

## References

Acar, F., Ozdemir, M., Bayrakli, F., Cirak, B., Coskun, E., & Burchiel, K. (2013). Management of medically intractable genitofemoral and ilioinguinal neuralgia. *Turkish Neurosurgery*, 23(6), 753-757.

Aim: To evaluate the effectiveness of invasive procedures in medically intractable genitofemoral and ilioinguinal neuralgia. Material and Methods: This is a prospective study of 20 patients with genitofemoral and ilioinguinal neuralgias who were treated at our medical center between 2007 and 2011. Genitofemoral and ilioinguinal nerve blocks were performed in all cases after medical treatment had failed to alleviate the patients' pain. Neurectomy was performed for the patients whose pain did not improve. Patient histories, physical examinations and visual analogue scale scores before and after treatments were analyzed. Results: Fourteen (70%) of the patients were treated with nerve blocks and six (30%) of the patients whose pain did not improve with nerve block application underwent neurectomy which resulted in pain relief. Conclusion: For patients with medically intractable genitofemoral and ilioinguinal neuralgias, nerve blocks and neurectomies can be applied safely for pain control.

Acott, T. S., Kelley, M. J., Keller, K. E., Vranka, J. A., Abu-Hassan, D. W., Li, X., et al. (2014).

Intraocular pressure homeostasis: Maintaining balance in a high-pressure environment. *Journal of Ocular Pharmacology and Therapeutics : The Official Journal of the Association for Ocular Pharmacology and Therapeutics*,

Abstract Although glaucoma is a relatively common blinding disease, most people do not develop glaucoma. A robust intraocular pressure (IOP) homeostatic mechanism keeps ocular pressures within relatively narrow acceptable bounds throughout most peoples' lives. The trabecular meshwork and/or Schlemm's canal inner wall cells respond to sustained IOP elevation and adjust the aqueous humor outflow resistance to restore IOP to acceptable levels. It appears that the cells sense IOP elevations as mechanical stretch or distortion of the actual outflow resistance and respond by initiating a complex extracellular matrix (ECM) turnover process that takes several days to complete. Although considerable information pertinent to this process is available, many aspects of the IOP homeostatic process remain to be elucidated. Components and mechanisms beyond ECM turnover could also be relevant to IOP homeostasis, but will not be addressed in

detail here. Known aspects of the IOP homeostasis process as well as possible ways that it might function and impact glaucoma are discussed.

Adachi, K., Enoki, T., Kawano, Y., Veraz, M., & Nakai, H. (2014). Drawing a high-resolution functional map of adeno-associated virus capsid by massively parallel sequencing. *Nature Communications*, 5, 3075.

Adeno-associated virus (AAV) capsid engineering is an emerging approach to advance gene therapy. However, a systematic analysis on how each capsid amino acid contributes to multiple functions remains challenging. Here we show proof-of-principle and successful application of a novel approach, termed AAV Barcode-Seq, that allows us to characterize phenotypes of hundreds of different AAV strains in a high-throughput manner and therefore overcomes technical difficulties in the systematic analysis. In this approach, we generate DNA barcode-tagged AAV libraries and determine a spectrum of phenotypes of each AAV strain by Illumina barcode sequencing. By applying this method to AAV capsid mutant libraries tagged with DNA barcodes, we can draw a high-resolution map of AAV capsid amino acids important for the structural integrity and functions including receptor binding, tropism, neutralization and blood clearance. Thus, Barcode-Seq provides a new tool to generate a valuable resource for virus and gene therapy research.

Agarwal, A., Mackenzie, R. J., Pippa, R., Eide, C. A., Oddo, J., Tyner, J. W., et al. (2014). Antagonism of SET using OP449 enhances the efficacy of tyrosine kinase inhibitors and overcomes drug resistance in myeloid leukemia. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

PURPOSE: The SET oncoprotein, a potent inhibitor of the protein phosphatase 2A (PP2A), is overexpressed in leukemia. We evaluated the efficacy of SET antagonism in chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) cell lines, a murine leukemia model, and primary patient samples using OP449, a specific, cell-penetrating peptide that antagonizes SET's inhibition of PP2A. EXPERIMENTAL DESIGN: In vitro cytotoxicity and specificity of OP449 in CML and AML cell lines and primary samples were measured using proliferation, apoptosis and colonogenic assays. Efficacy of target inhibition by OP449 is evaluated by immunoblotting and

PP2A assay. In vivo antitumor efficacy of OP449 was measured in human HL-60 xenografted murine model. RESULTS: We observed that OP449 inhibited growth of CML cells including those from patients with blastic phase disease and patients harboring highly drug-resistant BCR-ABL1 mutations. Combined treatment with OP449 and ABL1 tyrosine kinase inhibitors was significantly more cytotoxic to K562 cells and primary CD34+ CML cells. SET protein levels remained unchanged with OP449 treatment, but BCR-ABL1-mediated downstream signaling was significantly inhibited with the degradation of key signaling molecules such as BCR-ABL1, STAT5, and AKT. Similarly, AML cell lines and primary patient samples with various genetic lesions showed inhibition of cell growth after treatment with OP449 alone or in combination with respective kinase inhibitors. Finally, OP449 reduced the tumor burden of mice xenografted with human leukemia cells. CONCLUSIONS: We demonstrate a novel therapeutic paradigm of SET antagonism using OP449 in combination with tyrosine kinase inhibitors for the treatment of CML and AML.

Aicher, S. A., Hegarty, D. M., & Hermes, S. M. (2014). Corneal pain activates a trigemino-parabrachial pathway in rats. *Brain Research*,

Corneal pain is mediated by primary afferent fibers projecting to the dorsal horn of the medulla, specifically the trigeminal nucleus caudalis. In contrast to reflex responses, the conscious perception of pain requires transmission of neural activity to higher brain centers. Ascending pain transmission is mediated primarily by pathways to either the thalamus or parabrachial nuclei. We previously showed that some corneal afferent fibers preferentially contact parabrachial-projecting neurons in the rostral pole of the trigeminal nucleus caudalis, but the role of these projection neurons in transmitting noxious information from the cornea has not been established. In the present study, we show that noxious stimulation of the corneal surface activates neurons in the rostral pole of the nucleus caudalis, including parabrachially projecting neurons that receive direct input from corneal afferent fibers. We used immunocytochemical detection of c-Fos protein as an index of neuronal activation after noxious ocular stimulation. Animals had previously received injections of a retrograde tracer into either thalamic or parabrachial nuclei to identify projection neurons in the trigeminal dorsal horn. Noxious stimulation of the cornea induced c-Fos in neurons sending projections to parabrachial nuclei, but not thalamic nuclei. We also confirmed that

corneal afferent fibers identified with cholera toxin B preferentially target trigeminal dorsal horn neurons projecting to the parabrachial nucleus. The parabrachial region sends ascending projections to brain regions involved in emotional and homeostatic responses. Activation of the ascending parabrachial system may explain the extraordinary salience of stimulation of corneal nociceptors.

Aktas, R. G., Kayton, R. J., Caglar, M., & Oktayer, A. G. (2013). Quantitative analysis of immunogold labeling for basic fibroblast growth factor according to the activational stages of mast cells. *Analytical and Quantitative Cytology and Histology*, 35(6), 306-315.

OBJECTIVE: To analyze whether immunogold labeling density for basic fibroblastic growth factor in granules is compatible with the activation stage of mast cells. STUDY DESIGN: Cytoplasmic features and granules of 46 mast cells were examined at the ultrastructural level. The cells were classified according to their activation stage, namely, whether resting, initially activated, fully degranulated or piecemeal degranulated. Granules were classified as electron lucent, moderate or dense granules. Gold particles per secretory granules in the cells were counted. Recently described quantitative analysis techniques were used for evaluation. RESULTS: There is a statistically meaningful relationship between the activation stage of mast cells and their immunogold labeling density. The number of different types of granules encountered in a cell depends on the type of the cell. The distribution of gold particles among the secretory granules depends upon the cell. The type of granule does not have an individual effect on the number of particles, as indicated by an overall statistical analysis of granules, cells and their interaction effects. CONCLUSION: A count of gold particles in the cells can be used as a strong biological indicator. Therefore the number of gold particles might be very useful for comparative studies related to the secretion of this growth factor under different conditions. © Science Printers and Publishers, Inc.

Allemann, N., Coleman, D. J., Pavlin, C. J., & Huang, D. (2013). Imaging the anterior segment: High-frequency ultrasound and anterior segment OCT. *Journal of Ophthalmology*, 2013, 398715.

Alonso, E., Gonzalez-Otero, D., Aramendi, E., de Gauna, S. R., Ruiz, J., Ayala, U., et al. (2014). Can thoracic impedance monitor the depth of chest compressions during out-of-hospital

cardiopulmonary resuscitation? *Resuscitation*,

AIM: To analyze the relationship between the depth of the chest compressions and the fluctuation caused in the thoracic impedance (TI) signal in out-of-hospital cardiac arrest (OHCA). The ultimate goal was to evaluate whether it is possible to identify compressions with inadequate depth using information of the TI waveform. METHODS: 60 OHCA episodes were extracted, one per patient, containing both compression depth (CD) and TI signals. Every 5s the mean value of the maxima of the CD, Dmax, and three features characterizing the fluctuations caused by the compressions in the TI waveform (peak-to-peak amplitude, area and curve length) were computed. The linear relationship between Dmax and the TI features was tested using Pearson correlation coefficient (r) and univariate linear regression for the whole population, for each patient independently, and for series of compressions provided by a single rescuer. The power of the three TI features to classify each 5s-epoch as shallow/non-shallow was evaluated in terms of area under the curve, sensitivity and specificity. RESULTS: The r was 0.34, 0.36 and 0.37 for peak-to-peak amplitude, area and curve length respectively when the whole population was analyzed. Within patients the median r was 0.40, 0.43 and 0.47, respectively. The analysis of the series of compressions yielded a median r of 0.81 between Dmax and the peak-to-peak amplitude, but it decreased to 0.47 when all the series were considered jointly. The classifier based on the TI features showed 90.0%/37.1% and 86.2%/43.5% sensitivity/specificity values, and an area under the curve of 0.75 and 0.71 for the training and test set respectively. CONCLUSION: Low linearity between CD and TI was noted in OHCA episodes involving multiple rescuers. Our findings suggest that TI is unreliable as a predictor of Dmax and inaccurate in detecting shallow compressions.

Alt, J. A., Mace, J. C., Buniel, M. C., Soler, Z. M., & Smith, T. L. (2014). Predictors of olfactory dysfunction in rhinosinusitis using the brief smell identification test. *The Laryngoscope*, Objective: Associations between olfactory function to quality-of-life (QOL) and disease severity in patients with rhinosinusitis is poorly understood. We sought to evaluate and compare olfactory function between subgroups of patients with rhinosinusitis using the Brief Smell Identification Test (BSIT). Study Design: Cross-sectional evaluation of a multi-center cohort. Methods: Patients with recurrent acute sinusitis (RARS) and chronic rhinosinusitis (CRS) with and without nasal

polyposis were prospectively enrolled from three academic tertiary care sites. Each subject completed the BSIT, in addition to measures of disease-specific QOL. Patient demographics, comorbidities, and clinical measures of disease severity were compared between patients with normal (BSIT;  $\geq 9$ ) and abnormal (BSIT;  $< 9$ ) olfaction scores. Regression modeling was used to identify potential risk factors associated with olfactory impairment. Results: Patients with rhinosinusitis (n=445) were found to suffer olfactory dysfunction as measured by the BSIT (28.3%). Subgroups of rhinosinusitis differed in the degree of olfactory dysfunction reported. Worse disease severity, measured by computed tomography and nasal endoscopy, correlated to worse olfaction. Olfactory scores did not consistently correlate with Rhinosinusitis Disability Index or Sinonasal Outcome Test scores. Regression models demonstrated nasal polyposis was the strongest predictor of olfactory dysfunction. Recalcitrant disease and aspirin intolerance were strongly predictive of worse olfactory function. Conclusion: Olfactory dysfunction is a complex, multi-factorial process found to be differentially expressed within subgroups of rhinosinusitis. Olfaction was associated with disease severity as measured by imaging and endoscopy, with only weak associations to disease-specific QOL measures.

Ambert, K. H., Cohen, A. M., Burns, G. A., Boudreau, E., & Sonmez, K. (2013). Virk: An active learning-based system for bootstrapping knowledge base development in the neurosciences. *Frontiers in Neuroinformatics*, 7, 38.

The frequency and volume of newly-published scientific literature is quickly making manual maintenance of publicly-available databases of primary data unrealistic and costly. Although machine learning (ML) can be useful for developing automated approaches to identifying scientific publications containing relevant information for a database, developing such tools necessitates manually annotating an unrealistic number of documents. One approach to this problem, active learning (AL), builds classification models by iteratively identifying documents that provide the most information to a classifier. Although this approach has been shown to be effective for related problems, in the context of scientific databases curation, it falls short. We present Virk, an AL system that, while being trained, simultaneously learns a classification model and identifies documents having information of interest for a knowledge base. Our approach uses a support vector machine (SVM) classifier with input features derived from neuroscience-related

publications from the primary literature. Using our approach, we were able to increase the size of the Neuron Registry, a knowledge base of neuron-related information, by a factor of 90%, a knowledge base of neuron-related information, in 3 months. Using standard biocuration methods, it would have taken between 1 and 2 years to make the same number of contributions to the Neuron Registry. Here, we describe the system pipeline in detail, and evaluate its performance against other approaches to sampling in AL.

Azevedo, A., Oliveira, A., Fortunato, A. B., Zhang, J., & Baptista, A. M. (2014). A cross-scale numerical modeling system for management support of oil spill accidents. *Marine Pollution Bulletin*,

A flexible 2D/3D oil spill modeling system addressing the distinct nature of the surface and water column fluids, major oil weathering and improved retention/reposition processes in coastal zones is presented. The system integrates hydrodynamic, transport and oil weathering modules, which can be combined to offer different-complexity descriptions as required by applications across the river-to-ocean continuum. Features include accounting for different composition and rheology in the surface and water column mixtures, as well as spreading, evaporation, water-in-oil emulsification, shoreline retention, dispersion and dissolution. The use of unstructured grids provides flexibility and efficiency in handling spills in complex geometries and across scales. The use of high-order Eulerian-Lagrangian methods allows for computational efficiency and for handling key processes in ways consistent with their distinct mathematical nature and time scales. The modeling system is tested through a suite of synthetic, laboratory and realistic-domain benchmarks, which demonstrate robust handling of key processes and of 2D/3D couplings. The application of the modeling system to a spill scenario at the entrance of a port in a coastal lagoon illustrates the power of the approach to represent spills that occur in coastal regions with complex boundaries and bathymetry.

Bair-Merritt, M. H., Lewis-O'Connor, A., Goel, S., Amato, P., Ismailji, T., Jelley, M., et al. (2014).

Primary care-based interventions for intimate partner violence: A systematic review. *American Journal of Preventive Medicine*, 46(2), 188-194.

CONTEXT: Primary care providers are uniquely positioned to respond to patients' disclosure of

intimate partner violence (IPV). However, the research on primary care-based IPV interventions has not been systematically synthesized, making it difficult for providers, policymakers, and researchers to understand how to effectively intervene in the primary care setting. This systematic review summarizes primary care-based interventions for patients experiencing IPV. EVIDENCE ACQUISITION: PubMed, PsycINFO, and CINAHL were searched from their start through September 2012; this search was augmented by bibliographic review and consultation with experts. Eligible studies included English-language, peer-reviewed articles that assessed patient-level impact of IPV interventions that originated from patients' visits to a primary care provider. EVIDENCE SYNTHESIS: Of 80 potentially eligible studies, 17 met eligibility criteria. The majority of interventions recruited women from reproductive care sites. Interventions tended to be brief, delivered by nonphysicians, and focused on empowerment, empathetic listening, discussion of the cycle of violence and safety, and referral to community-based resources. Thirteen studies demonstrated at least one intervention-related benefit. Six of 11 articles measuring IPV persistence found reductions in future violence; two of five measuring safety-promoting behaviors found increases; and six of ten measuring IPV/community resource referrals found enhanced use. Some studies also documented health improvements. CONCLUSIONS: The majority of studies demonstrated patient-level benefit subsequent to primary care IPV interventions, with IPV/community referrals the most common positively affected outcome.

Ballesteros-Merino, C., Watanabe, M., Shigemoto, R., Fukazawa, Y., Adelman, J. P., & Luján, R. (2014). Differential subcellular localization of SK3-containing channels in the hippocampus.

*European Journal of Neuroscience,*

Small-conductance, Ca<sup>2+</sup>-activated K<sup>+</sup> (SK) channels are expressed in the hippocampus where they regulate synaptic responses, plasticity, and learning and memory. To investigate the expression of SK3 (KCNN3) subunits, we determined the developmental profile and subcellular distribution of SK3 in the developing mouse hippocampus using western blots, immunohistochemistry and high-resolution immunoelectron microscopy. The results showed that SK3 expression increased during postnatal development, and that the localization of SK3 changed from being mainly associated with the endoplasmic reticulum and intracellular sites during the first postnatal week to being progressively concentrated in dendritic spines during later stages. In

the adult, SK3 was localized mainly in postsynaptic compartments, both at extrasynaptic sites and along the postsynaptic density of excitatory synapses. Double labelling showed that SK3 co-localized with SK2 (KCNN2) and with N-methyl-D-aspartate receptors. Finally, quantitative analysis of SK3 density revealed two subcellular distribution patterns in different hippocampal layers, with SK3 being unevenly distributed in CA1 region of the hippocampus pyramidal cells and homogeneously distributed in dentate gyrus granule cells. Our results revealed a complex cell surface distribution of SK3-containing channels and a distinct developmental program that may influence different hippocampal functions. © 2014 Federation of European Neuroscience Societies and John Wiley & Sons Ltd.

Barewal, R. M., Stanford, C., & Weesner, T. C. (2012). A randomized controlled clinical trial comparing the effects of three loading protocols on dental implant stability. *The International Journal of Oral & Maxillofacial Implants*, 27(4), 945-956.

**PURPOSE:** The primary goal of this stratified randomized controlled trial (SRCT) was to compare the stability of dental implants placed under three different loading regimens during the first 16 weeks of healing following implant placement. Implants were loaded immediately, early (6 weeks), or with conventional/delayed timing (12 weeks). Secondary outcomes were to compare marginal bone adaptation for 3 years after placement. **MATERIALS AND METHODS:** Single posterior implant sites in the maxilla or mandible were examined. The insertion torque value was the primary determinant of load assignment. Resonance frequency analysis was performed at follow-up appointments for the first 16 weeks (with results provided as implant stability quotients [ISQs]). Marginal bone levels were assessed via radiographs. **RESULTS:** Forty patients each received a single 4.0-mm diameter dental implant between 2004 and 2007. One implant failure occurred in Lekholm and Zarb type 4 bone with insertion torque value (ITV) of < 8.1 Ncm; the cumulative success rate was 97.5%. All implants, when classified by bone and loading type, increased in stability over time, with a minor reduction of 1.3 ISQ units seen at 4 weeks in the immediate loading group. The mean marginal bone loss over 3 years was 0.22 mm. The mean ITVs at implant placement for bone types 1 and 2 (grouped together), 3, and 4 were 32, 17, and 10, respectively, and were significantly different ( $P < .05$ ). **CONCLUSIONS:** ITV was a good objective measure of bone type. Using an ITV of 20 Ncm as the determinant for immediate

loading and an ITV of 10 Ncm or greater as the determinant for early loading provided long-term success for this implant and led to no negative changes in tissue response. All bone type groups and loading groups showed no reduction in stability during the first 4 months of healing.

Bargo, P. R., Jacques, S. L., & Prael, S. A. (2012). Validation of a monte carlo model for determination of fluorophore concentration on scattering media. *Biomedical Optics, BIOMED 2012*, Miami, FL. Experimental validation of a Monte Carlo code for correcting the effect of optical properties on fluorescence measurements is presented. The error for predicting true concentration was 4% and 10% for absorbing-only and turbid samples, respectively. © OSA 2012.

Bayestehtashk, A., & Shafran, I. (2013). Parsimonious multivariate copula model for density estimation. *2013 38th IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2013*, Vancouver, BC. pp. 5750-5754.

The most common approaches for estimating multivariate density assume a parametric form for the joint distribution. The choice of this parametric form imposes constraints on the marginal distributions. Copula models disentangle the choice of marginals from the joint distributions, making it a powerful model for multivariate density estimation. However, so far, they have been widely studied mostly for low dimensional multivariate. In this paper, we investigate a popular Copula model - the Gaussian Copula model - for high dimensional settings. They however require estimation of a full correlation matrix which can cause data scarcity in this setting. One approach to address this problem is to impose constraints on the parameter space. In this paper, we present Toeplitz correlation structure to reduce the number of Gaussian Copula parameter. To increase the flexibility of our model, we also introduce mixture of Gaussian Copula as a natural extension of the Gaussian Copula model. Through empirical evaluation of likelihood on held-out data, we study the trade-off between correlation constraints and mixture flexibility, and report results on wine data sets from the UCI Repository as well as our corpus of monkey vocalizations. We find that mixture of Gaussian Copula with Toeplitz correlation structure models the data consistently better than Gaussian mixture models with equivalent number of parameters. © 2013 IEEE.

Bess, S., Line, B. G., Lafage, V., Schwab, F., Shaffrey, C. I., Hart, R. A., et al. (2014). Does recombinant human bone morphogenetic protein-2 use in adult spinal deformity increase complications and are complications associated with location of rhBMP-2 use? A prospective, multicenter study of 279 consecutive patients. *Spine*, 39(3), 233-242.

STUDY DESIGN: Multicenter, prospective analysis of consecutive patients with adult spinal deformity (ASD). OBJECTIVE: Evaluate complications associated with recombinant human bone morphogenetic protein-2 (rhBMP-2) use in ASD. SUMMARY OF BACKGROUND DATA: Off-label rhBMP-2 use is common; however, underreporting of rhBMP-2 associated complications has been recently scrutinized. METHODS: Patients with ASD consecutively enrolled into a prospective, multicenter database were evaluated for type and timing of acute perioperative complications. Inclusion criteria: age 18 years and older, ASD, spinal arthrodesis of more than 4 levels, and 3 or more months of follow-up. Patients were 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: A total of 279 patients (mean age: 57 yr; mean spinal levels fused: 12.0; and mean follow-up: 28.8 mo) 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 min), more osteotomies per patient (4.0 vs. 1.6), and greater percentage of anteroposterior fusion (APSF; 20.9% vs. 8.4%) than NOBMP, respectively (P 0.05). Multivariate analysis demonstrated small to nonexistent correlations between rhBMP-2 use and complications. CONCLUSION: RhBMP-2 use and location of rhBMP-2 use in ASD surgery, at reported doses, do not increase acute major, neurological, or wound complications. Research is needed for higher rhBMP-2 dosing and long-term follow-up. Level of Evidence: 2.

Bice, J. B., Leechawengwongs, E., & Montanaro, A. (2014). Biologic targeted therapy in allergic asthma. *Annals of Allergy, Asthma & Immunology : Official Publication of the American College of*

*Allergy, Asthma, & Immunology, 112(2), 108-115.*

**OBJECTIVE:** To review the structure, function, clinical utility, and safety of current biologic targeted therapies being used for the treatment of asthma. **DATA SOURCES:** Medical literature obtained from PubMed and OVID searches from June to November 2013. **STUDY SELECTIONS:** Studies were selected based on article impact, relevance, and clinical significance. Particular emphasis was placed on articles discussing therapies targeted at IgE, interleukin (IL)-4, IL-4 receptor, IL-5, IL-13, tumor necrosis factor-alpha, CRTh2, and toll-like receptors 7 and 9. **RESULTS:** Since the approval of omalizumab in 2003, the development of biologic asthma therapies has grown at a remarkable pace. With approximately 30 drugs currently in clinical trials and dozens more in development, the future of asthma biologic therapies is promising. Despite several well-publicized setbacks, researchers remain focused on elucidating the complex pathophysiology of asthma. The hope is that asthma biologic therapies will eventually be tailored to an individual's asthma phenotype. With more than 300 million people worldwide affected by asthma and with roughly 5% to 10% of this population living with severe, uncontrolled asthma, the need for new biologic therapies is great. **CONCLUSION:** The introduction of each new biologic therapy into clinical trials has been associated with great anticipation, but the outcome of these trials, in many cases, has led to disappointment. Given the lack of overwhelming positive responses, these results have emphasized that asthma is a complex clinical syndrome with multiple underlying genotypes and clinical phenotypes. It has become abundantly clear that it is very unlikely that there is one "magic bullet" to cure all patients with asthma.

Blum, W. F., Deal, C., Zimmermann, A. G., Shavrikova, E. P., Child, C. J., Quigley, C. A., et al. (2014). Development of additional pituitary hormone deficiencies in pediatric patients originally diagnosed with idiopathic isolated GH deficiency. *European Journal of Endocrinology, 170(1), 13-21.*

**Objective:** We assessed the characteristics of children initially diagnosed with idiopathic isolated GH deficiency (IGHD) who later developed additional (multiple) pituitary hormone deficiencies (MPHD). **Design:** Data were analyzed for 5805 pediatric patients with idiopathic IGHD, who were GH-naïve at baseline and GH-treated in the multinational, observational Genetics and Neuroendocrinology of Short Stature International Study. **Methods:** Development of MPHD was

assessed from investigator diagnoses, adverse events, and concomitant medications. Analyses were performed for all patients and for those who developed MPHD within 4.5 years or had  $\geq 3.5$  years, follow-up and continued to have IGHD (4-year cohort). Results: MPHD developed in 118/5805 (2.0%) children overall, and in 96/1757 (5.5%) in the 4-year cohort. Patients who developed MPHD had more profound GHD, with decreased height SDS, IGF1 SDS and peak stimulated GH, and greater height decrement vs target, compared with children who continued to have IGHD ( $P < 0.001$  for each variable). Delivery complications, congenital anomalies, and perinatal/neonatal adverse events occurred more frequently in patients who developed MPHD. The most frequent additional deficiency was TSH (82 patients overall); four patients developed two pituitary hormone deficiencies and one developed three deficiencies. Multivariable logistic regression indicated that years of follow-up (odds ratio 1.55), baseline age (1.17), baseline height SDS (0.69), and peak stimulated GH (0.64) were associated with the development of MPHD. Conclusions: MPHD is more likely to develop in patients with more severe idiopathic IGHD. Older baseline age, lower baseline height SDS, and longer follow-up duration are associated with increased risk of development of MPHD. © 2014 European Society of Endocrinology.

Bodhankar, S., Chen, Y., Vandembark, A. A., Murphy, S. J., & Offner, H. (2013). Treatment of experimental stroke with IL-10-producing B-cells reduces infarct size and peripheral and CNS inflammation in wild-type B-cell-sufficient mice. *Metabolic Brain Disease*, , 1-15.

