mechanism as represented by the

sickness behavior model. This study provides novel preliminary evidence of several distinct neurobiological changes in the posterior insula associated with PCRF in BC survivors. Future, longitudinal studies are needed to explore these distinct biological phenomena where changes through time in peripheral immune markers and brain metabolites are examined to determine if they correlate with changes in fatigue.