Clinical stroke induces inflammatory processes leading to cerebral and splenic injury and profound peripheral immunosuppression. IL-10 expression is elevated during major CNS diseases and limits inflammation in the brain. Recent evidence demonstrated that absence of B-cells led to larger infarct volumes and CNS damage after middle cerebral artery occlusion (MCAO) that could be prevented by transfer of IL-10+ B-cells. The purpose of this study was to determine if the beneficial immunoregulatory effects on MCAO of the IL-10+ B-cell subpopulation also extends to B-cell-sufficient mice that would better represent stroke subjects. CNS inflammation and infarct volumes were evaluated in male C57BL/6J (WT) mice that received either RPMI or IL-10+ B-cells and underwent 60 min of middle cerebral artery occlusion (MCAO) followed by 96 h of reperfusion. Transfer of IL-10+ B-cells markedly reduced infarct volume in WT recipient mice when given 24 h prior to or 4 h after MCAO. B-cell protected (24 h pre-MCAO) mice had

increased regulatory subpopulations in the periphery, reduced numbers of activated, inflammatory T-cells, decreased infiltration of T-cells and a less inflammatory milieu in the ischemic hemispheres of the IL-10+ B-cell-treated group. Moreover, transfer of IL-10+ B-cells 24 h before MCAO led to a significant preservation of regulatory immune subsets in the IL-10+ B-cell protected group presumably indicating their role in immunomodulatory mechanisms, post-stroke. Our studies are the first to demonstrate a major immunoregulatory role for IL-10+ regulatory B-cells in preventing and treating MCAO in WT mice and also implicating their potential role in attenuating complications due to post-stroke immunosuppression. © 2013 Springer Science+Business Media New York.

Boise, L., Tuepker, A., Gipson, T., Vigmenon, Y., Soule, I., & Onadeko, S. (2013). African refugee and immigrant health needs: Report from a community-based house meeting project. *Progress in Community Health Partnerships: Research, Education, and Action*, 7(4), 369-378.

Background: As in other communities in the United States, information is lacking about the health needs of Africans refugees and immigrants living in Portland, Oregon. In 2008, the African Partnership for Health coalition (APH) was formed to carry out research, advocacy and education to improve the health and well-being of Africans in Oregon. This was APH's initial project.

Objectives: The purposes of this study were to gather data about the perceived health needs and barriers to health care Africans encounter, and lay the foundation for a program of action to guide APH's future work. Methods: Community-based participatory research (CBPR) methods were used to collect data on how to improve the health of the African community in the Portland area and define an agenda for future projects. Popular education principles guided the engagement and training of African community members, who conducted nine house meetings with 56 Africans from 14 countries. The results were analyzed by African community members and researchers and prioritized at a community meeting. Results: Three themes emerged: The stressfulness of life in America, the challenges of gaining access to health care, and the pervasive feelings of disrespect and lack of understanding of Africans' health needs, culture, and life experiences by health providers and staff members. Conclusion: Using CBPR methods, we identified and prioritized the needs of the African community. This information provides a

framework for future work of the African Partnership for Health and other service and advocacy groups. © 2013 The Johns Hopkins University Press.

Boise, L., Tuepker, A., Gipson, T., Vigmenon, Y., Soule, I., & Onadeko, S. (2013). African refugee and immigrant health needs: Report from a community-based house meeting project. *Progress in Community Health Partnerships: Research, Education, and Action*, 7(4), 359-360.

Boone-Heinonen, J., Diez-Roux, A. V., Goff, D. C., Loria, C. M., Kiefe, C. I., Popkin, B. M., et al. (2013). The neighborhood energy balance equation: Does neighborhood food retail environment + physical activity environment = obesity? the CARDIA study. *PloS One*, 8(12), e85141.

BACKGROUND: Recent obesity prevention initiatives focus on healthy neighborhood design, but most research examines neighborhood food retail and physical activity (PA) environments in isolation. We estimated joint, interactive, and cumulative impacts of neighborhood food retail and PA environment characteristics on body mass index (BMI) throughout early adulthood. METHODS AND FINDINGS: We used cohort data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study [n=4,092; Year 7 (24-42 years, 1992-1993) followed over 5 exams through Year 25 (2010-2011); 12,921 person-exam observations], with linked time-varying geographic information system-derived neighborhood environment measures. Using regression with fixed effects for individuals, we modeled time-lagged BMI as a function of food and PA resource density (counts per population) and neighborhood development intensity (a composite density score). We controlled for neighborhood poverty, individual-level sociodemographics, and BMI in the prior exam; and included significant interactions between neighborhood measures and by sex. Using model coefficients, we simulated BMI reductions in response to single and combined neighborhood improvements. Simulated increase in supermarket density (from 25(th) to 75(th) percentile) predicted inter-exam reduction in BMI of 0.09 kg/m<sup>2</sup> [estimate (95% CI): -0.09 (-0.16, -0.02)]. Increasing commercial PA facility density predicted BMI reductions up to 0.22 kg/m<sup>2</sup> in men, with variation across other neighborhood features [estimate (95% CI) range: -0.14 (-0.29, 0.01) to -0.22 (-0.37, -0.08)]. Simultaneous increases in supermarket and commercial PA facility density predicted inter-exam BMI reductions up to 0.31 kg/m<sup>2</sup> in men [estimate (95% CI) range: -0.23 (-0.39, -0.06) to -0.31 (-0.47, -0.15)] but not women. Reduced

fast food restaurant and convenience store density and increased public PA facility density and neighborhood development intensity did not predict reductions in BMI. CONCLUSIONS: Findings suggest that improvements in neighborhood food retail or PA environments may accumulate to reduce BMI, but some neighborhood changes may be less beneficial to women.

Boudreau, R. L., Jiang, P., Gilmore, B. L., Spengler, R. M., Tirabassi, R., Nelson, J. A., et al. (2014). Transcriptome-wide discovery of microRNA binding sites in human brain. *Neuron*, *81*(2), 294-305.

The orchestration of brain function requires complex gene regulatory networks that are modulated, in part, by microRNAs (miRNAs). These noncoding RNAs associate with argonaute (Ago) proteins in order to direct posttranscriptional gene suppression via base pairing with target transcripts. In order to better understand how miRNAs contribute to human-specialized brain processes and neurological phenotypes, identifying their targets is of paramount importance. Here, we address the latter by profiling Ago2:RNA interactions using HITS-CLIP to generate a transcriptome-wide map of miRNA binding sites in human brain. We uncovered approximately 7,000 stringent Ago2 binding sites that are highly enriched for conserved sequences corresponding to abundant brain miRNAs. This interactome points to functional miRNA:target pairs across >3,000 genes and represents a valuable resource for accelerating our understanding of miRNA functions in brain. We demonstrate the utility of this map for exploring clinically relevant miRNA binding sites that may facilitate the translation of genetic studies of complex neuropsychiatric diseases into therapeutics.

Brace, R. A., Cheung, C. Y., & Anderson, D. F. (2014). Inhibitor of intramembranous absorption in ovine amniotic fluid. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology*, *306*(3), R185-9.

Intramembranous absorption increases during intra-amniotic infusion of physiological saline solutions. The increase may be due partly to the concomitant elevation in fetal urine production as fetal urine contains a stimulator of intramembranous absorption. In this study, we hypothesized that the increase in intramembranous absorption during intra-amniotic infusion is due, in part, to dilution of a nonrenal inhibitor of intramembranous absorption that is present in

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

Broberg, C. S., Van Woerkom, R. C., Swallow, E., Dimopoulos, K., Diller, G. -, Allada, G., et al.

(2014). Lung function and gas exchange in Eisenmenger syndrome and their impact on exercise capacity and survival. *International Journal of Cardiology*, 171(1), 73-77.

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

patients had a compensated respiratory alkalosis ( $\text{PaCO}_2$   $32 \pm 4.4$  mm Hg).  $\text{PaCO}_2$  was less reduced in older patients ( $r = 0.438$ ,  $P = 0.022$ ), and correlated independently with exercise duration ( $R = -0.463$ ,  $P = 0.03$ ), yet  $\text{PaO}_2$ , not  $\text{PaCO}_2$ , was associated with survival. Conclusions Eisenmenger patients show evidence of obstructive lung disease, diffusion abnormalities, and hypocapnia; likely from hyperventilation. Understanding expected lung mechanics and gas exchange may facilitate more appropriate clinical management. © 2013 Elsevier Ireland Ltd.

Bubalo, J., Carpenter, P. A., Majhail, N., Perales, M. A., Marks, D. I., Shaughnessy, P., et al. (2014).

Conditioning chemotherapy dose adjustment in obese patients: A review and position statement by the American Society for Blood and Marrow Transplantation Practice Guideline Committee.

*Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,*

Hematopoietic stem cell transplantation (HCT) is a potentially life-saving therapy for patients with malignant and non-malignant disease states. This article reviews the current published literature on the dosing of pharmacologic agents used for HCT-preparative regimens with specific focus on the obese patient population. The review found that dose adjustments for obesity have, to date, been based empirically or extrapolated from published data in the non-transplant patient population. As a result, the Committee determined that clear standards or dosing guidelines are unable to be made for the obese population because Level I and II evidence is unavailable at this time. Instead, the Committee provides a current published literature review to serve as a platform for conditioning agent dose selection in the setting of obesity. A necessary goal should be to encourage future prospective trials in this patient population because further information is needed to enhance our knowledge of the pharmacokinetics and pharmacodynamics of conditioning agents in the setting of obesity.

Buckley Prof., D. I., & Heneghan Prof., C. (2013). Erratum: Duration of symptoms of respiratory tract infections in children: Systematic review (BMJ (online) (2013) 347 (f7027)

DOI:10.1136/bmj.f7027). *BMJ (Online)*, 347

Bumsted, T. (2012). Hiring pediatric hospitalists: The process matters. *Hospital Pediatrics*, 2(1), 39-44.

Burnett, E. J., Grant, K. A., Davenport, A. T., Hemby, S. E., & Friedman, D. P. (2014). The effects of chronic ethanol self-administration on hippocampal 5-HT receptors in monkeys. *Drug and Alcohol Dependence*,

BACKGROUND: Chronic alcohol consumption reduces brain serotonin and alters the synaptic mechanisms involved in memory formation. Hippocampal 5-HT<sub>1A</sub> receptors modulate these mechanisms, but the neuroadaptive response of 5HT<sub>1A</sub> receptors to chronic alcohol self-administration is not well understood. METHODS: Hippocampal tissue from monkeys that voluntarily self-administered ethanol for 12 months (n=9) and accompanying controls (n=8) were prepared for in vitro receptor autoradiography and laser capture microdissection. The 5-HT<sub>1A</sub> receptor antagonist, [3H]MPPF, and the agonist, [3H]8-OH-DPAT, were used to measure total and G-protein coupled 5-HT<sub>1A</sub> receptors respectively. The expression of the genes encoding the 5-HT<sub>1A</sub> receptor and its trafficking protein Yif1B was measured in microdissected dentate gyrus (DG) granule cells and CA1 pyramidal neurons. RESULTS: An increase in G-protein coupled, but not total, receptors was observed in the posterior pyramidal cell layer of CA1 in ethanol drinkers compared to controls. Chronic ethanol self-administration was also associated with an up-regulation of total and G-protein coupled 5-HT<sub>1A</sub> receptors in the posterior DG polymorphic layer. Changes in receptor binding were not associated with concomitant changes in 5-HT<sub>1A</sub> receptor mRNA expression. Chronic ethanol self-administration was associated with a significant increase in Yif1B gene expression in posterior CA1 pyramidal neurons. CONCLUSIONS: Chronic, ethanol self-administration up-regulates hippocampal 5-HT<sub>1A</sub> receptor density in a region-specific manner that does not appear to be due to alterations at the level of transcription but instead may be due to increased receptor trafficking. Further exploration of the mechanisms mediating chronic ethanol-induced 5-HT<sub>1A</sub> receptor up-regulation and how hippocampal neurotransmission is altered is warranted.

Bush, B. O., & Kain, A. (2013). Estimating phoneme formant targets and coarticulation parameters of conversational and clear speech. *2013 38th IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2013, Vancouver, BC*. pp. 8017-8021.

We present a data-driven formant model and methodology for discovering its parameters, namely phoneme targets and coarticulation functions for consonant-vowel-consonant (CVC)

words from fully-automatic formant data. The model uses formant targets that are speaker dependent, but independent of speaking style and phonemic context. We used a global error measure to search for optimal formant targets for all phonemes, including classes of sounds where formants are not directly observable. Analysis of coarticulation parameters found significant differences in parameters between clear and conversational speech. Estimated formant targets were largely in agreement with acoustic-phonetic expectations. An intelligibility test validated that resynthesized CVC words using modeled formant trajectories were nearly as intelligible as resynthesized CVC words using observed formant trajectories. © 2013 IEEE.

Calderwood, A. H., Logan, J. R., Zurfluh, M., Lieberman, D. A., Jacobson, B. C., Heeren, T. C., et al. (2014). Validity of a web-based educational program to disseminate a standardized bowel preparation rating scale. *Journal of Clinical Gastroenterology*,  
GOALS:: Our goal was to assess the validity of a Web-based educational program on the Boston Bowel Preparation Scale (BBPS). BACKGROUND:: Data on Web-based education for improving the practice and quality of colonoscopy are limited. STUDY:: Endoscopists worldwide participated in the BBPS Educational Program. We assessed program completion rates, satisfaction, short-term (0 to 90 d) and long-term (91 to 180 d) uptake of the BBPS, and the validity of the program by measuring the reliability of the BBPS among participants. RESULTS:: A total of 207 endoscopists completed the program. Overall, 93% found the content relevant, 89% felt confident in using the BBPS, and 97% thought the quality was good or excellent. Uptake of the BBPS into clinical practice was robust with 91% and 98% of colonoscopy reports containing the BBPS at short-term and long-term follow-up, respectively. The interobserver and test-retest reliability of BBPS segment and total scores were both substantial. CONCLUSIONS:: A BBPS Web-based educational program facilitates adoption into clinical practice and teaches the BBPS to be used reliably by a diverse group of endoscopists worldwide.

Call, J. A., Prendergast, B. M., Jensen, L. G., Ord, C. B., Goodman, K. A., Jacob, R., et al. (2014). Intensity-modulated radiation therapy for anal cancer: Results from a multi-institutional retrospective cohort study. *American Journal of Clinical Oncology*,  
OBJECTIVES:: To assess toxicity and efficacy of intensity-modulated radiation therapy (IMRT) for

anal cancer. METHODS:: Records of 152 patients were reviewed retrospectively from multiple institutions. Data on disease control and toxicity were collected as well as patient and treatment characteristics. Acute ( $\leq 6$  mo) severe toxicity (grade  $\geq 3$ ) were graded. Four patients were excluded due to the presence of metastatic disease or stage TX. Late toxicity data were available for 120 patients. RESULTS:: Median cumulative IMRT dose was 51.25 Gy (median, 28 fractions). All but 2 patients received chemotherapy. With median follow-up of 26.8 months, local control at 3 years was 87%, worse for patients with T3-T4 than T1-T2 disease on univariate analysis (79% vs. 90%;  $P=0.04$ ). Regional control, distant control, and overall survival were 97%, 91%, and 87%, respectively, at 3 years. Nodal status was associated with regional control, distant control, and overall survival ( $P<0.01$  for each). Most common severe acute toxicity was hematologic (41%), skin (20%), and gastrointestinal tract (11%). Two grade 5 toxicities occurred (hematologic and gastrointestinal tract). Severe late toxicity affected skin (1%) and gastrointestinal tract (3%). CONCLUSIONS:: IMRT with chemotherapy resulted in excellent local control. Although T stage predicted worse local control, most T3-T4 disease was controlled with IMRT. Nodal status predicted regional and distant control and overall survival. Severe toxicity was acceptable.

Callaway, C. W., Schmicker, R. H., Brown, S. P., Albrich, J. M., Andrusiek, D. L., Aufderheide, T. P., et al. (2014). Early coronary angiography and induced hypothermia are associated with survival and functional recovery after out-of-hospital cardiac arrest. *Resuscitation*,  
BACKGROUND: The rate and effect of coronary interventions and induced hypothermia after out-of-hospital cardiac arrest (OHCA) are unknown. We measured the association of early ( $\leq 18$  years) hospitalized after OHCA with pulses sustained  $\geq 60$ min. We measured the association of early coronary catheterization, percutaneous coronary intervention, fibrinolysis, and induced hypothermia with survival to hospital discharge with favorable functional status (modified Rankin Score  $\leq 3$ ). RESULTS: From 16,875 OHCA subjects, 3981 (23.6%) arrived at 151 hospitals with sustained pulses. 1317 (33.1%) survived to hospital discharge, with 1006 (25.3%) favorable outcomes. Rates of early coronary catheterization (19.2%), coronary reperfusion (17.7%) or induced hypothermia (39.3%) varied among hospitals, and were higher in hospitals treating more subjects per year. Odds of survival and favorable outcome increased with hospital volume (per 5

subjects/year OR 1.06; 95%CI: 1.04-1.08 and OR 1.06; 95%CI: 1.04, 1.08, respectively).

Survival and favorable outcome were independently associated with early coronary angiography (OR 1.69; 95%CI 1.06-2.70 and OR 1.87; 95%CI 1.15-3.04), coronary reperfusion (OR 1.94; 95%CI 1.34-2.82 and OR 2.14; 95%CI 1.46-3.14), and induced hypothermia (OR 1.36; 95%CI 1.01-1.83 and OR 1.42; 95%CI 1.04-1.94). INTERPRETATION:: Early coronary intervention and induced hypothermia are associated with favorable outcome and are more frequent in hospitals that treat higher numbers of OHCA subjects per year.

Callegari, L. S., Darney, B. G., Godfrey, E. M., Sementi, O., Dunsmoor-Su, R., & Prager, S. W. (2014).

Evidence-based selection of candidates for the levonorgestrel intrauterine device (IUD). *Journal of the American Board of Family Medicine : JABFM*, 27(1), 26-33.

BACKGROUND: Recent evidence-based guidelines expanded the definition of appropriate candidates for the levonorgestrel-releasing intrauterine system (LNG-IUS). We investigated correlates of evidence-based selection of candidates for the LNG-IUS by physicians who offer insertion. METHODS: We conducted a mixed-mode (online and mail) survey of practicing family physicians and obstetrician-gynecologists in Seattle. RESULTS: A total of 269 physicians responded to the survey (44% response rate). Of the 217 respondents who inserted intrauterine devices, half or fewer routinely recommended the LNG-IUS to women who are nulliparous, younger than 20 years old, or have a history of sexually transmitted infections (STIs). In multivariable analyses, training/resident status was positively associated with recommending the LNG-IUS to women <20 years old (adjusted odds ratio [aOR], 3.6; 95% confidence interval [CI], 1.6-8.0) and women with history of STI (aOR, 3.7; 95% CI, 1.6-8.4). Perceived risk of infection or infertility was negatively associated with recommending the LNG-IUS to nulliparous women (aOR, 0.2; 95% CI, 0.1-0.5) and women with a history of STI (aOR, 0.3; 95% CI, 0.1-0.8). CONCLUSIONS: Many family physicians and obstetrician-gynecologists who insert the LNG-IUS are overly restrictive in selecting candidates, although those who train residents are more likely to follow evidence-based guidelines. Interventions that address negative bias and perceptions of risks, in addition to improving knowledge, are needed to promote wider use of the LNG-IUS.

Caughey, A. B., & Burchfield, D. J. (2014). Costs and cost-effectiveness of periviable care. *Seminars in Perinatology*, 38(1), 56-62.

With increasing concerns regarding rapidly expanding healthcare costs, cost-effectiveness analysis allows assessment of whether marginal gains from new technology are worth the increased costs. Particular methodologic issues related to cost and cost-effectiveness analysis in the area of neonatal and periviable care include how costs are estimated, such as the use of charges and whether long-term costs are included; the challenges of measuring utilities; and whether to use a maternal, neonatal, or dual perspective in such analyses. A number of studies over the past three decades have examined the costs and the cost-effectiveness of neonatal and periviable care. Broadly, while neonatal care is costly, it is also cost effective as it produces both life-years and quality-adjusted life-years (QALYs). However, as the gestational age of the neonate decreases, the costs increase and the cost-effectiveness threshold is harder to achieve. In the periviable range of gestational age (22-24 weeks of gestation), whether the care is cost effective is questionable and is dependent on the perspective. Understanding the methodology and salient issues of cost-effectiveness analysis is critical for researchers, editors, and clinicians to accurately interpret results of the growing body of cost-effectiveness studies related to the care of periviable pregnancies and neonates.

Chapman, C. H., Hwang, W. -, Both, S., Thomas, C. R., & Deville, C. (2014). Current status of diversity by race, hispanic ethnicity, and sex in diagnostic radiology. *Radiology*, 270(1), 232-240. Purpose: To assess the diversity of the U.S. diagnostic radiology physician workforce by race, Hispanic ethnicity, and sex in the context of the available pipeline of medical students. Materials and Methods: Institutional review board evaluation and exemption were granted for the study, as primary data were obtained from publicly available registry sources, with no identifiable private or protected information. Publicly available American Medical Association, American Association of Medical Colleges, and U.S. census registries were used to assess differences for 2010 among diagnostic radiology practicing physicians, academic faculty, residents, subspecialty trainees, residency applicants, medical school graduates, and U.S. population by using binomial tests; with adjustment for multiple comparisons among different groups, differences with P .01) representation, suggesting no dramatic change in future representation as practicing physicians.

Moreover, diagnostic radiology ranks 17th in female and 20th in URM representation among the 20 largest residency training specialties. Conclusion: Females and URM remain underrepresented in the diagnostic radiology physician workforce despite an available medical student pipeline. Given prevalent health care disparities and an increasingly diverse society, future research and training efforts should address increasing resident diversity with program directors and department chairs. © RSNA, 2013.

Cherala, G., Pearson, J., Dubois, B., & Mahmood, T. (2014). Lack of in vitro-in vivo correlation of adulthood cytochrome p450 activities in low-birth-weight rats. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, 42(3), 481.

Chiang, W. -., Chow-In Ko, P., Chang, A. M., Shih-Hung Liu, S., Wang, H. -., Yang, C. -., et al. (2013). Predictive performance of universal termination of resuscitation rules in an asian community: Are they accurate enough? *Emergency Medicine Journal*,  
Introduction: Prehospital termination of resuscitation (TOR) rules have not been widely validated outside of Western countries. This study evaluated the performance of TOR rules in an Asian metropolitan with a mixed-tier emergency medical service (EMS). Methods: We analysed the Utstein registry of adult, non-traumatic out-of-hospital cardiac arrests (OHCAs) in Taipei to test the performance of TOR rules for advanced life support (ALS) or basic life support (BLS) providers. ALS and BLS-TOR rules were tested in OHCAs among three subgroups: (1) resuscitated by ALS, (2) by BLS and (3) by mixed ALS and BLS. Outcome definition was in-hospital death. Sensitivity, specificity, positive predictive value (PPV), negative predictive value and decreased transport rate (DTR) among various provider combinations were calculated. Results: Of the 3489 OHCAs included, 240 were resuscitated by ALS, 1727 by BLS and 1522 by ALS and BLS. Overall survival to hospital discharge was 197 patients (5.6%). Specificity and PPV of ALS-TOR and BLS-TOR for identifying death ranged from 70.7% to 81.8% and 95.1% to 98.1%, respectively. Applying the TOR rules would have a DTR of 34.2-63.9%. BLS rules had better predictive accuracy and DTR than ALS rules among all subgroups. Conclusions: Application of the ALS and BLS TOR rules would have decreased OHCA transported to the hospital, and BLS rules are reasonable as the universal criteria in a mixed-tier EMS. However, 1.9-4.9% of those

who survived would be misclassified as non-survivors, raising concern of compromising patient safety for the implementation of the rules. © 2013 BMJ Publishing Group Ltd and the College of Emergency Medicine.

Chiang, W. -., Ko, P. C. I., Chang, A. M., Chen, W. -., Liu, S. S. H., Huang, Y. -., et al. (2014).

Bystander-initiated CPR in an asian metropolitan: Does the socioeconomic status matter? *Resuscitation*, 85(1), 53-58.

Objectives: To determine the association of neighborhood socioeconomic status (SES) with bystander-initiated cardiopulmonary resuscitation (CPR) and patient outcomes of out of hospital cardiac arrests (OHCAs) in an Asian metropolitan area. Methods: We performed a retrospective study in a prospectively collected cohort from the Utstein registry of adult non-traumatic OHCAs in Taipei, Taiwan. Average real estate value was assessed as the first proxy of SES. Twelve administrative districts in Taipei City were categorized into low versus high SES areas to test the association. The primary outcome was bystander-initiated CPR, and the secondary outcome was patient survival status. Factors associated with bystander-initiated CPR were adjusted for in multivariate analysis. The mean household income was assessed as the second proxy of SES to validate the association. Results: From January 1, 2008 to December 30, 2009, 3573 OHCAs received prehospital resuscitation in the community. Among these, 617 (17.3%) cases received bystander CPR. The proportion of bystander CPR in low-SES vs. high-SES areas was 14.5% vs. 19.6% ( $p < 0.01$ ). Odds ratio of receiving bystander-initiated CPR in low-SES areas was 0.72 (95% confidence interval: [0.60-0.88]) after adjusting for age, gender, witnessed status, public collapse, and OHCA unrecognized by the online dispatcher. Survival to discharge rate was significantly lower in low-SES areas vs. high-SES areas (4.3% vs. 6.8%;  $p < 0.01$ ). All results above remained consistent in the analyses by mean household income. Conclusions: Patients who experienced an OHCA in low-SES areas were less likely to receive bystander-initiated CPR, and demonstrated worse survival outcomes. © 2013 Elsevier Ireland Ltd.

Chiovaro, J., Douglas, V., Gaggar, A., & Dhaliwal, G. (2014). Exhausting the differential. *Journal of General Internal Medicine*,

Clayburgh, D. R., Stott, W., Cordiero, T., Park, R., Detwiller, K., Buniel, M., et al. (2013). Prospective study of venous thromboembolism in patients with head and neck cancer after surgery. *JAMA Otolaryngology-- Head & Neck Surgery*, 139(11), 1143-1150.

IMPORTANCE: Venous thromboembolism (VTE) is associated with significant morbidity and mortality in surgery patients, but little data exist on the incidence of VTE in head and neck cancer surgical patients. OBJECTIVE: To determine the incidence of VTE in postoperative patients with head and neck cancer. DESIGN, SETTING, AND PARTICIPANTS: A prospective study of 100 consecutive patients hospitalized at a tertiary care academic surgical center who underwent surgery to treat head and neck cancer. Routine chemoprophylaxis was not used. On postoperative day (POD) 2 or 3, participants received clinical examination and duplex ultrasonographic evaluation (US). Participants with negative findings on clinical examination and US were followed up clinically; participants with evidence of deep venous thrombosis (DVT) or pulmonary embolism (PE) were given therapeutic anticoagulation. Participants with superficial VTE underwent repeated US on POD 4, 5, or 6. Participants were monitored for 30 days after surgery. MAIN OUTCOME AND MEASURE: Total number of new cases of VTE (superficial and deep) identified within 30 days of surgery and confirmed on diagnostic imaging. RESULTS: Of the 111 participants enrolled, 11 withdrew before completing the study; thus, 100 participants were included. The overall incidence of VTE was 13%. Eight participants were identified with clinically significant VTE: 7 DVT and 1 PE. An additional 5 participants had asymptomatic lower extremity superficial VTE detected on US alone. Fourteen percent of patients received some form of postoperative anticoagulation therapy; the rate of bleeding complications in these patients (30.1%) was higher than that in patients without anticoagulation therapy (5.6%) ( $P = .01$ ). CONCLUSIONS AND RELEVANCE: Hospitalized patients with head and neck cancer not routinely receiving anticoagulation therapy after surgery have an increased risk of VTE. Bleeding complications are elevated in patients receiving postoperative anticoagulation.

Cleary, C., Li, Y., Tang, M., Samy El Gendy, N. M., & Huang, D. (2014). Predicting transepithelial phototherapeutic keratectomy outcomes using fourier domain optical coherence tomography. *Cornea*,

PURPOSE:: The aim of this study was to use Fourier domain optical coherence tomography to

predict transepithelial phototherapeutic keratectomy outcomes. METHODS:: This is a prospective case series. Subjects with anterior stromal corneal opacities underwent an excimer laser phototherapeutic keratectomy (PTK) combined with a photorefractive keratectomy using the VISX S4 excimer laser (AMO, Inc, Santa Ana, CA). Preoperative and postoperative Fourier domain optical coherence tomography images were used to develop a simulation algorithm to predict treatment outcomes. Main outcome measures included preoperative and postoperative uncorrected distance visual acuities and corrected distance visual acuity. RESULTS:: Nine eyes of 8 patients were treated. The nominal ablation depth was 75 to 177  $\mu\text{m}$  centrally and 62 to 185  $\mu\text{m}$  peripherally. Measured PTK ablation depths were 20% higher centrally and 26% higher peripherally, compared with those for laser settings. Postoperatively, the mean uncorrected distance visual acuity was 20/41 (range, 20/25-20/80) compared with 20/103 (range, 20/60-20/400) preoperatively. The mean corrected distance visual acuity was 20/29 (range, 20/15-20/60) compared with 20/45 (range, 20/30-20/80) preoperatively. The MRSE was +1.38 +/- 2.37 diopters (D) compared with -2.59 +/- 2.83 D (mean +/- SD). The mean astigmatism magnitude was 1.14 +/- 0.83 D compared with 1.40 +/- 1.18 D preoperatively. Postoperative MRSE correlated strongly with ablation settings, central and peripheral epithelial thickness ( $r = 0.99$ ,  $P < 0.00001$ ). Central islands remained difficult to predict and limited visual outcomes in some cases. CONCLUSIONS:: Optical coherence tomography measurements of opacity depth and 3-dimensional ablation simulation provide valuable guidance in PTK planning. Post-PTK refraction may be predicted with a regression formula that uses epithelial thickness measurements obtained by optical coherence tomography. The laser ablation rates described in this study apply only to the VISX laser.

Cohen, M. R., Huynh, K. W., Cawley, D., & Moiseenkova-Bell, V. Y. (2013). Understanding the cellular function of TRPV2 channel through generation of specific monoclonal antibodies. *PLoS One*, 8(12), e85392.

Transient receptor potential vanilloid 2 (TRPV2) is a  $\text{Ca}^{2+}$ -permeable nonselective cation channel proposed to play a critical role in a wide array of cellular processes. Although TRPV2 surface expression was originally determined to be sensitive to growth factor signaling, regulated trafficking of TRPV2 has remained controversial. TRPV2 has proven difficult to study due to the

lack of specific pharmacological tools to modulate channel activity; therefore, most studies of the cellular function of TRPV2 rely on immuno-detection techniques. Polyclonal antibodies against TRPV2 have not been properly validated and characterized, which may contribute to conflicting results regarding its function in the cell. Here, we developed monoclonal antibodies using full-length TRPV2 as an antigen. Extensive characterization of these antibodies and comparison to commonly used commercially available TRPV2 antibodies revealed that while monoclonal antibodies generated in our laboratory were suitable for detection of endogenous TRPV2 by western blot, immunoprecipitation and immunocytochemistry, the commercially available polyclonal antibodies we tested were not able to recognize endogenous TRPV2. We used our newly generated and validated TRPV2 antibodies to determine the effects of insulin-like growth factor 1 (IGF-1) on TRPV2 surface expression in heterologous and endogenous expression systems. We found that IGF-1 had little to no effect on trafficking and plasma membrane expression of TRPV2. Overall, these new TRPV2 monoclonal antibodies served to dispel the controversy of the effects of IGF-1 on TRPV2 plasma membrane expression and will clarify the role TRPV2 plays in cellular function. Furthermore, our strategy of using full-length tetrameric TRP channels may allow for the generation of antibodies against other TRP channels of unclear function.

Collin, P., Matsumura, N., Ladermann, A., Denard, P. J., & Walch, G. (2014). Relationship between massive chronic rotator cuff tear pattern and loss of active shoulder range of motion. *Journal of Shoulder and Elbow Surgery / American Shoulder and Elbow Surgeons ...[Et Al.]*,  
BACKGROUND: Management of massive chronic rotator cuff tears remains controversial, with no clearly defined clinical presentation as yet. The purpose of the study was to evaluate the effect of tear size and location on active motion in patients with chronic and massive rotator cuff tears with severe muscle degeneration. METHODS: One hundred patients with massive rotator cuff tears accompanied by muscle fatty infiltration beyond Goutallier stage 3 were prospectively included in this study. All patients were divided into 5 groups on the basis of tear pattern (supraspinatus, superior subscapularis, inferior subscapularis, infraspinatus, and teres minor). Active range of shoulder motion was assessed in each group and differences were analyzed. RESULTS: Active elevation was significantly decreased in patients with 3 tear patterns involved.

Pseudoparalysis was found in 80% of the cases with supraspinatus and complete subscapularis tears and in 45% of the cases with tears involving the supraspinatus, infraspinatus, and superior subscapularis. Loss of active external rotation was related to tears involving the infraspinatus and teres minor; loss of active internal rotation was related to tears of the subscapularis.

CONCLUSIONS: This study revealed that dysfunction of the entire subscapularis and supraspinatus or 3 rotator cuff muscles is a risk factor for pseudoparalysis. For function to be preserved in patients with massive chronic rotator cuff tears, it may be important to avoid fatty infiltration with anterior extension into the lower subscapularis or involvement of more than 2 rotator cuff muscles.

Colville-Ebeling, B., Freeman, M., Banner, J., & Lynnerup, N. (2014). *Autopsy practice in forensic pathology - evidence-based or experience-based? A review of autopsies performed on victims of traumatic asphyxia in a mass disaster*

Current autopsy practice in forensic pathology is to a large extent based on experience and individual customary practices as opposed to evidence and consensus based practices. As a result there is the potential for substantial variation in how knowledge is applied in each case. In the present case series, we describe the variation observed in autopsy reports by five different pathologists of eight victims who died simultaneously from traumatic asphyxia due to compression during a human stampede. We observed that there was no mention of the availability of medical charts in five of the reports, of potentially confounding resuscitation efforts in three reports, of cardinal signs in seven reports and of associated injuries to a various degree in all reports. Further, there was mention of supplemental histological examination in two reports and of pre-autopsy radiograph in six reports. We inferred that reliance on experience and individual customary practices led to disparities between the autopsy reports as well as omissions of important information such as cardinal signs, and conclude that such reliance increases the potential for error in autopsy practice. We suggest that pre-autopsy data-gathering and the use of check lists specific to certain injury causes are likely to result in less deviation from evidence-based practices in forensic pathology. Pre-autopsy data-gathering and check lists will help ensure a higher degree of standardization in autopsy reports thus enhancing the quality and accuracy of

the report as a legal document as well as rendering it more useful for data-gathering efforts. © 2013 Elsevier Ltd and Faculty of Forensic and Legal Medicine. All rights reserved.

Combs, C. A., Gravett, M., Garite, T. J., Hickok, D. E., Lapidus, J., Porreco, R., et al. (2013). Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. *American Journal of Obstetrics and Gynecology*,

Objective: The purpose of this study was to compare intraamniotic inflammation vs microbial invasion of the amniotic cavity (MIAC) as predictors of adverse outcome in preterm labor with intact membranes. Study Design: Interleukin-6 (IL-6) was measured in prospectively collected amniotic fluid from 305 women with preterm labor. MIAC was defined by amniotic fluid culture and/or detection of microbial 16S ribosomal DNA. Cases were categorized into 5 groups: infection (MIAC; IL-6,  $\geq 11.3$  ng/mL); severe inflammation (no MIAC; IL-6,  $\geq 11.3$  ng/mL); mild inflammation (no MIAC; IL-6, 2.6-11.2 ng/mL); colonization (MIAC; IL-6,  $< 2.6$  ng/mL); negative (no MIAC; IL-6,  $< 2.6$  ng/mL). Results: The infection (n = 27) and severe inflammation (n = 36) groups had similar latency (median,  $< 1$  day and 2 days, respectively) and similar rates of composite perinatal morbidity and mortality (81% and 72%, respectively). The colonization (n = 4) and negative (n = 195) groups had similar outcomes (median latency, 23.5 and 25 days; composite morbidity and mortality rates, 21% and 25%, respectively). The mild inflammation (n = 47) groups had outcomes that were intermediate to the severe inflammation and negative groups (median latency, 7 days; composite morbidity and mortality rates, 53%). In logistic regression adjusting for gestational age at enrollment, IL-6  $\geq 11.3$  and 2.6-11.2 ng/mL, but not MIAC, were associated significantly with composite morbidity and mortality rates (odds ratio [OR], 4.9; 95% confidence interval [CI], 2.2-11.2, OR, 3.1; 95% CI, 1.5-6.4, and OR, 1.8; 95% CI, 0.6-5.5, respectively). Conclusion: We confirmed previous reports that intraamniotic inflammation is associated with adverse perinatal outcomes whether or not intraamniotic microbes are detected. Colonization without inflammation appears relatively benign.

Intraamniotic inflammation is not simply present or absent but also has degrees of severity that correlate with adverse outcomes. We propose the designation amniotic inflammatory response syndrome to denote the adverse outcomes that are associated with intraamniotic inflammation.

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Conner, K. R., Huguet, N., Caetano, R., Giesbrecht, N., McFarland, B. H., Nolte, K. B., et al. (2014).

Acute use of alcohol and methods of suicide in a US national sample. *American Journal of Public Health, 104*(1), 171-178.

Objectives: We explored age, gender, and racial/ethnic differences with alcohol use and firearms, hanging or asphyxiation, and poisoning methods of suicide. Methods: We analyzed data for 37 993 suicide decedents aged 18 years and older from the 2005-2010 National Violent Death Reporting System database. Multinomial logistic regressions examined associations of method with alcohol use defined by blood alcohol content. Two-way interactions tested the effects of age, gender, and race/ethnicity on the associations between alcohol use and method of suicide.

Results: Alcohol was present among decedents who used the 3 leading methods of suicide: firearm (35.0%), hanging (36.8%), and poisoning (32.7%). Two-way interaction tests suggested that in young and middle adulthood, individuals were more likely to drink alcohol when they used a firearm or hanging (compared with poisoning), but in older adulthood, the reverse was true, with alcohol use more likely with poisoning. Interaction tests also suggested that Asians and Pacific Islanders were most likely to use alcohol in poisonings and that Blacks were least likely to use alcohol in hangings. Conclusions: The results suggested that alcohol use before suicide was influenced by several factors, including age, race/ethnicity, and suicide method.

Copelan, E. A., Hamilton, B. K., Avalos, B., Ahn, K. W., Bolwell, B. J., Zhu, X., et al. (2013). Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI. *Blood, 122*(24), 3863-3870.

Cyclophosphamide combined with total body irradiation (Cy/TBI) or busulfan (BuCy) are the most widely used myeloablative conditioning regimens for allotransplants. Recent data regarding their comparative effectiveness are lacking. We analyzed data from the Center for International Blood and Marrow Transplant Research for 1230 subjects receiving a first hematopoietic cell transplant from a human leukocyte antigen-matched sibling or from an unrelated donor during the years 2000 to 2006 for acute myeloid leukemia (AML) in first complete remission (CR) after conditioning with Cy/TBI or oral or intravenous (4) BuCy. Multivariate analysis showed significantly less nonrelapse mortality (relative risk [RR]= 0.58; 95% confidence interval [CI]: 0.39-0.86; P = .007), and relapse after, but not before, 1 year posttransplant (RR=0.23; 95%

CI: 0.08-0.65; P=.006), and better leukemia-free survival (RR=0.70; 95% CI: 0.55-0.88; P = .003) and survival (RR = 0.68; 95% CI: 0.52-0.88; P = .003) in persons receiving 4, but not oral, Bu compared with TBI. In combination with Cy, 4 Bu is associated with superior outcomes compared with TBI in patients with AML in first CR. © 2013 by The American Society of Hematology.

Corless, C. L. (2014). Gastrointestinal stromal tumors: What do we know now? *Modern Pathology : An Official Journal of the United States and Canadian Academy of Pathology, Inc, 27 Suppl 1*, S1-S16.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the GI tract, arising from the interstitial cells of Cajal, primarily in the stomach and small intestine. They manifest a wide range of morphologies, from spindle cell to epithelioid, but are immunopositive for KIT (CD117) and/or DOG1 in essentially all cases. Although most tumors are localized at presentation, up to half will recur in the abdomen or spread to the liver. The growth of most GISTs is driven by oncogenic mutations in either of two receptor tyrosine kinases: KIT (75% of cases) or PDGFRA (10%). Treatment with tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib, and regorafenib is effective in controlling unresectable disease; however, drug resistance caused by secondary KIT or PDGFRA mutations eventually develops in 90% of cases. Adjuvant therapy with imatinib is commonly used to reduce the likelihood of disease recurrence after primary surgery, and for this reason assessing the prognosis of newly resected tumors is one of the most important roles for pathologists. Approximately 15% of GISTs are negative for mutations in KIT and PDGFRA. Recent studies of these so-called wild-type GISTs have uncovered a number of other oncogenic drivers, including mutations in neurofibromatosis type I, RAS genes, BRAF, and subunits of the succinate dehydrogenase complex. Routine genotyping is strongly recommended for optimal management of GISTs, as the type and dose of TKI used for treatment is dependent on the mutation identified.

Cotts, T., Khairy, P., Opatowsky, A. R., John, A. S., Valente, A. M., Zaidi, A. N., et al. (2014). Clinical research priorities in adult congenital heart disease. *International Journal of Cardiology, 171*(3), 351-360.

**BACKGROUND:** Adult congenital heart disease (ACHD) clinicians are hampered by the paucity of data to inform clinical decision-making. The objective of this study was to identify priorities for clinical research in ACHD. **METHODS:** A list of 45 research questions was developed by the Alliance for Adult Research in Congenital Cardiology (AARCC), compiled into a survey, and administered to ACHD providers. Patient input was sought via the Adult Congenital Heart Association at community meetings and online forums. The 25 top questions were sent to ACHD providers worldwide via an online survey. Each question was ranked based on perceived priority and weighted based on time spent in ACHD care. The top 10 topics identified are presented and discussed. **RESULTS:** The final online survey yielded 139 responses. Top priority questions related to tetralogy of Fallot (timing of pulmonary valve replacement and criteria for primary prevention ICDs), patients with systemic right ventricles (determining the optimal echocardiographic techniques for measuring right ventricular function, and indications for tricuspid valve replacement and primary prevention ICDs), and single ventricle/Fontan patients (role of pulmonary vasodilators, optimal anticoagulation, medical therapy for preservation of ventricular function, treatment for protein losing enteropathy). In addition, establishing criteria to refer ACHD patients for cardiac transplantation was deemed a priority. **CONCLUSIONS:** The ACHD field is in need of prospective research to address fundamental clinical questions. It is hoped that this methodical consultation process will inform researchers and funding organizations about clinical research topics deemed to be of high priority.

Cozzoli, D. K., Courson, J., Wroten, M. G., Greentree, D. I., Lum, E. N., Campbell, R. R., et al. (2014).

Binge alcohol drinking by mice requires intact group1 metabotropic glutamate receptor signaling within the central nucleus of the amygdale. *Neuropsychopharmacology*, 39(2), 435-444.

Despite the fact that binge alcohol drinking (intake resulting in blood alcohol concentrations (BACs)  $\geq 80$  mg% within a 2-h period) is the most prevalent form of alcohol-use disorders (AUD), a large knowledge gap exists regarding how this form of AUD influences neural circuits mediating alcohol reinforcement. The present study employed integrative approaches to examine the functional relevance of binge drinking-induced changes in glutamate receptors, their associated scaffolding proteins and certain signaling molecules within the central nucleus of the amygdala (CeA). A 30-day history of binge alcohol drinking (for example, 4-5 g kg<sup>-1</sup> per 2 h<sup>-1</sup>) elevated

CeA levels of mGluR1, GluN2B, Homer2a/b and phospholipase C (PLC)  $\beta$ 3, without significantly altering protein expression within the adjacent basolateral amygdala. An intra-CeA infusion of mGluR1, mGluR5 and PLC inhibitors all dose-dependently reduced binge intake, without influencing sucrose drinking. The effects of co-infusing mGluR1 and PLC inhibitors were additive, whereas those of co-inhibiting mGluR5 and PLC were not, indicating that the efficacy of mGluR1 blockade to lower binge intake involves a pathway independent of PLC activation. The efficacy of mGluR1, mGluR5 and PLC inhibitors to reduce binge intake depended upon intact Homer2 expression as revealed through neuropharmacological studies of Homer2 null mutant mice. Collectively, these data indicate binge alcohol-induced increases in Group1 mGluR signaling within the CeA as a neuroadaptation maintaining excessive alcohol intake, which may contribute to the propensity to binge drink. © 2014 American College of Neuropsychopharmacology.

Crawford, J., Swanson, P., Schwarzenberger, P., Sandler, A., Prager, D., Zhang, K., et al. (2013). A phase 2 randomized trial of paclitaxel and carboplatin with or without panitumumab for first-line treatment of advanced non-small-cell lung cancer. *Journal of Thoracic Oncology*, 8(12), 1510-1518.

**Introduction:** This two-part phase 2 study evaluated the efficacy and safety of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, combined with carboplatin/paclitaxel in patients with previously untreated advanced non-small-cell lung cancer. **Methods:** In part 1, patients were sequentially enrolled to receive paclitaxel 200 mg/m<sup>2</sup> and carboplatin (area under the concentration-versus-time curve, 6 mg/min/ml) plus panitumumab (1.0, 2.0, or 2.5 mg/kg). In part 2, patients were randomized 2:1 to receive paclitaxel/carboplatin with (arm A) or without (arm B) the maximum tolerated dose of panitumumab identified in part 1. Primary endpoints in parts 1 and 2 were the incidence of dose-limiting toxicities and time to progression (TTP), respectively. **Results:** In part 1, four of 19 patients had dose-limiting toxicities: three at 2.0 mg/kg (fatigue, pain in extremity, dyspepsia) and one at 2.5 mg/kg (rash). The maximum tolerated dose was not reached; panitumumab 2.5 mg/kg was selected for part 2. In part 2, TTP was 18.1 weeks (95% confidence interval [CI], 13.6-23.3) in arm A and 23.0 weeks (95% CI, 15.9-24.1) in arm B (hazard ratio, 0.9; 90% CI, 0.66-1.21; p = 0.555). Progression-free survival in arms A and B was 17.6 weeks and 18.3

weeks, respectively, and the objective response rate was 15.2% and 11.1%. Adverse events occurring more frequently in arm A than in arm B included skin toxicity, diarrhea, stomatitis, vomiting, and dizziness. Exploratory analyses did not demonstrate associations between potential biomarkers and outcomes. Conclusion: Although toxicity was predictable and manageable, the addition of panitumumab to paclitaxel/carboplatin did not improve TTP in patients with previously untreated advanced non-small-cell lung cancer. Copyright © 2013 by the International Association for the Study of Lung Cancer.

Crawford, J. D., Perrone, K. H., Wong, V. W., Mitchell, E. L., Azarbal, A. F., Liem, T. K., et al. (2014).

A modern series of acute aortic occlusion. *Journal of Vascular Surgery*,

OBJECTIVE: Acute aortic occlusion (AAO) is a rare condition associated with substantial morbidity and mortality. The most recent large series was published over 15 years ago and included patients from the 1980s. Previous studies reported up to 50% of AAOs are caused by embolization, with a mortality rate approaching 50%. We reviewed our recent experience with AAOs to identify current etiologies and outcomes in a contemporary series of patients with AAOs.

METHODS: Current Procedural Terminology codes and data from a prospectively maintained vascular surgical database were used to identify patients with acute occlusion of the native aorta between 2005 and July 2013. AAOs secondary to trauma, dissection, or graft occlusion were excluded. RESULTS: We identified 29 patients with AAOs treated at our institution. Twenty-three patients were transferred from referring hospitals with a mean transfer time of 3.9 hours (range, 0.5-7.5 hours). Twenty-two presented with occlusion below the renal arteries and seven with occlusion extending above the renal arteries. Resting motor/sensory lower extremity deficits were noted in 17 patients. Eight patients presented with complete paraplegia. Etiology was felt to be aortoiliac thrombosis in 22 cases, embolic occlusion in 2, and indeterminate in 5. Surgical revascularization was performed in 26 cases (extra-anatomic bypass in 18, thromboembolectomy in 5, and aortobifemoral bypass in 3 patients). Three patients had no intervention. Acute renal failure developed in 15 patients and rhabdomyolysis in 10 patients. Fasciotomy was performed in 19 extremities. Nine extremities were amputated in six patients. Overall mortality was 34% with a 30-day mortality of 24% and a postprocedure mortality of 15%. CONCLUSIONS: AAO is an infrequent but devastating event. The dominant etiology of AAOs is now thrombotic occlusion.

Despite advances in vascular surgery and critical care over the past 2 decades, associated morbidity and mortality remain substantial with high rates of limb loss, acute renal failure, rhabdomyolysis, and death. Mortality may be improved with expeditious extra-anatomic bypass.

Crawford, J. D., Wong, V. W., Deloughery, T. G., Mitchell, E. L., Liem, T. K., Landry, G. J., et al.

(2014). Paroxysmal nocturnal hemoglobinuria: A red clot syndrome. *Annals of Vascular Surgery*, 28(1), 122.e5-122.e10.

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. © 2014 by Elsevier Inc. All rights reserved.

Cservenka, A., Casimo, K., Fair, D. A., & Nagel, B. J. (2013). Resting state functional connectivity of

the nucleus accumbens in youth with a family history of alcoholism. *Psychiatry Research*, Adolescents with a family history of alcoholism (FHP) are at heightened risk for developing alcohol use disorders (AUDs). The nucleus accumbens (NAcc), a key brain region for reward processing, is implicated in the development of AUDs. Thus, functional connectivity of the NAcc may be an important marker of risk in FHP youth. Resting state functional magnetic resonance imaging (rs-fcMRI) was used to examine the intrinsic connectivity of the NAcc in 47 FHP and 50

family history negative (FHN) youth, ages 10-16 years old. FHP and FHN adolescents showed significant group differences in resting state synchrony between the left NAcc and bilateral inferior frontal gyri and the left postcentral gyrus (PG). Additionally, FHP youth differed from FHN youth in right NAcc functional connectivity with the left orbitofrontal cortex (OFC), left superior temporal gyrus, right cerebellum, left PG, and right occipital cortex. These results indicate that FHP youth have less segregation between the NAcc and executive functioning brain regions, and less integration with reward-related brain areas, such as the OFC. The findings of the current study highlight that premorbid atypical connectivity of appetitive systems, in the absence of heavy alcohol use, may be a risk marker in FHP adolescents.

Cservenka, A., Casimo, K., Fair, D. A., & Nagel, B. J. (2014). Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism. *Psychiatry Research - Neuroimaging*,

Adolescents with a family history of alcoholism (FHP) are at heightened risk for developing alcohol use disorders (AUDs). The nucleus accumbens (NAcc), a key brain region for reward processing, is implicated in the development of AUDs. Thus, functional connectivity of the NAcc may be an important marker of risk in FHP youth. Resting state functional magnetic resonance imaging (rs-fcMRI) was used to examine the intrinsic connectivity of the NAcc in 47 FHP and 50 family history negative (FHN) youth, ages 10-16 years old. FHP and FHN adolescents showed significant group differences in resting state synchrony between the left NAcc and bilateral inferior frontal gyri and the left postcentral gyrus (PG). Additionally, FHP youth differed from FHN youth in right NAcc functional connectivity with the left orbitofrontal cortex (OFC), left superior temporal gyrus, right cerebellum, left PG, and right occipital cortex. These results indicate that FHP youth have less segregation between the NAcc and executive functioning brain regions, and less integration with reward-related brain areas, such as the OFC. The findings of the current study highlight that premorbid atypical connectivity of appetitive systems, in the absence of heavy alcohol use, may be a risk marker in FHP adolescents. © 2013 Elsevier Ireland Ltd. All rights reserved.

Culbert, K. M., Burt, S. A., Sisk, C. L., Nigg, J. T., & Klump, K. L. (2014). The effects of circulating testosterone and pubertal maturation on risk for disordered eating symptoms in adolescent males. *Psychological Medicine*, 1-16.

**BACKGROUND:** Testosterone may be a biological factor that protects males against eating disorders. Elevated prenatal testosterone exposure is linked to lower levels of disordered eating symptoms, but effects emerge only after mid-puberty. Whether circulating levels of testosterone account for decreased risk for disordered eating in boys after mid-puberty is currently unknown; however, animal data support this possibility. In rodents, prenatal testosterone's masculinizing effects on sex-differentiated behaviors emerge during puberty when circulating levels of testosterone increase and 'activate' the expression of masculinized phenotypes. This study investigated whether higher levels of circulating testosterone predict lower levels of disordered eating symptoms in adolescent boys, and in particular whether effects are associated with advancing pubertal maturation. **METHOD:** Participants were 213 male twins from the Michigan State University Twin Registry. The Minnesota Eating Behavior Survey and Eating Disorder Examination Questionnaire assessed several disordered eating symptoms. The Pubertal Development Scale assessed pubertal status. Afternoon saliva samples were assayed for testosterone using enzyme immunoassays. **RESULTS:** Consistent with animal data, higher levels of circulating testosterone predicted lower levels of disordered eating symptoms in adolescent boys and effects emerged with advancing puberty. Results were not accounted for by several important covariates, including age, adiposity, or mood/anxiety symptoms. **CONCLUSIONS:** Findings suggest that elevated circulating testosterone may be protective and underlie decreased risk for eating pathology in males during/after puberty, whereas lower levels of testosterone may increase risk and explain why some, albeit relatively few, males develop eating disorders.

Cullen, T. J., McCarthy, M. P., Lasarev, M. R., Barry, J. M., & Stadler, D. D. (2014). Body mass index and the development of new-onset diabetes mellitus or the worsening of pre-existing diabetes mellitus in adult kidney transplant patients. *Journal of Renal Nutrition : The Official Journal of the Council on Renal Nutrition of the National Kidney Foundation*,

**OBJECTIVE:** The purpose of this study was to determine the relationship between body mass index (BMI) and the development of new-onset diabetes after transplant (NODAT) as well as the

worsening of pre-existing diabetes mellitus (DM) in adults after kidney transplantation. DESIGN AND SUBJECTS: A medical record review was conducted using the records of 204 adult patients who underwent a first renal transplant between September 2009 and February 2011 at a single transplant center. Patients who received simultaneous transplantation of another organ, who were immunosuppressed for nontransplant reasons, or those who were less than 18 years of age were excluded. MAIN OUTCOME MEASURES: Outcome data collected at the time of hospital discharge and at 3, 6, and 12 months after kidney transplantation included the development of NODAT and the components of DM treatment regimens. RESULTS: The cumulative incidence of NODAT at discharge and 3, 6, and 12 months post-transplantation was 14.2%, 19.4%, 20.1%, and 19.4%, respectively. The odds of developing NODAT by discharge or 3 or 6 months post-transplantation increased by a factor of 1.11 (95% confidence interval [CI]: 1.0-1.23), 1.13 (95% CI: 1.03-1.24), and 1.15 (95% CI: 1.05-1.27), respectively, per unit increase in pretransplantation BMI. The need for more aggressive DM treatment (suggesting a worsening of DM status) was most usually seen between discharge and 3 months; 50% of patients with preexisting DM required more aggressive DM treatment post-transplantation ( $X^2 = 13.25$ ;  $P = .001$ ). CONCLUSION: The odds of developing NODAT at discharge and 3 and 6 months post-transplantation increased per unit of pretransplantation BMI. The most common time for NODAT to develop or for preexisting DM to worsen was within 3 months of kidney transplantation.

Daldoul, H., Denguezli, M., Jithoo, A., Gnatiuc, L., Buist, S., Burney, P., et al. (2013). Prevalence of COPD and tobacco smoking in Tunisia - results from the BOLD study. *International Journal of Environmental Research and Public Health*, 10(12), 7257-7271.

In Tunisia, there is a paucity of population-based data on Chronic Obstructive Pulmonary Disease (COPD) prevalence. To address this problem, we estimated the prevalence of COPD following the Burden of Lung Disease Initiative. We surveyed 807 adults aged 40+ years and have collected information on respiratory history and symptoms, risk factors for COPD and quality of life. Post-bronchodilator spirometry was performed and COPD and its stages were defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Six hundred and sixty one (661) subjects were included in the final analysis. The prevalence of GOLD Stage I and II or higher COPD were 7.8% and 4.2%, respectively (Lower Limit of Normal modified stage I and II or

higher COPD prevalence were 5.3% and 3.8%, respectively). COPD was more common in subjects aged 70+ years and in those with a BMI < 20 kg/m<sup>2</sup>. Prevalence of stage I+ COPD was 2.3% in <10 pack years smoked and 16.1% in 20+ pack years smoked. Only 3.5% of participants reported doctor-diagnosed COPD. In this Tunisian population, the prevalence of COPD is higher than reported before and higher than self-reported doctor-diagnosed COPD. In subjects with COPD, age is a much more powerful predictor of lung function than smoking. © 2013 by the authors; licensee MDPI, Basel, Switzerland.

Damania, D., Subramanian, H., Backman, V., Anderson, E. C., Wong, M. H., McCarty, O. J., et al.

(2014). Network signatures of nuclear and cytoplasmic density alterations in a model of pre and postmetastatic colorectal cancer. *Journal of Biomedical Optics*, 19(1), 16016.

**ABSTRACT.** Cells contributing to the pathogenesis of cancer possess cytoplasmic and nuclear structural alterations that accompany their aberrant genetic, epigenetic, and molecular perturbations. Although it is known that architectural changes in primary and metastatic tumor cells can be quantified through variations in cellular density at the nanometer and micrometer spatial scales, the interdependent relationships among nuclear and cytoplasmic density as a function of tumorigenic potential has not been thoroughly investigated. We present a combined optical approach utilizing quantitative phase microscopy and partial wave spectroscopic microscopy to perform parallel structural characterizations of cellular architecture. Using the isogenic SW480 and SW620 cell lines as a model of pre and postmetastatic transition in colorectal cancer, we demonstrate that nuclear and cytoplasmic nanoscale disorder, micron-scale dry mass content, mean dry mass density, and shape metrics of the dry mass density histogram are uniquely correlated within and across different cellular compartments for a given cell type. The correlations of these physical parameters can be interpreted as networks whose nodal importance and level of connection independence differ according to disease stage. This work demonstrates how optically derived biophysical parameters are linked within and across different cellular compartments during the architectural orchestration of the metastatic phenotype.

D'Angio, C. T., Murray, T. E., Li, L., Heyne, R. J., O'Shea, T. M., Schelonka, R. L., et al. (2013).

Immunogenicity of haemophilus influenzae type b protein conjugate vaccines in very low birth weight infants. *Pediatric Infectious Disease Journal*, 32(12), 1400-1402.

Darney, B. G., & Caughey, A. B. (2014). In reply. *Obstetrics and Gynecology*, 123(2 Pt 1), 361-364.

Daughtry, B., & Mitalipov, S. (2014). Concise review: Parthenote stem cells for regenerative medicine:

Genetic, epigenetic, and developmental features. *Stem Cells Translational Medicine*,

Embryonic stem cells (ESCs) have the potential to provide unlimited cells and tissues for regenerative medicine. ESCs derived from fertilized embryos, however, will most likely be rejected by patient's immune system unless appropriately immunomatched. Pluripotent stem cells (PSCs) genetically identical to a patient can now be established by reprogramming of somatic cells. However, practical applications of PSCs for personalized therapies are projected to be unfeasible because of the enormous cost and time required to produce clinical-grade cells for each patient. ESCs derived from parthenogenetic embryos (pESCs) that are homozygous for human leukocyte antigens may serve as an attractive alternative for immunomatched therapies for a large population of patients. In this study, we describe the biology and genetic nature of mammalian parthenogenesis and review potential advantages and limitations of pESCs for cell-based therapies.

Davis, M., Balasubramanian, B. A., Waller, E., Miller, B. F., Green, L. A., & Cohen, D. J. (2014). Re:

Integrating behavioral and physical health care in the real world: Early lessons from advancing care together. *Journal of the American Board of Family Medicine : JABFM*, 27(1), 161.

Davis, M. M., Currey, J. M., Howk, S., Desordi, M. R., Boise, L., Fagnan, L. J., et al. (2014). A

qualitative study of rural primary care clinician views on remote monitoring technologies. *The Journal of Rural Health : Official Journal of the American Rural Health Association and the National Rural Health Care Association*, 30(1), 69-78.

PURPOSE: Remote monitoring technologies (RMTs) may improve the quality of care, reduce access barriers, and help control medical costs. Despite the role of primary care clinicians as potential key users of RMTs, few studies explore their views. This study explores rural primary

care clinician interest and the resources necessary to incorporate RMTs into routine practice.

**METHODS:** We conducted 15 in-depth interviews with rural primary care clinician members of the Oregon Rural Practice-based Research Network (ORPRN) from November 2011 to April 2012. Our multidisciplinary team used thematic analysis to identify emergent themes and a cross-case comparative analysis to explore variation by participant and practice characteristics. **RESULTS:** Clinicians expressed interest in RMTs most relevant to their clinical practice, such as supporting chronic disease management, noting benefits to patients of all ages. They expressed concern about the quantity of data, patient motivation to utilize equipment, and potential changes to the patient-clinician encounter. Direct data transfer into the clinic's electronic health record (EHR), availability in multiple formats, and review by ancillary staff could facilitate implementation. Although participants acknowledged the potential system-level benefits of using RMTs, adoption would be difficult without payment reform. **CONCLUSIONS:** Adoption of RMTs by rural primary care clinicians may be influenced by equipment purpose and functionality, implementation resources, and payment. Clinician and staff engagement will be critical to actualize RMT use in routine primary care.

DeBarber, A. E., Luo, J., Star-Weinstock, M., Purkayastha, S., Geraghty, M. T., Chiang, J., et al.

(2014). A blood test for cerebrotendinous xanthomatosis with potential for disease detection in newborns. *Journal of Lipid Research*, 55(1), 146-154.

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 because 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 5 $\alpha$ -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 was compared with 5 $\alpha$ -cholestanol. 7 $\alpha$ ,12 $\alpha$ -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 - 10-fold higher than in unaffected newborn DBS ( $16.4 \pm 6.0$  ng/ml), such that quantification of this ketosterol 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 by preventing morbidity and mortality. Copyright © 2014 by the American Society for Biochemistry and Molecular Biology, Inc.

Deconde, A. S., Mace, J. C., & Smith, T. L. (2014). The impact of comorbid migraine on quality of life outcomes after endoscopic sinus surgery. *The Laryngoscope*,  
Objectives: Chronic rhinosinusitis (CRS) and migraine are common entities with overlapping symptomatology yet little research exists which investigates the intersection of the two. This study seeks to investigate whether patients with CRS with and without a migraine history experience comparable quality-of-life (QOL) improvement after endoscopic sinus surgery (ESS).  
Study Design: Retrospective analysis of a prospective cohort  
Methods: An adult population (n=229) with medically refractory CRS was prospectively evaluated following ESS using disease-specific QOL surveys: the Rhinosinusitis Disability Index (RSDI), the Chronic Sinusitis Survey (CSS), and the Sinonasal Outcome Test-22 (SNOT-22). History of comorbid migraine was identified (n=46) and pre- and postoperative QOL was compared to patients without migraine (n=183).  
Results: Patients with migraine and CRS were more likely to be female (p=0.023), experience allergies (p=0.024), fibromyalgia (p=0.009), depression (p=0.010), and be less likely to have nasal polyposis (p=0.003). Objective measures of disease (endoscopy and computed tomography scores) were significantly lower in patients with migraine (p=0.027 and p=0.002, respectively), yet these patients scored lower on baseline RSDI and SNOT-22 scores (p=0.025 and p=0.019, respectively). QOL in both patients with and without migraine improved significantly after ESS (p=0.062).  
Conclusion: Patients with comorbid migraine and CRS are more likely to have less severe evidence of disease and worse preoperative baseline QOL scores. This may imply that comorbid migraine disorder, in the setting of CRS, compels these patients to seek surgical management earlier in the disease process. Regardless, ESS provides comparable improvement for both patients with and without comorbid migraine.

Deininger, M. W., Kopecky, K. J., Radich, J. P., Kamel-Reid, S., Stock, W., Paietta, E., et al. (2014).

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*, 164(2), 223-232.

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.

Delamater, A. R., & Matthew Lattal, K. (2014). The study of associative learning: Mapping from psychological to neural levels of analysis. *Neurobiology of Learning and Memory*,

One of the major achievements of the last century of research in experimental psychology is the identification of a coherent set of theories and principles to characterize the nature of simple forms of associative learning. Major advances are also currently being made at a rapid pace in the neurobiology of associative learning, and, interestingly, we are beginning to see how a mapping from a psychological level of analysis to underlying neurobiological mechanisms is possible. This collection of papers honors the illustrative careers of four major learning theorists from the experimental psychology tradition (Robert Rescorla, Allan Wagner, Nicholas Mackintosh, Anthony Dickinson) who have helped shape our understanding of behavioral principles. The

collection of works in this special issue reflects common interests among researchers working at both psychological and neurobiological levels of analysis towards a more comprehensive understanding of basic associative learning processes as they relate to several key issues identified and intensively studied by these influential learning theorists. These consist of the questions regarding (1) the critical conditions enabling learning, (2) the contents of learning, and (3) the rules that translate learning into performance. In one way or another, the separate contributions in this issue address these fundamental questions as they relate to a wide variety of currently exciting topics in the study of the neurobiology of learning and memory. © 2013.

DeLoughery, T. (2013). Review: Contemporary oral contraceptives are associated with venous thromboembolism and stroke. *Annals of Internal Medicine*, 159(12)

Desai, R. I., Grandy, D. K., Lupica, C. R., & Katz, J. L. (2014). Pharmacological characterization of a dopamine transporter ligand that functions as a cocaine antagonist. *Journal of Pharmacology and Experimental Therapeutics*, 348(1), 106-115.

An N-butyl analog of bupropion, JHW007 [N-(n-butyl)-3a-[bis(4-fluorophenyl)methoxy]-tropane], binds to dopamine transporters (DAT) but has reduced cocaine-like behavioral effects and antagonizes various effects of cocaine. The present study further examined mechanisms underlying these effects. Cocaine dose-dependently increased locomotion, whereas JHW007 was minimally effective but increased activity 24 hours after injection. JHW007 (3-10 mg/kg) dose-dependently and fully antagonized the locomotor-stimulant effects of cocaine (5-60 mg/kg), whereas N-methyl and N-allyl analogs and the dopamine (DA) uptake inhibitor GBR12909 [1-(2-[bis(4-fluorophenyl)methoxy]ethyl)-4-(3-phenylpropyl)piperazine dihydrochloride] stimulated activity and failed to antagonize effects of cocaine. JHW007 also blocked the locomotor-stimulant effects of the DAT inhibitor GBR12909 but not stimulation produced by the d-opioid agonist SNC 80 [4-[(R)-[(2S,5R)-4-allyl-2,5-dimethylpiperazin-1-yl](3-methoxyphenyl)methyl]-N,N-diethylbenzamide], which increases activity through nondopaminergic mechanisms. JHW007 blocked locomotor-stimulant effects of cocaine in both DA D2- and CB1-receptor knockout and wild-type mice, indicating a lack of involvement of these targets. Furthermore, JHW007 blocked effects of cocaine on stereotyped rearing but enhanced stereotyped sniffing, suggesting that

interference with locomotion by enhanced stereotypies is not responsible for the cocaine antagonist effects of JHW007. Time-course data indicate that administration of JHW007 antagonized the locomotor-stimulant effects of cocaine within 10 minutes of injection, whereas occupancy at the DAT, as determined in vivo, did not reach a maximum until 4.5 hours after injection. The  $\sigma_1$ -receptor antagonist BD 1008 [N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl) ethylamine dihydrobromide] blocked the locomotor stimulant effects of cocaine. Overall, these findings suggest that JHW007 has cocaine-antagonist effects that deviate from its DAT occupancy and that some other mechanism, possibly  $\sigma$ -receptor antagonist activity, may contribute to the cocaine antagonist effect of JHW007 and like drugs. Copyright © 2013 by The American Society for Pharmacology and Experimental Therapeutics.

Deshpande, A., Nelson, D., Corless, C. L., Deshpande, V., & O'Brien, M. J. (2014). Leiomyoma of the gastrointestinal tract with interstitial cells of Cajal: A mimic of gastrointestinal stromal tumor. *American Journal of Surgical Pathology*, 38(1), 72-77.

Leiomyomas (LMs) of the gastrointestinal tract arise within the muscularis mucosae (superficial) and muscularis propria (deep). There are isolated reports of KIT-positive cells, presumed interstitial cells of Cajal (ICCs), within gastrointestinal LMs. We have encountered esophageal LMs with a high proportion of KIT-positive and DOG1-positive spindle-shaped cells, an appearance that mimicked gastrointestinal stromal tumor. Our aim was to explore the prevalence of ICCs in LMs of the gastrointestinal tract and the etiopathogenic significance of these cells in this benign neoplasm. We identified 34 esophageal LMs (28 deep, 6 superficial), 8 gastric LMs, and 5 small-bowel LMs (all lesions in muscularis propria). We performed immunohistochemical staining studies for desmin, DOG1, and KIT on these neoplasms. We also evaluated 12 superficial colonic LMs. ICCs were distinguished from mast cells on the basis of morphology (elongated and occasionally branching spindle-shaped cells) and the presence of DOG1 reactivity. Four cases were screened for mutations in PDGFRA exons 12, 14, and 18 and KIT exons 9, 11, 13, and 17. ICCs were identified in all deep esophageal LMs and constituted an average of 20% of the lesional cells; focally, these cells comprised >50% of cells. The density of these cells was significantly higher than the background muscularis propria, and hyperplasia of ICCs was not identified in the adjacent muscle. ICCs were identified in 6 of 8 gastric LMs and 1 of 5 small-

bowel LMs and were entirely absent in all superficial esophageal and colonic/rectal LMs. There were no mutations in KIT or PDGFRA. ICCs are universally present in deep esophageal LMs, and thus these neoplasms could be mistaken for gastrointestinal stromal tumors, particularly on biopsy samples, an error associated with adverse clinical consequences. ICCs are also identified in gastric and intestinal LMs, albeit in a smaller proportion of cases. Colonization and hyperplasia by non-neoplastic ICCs likely account for this phenomenon. © 2013 by Lippincott Williams and Wilkins.

Ditzenberger, G. R., Wallen, L. D., Phelan, L., Escoe, S., & Collins, S. D. (2013). Supplemental protein and postnatal growth of very low birth weight infants: A randomized trial. *Journal of Neonatal-Perinatal Medicine*, 6(4), 285-294.

**BACKGROUND:** Providing adequate nutritional support to promote optimal postnatal growth for very low birth weight (VLBW) infants has been a difficult problem to surmount in the NICU. During the past 4 decades, improvements in neonatal critical care have made it possible for more VLBW infants to survive to discharge from NICUs. The NICHD Neonatal Network reported that while intrauterine growth restriction was present in 22% of VLBW infants at birth, 91% demonstrated postnatal growth restriction by 36 weeks post menstrual age. The persistence of this nearly universal growth deficit is associated with the inadequacy of protein and energy intake, which may account for 45-50% of the postnatal growth restriction. **OBJECTIVE:** The purpose of this study was to assess whether increasing enteral intake, using supplemental protein, would improve postnatal growth for VLBW infants. **STUDY DESIGN:** Randomized clinical trial. Sixty-four infants were enrolled (34 in control group with 15 infants <1000 g, and 30 in intervention group with 13 infants <1000 g). **RESULT:** There were no sustained statistical differences between weekly measurements of weight, length, head circumference, and skinfold thickness between groups. There were no significant differences between laboratory results except blood urea nitrogen at time of peak protein intake for intervention group. **CONCLUSIONS:** Supplemental enteral protein had minimal to no effect on postnatal weight, length, head circumference, body mass, or length of stay. It may be most important to provide consistent sustained nutritional support with protein from birth to reduce postnatal growth restriction, especially for those infants <1000 g at birth.

Doohan, N. C., Duane, M., Harrison, B., Lesko, S., & Devoe, J. E. (2014). The future of family medicine version 2.0: Reflections from pisacano scholars. *Journal of the American Board of Family Medicine : JABFM*, 27(1), 142-150.

The Future of Family Medicine (FFM) project has helped shape and direct the evolution of primary care medicine over the past decade. Pisacano Scholars, a group of leaders in family medicine supported by the American Board of Family Medicine, gathered for a 2-day symposium in April 2013 to explore the history of the FFM project and outline a vision for the next phase of this work-FFM version 2.0 (v2.0). After learning about the original FFM project (FFM v1.0), the group held interactive discussions using the World Cafe approach to conversational leadership. This commentary summarizes the discussions and highlights major themes relevant to FFM v2.0 identified by the group. The group endorsed the FFM v1.0 recommendations as still relevant and marveled at the progress made toward achieving many of those goals. Most elements of FFM v1.0 have moved forward, and some have been incorporated into policy blueprints for reform. Now is the time to refocus attention on facets of FFM v1.0 not yet realized and to identify key aspects missing from FFM v1.0. The Pisacano Scholars are committed to moving the FFM goals forward and hope that this expression of the group's vision will help to do so.

Doss, A., & Pereira, L. (2014). Strip of the month: January 2014. *Neoreviews*, 15(1), e37-e44.

Druker, B. J. (2014). Janet rowley (1925-2013). *Nature*, 505(7484), 484.

D'Souza, N. (2014). Transition to DSM-5: The resident perspective. *Academic Psychiatry : The Journal of the American Association of Directors of Psychiatric Residency Training and the Association for Academic Psychiatry*,

Dufour, B. D., Smith, C. A., Clark, R. L., Walker, T., & McBride, J. L. (2014). Intra-jugular vein delivery of AAV9-RNAi prevents neuropathological changes and weight loss in huntington's disease mice. *Molecular Therapy : The Journal of the American Society of Gene Therapy*,  
Huntington's disease (HD) is a fatal neurological disorder caused by a CAG repeat expansion in the HTT gene, which encodes a mutant huntingtin protein (mHTT). The mutation confers a toxic gain of function on huntingtin, leading to widespread neurodegeneration and inclusion formation

in many brain regions. Although the hallmark symptom of HD is hyperkinesia stemming from striatal degeneration, several other brain regions are affected which cause psychiatric, cognitive and metabolic symptoms. Additionally, mHTT expression in peripheral tissue is associated with skeletal muscle atrophy, cardiac failure, weight loss and diabetes. We, and others, have demonstrated a prevention of motor symptoms in HD mice following direct striatal injection of AAV serotype 1 encoding an RNA interference (RNAi) construct targeting mutant HTT mRNA (mHTT). Here, we expand these efforts and demonstrate that an intra-jugular vein injection of AAV serotype 9 expressing a mutant HTT-specific RNAi construct significantly reduced mHTT expression in multiple brain regions and peripheral tissues affected in HD. Correspondingly, this approach prevented atrophy and inclusion formation in key brain regions as well as the severe weight loss germane to HD transgenic mice. These results demonstrate that systemic delivery of AAV9-RNAi may provide more widespread clinical benefit for patients suffering from HD. *Molecular Therapy* (2014); doi:10.1038/mt.2013.289.

Dusi, S., Valletta, L., Haack, T. B., Tsuchiya, Y., Venco, P., Pasqualato, S., et al. (2014). Exome sequence reveals mutations in CoA synthase as a cause of neurodegeneration with brain iron accumulation. *American Journal of Human Genetics*, 94(1), 11-22.

Neurodegeneration with brain iron accumulation (NBIA) comprises a clinically and genetically heterogeneous group of disorders with progressive extrapyramidal signs and neurological deterioration, characterized by iron accumulation in the basal ganglia. Exome sequencing revealed the presence of recessive missense mutations in COASY, encoding coenzyme A (CoA) synthase in one NBIA-affected subject. A second unrelated individual carrying mutations in COASY was identified by Sanger sequence analysis. CoA synthase is a bifunctional enzyme catalyzing the final steps of CoA biosynthesis by coupling phosphopantetheine with ATP to form dephospho-CoA and its subsequent phosphorylation to generate CoA. We demonstrate alterations in RNA and protein expression levels of CoA synthase, as well as CoA amount, in fibroblasts derived from the two clinical cases and in yeast. This is the second inborn error of coenzyme A biosynthesis to be implicated in NBIA. © 2014 The American Society of Human Genetics.

Duty, B. D., Kreshover, J. E., Richstone, L., & Kavoussi, L. R. (2014). Review of appendiceal on-lay flap in the management of complex ureteral strictures in six patients. *BJU International*,

OBJECTIVES: Evaluation of appendiceal on-lay flap ureteroplasty for repairing complex right proximal and mid ureteral strictures. PATIENTS AND METHODS: Between August 2006 and August 2012 four women and two men (mean age 34.2 years) underwent right laparoscopic appendiceal on-lay flap ureteroplasty. Mean stricture length was 2.5 cm. Stricture formation was secondary to impacted ureteral stones in three patients and failed pyeloplasty for congenital ureteropelvic junction obstruction in the remaining three. Each patient had ipsilateral flank pain prior to surgery. RESULTS: Mean operative time, estimated blood loss and hospital stay were 244 minutes, 175 ml, and 3.2 days, respectively. No intraoperative or perioperative complications were noted. The objective success rate was 100% (all patients had radiographic and/or endoscopic resolution of their ureteral strictures). The subjective success rate was 66%, (two patients developed recurrent discomfort, which upon exploration was found to be due to fibrosis away from the appendiceal on-lay graft where the gonadal vessels crossed the ureter). Both patients with recurrent pain underwent laparoscopic ureterolysis and bladder advancement flap proximal to the appendiceal on-lay, which markedly improved one patient's pain but the other patient continued to have discomfort ultimately resulting in a laparoscopic nephroureterectomy. CONCLUSIONS: Appendiceal on-lay ureteroplasty is a viable treatment option for patients with complex right proximal and mid ureteral strictures, while minimizing the potential morbidity of appendiceal and ileal interposition.

El-Gohary, M., Pearson, S., McNames, J., Mancini, M., Horak, F., Mellone, S., et al. (2014). Continuous monitoring of turning in patients with movement disability. *Sensors (Switzerland)*, *14*(1), 356-369.

Difficulty with turning is a major contributor to mobility disability and falls in people with movement disorders, such as Parkinson's disease (PD). Turning often results in freezing and/or falling in patients with PD. However, asking a patient to execute a turn in the clinic often does not reveal their impairments. Continuous monitoring of turning with wearable sensors during spontaneous daily activities may help clinicians and patients determine who is at risk of falls and could benefit from preventative interventions. In this study, we show that continuous monitoring

of natural turning with wearable sensors during daily activities inside and outside the home is feasible for people with PD and elderly people. We developed an algorithm to detect and characterize turns during gait, using wearable inertial sensors. First, we validate the turning algorithm in the laboratory against a Motion Analysis system and against a video analysis of 21 PD patients and 19 control (CT) subjects wearing an inertial sensor on the pelvis. Compared to Motion Analysis and video, the algorithm maintained a sensitivity of 0.90 and 0.76 and a specificity of 0.75 and 0.65, respectively. Second, we apply the turning algorithm to data collected in the home from 12 PD and 18 CT subjects. The algorithm successfully detects turn characteristics, and the results show that, compared to controls, PD subjects tend to take shorter turns with smaller turn angles and more steps. Furthermore, PD subjects show more variability in all turn metrics throughout the day and the week. © 2013 by the authors; licensee MDPI, Basel, Switzerland.

El-Khoueiry, A. B., Rankin, C., Siegel, A. B., Iqbal, S., Gong, I. Y., Micetich, K. C., et al. (2014).

S0941: A phase 2 SWOG study of sorafenib and erlotinib in patients with advanced gallbladder carcinoma or cholangiocarcinoma. *British Journal of Cancer*,

Background: Gallbladder cancers and cholangiocarcinomas make up a heterogeneous group of tumours with a poor prognosis in advanced stages. On the basis of evidence of dysregulation of the epidermal growth factor receptor, vascular endothelial growth factor and mitogen-activated protein kinase pathways in biliary cancers, we performed a phase 2 trial of sorafenib and erlotinib in patients with advanced biliary cancers. Methods: Eligible patients were previously untreated in the advanced setting with adequate hepatic and bone marrow function. Sorafenib and erlotinib were administered continuously at 400 mg BID and 100 mg daily, respectively. Results: Thirty-four eligible patients were recruited. The study was terminated after the first stage of accrual owing to failure to meet the predetermined number of patients who were alive and progression free at 4 months. There were two unconfirmed partial responses (6%, 95% CI: 1-20%), with a median progression-free survival of 2 months (95% CI: 2-3), and median overall survival of 6 months (95% CI: 3-8 months). Grade 3 and 4 adverse events included hypertension, AST/ALT increase, bilirubin increase, diarrhoea, hypokalaemia, hypophosphatemia and rash. Conclusions: Despite compelling preclinical rationale, the combination of sorafenib and erlotinib does not have

promising clinical activity in an unselected population of patients with biliary cancers. Improved patient selection based on tumour biology and molecular markers is critical for future evaluation of targeted therapies in this disease. *British Journal of Cancer* advance online publication 14 January 2014; doi:10.1038/bjc.2013.801 [www.bjcancer.com](http://www.bjcancer.com).

Elliot, D. L., Goldberg, L., & Goldberg, M. J. (2014). Digital video technology and production 101: Lights, camera, action. *Health Promotion Practice, 15*(1), 86-90.

Videos are powerful tools for enhancing the reach and effectiveness of health promotion programs. They can be used for program promotion and recruitment, for training program implementation staff/volunteers, and as elements of an intervention. Although certain brief videos may be produced without technical assistance, others often require collaboration and contracting with professional videographers. To get practitioners started and to facilitate interactions with professional videographers, this Tool includes a guide to the jargon of video production and suggestions for how to integrate videos into health education and promotion work. For each type of video, production principles and issues to consider when working with a professional videographer are provided. The Tool also includes links to examples in each category of video applications to health promotion. © 2013 Society for Public Health Education.

Farr, J., Crawford, D. C., Diduch, D. R., Arendt, E. A., Ma, C. B., & Li, C. S. (2013). Prospective, multicenter, pilot study to evaluate symptom relief in patients with medial knee osteoarthritis (OA) treated with the KineSpring® knee implant for load reduction - the SOAR protocol. *Journal of Long-Term Effects of Medical Implants, 23*(2-3), 161-173.

The study described here is designed as a prospective, multicenter, open-label, single-arm pilot study. Eligible subjects with symptomatic osteoarthritis of the medial compartment of the knee will be enrolled in the study and will receive the KineSpring® Knee Implant System. The study population will consist of adult patients between 25 and 80 years of age that have been diagnosed with medial knee osteoarthritis and have failed to improve after at least 6 months of conservative medical treatment. A patient is considered to have a clinically important change in OA pain and function with a minimum improvement of 20% compared to baseline measures. We will collect data on the safety and effectiveness of the KineSpring in patients with primarily

unicompartmental medial knee osteoarthritis through 24 months of postoperative follow-up. These data will provide insights on the overall clinical success and safety outcome of KineSpring System. © 2013 by Begell House, Inc.

Filtz, T. M., Vogel, W. K., & Leid, M. (2014). Regulation of transcription factor activity by interconnected post-translational modifications. *Trends in Pharmacological Sciences*, 35(2), 76-85.

Transcription factors comprise just over 7% of the human proteome and serve as gatekeepers of cellular function, integrating external signal information into gene expression programs that reconfigure cellular physiology at the most basic levels. Surface-initiated cell signaling pathways converge on transcription factors, decorating these proteins with an array of post-translational modifications (PTMs) that are often interdependent, being linked in time, space, and combinatorial function. These PTMs orchestrate every activity of a transcription factor over its entire lifespan—from subcellular localization to protein-protein interactions, sequence-specific DNA binding, transcriptional regulatory activity, and protein stability—and play key roles in the epigenetic regulation of gene expression. The multitude of PTMs of transcription factors also offers numerous potential points of intervention for development of therapeutic agents to treat a wide spectrum of diseases. We review PTMs most commonly targeting transcription factors, focusing on recent reports of sequential and linked PTMs of individual factors.

Fischer, J. M., Schepers, A. G., Clevers, H., Shibata, D., & Liskay, R. M. (2014). Occult progression by *apc*-deficient intestinal crypts as a target for chemoprevention. *Carcinogenesis*, 35(1), 237-246. Although *Apc* mutation is widely considered an initiating event in colorectal cancer, little is known about the earliest stages of tumorigenesis following sporadic *Apc* loss. Therefore, we have utilized a novel mouse model that facilitates the sporadic inactivation of *Apc* via frameshift reversion of *Cre* in single, isolated cells and subsequently tracks the fates of *Apc*-deficient intestinal cells. Our results suggest that consistent with *Apc* being a 'gatekeeper', loss of *Apc* early in life during intestinal growth leads to adenomas or increased crypt fission, manifested by fields of mutant but otherwise normal-appearing crypts. In contrast, *Apc* loss occurring later in life has minimal consequences, with mutant crypts being less prone to either increased crypt fission or adenoma

formation. Using the stem cell-specific Lgr5-CreER mouse, we generated different sized fields of Apc-deficient crypts via independent recombination events and found that field size correlates with progression to adenoma. To evaluate this early stage prior to adenoma formation as a therapeutic target, we examined the chemopreventive effects of sulindac on Apc-deficient occult crypt fission. We found that sulindac treatment started early in life inhibits the morphologically occult spread of Apc-deficient crypts and thus reduces adenoma numbers. Taken together these results suggest that: (i) earlier Apc loss promotes increased crypt fission, (ii) a field of Apc-deficient crypts, which can form via occult crypt fission or independent neighboring events, is an important intermediate between loss of Apc and adenoma formation and (iii) normal-appearing Apc-deficient crypts are potential unappreciated targets for cancer screening and chemoprevention. © The Author 2013. Published by Oxford University Press. All rights reserved.

Fleischman, A. G., & Tyner, J. W. (2013). Causal role for JAK2 V617F in thrombosis. *Blood*, *122*(23), 3705-3706.

The article by Takahashi and colleagues is impactful because it helps validate the decision of both sets of response criteria that focus on peripheral blood analysis for the assessment of the JAK2 V617F allele burden. The quality demonstration in a high number of samples across MPNs demonstrating the interchangeable nature of measuring alleleburden in blood and bone marrow will be very helpful in clinical trials moving forward, as well as potentially clinical practice as we further validate the impact that reduction in allele burden is helpful. In addition, it helps validate the practice even today of monitoring the JAK2 V617F allele burden in patients post stem cell transplantation in terms of monitoring for both response and relapse. As the current clinical trials of MPNs are evolving from single agent to combination strategies, the ability to dynamically follow allele burden in the course of these trials through the peripheral blood is an important advancement. Whether in the future monitoring the lower prevalence MPN molecular mutations will be helpful in assessment of therapeutic response remains a question to be answered. © 2013 by The American Society of Hematology.

Fleseriu, M. (2014). Insight into cardiovascular risk factors in patients with acromegaly. *Endocrine*,

Floc'H, J. L., Tan, W., Telang, R. S., Vlajkovic, S. M., Nuttall, A., Rooney, W. D., et al. (2014). Markers of cochlear inflammation using MRI. *Journal of Magnetic Resonance Imaging*, 39(1), 150-161.

Purpose To quantify spatial and temporal inflammation-induced changes in vascular permeability and macrophage infiltration in guinea-pig (GP) cochlea using MRI. Materials and Methods GPs were injected with lipopolysaccharide (LPS) to induce cochlear inflammation. One group was injected with a gadolinium based contrast agent (GBCA) and dynamic contrast enhanced (DCE)-MRI was performed at 4, 7, and 10 days after LPS treatment. A two-compartment pharmacokinetic model was used to determine the apparent rate constant of GBCA extravasation ( $K_{trans}$ ). A second group was injected with ultrasmall superparamagnetic iron oxide particles (USPIOs) and studied at 2, 3, and 7 days after LPS treatment to detect tissue USPIO uptake and correlate with histology. For both groups, control GPs were scanned similarly. Results The signal enhancement increased substantially and more rapidly at day 4 in LPS-treated than in control cochlea shortly following GBCA injection.  $K_{trans}$  of LPS-treated cochlea was maximum on day 4 at  $0.0218 \pm 0.0032 \text{ min}^{-1}$  and then decreased to control level at  $0.0036 \pm 0.0004 \text{ min}^{-1}$  by day 10. In the second group, the relative signal intensity and T2 in cochlear perilymphatic spaces on day 2 decreased, on average, by 54% and 45%, respectively, compared with baseline and then remained under control levels by day 7. This suggests the infiltration of inflammatory cells, although unconfirmed by histology. Conclusion This provides the first measurement of cochlear vascular permeability using MRI and a quantitative evaluation of the development of cochlear inflammation. MRI holds considerable potential for the assessment of disease processes such as clinical diagnosis of conditions such as labyrinthitis. *J. Magn. Reson. Imaging* 2014;39:150-161. © 2013 Wiley Periodicals, Inc. Copyright © 2013 Wiley Periodicals, Inc.

Gallun, F. J., Diedesch, A. C., Kempel, S. D., & Jakien, K. M. (2013). Independent impacts of age and hearing loss on spatial release in a complex auditory environment. *Frontiers in Neuroscience*, 7, 252.

Listeners in complex auditory environments can benefit from the ability to use a variety of spatial and spectrotemporal cues for sound source segregation. Probing these abilities is an essential part of gaining a more complete understanding of why listeners differ in navigating the auditory environment. Two fundamental processes that can impact the auditory systems of individual

listeners are aging and hearing loss. One difficulty with uncovering the independent effects of age and hearing loss on spatial release is the commonly observed phenomenon of age-related hearing loss. In order to reveal the effects of aging on spatial hearing, it is essential to develop testing methods that reduce the influence of hearing loss on the outcomes. The statistical power needed for such testing generally requires a larger number of participants than can easily be tested using traditional behavioral methods. This work describes the development and validation of a rapid method by which listeners can be categorized in terms of their ability to use spatial and spectrotemporal cues to separate competing speech streams. Results show that when age and audibility are not covarying, age alone can be shown to substantially reduce spatial release from masking. These data support the hypothesis that aging, independent of an individual's hearing threshold, can result in changes in the cortical and/or subcortical structures essential for spatial hearing.

Ganzini, L. (2014). Psychiatric evaluations for individuals requesting assisted death in Washington and Oregon should not be mandatory. *General Hospital Psychiatry*, 36(1), 10-12.

Gardner, C. J., Trisnadi, J., Kim, T. K., Brammer, K., Reiss, L., Chen, L. H., et al. (2013). Controlled metallic nanopillars for low impedance biomedical electrode. *Acta Biomaterialia*, Radial metallic nanopillar/nanowire structures can be created by a controlled radiofrequency (RF) plasma processing technique on the surface of certain alloy wires, including important biomedical alloys such as MP35N (Co-Ni-Cr-Mo alloy), platinum-iridium and stainless steel. In electrode applications such as pacemakers or neural stimulators, the increase in surface area in elongated MP35N nanopillars allows for decreased surface impedance and greater current density. However, the nanopillar height on MP35N alloy tends to be self-limiting at approximately 1-3µm. The objective of this study was to further elongate the radial nanopillars so as to reduce electrode impedance for biomedical electrode applications. Intelligent experimental design allowed for efficient investigation of processing parameters, including plasma material, process duration, power, pressure and repetition. It was found that multi-step repeated processing in the parameter-controlled RF environment could increase nanopillar height to approximately 10µm, a 400% improvement, while the RF plasma processing with identical total duration but in a single

step did not lead to desired nanopillar elongation. Measurement of electrode impedance in phosphate-buffered saline solution showed an associated decrease to one-fifth of the surface impedance of unprocessed wire for signals below 100Hz. For the purposes of this study, MP35N and Pt-Ir wires were characterized and demonstrated augmented surface impedance properties which, in combination with superior cell integration, enhanced biomedical electrode performance.

Gardner, C. J., Trisnadi, J., Kim, T. K., Brammer, K., Reiss, L., Chen, L. -, et al. (2014). Controlled metallic nanopillars for low impedance biomedical electrode. *Acta Biomaterialia*, Radial metallic nanopillar/nanowire structures can be created by a controlled radiofrequency (RF) plasma processing technique on the surface of certain alloy wires, including important biomedical alloys such as MP35N (Co-Ni-Cr-Mo alloy), platinum-iridium and stainless steel. In electrode applications such as pacemakers or neural stimulators, the increase in surface area in elongated MP35N nanopillars allows for decreased surface impedance and greater current density. However, the nanopillar height on MP35N alloy tends to be self-limiting at ~1-3  $\mu\text{m}$ . The objective of this study was to further elongate the radial nanopillars so as to reduce electrode impedance for biomedical electrode applications. Intelligent experimental design allowed for efficient investigation of processing parameters, including plasma material, process duration, power, pressure and repetition. It was found that multi-step repeated processing in the parameter-controlled RF environment could increase nanopillar height to ~10  $\mu\text{m}$ , a 400% improvement, while the RF plasma processing with identical total duration but in a single step did not lead to desired nanopillar elongation. Measurement of electrode impedance in phosphate-buffered saline solution showed an associated decrease to one-fifth of the surface impedance of unprocessed wire for signals below 100 Hz. For the purposes of this study, MP35N and Pt-Ir wires were characterized and demonstrated augmented surface impedance properties which, in combination with superior cell integration, enhanced biomedical electrode performance. © 2013 Acta Materialia Inc.

Gathey, D., Zhu, A. Y., Stagner, A., Terry, M. A., & Jun, A. S. (2014). Fuchs endothelial corneal dystrophy in patients with myotonic dystrophy: A case series. *Cornea*, 33(1), 96-98.

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. Copyright © 2013 by Lippincott Williams & Wilkins.

Gausche-Hill, M., Brown, K. M., Oliver, Z. J., Sasson, C., Dayan, P. S., Eschmann, N. M., et al. (2014). An evidence-based guideline for prehospital analgesia in trauma. *Prehospital Emergency Care*, 18(SUPPL.1), 25-34.

Background. The management of acute traumatic pain is a crucial component of prehospital care and yet the assessment and administration of analgesia is highly variable, frequently suboptimal, and often determined by consensus-based regional protocols. Objective. To develop an evidence-based guideline (EBG) for the clinical management of acute traumatic pain in adults and children by advanced life support (ALS) providers in the prehospital setting. Methods. We recruited a multi-stakeholder panel with expertise in acute pain management, guideline development, health informatics, and emergency medical services (EMS) outcomes research. Representatives of the National Highway Traffic Safety Administration (sponsoring agency) and a major children's

research center (investigative team) also contributed to the process. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to guide the process of question formulation, evidence retrieval, appraisal/synthesis, and formulation of recommendations. The process also adhered to the National Prehospital Evidence-Based Guideline (EBG) model process approved by the Federal Interagency Council for EMS and the National EMS Advisory Council. Results. Four strong and three weak recommendations emerged from the process; two of the strong recommendations were linked to high-and moderate-quality evidence, respectively. The panel recommended that all patients be considered candidates for analgesia, regardless of transport interval, and that opioid medications should be considered for patients in moderate to severe pain. The panel also recommended that all patients should be reassessed at frequent intervals using a standardized pain scale and that patients should be re-dosed if pain persists. The panel suggested the use of specific age-appropriate pain scales. Conclusion. GRADE methodology was used to develop an evidence-based guideline for prehospital analgesia in trauma. The panel issued four strong recommendations regarding patient assessment and narcotic medication dosing. Future research should define optimal approaches for implementation of the guideline as well as the impact of the protocol on safety and effectiveness metrics. © 2014 National Association of EMS Physicians.

Gibbs, D. L., Gralinski, L., Baric, R. S., & McWeeney, S. K. (2014). Multi-omic network signatures of disease. *Frontiers in Genetics, 4*, 309.

To better understand dynamic disease processes, integrated multi-omic methods are needed, yet comparing different types of omic data remains difficult. Integrative solutions benefit experimenters by eliminating potential biases that come with single omic analysis. We have developed the methods needed to explore whether a relationship exists between co-expression network models built from transcriptomic and proteomic data types, and whether this relationship can be used to improve the disease signature discovery process. A naive, correlation based method is utilized for comparison. Using publicly available infectious disease time series data, we analyzed the related co-expression structure of the transcriptome and proteome in response to SARS-CoV infection in mice. Transcript and peptide expression data was filtered using quality scores and subset by taking the intersection on mapped Entrez IDs. Using this data set,

independent co-expression networks were built. The networks were integrated by constructing a bipartite module graph based on module member overlap, module summary correlation, and correlation to phenotypes of interest. Compared to the module level results, the naive approach is hindered by a lack of correlation across data types, less significant enrichment results, and little functional overlap across data types. Our module graph approach avoids these problems, resulting in an integrated omic signature of disease progression, which allows prioritization across data types for down-stream experiment planning. Integrated modules exhibited related functional enrichments and could suggest novel interactions in response to infection. These disease and platform-independent methods can be used to realize the full potential of multi-omic network signatures. The data (experiment SM001) are publically available through the NIAID Systems Virology (<https://www.systemsvirology.org>) and PNNL (<http://omics.pnl.gov>) web portals. Phenotype data is found in the supplementary information. The ProCoNA package is available as part of Bioconductor 2.13.

Gilmour, H., Stranges, S., Kaplan, M., Feeny, D., McFarland, B., Huguet, N., et al. (2013).

Longitudinal trajectories of sleep duration in the general population. *Health Reports*, 24(11), 1-9. Background Sleep duration has been associated with overall health status, health behaviours, and mortality. Little is known about habitual longitudinal patterns of sleep in the general population. Furthermore, evidence about whether sleep duration has declined in recent years is contradictory. Data and methods The study was based on 8,673 adults aged 18 or older in 2002/2003 (cycle 5 of the National Population Health Survey) and used five self-reported biennial measurements of sleep duration spanning eight years. Multiple distinct trajectories of sleep duration were estimated using latent class growth modeling. Results Four modelled trajectories of sleep duration were identified: short (11.1% of the population); low-normal (49.4%); high-normal (37.0%); and long (2.4%). The short, low-normal and highnormal sleep trajectories each exhibited a slight linear decline in hours of sleep over the eight years of follow-up. Poor sleep was predictive of trajectory group membership and associated with a decrease in sleep duration for three of the four groups. Age and sex were also significant predictors of trajectory group membership. Interpretation Trajectory analysis is a useful descriptive tool in the investigation of sleep duration over time. © Minister of Industry, 2013.

Goldthwaite, L. M., Baldwin, M. K., Page, J., Micks, E. A., Nichols, M. D., Edelman, A. B., et al. (2013).

Comparison of interventions for pain control with tenaculum placement: A randomized clinical trial. *Contraception*,

OBJECTIVE: Although previous studies have demonstrated that a variety of local anesthetics are effective to decrease pain associated with tenaculum placement, no studies directly compare an injection with a topical anesthetic. The objective of this study was therefore to compare mean pain scores with tenaculum placement after an intracervical lidocaine injection or topical lidocaine gel. STUDY DESIGN: A randomized, single-blinded trial of women presenting for office gynecologic procedures that required a tenaculum. Women aged 18 years or older were randomized to receive either a 1% lidocaine intracervical injection or topical application of 2% lidocaine gel to the cervix immediately prior to tenaculum placement. The primary outcome was pain at the time of tenaculum placement, measured on a 100 mm Visual Analog Scale. Secondary outcomes included pain with the intervention and satisfaction with tenaculum placement.

RESULTS: Seventy-four women were enrolled and randomized; 35 subjects in each group met criteria for analysis. The two groups had similar socio-demographic characteristics. Women who received the injection had lower mean pain levels at tenaculum placement [12.3 mm (S.D. 17.4 mm) versus 36.6 mm (S.D. 23.0 mm),  $p < .001$ ] but higher mean pain levels with study drug application [20.4 mm (S.D. 19.4 mm) versus 5.9 mm (S.D. 8.6 mm),  $p < .001$ ]. Satisfaction with tenaculum placement was similar for the two groups. CONCLUSION: Mean pain with tenaculum placement is lower after receiving a lidocaine injection than after receiving a topical lidocaine gel. Satisfaction with tenaculum placement is similar with both interventions.

Goldthwaite, L. M., Baldwin, M. K., Page, J., Micks, E. A., Nichols, M. D., Edelman, A. B., et al. (2014).

Comparison of interventions for pain control with tenaculum placement: A randomized clinical trial. *Contraception*,

Objective: Although previous studies have demonstrated that a variety of local anesthetics are effective to decrease pain associated with tenaculum placement, no studies directly compare an injection with a topical anesthetic. The objective of this study was therefore to compare mean pain scores with tenaculum placement after an intracervical lidocaine injection or topical lidocaine gel. Study Design: A randomized, single-blinded trial of women presenting for office gynecologic

procedures that required a tenaculum. Women aged 18 years or older were randomized to receive either a 1% lidocaine intracervical injection or topical application of 2% lidocaine gel to the cervix immediately prior to tenaculum placement. The primary outcome was pain at the time of tenaculum placement, measured on a 100 mm Visual Analog Scale. Secondary outcomes included pain with the intervention and satisfaction with tenaculum placement. Results: Seventy-four women were enrolled and randomized; 35 subjects in each group met criteria for analysis. The two groups had similar socio-demographic characteristics. Women who received the injection had lower mean pain levels at tenaculum placement [12.3 mm (S.D. 17.4 mm) versus 36.6 mm (S.D. 23.0 mm),  $p < .001$ ] but higher mean pain levels with study drug application [20.4 mm (S.D. 19.4 mm) versus 5.9 mm (S.D. 8.6 mm),  $p < .001$ ]. Satisfaction with tenaculum placement was similar for the two groups. Conclusion: Mean pain with tenaculum placement is lower after receiving a lidocaine injection than after receiving a topical lidocaine gel. Satisfaction with tenaculum placement is similar with both interventions. © 2014 Elsevier Inc. All rights reserved.

Gray, N. E., Morre, J., Kelley, J., Maier, C. S., Stevens, J. F., Quinn, J. F., et al. (2014). Caffeoylquinic acids in centella asiatica protect against amyloid-beta toxicity. *Journal of Alzheimer's Disease : JAD*,

The accumulation of amyloid-beta (A $\beta$ ) is a hallmark of Alzheimer's disease and is known to result in neurotoxicity both in vivo and in vitro. We previously demonstrated that treatment with the water extract of *Centella asiatica* (CAW) improves learning and memory deficits in Tg2576 mice, an animal model of A $\beta$  accumulation. However the active compounds in CAW remain unknown. Here we used two in vitro models of A $\beta$  toxicity to confirm this neuroprotective effect and identify several active constituents of the CAW extract. CAW reduced A $\beta$ -induced cell death and attenuated A $\beta$ -induced changes in tau expression and phosphorylation in both the MC65 and SH-SY5Y neuroblastoma cell lines. We confirmed and quantified the presence of several mono- and dicaffeoylquinic acids (CQAs) in CAW using chromatographic separation coupled to mass spectrometry and ultraviolet spectroscopy. Multiple dicaffeoylquinic acids showed efficacy in protecting MC65 cells against A $\beta$ -induced cytotoxicity. Isochlorogenic acid A and 1,5-dicaffeoylquinic acid were found to be the most abundant CQAs in CAW, and the most active in protecting MC65 cells from A $\beta$ -induced cell death. Both compounds showed

neuroprotective activity in MC65 and SH-SY5Y cells at concentrations comparable to their levels in CAW. Each compound not only mitigated Abeta-induced cell death, but was able to attenuate Abeta-induced alterations in tau expression and phosphorylation in both cell lines, as seen with CAW. These data suggest that CQAs are active neuroprotective components in CAW, and therefore are important markers for future studies on CAW standardization, bioavailability, and dosing.

Greninger, D. A., Lowry, E. A., Porco, T. C., Naseri, A., Stamper, R. L., & Han, Y. (2014). Resident-performed selective laser trabeculoplasty in patients with open-angle glaucoma. *JAMA Ophthalmology*,

IMPORTANCE To our knowledge, this is the first study to investigate effectiveness and complication rates of resident-performed selective laser trabeculoplasty (SLT). OBJECTIVES To evaluate the effectiveness and complications of SLT performed by resident ophthalmologists and to identify predictors for success. DESIGN, SETTING, AND PARTICIPANTS Retrospective case series of 81 patients with open-angle glaucoma undergoing 110 SLT procedures from November 17, 2009, through December 16, 2011, at the San Francisco Veterans Affairs Medical Center. INTERVENTION Resident-performed SLT. MAIN OUTCOMES AND MEASURES Intraocular pressure (IOP) reduction. Secondary outcomes included change in eyedrop medications, complication rates, and predictors of SLT success defined as a 20% reduction in IOP. RESULTS The mean IOP at baseline, defined as the average IOP of the 2 appointments prior to the SLT procedure, was 18.7 mm Hg. The mean decrease in postoperative IOP compared with baseline was 2.2 mm Hg (12%; 95% CI, 5%-19%) at 12 months and 3.3 mm Hg (18%; 95% CI, 13%-23%), 2.8 mm Hg (15%; 95% CI, 10%-21%), and 3.6 mm Hg (19%; 95% CI, 11%-27%) at 3, 6, and 24 months, respectively (all  $P < .001$ , linear mixed-effects regression). Success rates were 36% (95% CI, 27%-47%) at 12 months and 41% (95% CI, 31%-53%), 50% (95% CI, 40%-60%), and 39% (95% CI, 26%-53%) at 3, 6, and 24 months, respectively. The most common complication was a temporary IOP spike, with increases of at least 6 mm Hg occurring in 7% (95% CI, 4%-14%) of the population. The largest IOP spike was 11 mm Hg. Increased number of laser shots performed was not associated with better IOP control but was associated with a reduction in number of eyedrop medications ( $P = .02$ ). Increased baseline IOP was associated with an odds ratio for

success of 1.24 (95% CI, 1.08-1.44) at 3 months, 1.20 (95% CI, 1.05-1.37) at 6 months, and 1.31 (95% CI, 1.13-1.53) at 12 months of follow-up ( $P = .003$ ,  $P = .006$ , and  $P < .001$ , respectively, logistic regression). In a multivariate analysis, baseline IOP remained the greatest predictor of effectiveness. CONCLUSIONS AND RELEVANCE Resident-performed SLT obtains outcomes similar to the IOP reduction reported in the literature for attending-performed SLT with low levels of complications. Increasing the number of shots in a treatment session may lead to less long-term need for eyedrop medications. In this patient group, higher baseline IOP was the strongest predictor of treatment effectiveness.

Gross, A. F., & Stern, T. A. (2014). Neuropsychiatric conditions associated with anesthesia exposure. *Psychosomatics*, *55*(1), 21-28.

Background: Although anesthetics have been used for more than a century, their mechanisms of action remain poorly understood. Given that a number of intraoperative and postoperative neuropsychiatric syndromes have been linked to the use of anesthetics, practitioners should familiarize themselves with these conditions. Methods: Basic concepts about anesthesia are reviewed and neuropsychiatric syndromes associated with anesthesia exposure described. Conclusions: Emergence delirium, postoperative delirium, postoperative cognitive dysfunction, and intraoperative awareness can develop in association with use of inhalation anesthetics and intravenously administered anesthetics. © 2014 The Academy of Psychosomatic Medicine.

Grunwald, J. E., Daniel, E., Huang, J., Ying, G. -, Maguire, M. G., Toth, C. A., et al. (2014). Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*, *121*(1), 150-161.

Purpose To describe risk factors for geographic atrophy (GA) in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT). Design Cohort within a randomized clinical trial. Participants We analyzed 1024 CATT patients with no GA visible on color fundus photographs (CFPs) and/or fluorescein angiograms (FAs) at enrollment. Methods Eyes were assigned to ranibizumab (0.5 mg) or bevacizumab (1.25 mg) treatment and to a 2-year monthly or pro re nata (PRN) injection regimen, or monthly injections for 1 year and PRN for 1 year. Demographic, genetic, and baseline ocular characteristics and lesion features of CFP/FA and optical coherence

tomography (OCT) were evaluated as risk factors for GA through 2 years of follow-up. Time-dependent Cox proportional hazard models were used to estimate adjusted hazard ratios (aHRs). Main Outcome Measures Development of GA. Results By 2 years, GA developed in 187 of 1024 patients (18.3%). Baseline risk factors for GA development included baseline visual acuity (VA)  $\leq 20/200$  (aHR, 2.65; 95% confidence interval [CI], 1.43-4.93), retinal angiomatous proliferation (RAP; aHR, 1.69; 95% CI, 1.16-2.47), GA in the fellow eye (aHR, 2.07; 95% CI, 1.40-3.08), and intraretinal fluid at the foveal center (aHR, 2.10; 95% CI, 1.34-3.31). Baseline factors associated with lower risk for GA development included blocked fluorescence (aHR, 0.49; 95% CI, 0.29-0.82), OCT measurements of subretinal fluid thickness of  $>25 \mu$  (aHR, 0.52; 95% CI, 0.35-0.78), subretinal tissue complex thickness of  $>275$  compared with  $\leq 75 \mu$  (aHR, 0.31; 95% CI, 0.19-0.50), and vitreomacular attachment (aHR, 0.55; 95% CI, 0.31-0.97). Ranibizumab compared with bevacizumab had a higher risk (aHR, 1.43; 95% CI, 1.06-1.93), and monthly dosing had a higher risk (aHR, 1.59; 95% CI, 1.17-2.16) than PRN dosing. There were no strong associations between development of GA and the presence of risk alleles for CFH, ARMS 2, HTRA1, C3, or TLR3. Conclusions Approximately one fifth of CATT patients developed GA within 2 years of treatment. Independent baseline risk factors included poor VA, RAP, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. Anti-vascular endothelial growth factor therapy may have a role in the development of GA. © 2014 by the American Academy of Ophthalmology.

Gupta, S., & Cigarroa, J. E. (2014). Bleeding, a call to action. *Catheterization and Cardiovascular Interventions : Official Journal of the Society for Cardiac Angiography & Interventions*, 83(2), 190-191.

Gupta, V., Malone, A. K., Hari, P. N., Ahn, K. W., Hu, Z. -, Gale, R. P., et al. (2014). Reduced-intensity hematopoietic cell transplantation for patients with primary myelofibrosis: A cohort analysis from the center for international blood and marrow transplant research. *Biology of Blood and Marrow Transplantation*, 20(1), 89-97.

We evaluated outcomes and associated prognostic factors in 233 patients undergoing allogeneic hematopoietic cell transplantation (HCT) for primary myelofibrosis (MF) using reduced-intensity conditioning (RIC). The median age at RIC HCT was 55 yr. Donors were a matched sibling donor

(MSD) in 34% of RIC HCTs, an HLA well-matched unrelated donor (URD) in 45%, and a partially matched/mismatched URD in 21%. Risk stratification according to the Dynamic International Prognostic Scoring System (DIPSS) was 12% low, 49% intermediate-1, 37% intermediate-2, and 1% high. The probability of survival at 5 yr was 47% (95% confidence interval [CI], 40% to 53%). In a multivariate analysis, donor type was the sole independent factor associated with survival. Adjusted probabilities of survival at 5-yr were 56% (95% CI, 44% to 67%) for MSD, 48% (95% CI, 37% to 58%) for well-matched URD, and 34% (95% CI, 21% to 47%) for partially matched/mismatched URD (P=002). The relative risk (RR) for NRM was 3.92 (P= .006) for well-matched URD and 9.37 (P < .0001) for partially matched/mismatched URD. Trends toward increased NRM (RR, 1.7; P= .07) and inferior survival (RR, 1.37; P= .10) were observed in DIPSS intermediate-2/high-risk patients compared with DIPSS low/intermediate-1 risk patients. Our data indicate that RIC HCT is a potentially curative option for patients with MF, and that donor type is the most important factor influencing survival in these patients. © 2014 American Society for Blood and Marrow Transplantation.

Gyurkocza, B., Gutman, J., Nemecek, E. R., Bar, M., Milano, F., Ramakrishnan, A., et al. (2014).

Treosulfan, fludarabine, and 2-gy total body irradiation followed by allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome and acute myeloid leukemia. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

Allogeneic hematopoietic cell transplantation (HCT) offers curative therapy for many patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). However, post-HCT relapse remains a major problem, particularly in patients with high-risk cytogenetics. In this prospective phase II trial, we assessed the efficacy and toxicity of treosulfan, fludarabine, and 2-Gy total body irradiation (TBI) as conditioning for allogeneic HCT in patients with MDS or AML. Ninety-six patients with MDS (n = 36: 15 refractory cytopenia with multilineage dysplasia, 15 refractory anemia with excess blasts type 1, 10 refractory anemia with excess blasts type 2, 1 chronic myelomonocytic leukemia type 1) or AML (n = 60: 35 first complete remission [CR], 18 second CR, 3 advanced CR, 4 refractory relapse) were enrolled; median age was 51 (range, 1 to 60) years. Twelve patients had undergone a prior HCT with high-intensity conditioning. Patients

received 14 g/m<sup>2</sup>/day treosulfan i.v. on days -6 to -4, 30 mg/m<sup>2</sup>/day fludarabine i.v. on days -6 to -2, and 2-Gy TBI on day 0, followed by infusion of hematopoietic cells from related (n = 27) or unrelated (n = 69) donors. Graft-versus-host disease prophylaxis consisted of tacrolimus and methotrexate. With a median follow-up of 30 months, the 2-year overall survival (OS), relapse incidence, and nonrelapse mortality were 73%, 27%, and 8%, respectively. The incidences of grades II to IV (III to IV) acute and chronic graft-versus-host disease were 59% (10%) and 47%, respectively. Two-year OS was not significantly different between MDS patients with poor-risk and good/intermediate-risk cytogenetics (69% and 85%, respectively) or between AML patients with unfavorable and favorable/intermediate-risk cytogenetics (64% and 76%, respectively). In AML patients, minimal residual disease (MRD; n = 10) at the time of HCT predicted higher relapse incidence (70% versus 18%) and lower OS (41% versus 79%) at 2 years when compared with patients without MRD. In conclusion, treosulfan, fludarabine, and low-dose TBI provided effective conditioning for allogeneic HCT in patients with MDS or AML and resulted in low relapse incidence, regardless of cytogenetic risk. In patients with AML, MRD at the time of HCT remained a risk factor for post-HCT relapse.

Haley, G. E., & Raber, J. (2012). *Neurobiological correlates of behavioral and cognitive performance in nonhuman primates* Nova Science Publishers, Inc.

Animals in experiments are traditionally grouped by experimental treatment. Although this is a valuable way to differentiate the groups, alternatively, groups can be distinguished based on cognitive performance. Performance based analysis can yield valuable insights, corresponding to behavior and/or cognition, that might not otherwise be observed. As an example of such an analysis, we discuss a cohort of elderly female rhesus macaques who participated in a spatial food port maze navigational test. Circadian activity and pharmacological MRI (phMRI) were assessed in these monkeys in vivo and radioligand binding was assessed in post-mortem tissue. Based on cognitive performance in the spatial maze, the cohort of monkeys was divided into Good Spatial Performers (GSP) and Poor Spatial Performers (PSP). GSP animals were more active during the day and less active at night compared to PSP animals. In addition, GSP animals had a higher percentage change in blood-oxygen-level-dependent (BOLD) signal after a scopolamine challenge, a non-specific muscarinic receptor antagonist, compared to PSP animals. Post-mortem

radioligand experiments demonstrated that hippocampal muscarinic type 1 (M1) maximum receptor binding and receptor binding affinity, hypothesized to have an integral role in spatial learning and memory, was significantly greater in the hippocampus of GSP than PSP animals. In contrast to the hippocampus, M1 receptor binding was not significantly different in the prefrontal cortex (PFC). Muscarinic type 2 (M2) maximum receptor binding and receptor binding affinity were not significantly different between the two groups in either brain region. Finally, there were positive correlations between circadian measures and the percentage change in BOLD signal following the scopolamine challenge, as well as M1 receptor binding measures. Thus, GSP animals sleep more and have an enhanced M1 receptor function. These data demonstrate the close relationship between BOLD signal changes, circadian activity, and M1 receptor binding parameters. Distinguishing groups based on cognitive or behavioral performance is valuable for studying neurobiological correlates of performance in nonhuman primates. © 2012 Nova Science Publishers, Inc. All rights reserved.

Handel, D. A., Fu, R., Vu, E., Augustine, J. J., Hsia, R. Y., Shufflebarger, C. M., et al. (2014).

Association of emergency department and hospital characteristics with elopements and length of stay. *The Journal of Emergency Medicine*,

BACKGROUND: As the Centers for Medicare & Medicaid Services (CMS) core measures in 2013 compare Emergency Department (ED) treatment time intervals, it is important to identify ED and hospital characteristics associated with these metrics to facilitate accurate comparisons. STUDY OBJECTIVES: The objective of this study is to assess differences in operational metrics by ED and hospital characteristics. ED-level characteristics included annual ED volume, percentage of patients admitted, percentage of patients presenting by ambulance, and percentage of pediatric patients. Hospital-level characteristics included teaching hospital status, trauma center status, hospital ownership (nonprofit or for-profit), inpatient bed capacity, critical access status, inpatient bed occupancy, and rural vs. urban location area. METHODS: Data from the ED Benchmarking Alliance from 2004 to 2009 were merged with the American Hospital Association's Annual Survey Database to include hospital characteristics that may impact ED throughput. Overall median length of stay (LOS) and left before treatment is complete (LBTC) were the primary outcome variables, and a linear mixed model was used to assess the association between outcome

variables and ED and hospital characteristics, while accounting for correlations among multiple observations within each hospital. All data were at the hospital level on a yearly basis. RESULTS: There were 445 EDs included in the analysis, from 2004 to 2009, with 850 observations over 6 years. Higher-volume EDs were associated with higher rates of LBTC and LOS. For-profit hospitals had lower LBTC and LOS. Higher inpatient bed occupancies were associated with a higher LOS. Increasing admission percentages were positively associated with overall LOS for EDs, but not with rates of LBTC. CONCLUSIONS: Higher-volume EDs are associated with higher LBTC and LOS, and for-profit hospitals appear more favorably in these metrics compared with their nonprofit counterparts. It is important to appreciate that hospitals have different baselines for performance that may be more tied to volume and capacity, and less to quality of care.

Hartung, D. M., Zerzan, J., Yamashita, T., Tong, S., Morden, N. E., & Libby, A. M. (2014).

Characteristics and trends of low-dose quetiapine use in two western state medicaid programs. *Pharmacoepidemiology and Drug Safety*, 23(1), 87-94.

Purpose: Medicaid programs are concerned about inappropriate, potentially hazardous, and costly off-label use of second-generation antipsychotics (SGAs). Several states are exploring policies aimed at managing low-dose quetiapine, commonly prescribed for off-label conditions. This study aimed to characterize longitudinal trends and patient characteristics associated with low-dose quetiapine in two state Medicaid programs. We further aimed to quantify changes in the use of quetiapine associated with a legal settlement that curtailed off-label promotion of this product.

Methods: Using administrative data from two state Medicaid programs, Oregon and Colorado, we identified SGA initiators and determined patient level factors associated with receipt of low-dose SGAs. We evaluated changes in low-dose quetiapine initiation during and after a period in which quetiapine was being promoted illegally for off-label purposes. Results: We identified 14763 new SGA starts during the study period. Low-dose (versus therapeutic dose) SGA use was common in both states, representing 53% to 56% of initiators. Quetiapine was the most commonly used SGA in both states and both dose ranges. Diagnoses of schizophrenia, bipolar disorder, posttraumatic stress disorder, anxiety disorder, and use of newer sedative hypnotics were associated with lower likelihood of initiating low-dose quetiapine. Initiation of low-dose quetiapine as a proportion of all SGA initiation and of all quetiapine initiation significantly declined in Oregon following suspension

of off-label promotional activities. Conclusions: Low-dose SGA and specifically low-dose quetiapine use remains common. Medicaid programs must set policies carefully to maximize the net safety of prescription use while optimizing disease management considering the potential for substitution effects. © 2013 John Wiley & Sons, Ltd.

Havmoeller, R., Reinier, K., Teodorescu, C., Ahmadi, N., Kwok, D., Uy-Evanado, A., et al. (2014).

Elevated plasma free fatty acids are associated with sudden death: A prospective community-based evaluation at the time of cardiac arrest. *Heart Rhythm : The Official Journal of the Heart Rhythm Society*,

BACKGROUND: In cohort studies, elevated plasma levels of non-esterified free fatty acids (P-NEFA) have been associated with increased risk of sudden cardiac death (SCD) in men, but blood samples were drawn several years prior to SCD. OBJECTIVE: We sought to confirm this relationship by evaluating P-NEFA at the time of the SCD event in a group of both men and women. METHODS: From the ongoing Oregon Sudden Unexpected Death Study, we compared P-NEFA in 149 SCD cases presenting with ventricular fibrillation (mean age 64+/-12 yrs, 73% male) and 149 age and sex-matched controls with coronary artery disease. Plasma was processed from blood drawn at the time of arrest (cases) and at a routine visit (controls). P-NEFA levels were compared after categorizing into quartiles based on control values. Conditional logistic regression was used to predict adjusted odds of SCD associated with P-NEFA levels per increased quartile. RESULTS: P-NEFA was significantly higher in SCD cases compared to controls (median 0.39; interquartile range 0.28-0.60 vs. 0.32 mmol/L; 0.20-0.49, P=0.002). There were no significant differences in body mass index, smoking, or diabetes. The odds of SCD were 1.42 (95% CI 1.14-1.78) per quartile increase in P-NEFA level (P=0.002). Individuals with P-NEFA levels above the pre-specified cut-off point of 0.32 mmol/L were at increased risk of SCD [OR 2.00 (1.20-3.34) P=0.008]. CONCLUSIONS: These findings strengthen the role of P-NEFA as a potential biomarker for assessment of SCD risk.

Hawkes, J. E., Campbell, J., Garvin, D., Cannon-Albright, L., Cassidy, P., & Leachman, S. A. (2013).

Lack of GNAQ and GNA11 germ-line mutations in familial melanoma pedigrees with uveal melanoma or blue nevi. *Frontiers in Oncology*, 3 JUN

Approximately 10% of melanoma cases are familial, but only 25-40% of familial melanoma cases can be attributed to germ-line mutations in the CDKN2A - the most significant high-risk melanoma susceptibility locus identified to date. The pathogenic mutation(s) in most of the remaining familial melanoma pedigrees have not yet been identified. The most common mutations in nevi and sporadic melanoma are found in BRAF and NRAS, both of which result in constitutive activation of the MAPK pathway. However, these mutations are not found in uveal melanomas or the intradermal melanocytic proliferations known as blue nevi. Rather, multiple studies report a strong association between these lesions and somatic mutations in Guanine nucleotide-binding protein G(q) subunit alpha (GNAQ), Guanine nucleotide-binding protein G(q) subunit alpha-11 (GNA11), and BRCA1-associated protein-1 (BAP1). Recently, germ-line mutations in BAP1, the gene encoding a tumor suppressing deubiquitinating enzyme, have been associated with predisposition to a variety of cancers including uveal melanoma, but no studies have examined the association of germ-line mutations in GNAQ and GNA11 with uveal melanoma and blue nevi. We have now done so by sequencing exon 5 of both of these genes in 13 unique familial melanoma pedigrees, members of which have had either uveal or cutaneous melanoma and/or blue nevi. Germ-line DNA from a total of 22 individuals was used for sequencing; however no deleterious mutations were detected. Nevertheless, such candidate gene studies and the discovery of novel germ-line mutations associated with an increased MM susceptibility can lead to a better understanding of the pathways involved in melanocyte transformation, formulation of risk assessment, and the development of specific drug therapies. © 2013 Hawkes, Campbell, Garvin, Cannon-Albright, Cassidy and Leachman.

He, Z., O'Roak, B. J., Smith, J. D., Wang, G., Hooker, S., Santos-Cortez, R. L. P., et al. (2014). Rare-variant extensions of the transmission disequilibrium test: Application to autism exome sequence data. *American Journal of Human Genetics*, 94(1), 33-46.

Many population-based rare-variant (RV) association tests, which aggregate variants across a region, have been developed to analyze sequence data. A drawback of analyzing population-based data is that it is difficult to adequately control for population substructure and admixture, and spurious associations can occur. For RVs, this problem can be substantial, because the spectrum of rare variation can differ greatly between populations. A solution is to analyze parent-

child trio data, by using the transmission disequilibrium test (TDT), which is robust to population substructure and admixture. We extended the TDT to test for RV associations using four commonly used methods. We demonstrate that for all RV-TDT methods, using proper analysis strategies, type I error is well-controlled even when there are high levels of population substructure or admixture. For trio data, unlike for population-based data, RV allele-counting association methods will lead to inflated type I errors. However type I errors can be properly controlled by obtaining p values empirically through haplotype permutation. The power of the RV-TDT methods was evaluated and compared to the analysis of case-control data with a number of genetic and disease models. The RV-TDT was also used to analyze exome data from 199 Simons Simplex Collection autism trios and an association was observed with variants in ABCA7. Given the problem of adequately controlling for population substructure and admixture in RV association studies and the growing number of sequence-based trio studies, the RV-TDT is extremely beneficial to elucidate the involvement of RVs in the etiology of complex traits. © 2014 The American Society of Human Genetics.

Helms, C. M., Rau, A., Shaw, J., Stull, C., Gonzales, S. W., & Grant, K. A. (2014). The effects of age at the onset of drinking to intoxication and chronic ethanol self-administration in male rhesus macaques. *Psychopharmacology*,

RATIONALE: Consumption of alcohol begins during late adolescence in a majority of humans, and the greatest drinking occurs at 18-25 years then decreases with age. OBJECTIVES: The present study measured the differences in ethanol intake in relation to age at the onset of ethanol access among nonhuman primates to control for self-selection in humans and isolate age effects on heavy drinking. METHODS: Male rhesus macaques were assigned first access to ethanol during late adolescence (n = 8), young adulthood (n = 8), or early middle age (n = 11). The monkeys were induced to drink ethanol (4 % w/v in water) in increasing doses (water then 0.5, 1.0, 1.5 g/kg ethanol) using a fixed-time (FT) 300-s schedule of food delivery, followed by 22 h/day concurrent access to ethanol and water for 12 months. Age-matched controls consumed isocaloric maltose-dextrin solution yoked to the late adolescents expected to be rapidly maturing (n = 4). RESULTS: Young adult monkeys had the greatest daily ethanol intake and blood-ethanol concentration (BEC). Only late adolescents escalated their intake (ethanol, not water) during the

second compared to the first 6 months of access. On average, plasma testosterone level was consistent with age differences in maturation and tended to increase throughout the experiment more for control than ethanol-drinking adolescent monkeys. CONCLUSIONS: Young adulthood in nonhuman primates strongly disposes toward heavy drinking, which is independent of sociocultural factors present in humans. Ethanol drinking to intoxication during the critical period of late adolescence is associated with escalation to heavy drinking.

Henares, B., Kommineni, S., Chumsakul, O., Ogasawara, N., Ishikawa, S., & Nakano, M. M. (2014).

The ResD response regulator, through functional interaction with NsrR and fur, plays three distinct roles in bacillus subtilis transcriptional control. *Journal of Bacteriology*, 196(2), 493-503.

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 quantitative PCR (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 antirepressor of Fur and a corepressor 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. © 2014, American Society for Microbiology.

Hermes, S. M., Colbert, J. F., & Aicher, S. A. (2014). *Differential content of vesicular glutamate transporters in subsets of vagal afferents projecting to the nucleus tractus solitarius in the rat*

The vagus nerve contains primary visceral afferents that convey sensory information from cardiovascular, pulmonary, and gastrointestinal tissues to the nucleus tractus solitarius (NTS). The

heterogeneity of vagal afferents and their central terminals within the NTS is a common obstacle for evaluating functional groups of afferents. To determine whether different anterograde tracers can be used to identify distinct subpopulations of vagal afferents within NTS, we injected cholera toxin B subunit (CTb) and isolectin B4 (IB4) into the vagus nerve. Confocal analyses of medial NTS following injections of both CTb and IB4 into the same vagus nerve resulted in labeling of two exclusive populations of fibers. The ultrastructural patterns were also distinct. CTb was found in both myelinated and unmyelinated vagal axons and terminals in medial NTS, whereas IB4 was found only in unmyelinated afferents. Both tracers were observed in terminals with asymmetric synapses, suggesting excitatory transmission. Because glutamate is thought to be the neurotransmitter at this first primary afferent synapse in NTS, we determined whether vesicular glutamate transporters (VGLUTs) were differentially distributed among the two distinct populations of vagal afferents. Anterograde tracing from the vagus with CTb or IB4 was combined with immunohistochemistry for VGLUT1 or VGLUT2 in medial NTS and evaluated with confocal microscopy. CTb-labeled afferents contained primarily VGLUT2 (83%), whereas IB4-labeled afferents had low levels of vesicular transporters, VGLUT1 (5%) or VGLUT2 (21%). These findings suggest the possibility that glutamate release from unmyelinated vagal afferents may be regulated by a distinct, non-VGLUT, mechanism. *J. Comp. Neurol.* 522:642-653, 2014. © 2013 Wiley Periodicals, Inc.

Hernandez-Diaz, S., Mittendorf, R., Smith, C. R., Hauser, W. A., Yerby, M., Holmes, L. B., et al. (2014). Association between topiramate and zonisamide use during pregnancy and low birth weight. *Obstetrics and Gynecology*, 123(1), 21-28.

OBJECTIVE: To assess the possible effects of topiramate and zonisamide use during pregnancy on fetal growth. METHODS: The study population was the singleton liveborns born to women who enrolled in the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2012. Data were collected through telephone interviews at enrollment, 7 months of gestation, and postpartum. The prevalence of small for gestational age at birth among neonates exposed to topiramate and to zonisamide when either was used as monotherapy during pregnancy was compared with that among neonates exposed to lamotrigine monotherapy, a weight-neutral therapy, and the most common antiepileptic drug in the Registry. Relative risks (RRs) and 95%

confidence intervals (CIs) were estimated with multivariable log-binomial regression to control for potential confounders. RESULTS: Data were available for 347 topiramate, 98 zonisamide, and 1,581 lamotrigine-exposed neonates. The mean gestational length was 39 weeks for all comparison groups. Prenatal exposure to topiramate or zonisamide was associated with a mean lower birth weight of 221 and 202 g, respectively, and a mean lesser neonatal length of 1 cm as compared with lamotrigine exposure ( $p < .01$ ). The prevalence of small for gestational age was 6.8% for lamotrigine, 17.9% for topiramate (RR 2.4, 95% CI 1.8-3.3) and 12.2% for zonisamide (RR 1.6, 0.9-2.8). Similar results were found when a group of 457 unexposed neonates was used as the reference. CONCLUSIONS: Topiramate and zonisamide have been shown to reduce weight in adults. Our finding of a decrease in mean birth weight and length among neonates exposed in utero raises concern. LEVEL OF EVIDENCE: : II.

Herting, M. M., Colby, J. B., Sowell, E. R., & Nagel, B. J. (2014). White matter connectivity and aerobic fitness in male adolescents. *Developmental Cognitive Neuroscience, 7*, 65-75.

Exercise has been shown to have positive effects on the brain and behavior throughout various stages of the lifespan. However, little is known about the impact of exercise on neurodevelopment during the adolescent years, particularly with regard to white matter microstructure, as assessed by diffusion tensor imaging (DTI). Both tract-based spatial statistics (TBSS) and tractography-based along-tract statistics were utilized to examine the relationship between white matter microstructure and aerobic exercise in adolescent males, ages 15-18. Furthermore, we examined the data by both (1) grouping individuals based on aerobic fitness self-reports (high fit (HF) vs. low fit (LF)), and (2) using VO<sub>2</sub> peak as a continuous variable across the entire sample. Results showed that HF youth had an overall higher number of streamline counts compared to LF peers, which was driven by group differences in corticospinal tract (CST) and anterior corpus callosum (Fminor). In addition, VO<sub>2</sub> peak was negatively related to FA in the left CST. Together, these results suggest that aerobic fitness relates to white matter connectivity and microstructure in tracts carrying frontal and motor fibers during adolescence. Furthermore, the current study highlights the importance of considering the environmental factor of aerobic exercise when examining adolescent brain development. © 2013 The Authors. Published by Elsevier Ltd. All rights reserved.

Hitzemann, R., Bottomly, D., Iancu, O., Buck, K., Wilmot, B., Mooney, M., et al. (2013). The genetics of gene expression in complex mouse crosses as a tool to study the molecular underpinnings of behavior traits. *Mammalian Genome*, 1-11.

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

Holliday, E. B., Jaggi, R., Thomas Jr., C. R., Wilson, L. D., & Fuller, C. D. (2014). Standing on the shoulders of giants: Results from the radiation oncology academic development and mentorship assessment project (ROADMAP). *International Journal of Radiation Oncology Biology Physics*, 88(1), 18-24.

**Purpose** To analyze survey information regarding mentorship practices and cross-correlate the results with objective metrics of academic productivity among academic radiation oncologists at US Accreditation Council for Graduate Medical Education (ACGME)-accredited residency training programs. **Methods and Materials** An institutional review board-approved survey for the Radiation Oncology Academic Development and Mentorship Assessment Project (ROADMAP) was sent to 1031 radiation oncologists employed at an ACGME-accredited residency training program and administered using an international secure web application designed exclusively to support data capture for research studies. Data collected included demographics, presence of mentorship, and the nature of specific mentoring activities. Productivity metrics, including number of publications, number of citations, h-index, and date of first publication, were collected for each survey respondent from a commercially available online database, and m-index was calculated. **Results** A total of 158 academic radiation oncologists completed the survey, 96 of whom reported having an academic/scientific mentor. Faculty with a mentor had higher numbers of publications, citations, and h- and m-indices. Differences in gender and race/ethnicity were not associated with significant differences in mentorship rates, but those with a mentor were more likely to have a PhD degree and were more likely to have more time protected for research. Bivariate fit regression modeling showed a positive correlation between a mentor's h-index and their

mentee's h-index ( $R^2 = 0.16$ ;  $P < .001$ ). Linear regression also showed significant correlates of higher h-index, in addition to having a mentor ( $P = .001$ ), included a longer career duration ( $P < .001$ ) and fewer patients in treatment ( $P = .02$ ). Conclusions Mentorship is widely believed to be important to career development and academic productivity. These results emphasize the importance of identifying and striving to overcome potential barriers to effective mentorship. © 2014 Elsevier Inc. All rights reserved.

Horner-Johnson, W., Dobbertin, K., Andresen, E. M., & Iezzoni, L. I. (2014). Breast and cervical cancer screening disparities associated with disability severity. *Women's Health Issues : Official Publication of the Jacobs Institute of Women's Health*, 24(1), e147-53.

BACKGROUND: Prior research has noted disparities between women with and without disabilities in receipt of timely screening for breast and cervical cancer. Some studies suggest greater disparities for women with more severe disabilities, but the research to date has yielded inconsistent findings. Our purpose was to further examine differences in receipt of breast and cervical cancer screening in relation to severity of disability. METHODS: We analyzed Medical Expenditure Panel Survey annual data files from 2002 to 2008. Logistic regression analyses examined whether Pap smears and mammograms had been received within the recommended timeframe according to U.S. Preventive Services Task Force Guidelines. We compared four groups of women aged 18 to 64 years, categorized by presence and complexity of disability: 1) No limitations, 2) basic action difficulties only, 3) complex activity limitations only, and 4) both basic and complex activity limitations. FINDINGS: Women both with and without disabilities fell short of Healthy People 2020 goals for breast and cervical cancer screening. Overall, women with disabilities were less likely to be up to date with both mammograms and Pap tests. The magnitude of disparities was greater for women with complex limitations. Disparities in Pap testing, but not mammography, remained significant when controlling for demographic, geographic, and socioeconomic factors. CONCLUSIONS: Women with more complex or severe disability were less likely to be up to date with breast and cervical cancer screenings. Targeted efforts are needed to reduce barriers to breast and cervical cancer screening for women with significant disabilities, especially those who also experience other socioecological disadvantages.

Hostetler, C. M., Hitchcock, L. N., Anacker, A. M., Young, L. J., & Ryabinin, A. E. (2013). Comparative distribution of central neuropeptide Y (NPY) in the prairie (*Microtus ochrogaster*) and meadow (*M. pennsylvanicus*) vole. *Peptides*, *40*, 22-29.

Neuropeptide Y (NPY) has been implicated as a modulator of social behavior, often in a species-specific manner. Comparative studies of closely related vole species are particularly useful for identifying neural systems involved in social behaviors in both voles and humans. In the present study, immunohistochemistry was performed to compare NPY-like immunoreactivity (-ir) in brain tissue of the socially monogamous prairie vole and non-monogamous meadow vole. Species differences in NPY-ir were observed in a number of regions including the cortex, extended amygdala, septal area, suprachiasmatic nucleus, and intergeniculate leaf. Meadow voles had higher NPY-ir in all these regions as compared to prairie voles. No differences were observed in the striatum or hippocampus. The extended amygdala and lateral septum are regions that play a key role in regulation of monogamous behaviors such as pair bonding and paternal care. The present study suggests NPY in these regions may be an additional modulator of these species-specific social behaviors. Meadow voles had moderately higher NPY-ir in a number of hypothalamic regions, especially in the suprachiasmatic nucleus. Meadow voles also had much higher levels of NPY-ir in the intergeniculate leaflet, another key region in the regulation of circadian rhythms. Overall, species differences in NPY-ir were observed in a number of brain regions implicated in emotion, stress, circadian, and social behaviors. These findings provide additional support for a role for the NPY system in species-typical social behaviors.

Hu, W., Whitten, B., Sedgley, C., & Svec, T. (2014). Effect of three NiTi-files on transportation of the apical foramen. *International Endodontic Journal*,

AIM: To compare landed and non-landed rotary file overinstrumentation on transportation of the apical foramen in the curved canals of extracted teeth. METHODOLOGY: Severely curved molar root canals (n=45) were distributed into three equal groups (n=15) according to angle (mean 54 degrees ) and radius of curvature (mean 5 mm). Canals were overinstrumented 0.5 mm beyond the foramen to a size 35 master apical file using landed (ProFile ISO), non-landed (ProFile Vortex), or non-landed, reduced shape memory (Vortex Blue) files. Post-instrumentation images of the apical foramen were compared to pre-instrumentation control images for differences in

area, circularity, and ratio of Feret's diameters. Groups were compared by using ANOVA or Kruskal-Wallis tests with significance of  $P < 0.05$ . RESULTS: There were no differences between pre-treatment groups in the parameters tested. All groups demonstrated alterations in the geometry of the apical foramen. There were no significant differences between ProFile ISO, ProFile Vortex, or Vortex Blue in area, circularity, and ratio of Feret's diameters. CONCLUSIONS: Landed, non-landed, and non-landed reduced shape memory files all produced transportation of the apical foramen when overinstrumented by 0.5 mm in severely curved canals. There was no difference between these file systems with regard to the degree of this effect. This article is protected by copyright. All rights reserved.

Huguet, N., Kaplan, M. S., & McFarland, B. H. (2014). The effects of misclassification biases on veteran suicide rate estimates. *American Journal of Public Health, 104*(1), 151-155.

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.

Huisinga, J. M., St George, R. J., Spain, R., Overs, S., & Horak, F. B. (2014). Postural response latencies are related to balance control during standing and walking in patients with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation,*

OBJECTIVE: To understand examined the relationship between postural response latencies

obtained during postural perturbations and representative measures of balance during standing (sway variables) and during walking (trunk motion). DESIGN: Cross-sectional SETTING: University medical center balance disorders laboratory PARTICIPANTS: Forty persons with MS were compared with 20 similar aged control subjects. Twenty subjects with MS had normal walking velocity group and 20 had slow walking velocity based on the 25-foot walk time greater than 5 seconds. INTERVENTIONS: None MAIN OUTCOME MEASURES: Postural response latency, sway variables, trunk motion variables RESULTS: We found that subjects with MS with either slow or normal walking velocities had significantly longer postural response latencies than the healthy control group. Postural response latency was not correlated with the 25-ft walk time. Postural response latency was significantly correlated with center of pressure sway variables during quiet standing: root mean square ( $\rho = 0.334, p=0.040$ ), range ( $\rho=0.385, p=0.017$ ), mean velocity ( $\rho=0.337, p=0.038$ ), and total sway area ( $\rho=0.393, p=0.015$ ). Postural response latency was also significantly correlated with motion of the trunk during walking: sagittal plane range of motion ( $\rho=0.316, p=0.050$ ) and standard deviation of transverse plane range of motion ( $\rho=-0.430, p=0.006$ ). CONCLUSIONS: These findings clearly indicate that slow postural responses to external perturbations in patients with MS contribute to disturbances in balance control, both during standing and walking.

Inge, T. H., King, W. C., Jenkins, T. M., Courcoulas, A. P., Mitsnefes, M., Flum, D. R., et al. (2013).

The effect of obesity in adolescence on adult health status. *Pediatrics*, 132(6), 1098-1104.

OBJECTIVE: To test the hypothesis that adolescent obesity would be associated with greater risks of adverse health in severely obese adults. METHODS: Before weight loss surgery, adult participants in the Longitudinal Assessment of Bariatric Surgery-2 underwent detailed anthropometric and comorbidity assessment. Weight status at age 18 was retrospectively determined. Participants who were  $\geq 80\%$  certain of recalled height and weight at age 18 (1502 of 2308) were included. Log binomial regression was used to evaluate whether weight status at age 18 was independently associated with risk of comorbid conditions at time of surgery controlling for potential confounders. RESULTS: Median age and adult body mass index (BMI) were 47 years and 46, respectively. At age 18, 42% of subjects were healthy weight, 29% overweight, 16% class 1 obese, and 13% class  $\geq 2$  obese. Compared with healthy weight at age

18, class  $\geq 2$  obesity at age 18 independently increased the risk of lower-extremity venous edema with skin manifestations by 435% (P 0001), severe walking limitation by 321% (P 0001), abnormal kidney function by 302% (P 0001), polycystic ovary syndrome by 74% (P = .03), asthma by 48% (P = .01), diabetes by 42% (P 01), obstructive sleep apnea by 25% (P 01), and hypertension (by varying degrees based on age and gender). Conversely, the associated risk of hyperlipidemia was reduced by 61% (P 01). CONCLUSIONS: Severe obesity at age 18 was independently associated with increased risk of several comorbid conditions in adults undergoing bariatric surgery. © 2013 by the American Academy of Pediatrics.

Jakopovic, M., Thomas, A., & Lopez-Chavez, A. (2014). From platinum compounds to targeted therapies in advanced thoracic malignancies. *Anticancer Research*, 34(1), 477-482.

Improved understanding of the molecular mechanisms involved in development, growth and spread of cancer have led to development of targeted therapies for many cancers. Based on their superior tolerability and efficacy, targeted therapies with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) or crizotinib are preferred first-line treatments over platinum-based chemotherapies in patients whose tumours harbour EGFR-activating mutations and anaplastic lymphoma kinase (ALK) translocations, respectively. Active areas of research in EGFR-mutant and ALK-translocated NSCLC include identification of mechanisms of resistance and overcoming them. Therapeutic targeting of several other targets including ROS, RET and discoidin domain receptor 2 (DDR2) tyrosine kinases are in early phases of clinical evaluation. Despite the advances in tumour genomic sequencing, a substantial fraction of patients with non-small cell lung cancer (NSCLC) do not have any targetable genetic alteration. Ongoing research is focused on identifying mechanisms of carcinogenesis in these patients. Targeted therapies in small cell lung cancer (SCLC) and thymic malignancies have not yielded meaningful clinical benefits, and platinum-based therapies remain the cornerstone of treating patients with advanced disease.

James, M. L., Dority, J., Gray, M. C., Bellows, S. T., McDonagh, D. L., & Brambrink, A. M. (2014).

Survey of anesthesiologists practicing in american neurointensive care units as neurointensivists. *Journal of Neurosurgical Anesthesiology*, 26(1), 11-16.

BACKGROUND:: A group of anesthesiologists practice as intensivists in neurointensive care units

(NeuroICU). The current nature and implications of the role of anesthesiology-based neurointensivist remain unclear. The purpose of this survey was to assess today's practice environment of anesthesiology-based neurointensivists as a framework for future study.

**METHODS::** During the period between January 2011 and March 2011, we identified anesthesiologists who provide patient care in specialized NeuroICUs in the United States. We used an online, 15-question survey to gauge the environment and their role in the delivery of care to critically ill patients admitted to NeuroICUs.

**RESULTS::** Of the 104 NeuroICUs in the United States, 22 institutions include anesthesiology-based neurointensivists (n=41). With a response from 33 of 41 requested surveys, anesthesiology-based neurointensivists reported that background training and roles for providing patient care in the NeuroICU setting varied widely between institutions. In contrast, these practices were similar in providing 24-hour coverage (76%), working with neurosurgical (88%) and anesthesiology residents (85%), and having critical-care fellowship training (97%). Almost all surveyed individuals practice both neurocritical care and anesthesia in the operating room, and 76% reported satisfaction with their working environment in the NeuroICU relative to other responsibilities.

**CONCLUSIONS::** Anesthesiology-based neurointensivists currently represent a small subgroup within the rapidly growing neurointensivist workforce in the United States and consider neurocritical care a valuable aspect of their career. Promoting subspecialty training in neurocritical care among anesthesiologists may provide an opportunity for new patient-care frontiers and address the increasing need for NeuroICU physicians. © 2013 by Lippincott Williams and Wilkins.

Jansen, L. A., & Wall, S. (2013). Rethinking exploitation: A process-centered account. *Kennedy Institute of Ethics Journal*, 23(4), 381-410.

Exploitation has become an important topic in recent discussions of biomedical and research ethics. This is due in no small measure to the influence of Alan Wertheimer's path-breaking work on the subject. This paper presents some objections to Wertheimer's account of the concept. The objections attempt to show that his account places too much emphasis on outcome-based considerations and too little on process-based considerations. Building on these objections, the paper develops an alternative process-centered account of the concept. This alternative account of exploitation takes as its point of departure the broadly Kantian notion that it is wrong to use

another as an instrument for the advancement of one's own ends. It sharpens this slippery notion and adds a number of refinements to it. The paper concludes by arguing that process-centered accounts of exploitation better illuminate the ethical challenges posed by research on human subjects than outcome-centered accounts. © 2013 by The Johns Hopkins University Press.

Jenkins, D. H., Rappold, J. F., Badloe, J. F., Berseus, O., Blackbourne, L., Brohi, K. H., et al. (2014). THOR position paper on remote damage control resuscitation: Definitions, current practice and knowledge gaps. *Shock (Augusta, Ga.)*,

Jiang, Y., Lin, C., Meng, W., Yu, C., Cohen, A. M., & Smalheiser, N. R. (2014). Rule-based deduplication of article records from bibliographic databases. *Database : The Journal of Biological Databases and Curation*, 2014, bat086.

We recently designed and deployed a metasearch engine, Metta, that sends queries and retrieves search results from five leading biomedical databases: PubMed, EMBASE, CINAHL, PsycINFO and the Cochrane Central Register of Controlled Trials. Because many articles are indexed in more than one of these databases, it is desirable to deduplicate the retrieved article records. This is not a trivial problem because data fields contain a lot of missing and erroneous entries, and because certain types of information are recorded differently (and inconsistently) in the different databases. The present report describes our rule-based method for deduplicating article records across databases and includes an open-source script module that can be deployed freely. Metta was designed to satisfy the particular needs of people who are writing systematic reviews in evidence-based medicine. These users want the highest possible recall in retrieval, so it is important to err on the side of not deduplicating any records that refer to distinct articles, and it is important to perform deduplication online in real time. Our deduplication module is designed with these constraints in mind. Articles that share the same publication year are compared sequentially on parameters including PubMed ID number, digital object identifier, journal name, article title and author list, using text approximation techniques. In a review of Metta searches carried out by public users, we found that the deduplication module was more effective at identifying duplicates than EndNote without making any erroneous assignments.

Johnson, J. P. (2014). Reimagining charlotte's web as the creative experience of play. *Clinical Child Psychology and Psychiatry, 19*(1), 154-160.

Johnson, L. A., Olsen, R. H., Merkens, L. S., Debarber, A., Steiner, R. D., Sullivan, P. M., et al. (2014). Apolipoprotein E-low density lipoprotein receptor interaction affects spatial memory retention and brain ApoE levels in an isoform-dependent manner. *Neurobiology of Disease*, Human apolipoprotein E (apoE) exists in three isoforms: apoE2, apoE3 and apoE4. APOE epsilon4 (E4) is a major genetic risk factor for cardiovascular disease (CVD) and Alzheimer's disease (AD). ApoE mediates cholesterol metabolism by binding various receptors. The low-density lipoprotein receptor (LDLR) has a high affinity for apoE, and is the only member of its receptor family to demonstrate an apoE isoform specific binding affinity (E4>E3>>E2). Evidence suggests that a functional interaction between apoE and LDLR influences the risk of CVD and AD. We hypothesize that the differential cognitive effects of the apoE isoforms are a direct result of their varying interactions with LDLR. To test this hypothesis, we have employed transgenic mice that express human apoE2, apoE3, or apoE4, and either human LDLR (hLDLR) or no LDLR (LDLR<sup>-/-</sup>). Our results show that plasma and brain apoE levels, cortical cholesterol, and spatial memory are all regulated by isoform-dependent interactions between apoE and LDLR. Conversely, both anxiety-like behavior and cued associative memory are strongly influenced by APOE genotype, but these processes appear to occur via an LDLR-independent mechanism. Both the lack of LDLR and the interaction between E4 and the LDLR were associated with significant impairments in the retention of long term spatial memory. Finally, levels of hippocampal apoE correlate with long term spatial memory retention in mice with human LDLR. In summary, we demonstrate that the apoE-LDLR interaction affects regional brain apoE levels, brain cholesterol, and cognitive function in an apoE isoform-dependent manner.

Jothi, M., Mal, M., Keller, C., & Mal, A. K. (2013). Small molecule inhibition of PAX3-FOXO1 through AKT activation suppresses malignant phenotypes of alveolar rhabdomyosarcoma. *Molecular Cancer Therapeutics, 12*(12), 2663-2674.

Alveolar rhabdomyosarcoma comprises a rare highly malignant tumor presumed to be associated with skeletal muscle lineage in children. The hallmark of the majority of alveolar

rhabdomyosarcoma is a chromosomal translocation that generates the PAX3-FOXO1 fusion protein, which is an oncogenic transcription factor responsible for the development of the malignant phenotype of this tumor. Alveolar rhabdomyosarcoma cells are dependent on the oncogenic activity of PAX3-FOXO1, and its expression status in alveolar rhabdomyosarcoma tumors correlates with worst patient outcome, suggesting that blocking this activity of PAX3-FOXO1 may be an attractive therapeutic strategy against this fusion-positive disease. In this study, we screened small molecule chemical libraries for inhibitors of PAX3-FOXO1 transcriptional activity using a cell-based readout system. We identified the Sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPases (SERCA) inhibitor thapsigargin as an effective inhibitor of PAX3-FOXO1. Subsequent experiments in alveolar rhabdomyosarcoma cells showed that activation of AKT by thapsigargin inhibited PAX3-FOXO1 activity via phosphorylation. Moreover, this AKT activation appears to be associated with the effects of thapsigargin on intracellular calcium levels. Furthermore, thapsigargin inhibited the binding of PAX3-FOXO1 to target genes and subsequently promoted its proteasomal degradation. In addition, thapsigargin treatment decreases the growth and invasive capacity of alveolar rhabdomyosarcoma cells while inducing apoptosis in vitro. Finally, thapsigargin can suppress the growth of an alveolar rhabdomyosarcoma xenograft tumor in vivo. These data reveal that thapsigargin-induced activation of AKT is an effective mechanism to inhibit PAX3-FOXO1 and a potential agent for targeted therapy against alveolar rhabdomyosarcoma. © 2013 AACR.

Kachalia, A., Little, A., Isavoran, M., Crider, L. -, & Smith, J. (2014). Greatest impact of safe harbor rule may be to improve patient safety, not reduce liability claims paid by physicians. *Health Affairs*, 33(1), 59-66.

"Safe harbor" legislation that provides liability protection to physicians when they follow designated guidelines is often proposed as a way to reform the malpractice system while improving patient safety. However, published evidence provides little policy guidance on implementing safe harbors. With the support of an Agency for Healthcare Research and Quality planning grant, we conducted an empirical analysis of closed liability claims in Oregon to determine the potential effects of hypothetical safe harbor legislation. We found that such legislation would have changed the liability outcome in favor of the physician defendant in only 1

percent of 266 claims from the period 2002-09 that we reviewed. Nevertheless, if safe harbors can induce greater physician adherence to care guidelines, they have the potential to improve patient safety. Implementing safe harbor legislation, however, requires overcoming a number of hurdles, including selecting and updating approved guidelines, obtaining broad stakeholder support, and withstanding challenges to the legal validity of the legislation. More experimentation with safe harbors is needed to determine their effects on the performance of the liability system and on health care quality and costs © 2014 Project HOPE- The People-to-People Health Foundation, Inc.

Kajino, K., Kitamura, T., Iwami, T., Daya, M., Ong, M. E. H., Nishiyama, C., et al. (2014). Impact of the number of on-scene emergency life-saving technicians and outcomes from out-of-hospital cardiac arrest in Osaka city. *Resuscitation*, 85(1), 59-64.

Backgrounds: In Japan, ambulance staffing for cardiac arrest responses consists of a 3-person unit with at least one emergency life-saving technician (ELST). Recently, the number of ELSTs on ambulances has increased since it is believed that this improves the quality of on-scene care leading to better outcomes from out-of-hospital cardiac arrest (OHCA). The objective of this study was to evaluate the association between the number of on-scene ELSTs and OHCA outcome. Methods: This was a prospective cohort study of all bystander-witnessed OHCA patients aged  $\geq 18$  years in Osaka City from January 2005 to December 2007 using an Utstein-style database. The primary outcome measure was one-month survival with favorable neurological outcome defined as a cerebral performance category  $\geq 2$ . Multivariable logistic regression models were used to assess the contribution of the number of on-scene ELSTs to the outcome after adjusting for confounders. Results: Of the 2408 bystander-witnessed OHCA patients, one ELST group was present in 639 (26.5%), two ELST were present in 1357 (56.4%), and three ELST group in 412 (17.1%). The three ELST group had a significantly higher rate of one-month survival with favorable neurological outcome compared with the one ELST group (8.0% versus 4.5%, adjusted OR 2.26, 95% CI 1.27-4.04), while the two ELST group did not (5.4% versus 4.5%, adjusted OR 1.34, 95% CI 0.82-2.19). Conclusions: Compared with the one on-scene ELST group, the three on-scene ELST group was associated with the improved one-month

survival with favorable neurological outcome from OHCA in Osaka City. © 2013 Elsevier Ireland Ltd.

Kanchi, K. L., Johnson, K. J., Lu, C., McLellan, M. D., Leiserson, M. D., Wendl, M. C., et al. (2014).

Integrated analysis of germline and somatic variants in ovarian cancer. *Nature Communications*, 5, 3156.

We report the first large-scale exome-wide analysis of the combined germline-somatic landscape in ovarian cancer. Here we analyse germline and somatic alterations in 429 ovarian carcinoma cases and 557 controls. We identify 3,635 high confidence, rare truncation and 22,953 missense variants with predicted functional impact. We find germline truncation variants and large deletions across Fanconi pathway genes in 20% of cases. Enrichment of rare truncations is shown in BRCA1, BRCA2 and PALB2. In addition, we observe germline truncation variants in genes not previously associated with ovarian cancer susceptibility (NF1, MAP3K4, CDKN2B and MLL3).

Evidence for loss of heterozygosity was found in 100 and 76% of cases with germline BRCA1 and BRCA2 truncations, respectively. Germline-somatic interaction analysis combined with extensive bioinformatics annotation identifies 222 candidate functional germline truncation and missense variants, including two pathogenic BRCA1 and 1 TP53 deleterious variants. Finally, integrated analyses of germline and somatic variants identify significantly altered pathways, including the Fanconi, MAPK and MLL pathways.

Karamlou, T., Welke, K. F., McMullan, D. M., Cohen, G. A., Gelow, J., Tibayan, F. A., et al. (2014).

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*, 147(1), 456-461.e1.

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 ( $8.4 \pm 0.04$  years) and HKTx recipients ( $7.7 \pm 0.2$  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 ( $7.1 \pm 0.07$  vs  $7.7 \pm 0.2$ ;  $P < .001$ ). 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. Copyright © 2014 by The American Association for Thoracic Surgery.

Kaye, J., Mattek, N., Dodge, H. H., Campbell, I., Hayes, T., Austin, D., et al. (2014). Unobtrusive measurement of daily computer use to detect mild cognitive impairment. *Alzheimer's and Dementia*, 10(1), 10-17.

Background: Mild disturbances of higher order activities of daily living are present in people diagnosed with mild cognitive impairment (MCI). These deficits may be difficult to detect among those still living independently. Unobtrusive continuous assessment of a complex activity such as home computer use may detect mild functional changes and identify MCI. We sought to determine whether long-term changes in remotely monitored computer use differ in persons with MCI in comparison with cognitively intact volunteers. Methods: Participants enrolled in a longitudinal cohort study of unobtrusive in-home technologies to detect cognitive and motor decline in independently living seniors were assessed for computer use (number of days with use, mean daily use, and coefficient of variation of use) measured by remotely monitoring computer

session start and end times. Results: More than 230,000 computer sessions from 113 computer users (mean age, 85 years; 38 with MCI) were acquired during a mean of 36 months. In mixed-effects models, there was no difference in computer use at baseline between MCI and intact participants controlling for age, sex, education, race, and computer experience. However, over time, between MCI and intact participants, there was a significant decrease in number of days with use ( $P = .01$ ), mean daily use ( $\sim 1\%$  greater decrease/month;  $P = .009$ ), and an increase in day-to-day use variability ( $P = .002$ ). Conclusions: Computer use change can be monitored unobtrusively and indicates individuals with MCI. With 79% of those 55 to 64 years old now online, this may be an ecologically valid and efficient approach to track subtle, clinically meaningful change with aging. © 2014 The Alzheimer's Association. All rights reserved.

Keller, K. E., Yang, Y. F., Sun, Y. Y., Sykes, R., Gaudette, N. D., Samples, J. R., et al. (2014).

Interleukin-20 receptor expression in the trabecular meshwork and its implication in glaucoma. *Journal of Ocular Pharmacology and Therapeutics : The Official Journal of the Association for Ocular Pharmacology and Therapeutics*,

Abstract Purpose: To determine whether interleukin-20 receptors (IL-20R) are expressed in trabecular meshwork cells and the effect of a T104M mutation in IL-20R2 on downstream cellular functions. Methods: Evaluation of signal transducer and activator of transcription (STAT)3 phosphorylation and generic matrix metalloproteinase (MMP) activity in primary open angle glaucoma (POAG) dermal fibroblasts (pHDF) with the T104M IL-20R2 mutation were compared with normal human dermal fibroblasts (HDF). Expression of IL-20R1 and IL-20R2 in human trabecular meshwork (HTM) cells was determined by immunohistochemistry and western immunoblotting. Results: A T104M mutation in IL20-R2 was identified in a large POAG family in which the GLC1C locus was originally mapped. pHDFs harboring this mutation had significantly increased phosphorylated STAT3 (pSTAT3) activity compared with normal HDFs. However, stimulation with either IL-19 or IL-20 for 15 min resulted in significantly decreased levels of pSTAT3 in pHDFs compared with controls. Generic MMP activity was significantly decreased in pHDFs compared with controls after stimulation with IL-20 for 24 h. Both IL-20R1 and IL-20R2 receptors were expressed in HTM cells by western immunoblot and immunofluorescence, and they appeared to be up-regulated in response to cytokine treatment. Conclusions: A T104M

mutation in IL-20R2 significantly impacts the function of this receptor as shown by decreased pSTAT3 levels and generic MMP activity. Reduced MMP activity may affect the ability of glaucoma patients to alter outflow resistance in response to elevated intraocular pressure.

Kelly, S. P., Shoun, P., Mikol, J., & Steelman, R. (2014). Ventricular fibrillation following synchronized cardioversion in junctional ectopic tachycardia: A pediatric case report. *AACN Advanced Critical Care, 25*(1), 20-22.

Kikuchi, K., Hettmer, S., Aslam, M. I., Michalek, J. E., Laub, W., Wilky, B. A., et al. (2014). Cell-cycle dependent expression of a translocation-mediated fusion oncogene mediates checkpoint adaptation in rhabdomyosarcoma. *PLoS Genetics, 10*(1), e1004107.

Rhabdomyosarcoma is the most commonly occurring soft-tissue sarcoma in childhood. Most rhabdomyosarcoma falls into one of two biologically distinct subgroups represented by alveolar or embryonal histology. The alveolar subtype harbors a translocation-mediated PAX3:FOXO1A fusion gene and has an extremely poor prognosis. However, tumor cells have heterogeneous expression for the fusion gene. Using a conditional genetic mouse model as well as human tumor cell lines, we show that that Pax3:Foxo1a expression is enriched in G2 and triggers a transcriptional program conducive to checkpoint adaptation under stress conditions such as irradiation in vitro and in vivo. Pax3:Foxo1a also tolerizes tumor cells to clinically-established chemotherapy agents and emerging molecularly-targeted agents. Thus, the surprisingly dynamic regulation of the Pax3:Foxo1a locus is a paradigm that has important implications for the way in which oncogenes are modeled in cancer cells.

Kimura, S., Streiff, C., Zhu, M., Shimada, E., Datta, S., Ashraf, M., et al. (2014). Evaluation of a new 3-dimensional color doppler flow method to quantify flow across the mitral valve and in the left ventricular outflow tract: An in vitro study. *Journal of Ultrasound in Medicine : Official Journal of the American Institute of Ultrasound in Medicine, 33*(2), 265-271.

Objectives- The aim of this study was to assess the accuracy, feasibility, and reproducibility of determining stroke volume from a novel 3-dimensional (3D) color Doppler flow quantification method for mitral valve (MV) inflow and left ventricular outflow tract (LVOT) outflow at different stroke volumes when compared with the actual flow rate in a pumped porcine cardiac model.

Methods- Thirteen freshly harvested pig hearts were studied in a water tank. We inserted a latex balloon into each left ventricle from the MV annulus to the LVOT, which were passively pumped at different stroke volumes (30-80 mL) using a calibrated piston pump at increments of 10 mL. Four-dimensional flow volumes were obtained without electrocardiographic gating. The digital imaging data were analyzed offline using prototype software. Two hemispheric flow-sampling planes for color Doppler velocity measurements were placed at the MV annulus and LVOT. The software computed the flow volumes at the MV annulus and LVOT within the user-defined volume and cardiac cycle. Results- This novel 3D Doppler flow quantification method detected incremental increases in MV inflow and LVOT outflow in close agreement with pumped stroke volumes (MV inflow,  $r = 0.96$ ; LVOT outflow,  $r = 0.96$ ;  $P < .01$ ). Bland-Altman analysis demonstrated overestimation of both (MV inflow, 5.42 mL; LVOT outflow, 4.46 mL) with 95% of points within 95% limits of agreement. Interobserver variability values showed good agreement for all stroke volumes at both the MV annulus and LVOT. Conclusions- This study has shown that the 3D color Doppler flow quantification method we used is able to compute stroke volumes accurately at the MV annulus and LVOT in the same cardiac cycle without electrocardiographic gating. This method may be valuable for assessment of cardiac output in clinical studies.

Kita, S., Yaeko, K., & Porter, S. E. (2013). Prevalence and risk factors of intimate partner violence among pregnant women in Japan. *Health Care for Women International*, Intimate partner violence (IPV) during pregnancy can result in adverse outcomes for both mothers and their infants. This cross-sectional study examined the prevalence and risk factors of IPV associated with abuse during pregnancy via a self-administered questionnaire completed by 302 healthy pregnant women. Demographic information was also collected from medical records to analyze risk factors for abuse. Of the 302 women, 48 (15.9%) were identified as experiencing IPV. The identified risk factors were age over 30, multipara, previous abortion experience, and male partner aged under 30. © 2013 Copyright Taylor and Francis Group, LLC.

Köhler, S., Doelken, S. C., Mungall, C. J., Bauer, S., Firth, H. V., Bailleul-Forestier, I., et al. (2014). The human phenotype ontology project: Linking molecular biology and disease through phenotype data. *Nucleic Acids Research*, 42(D1), D966-D974.

The Human Phenotype Ontology (HPO) project, available at <http://www.human-phenotype-ontology.org>, provides a structured, comprehensive and well-defined set of 10,088 classes (terms) describing human phenotypic abnormalities and 13,326 subclass relations between the HPO classes. In addition we have developed logical definitions for 46% of all HPO classes using terms from ontologies for anatomy, cell types, function, embryology, pathology and other domains. This allows interoperability with several resources, especially those containing phenotype information on model organisms such as mouse and zebrafish. Here we describe the updated HPO database, which provides annotations of 7,278 human hereditary syndromes listed in OMIM, Orphanet and DECIPHER to classes of the HPO. Various meta-attributes such as frequency, references and negations are associated with each annotation. Several large-scale projects worldwide utilize the HPO for describing phenotype information in their datasets. We have therefore generated equivalence mappings to other phenotype vocabularies such as LDDB, Orphanet, MedDRA, UMLS and phenoDB, allowing integration of existing datasets and interoperability with multiple biomedical resources. We have created various ways to access the HPO database content using flat files, a MySQL database, and Web-based tools. All data and documentation on the HPO project can be found online. © 2013 The Author(s). Published by Oxford University Press.

Koilkonda, R. D., Yu, H., Chou, T. H., Feuer, W. J., Ruggeri, M., Porciatti, V., et al. (2014). Safety and effects of the vector for the leber hereditary optic neuropathy gene therapy clinical trial. *JAMA Ophthalmology*,

**IMPORTANCE** We developed a novel strategy for treatment of Leber hereditary optic neuropathy (LHON) caused by a mutation in the nicotinamide adenine dinucleotide dehydrogenase subunit IV (ND4) mitochondrial gene. **OBJECTIVE** To demonstrate the safety and effects of the gene therapy vector to be used in a proposed gene therapy clinical trial. **DESIGN AND SETTING** In a series of laboratory experiments, we modified the mitochondrial ND4 subunit of complex I in the nuclear genetic code for import into mitochondria. The protein was targeted into the organelle by agency of a targeting sequence (allotopic expression). The gene was packaged into adeno-associated viral vectors and then vitreally injected into rodent, nonhuman primate, and ex vivo human eyes that underwent testing for expression and integration by immunohistochemical analysis and blue

native polyacrylamide gel electrophoresis. During serial follow-up, the animal eyes underwent fundus photography, optical coherence tomography, and multifocal or pattern electroretinography. We tested for rescue of visual loss in rodent eyes also injected with a mutant G11778A ND4 homologue responsible for most cases of LHON. EXPOSURE Ocular infection with recombinant adeno-associated viral vectors containing a wild-type allotopic human ND4 gene. MAIN OUTCOMES AND MEASURES Expression of human ND4 and rescue of optic neuropathy induced by mutant human ND4. RESULTS We found human ND4 expressed in almost all mouse retinal ganglion cells by 1 week after injection and ND4 integrated into the mouse complex I. In rodent eyes also injected with a mutant allotopic ND4, wild-type allotopic ND4 prevented defective adenosine triphosphate synthesis, suppressed visual loss, reduced apoptosis of retinal ganglion cells, and prevented demise of axons in the optic nerve. Injection of ND4 in the ex vivo human eye resulted in expression in most retinal ganglion cells. Primates undergoing vitreal injection with the ND4 test article and followed up for 3 months had no serious adverse reactions. CONCLUSIONS AND RELEVANCE Expression of our allotopic ND4 vector in the ex vivo human eye, safety of the test article, rescue of the LHON mouse model, and the severe irreversible loss of visual function in LHON support clinical testing with mutated G11778A mitochondrial DNA in our patients.

Komazin-Meredith, G., Chou, S., Prichard, M. N., Hartline, C. B., Cardinale, S. C., Comeau, K., et al. (2014). Human cytomegalovirus UL97 kinase is involved in the mechanism of action of methylenecyclopropane analogs with 6-ether and -thioether substitutions. *Antimicrobial Agents and Chemotherapy*, 58(1), 274-278.

Methylenecyclopropane nucleoside (MCPN) analogs are being investigated for treatment of human cytomegalovirus (HCMV) infection because of favorable preclinical data and limited ganciclovir cross-resistance. Monohydroxymethyl MCPNs bearing ether and thioether functionalities at the purine 6 position have antiviral activity against herpes simplex virus (HSV) and varicella-zoster virus (VZV) in addition to HCMV. The role of the HCMV UL97 kinase in the mechanism of action of these derivatives was examined. When tested against a kinase-inactive UL97 K355M virus, a moderate 5- to 7-fold increase in 50% effective concentration (EC<sub>50</sub>) was observed, in comparison to a 13- to 25-fold increase for either cyclopropavir or ganciclovir. Serial

propagation of HCMV under two of these compounds selected for three novel UL97 mutations encoding amino acid substitutions D456N, C480R, and Y617del. When transferred to baseline laboratory HCMV strains, these mutations individually conferred resistance to all of the tested MCPNs, ganciclovir, and maribavir. However, the engineered strains also demonstrated severe growth defects and abnormal cytopathic effects similar to the kinase-inactive mutant. Expressed and purified UL97 kinase showed in vitro phosphorylation of the newly tested MCPNs. Thus, HCMV UL97 kinase is involved in the antiviral action of these MCPNs, but the in vitro selection of UL97-defective viruses suggests that their activity against more typical ganciclovir-resistant growth-competent UL97 mutants may be relatively preserved. Copyright © 2014, American Society for Microbiology. All Rights Reserved.

Kret, M. R., Cheng, D., Azarbal, A. F., Mitchell, E. L., Liem, T. K., Moneta, G. L., et al. (2014). Utility of direct angiosome revascularization and runoff scores in predicting outcomes in patients undergoing revascularization for critical limb ischemia. *Journal of Vascular Surgery*, 59(1), 121-128.

**Objective** Both runoff scores and direct (DR) vs indirect revascularization (IR) according to pedal angiosomes have unclear impact on outcome for patients with critical limb ischemia (CLI). We compared DR vs IR and runoff scores in CLI patients undergoing infrapopliteal bypass for foot wounds. **Methods** Patients who had tibial/pedal bypass for a foot/ankle wound from 2005-2011 were identified and operations classified as DR or IR based on wound location and bypass target. A blinded observer reviewed angiograms for an intact pedal arch and calculated standard Society for Vascular Surgery (single tibial) and modified (composite tibial) runoff scores. Comorbidities, wound characteristics, wound healing, major amputation, and overall survival were determined. **Results** A total of 106 limbs were revascularized in 97 patients; 54 limbs had DR and 52 had IR, although only 36% of wounds corresponded to a single, distinct angiosome. Wound characteristics and comorbidities were similar between groups. Mean standard (7.9 vs 7.2;  $P = .001$ ) and modified (22.2 vs 20.0;  $P = .02$ ) runoff scores were worse (higher number indicates worse runoff) in the IR vs DR groups; 33% had a complete pedal arch. Complete wound healing (78% vs 46%;  $P = .001$ ) and time to complete healing (99 vs 195 days;  $P = .002$ ) were superior with DR vs IR but were not influenced by runoff score, modified runoff score or presence of

complete plantar arch. In multivariate models controlling for runoff score, DR remained a significant predictor for wound healing (odds ratio, 2.9; 95% confidence interval, 1.1-7.4;  $P = .028$ ) and reduced healing time (hazard ratio, 2.1; 95% confidence interval, 1.2-3.7;  $P = .012$ ). Mean amputation-free survival (75 vs 71 months for DR vs IR;  $P = .82$ ) and median survival (36 vs 33 months DR vs IR;  $P = .22$ ) were not different for DR vs IR. Conclusions DR according to pedal angiosomes provides more efficient wound healing, but is possible in only one-half of the patients and does not affect amputation-free or overall survival. DR is associated with improved runoff scores, but current runoff scores have little clinical utility in predicting outcomes in CLI patients. Copyright © 2014 by the Society for Vascular Surgery.

Kusano, A. S., Thomas Jr., C. R., Bonner, J. A., Dewese, T. L., Formenti, S. C., Hahn, S. M., et al. (2014). Burnout in united states academic chairs of radiation oncology programs. *International Journal of Radiation Oncology Biology Physics*, 88(2), 363-368.

**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. © 2014 Elsevier Inc.

Labadie, C., Lee, J. -, Rooney, W. D., Jarchow, S., Aubert-Frécon, M., Springer Jr., C. S., et al.

(2014). Myelin water mapping by spatially regularized longitudinal relaxographic imaging at high magnetic fields. *Magnetic Resonance in Medicine*, 71(1), 375-387.

Purpose Magnetic resonance T1-weighted images are routinely used for human brain segmentation, brain parcellation, and clinical diagnosis of demyelinating diseases. Myelin is thought to influence the longitudinal relaxation commonly described by a mono-exponential recovery, although reports of bi-exponential longitudinal relaxation have been published. The purpose of this work was to investigate if a myelin water T1 contribution could be separated in geometrically sampled Look-Locker trains of low flip angle gradient echoes. Methods T1 relaxograms from normal human brain were computed by a spatially regularized inverse Laplace transform after estimating the apparent inversion efficiency. Results With sufficiently long inversion-time sampling (ca.  $5 \times T1$  of cerebrospinal fluid), the T1 relaxogram revealed a short-T1 peak (106-225 ms). The apparent fraction of this water component increased in human brain white matter from 8.3% at 3 T, to 11.3% at 4 T and 15.0% at 7 T. The T2\* of the short-T1 peak at 3 T was shorter,  $27.9 \pm 13.0$  ms, than that of the long-T1 peak,  $51.3 \pm 5.6$  ms. Conclusion The short-T1 fraction is interpreted as the water resident in myelin. Its detection is facilitated by longer T1 of axoplasmic water at higher magnetic field. © 2013 Wiley Periodicals, Inc.

Landier, W., Knight, K., Wong, F. L., Lee, J., Thomas, O., Kim, H., et al. (2014). Ototoxicity in children

with high-risk neuroblastoma: Prevalence, risk factors, and concordance of grading scales--A report from the children's oncology group. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

PURPOSE: Platinum-based therapy is the mainstay for management of high-risk neuroblastoma.

Prevalence of platinum-related ototoxicity has ranged from 13% to 95% in previous reports; variability is attributable to small samples and disparate grading scales. There is no consensus regarding optimal ototoxicity grading. Furthermore, prevalence and predictors of hearing loss in a

large uniformly treated high-risk neuroblastoma population are unknown. We address these gaps in our study. PATIENTS AND METHODS: Audiologic testing was completed after administration of cisplatin alone (< 400 mg/m<sup>2</sup>; exposure one) or after cisplatin (400 mg/m<sup>2</sup>) plus carboplatin (1,700 mg/m<sup>2</sup>; exposure two). Hearing loss was graded using four scales (American Speech-Language-Hearing Association; Brock; Chang; and Common Terminology Criteria for Adverse Events, version 3 [CTCAEv3]). RESULTS: Of 489 eligible patients, 333 had evaluable audiologic data. Median age at diagnosis was 3.3 years. Prevalence of severe hearing loss differed by scale. For those in the exposure-one group, prevalence ranged from 8% per Brock to 47% per CTCAEv3 (Brock v CTCAEv3 and Chang, P < .01; CTCAEv3 v Chang, P = .16); for those in the exposure-two group, prevalence ranged from 30% per Brock to 71% per CTCAEv3 (all pair-wise comparisons, P < .01). In patients requiring hearing aids, hearing loss was graded as severe in 49% (Brock), 91% (Chang), and 100% (CTCAEv3). Risk factors for severe hearing loss included exposure to cisplatin and carboplatin compared with cisplatin alone and hospitalization for infection. CONCLUSION: Severe hearing loss is prevalent among children with high-risk neuroblastoma. Exposure to cisplatin combined with myeloablative carboplatin significantly increases risk. The Brock scale underestimates severe hearing loss and should be used with caution in this setting.

Larkin, K. L., Saboo, U. S., Comer, G. M., Forooghian, F., Mackensen, F., Merrill, P., et al. (2014). Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. *British Journal of Ophthalmology*, 98(1), 99-103.

Aim: Vitreoretinal lymphoma is a diffuse large B cell non-Hodgkin lymphoma. Targeting malignant cells with rituximab is being used increasingly as local chemotherapy, but information on this treatment is scant. We aimed to describe current therapeutic approaches, as well as responses to and complications of, intravitreal rituximab in patients with vitreoretinal lymphoma. Methods: Clinical data were collected in a standardised manner retrospectively on patients with vitreoretinal lymphoma treated with intravitreal rituximab. Results: 48 eyes (34 patients) with vitreoretinal lymphoma were treated with a median of 3.5 intravitreal injections of rituximab (1 mg/0.1 mL) for new diagnosis (68.8%), progressive disease (29.9%) and maintenance therapy (2.1%). Intravitreal rituximab±methotrexate was the sole treatment in 19 eyes (39.6%). 31 eyes

(64.6%) eyes achieved complete remission, after a median of 3 injections; 7 of these eyes developed recurrent disease. 11 eyes (22.9%) achieved partial remission. Although rituximab may have contributed to complications reported in 12 eyes (25.0%), a 2-line loss of Snellen visual acuity occurred in only 2 of those eyes (4.2%). Conclusions: Approaches in rituximab-based intravitreal chemotherapy vary widely, but our findings suggest that this treatment may be safe and effective in inducing remission in a majority of eyes with vitreoretinal lymphoma.

Lawrence, P. F., Harlander-Locke, M. P., Oderich, G. S., Humphries, M. D., Landry, G. J., Ballard, J. L., et al. (2014). The current management of isolated degenerative femoral artery aneurysms is too aggressive for their natural history. *Journal of Vascular Surgery*, 59(2), 343-349.

**BACKGROUND:** Previous studies have combined anastomotic, catheter-induced, and atherosclerotic isolated femoral artery aneurysms (FAAs) to achieve adequate numbers for analysis and have recommended repair of asymptomatic FAAs with diameters  $\geq 2.5$  cm and all symptomatic FAAs. This study evaluated the contemporary management of isolated FAAs.

**METHODS:** Patients with FAAs were evaluated using a standardized, prospectively maintained database by a research consortium. **RESULTS:** From 2002 to 2012, 236 FAAs were identified in 182 patients (mean age, 72 years; male-to-female ratio, 16:1) at eight institutions. The mean nonoperative mean diameter was  $2.8 \pm 0.7$  cm, and the operative diameter was  $3.3 \pm 1.5$  cm. FAA location was the common femoral artery in 191, superficial femoral artery (SFA) in 34, and profunda femoris artery in 11. Synchronous aneurysms (mean, 1.7 per patient) occurred in the aorta ( $n = 113$ ), in the iliac ( $n = 109$ ), popliteal ( $n = 86$ ), and hypogastric ( $n = 56$ ) arteries, and in the contralateral common femoral artery ( $n = 34$ ), SFA ( $n = 9$ ), and profunda femoris artery ( $n = 2$ ). Of the aneurysms repaired, 66% were asymptomatic; other indications for repair were claudication (18%), local pain (8%), nerve compression (3%), rupture (2%), acute thrombosis (1%), and rest pain (0.5%). Acute aneurysm-related complications (rupture, thrombosis, embolus) were associated ( $P < 4$  cm and intraluminal thrombus, but not location. Mean diameter of asymptomatic aneurysms that developed acute complications was  $5.7 \pm 1.3$  cm for rupture,  $4 \pm 1.1$  cm for thrombosis, and 3.5 cm for embolus. Repair was by interposition or bypass graft in 177 FAAs and by endovascular repair in three SFA aneurysms. Two perioperative deaths, of myocardial infarction and multisystem organ failure, occurred at 30 days. Operative

complications included wound infection (6%), seroma (3%), and bleeding (2%). No amputations occurred through 5 years in the operative or nonoperative groups. Survival in operated-on patients was 99% (n = 138) at 3 months, 92% at 1 year, and 81% (n = 20) at 5 years.

CONCLUSIONS: This largest study of isolated FAAs demonstrates that (1) acute complications did not occur in FAAs 3.5 cm, and chronic intraluminal thrombus should reduce the threshold for repair, and that (2) current indications for symptomatic FAA repair result in low morbidity and should remain unchanged.

Lebwohl, B., Blaser, M. J., Ludvigsson, J. F., Green, P. H. R., Rundle, A., Sonnenberg, A., et al.

(2013). Decreased risk of celiac disease in patients with helicobacter pylori colonization.

*American Journal of Epidemiology*, 178(12), 1721-1730.

The prevalence of celiac disease (CD) has increased in recent decades without a clear explanation. The "hygiene hypothesis" theorizes that decreased exposure to bacterial antigens may trigger autoimmunity. We aimed to determine whether *Helicobacter pylori* infection and CD were associated among patients undergoing upper gastrointestinal endoscopy. We performed a cross-sectional study of patients who underwent esophagogastroduodenoscopy with submission of gastric and duodenal biopsies to Miraca Life Sciences, Inc. (Irving, Texas), a US commercial pathology laboratory, during a 4.5-year period (January 2008-June 2012). We compared the prevalence of *H. pylori* in CD patients with that in persons without CD. We performed multiple logistic regression analysis, adjusting odds ratios for patient age, gender, and racial, ethnic, and socioeconomic factors. Among 136,179 patients, a total of 2,689 (2.0%) had CD. *H. pylori* prevalence was significantly lower in patients with CD (4.4%) than in those without CD (8.8%;  $P < 0.0001$ ). After adjustment for the above covariates, this inverse relationship remained strong (adjusted odds ratio (OR) = 0.48, 95% confidence interval (CI): 0.40, 0.58). The relationships were similar in men (unadjusted OR = 0.51, 95% CI: 0.38, 0.69) and women (unadjusted OR = 0.46, 95% CI: 0.36, 0.58) and in all age groups. We conclude that *H. pylori* presence and CD are inversely associated, a relationship that persists after adjustment for socioeconomic factors.

Future studies should address whether *H. pylori* modulates immune responses to ingested gluten.

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Leder, H. A., Campbell, J. P., Sepah, Y. J., Gan, T., Dunn, J. P., Hatef, E., et al. (2013). Ultra-wide-field retinal imaging in the management of non-infectious retinal vasculitis. *Journal of Ophthalmic Inflammation and Infection*, 3(1), 1-6.

Background: The purpose of this study is to describe and quantify the benefit of ultra-wide-field imaging and fluorescein angiography (FA) in the management of non-infectious retinal vasculitis. In this prospective observational cohort series, patients with non-infectious retinal vasculitis were evaluated and enrolled by four investigators from the Divisions of Retina and Ocular Immunology at the Wilmer Eye Institute. In each patient, disease activity and the need for management changes were assessed, based on clinical examination with or without standard (60°) imaging and then with the addition of ultra-wide-field pseudo-color scanning laser ophthalmoscope (SLO) images and FA using the Optos ultra-wide-field SLO (Optos Panoramic 200MA™, Optos PLC, Dunfermline, Scotland, UK). A standardized questionnaire was completed by each investigator at the time of the clinical evaluation. The primary outcome was the percentage of patients whose management was changed by clinical examination and standard FA, compared with clinical examination plus ultra-wide-field imaging. The secondary outcome was the percentage of patients whose disease was determined to be active based on each modality. Results: Seventy-one visits from 23 patients were reviewed and analyzed. Based on examination plus ultra-wide-field imaging and ultra-wide-field angiography, disease activity was detected in 48/71 (68%) compared with 32/71 (45%) based on examination and standard FA ( $P = 0.0095$ ). Based on the clinical examination alone, the decision to alter management was made in 4 of 71 visits (6%), and an additional 3 of 71 (4%) based on simulated standard FA. The addition of ultra-wide-field SLO pseudo-color images altered management in an additional 10/71 visits (14%), and 36/71 (51%) with the addition of ultra-wide-field FA. Conclusions: Ultra-wide-field fluorescein imaging and angiography can provide additional information that may be important and relevant in the management of retinal vasculitis. © 2013 Leder et al.

Lee, T. H., McCully, S. P., McCully, B. H., Sands, C., Hampton, D. A., Louis, S. G., et al. (2014). Comparison of the hemostatic efficacy of low-volume lyophilized plasma reconstituted using sterile water, lactated ringer's, normal saline, and hextend solutions. *The Journal of Trauma and Acute Care Surgery*, 76(2), 264-272.

**BACKGROUND:** Low-volume ascorbic acid-buffered reconstituted lyophilized plasma (LP) provides logistic advantages, reduces the risks for large-volume resuscitation, modulates inflammation, and is equally effective for hemostatic resuscitation as full-volume LP. We compared the physiologic effects of resuscitation using LP reconstituted with sterile water (LP-SW), lactated Ringer's solution (LP-LR), normal saline (LP-NS), and Hextend (LP-Hx). **METHODS:** Plasma was collected from swine, lyophilized, and then reconstituted into four test solutions: LP-SW, LP-LR, LP-NS, or LP-Hx. Forty swine were anesthetized and subjected to a validated model of polytrauma and hemorrhagic shock (including a Grade V liver injury), then randomized to receive one of the four test solutions. Physiologic parameters, blood loss, lactate, and hematocrit were followed up. Coagulation status was evaluated using thrombelastography. Inflammatory mediator expression was evaluated by multiplex serum assay. **RESULTS:** Forty animals were included in the study (10 animals per group). One animal died following LP-Hx resuscitation. There was less blood loss in the LP-SW and LP-LR groups compared with the LP-NS and LP-Hx groups ( $p < 0.05$ ). The LP-SW group exhibited less early coagulopathic changes by thrombelastography, and the LP-Hx group had persistently elevated international normalized ratios at the end of the study period ( $p < 0.05$ ). Serum interleukin 6 was lower after 4 hours in the LP-SW group compared with LP-NS ( $p < 0.05$ ). **CONCLUSION:** Resuscitation using low-volume LP-SW and LP-LR buffered with ascorbic acid confers an anti-inflammatory benefit and results in less blood loss. Sterile water is a safe, cost-effective, and universally available fluid for creating a low-volume hemostatic LP resuscitation solution.

Lesiak, A., Zhu, M., Chen, H., Appleyard, S. M., Impey, S., Lein, P. J., et al. (2014). The environmental neurotoxicant PCB 95 promotes synaptogenesis via ryanodine receptor-dependent miR132 upregulation. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 34(3), 717-725.

Non-dioxin-like (NDL) polychlorinated biphenyls (PCBs) are widespread environmental contaminants linked to neuropsychological dysfunction in children. NDL PCBs increase spontaneous Ca(2+) oscillations in neurons by stabilizing ryanodine receptor (RyR) calcium release channels in the open configuration, which results in CREB-dependent dendritic outgrowth. In this study, we address the question of whether activation of CREB by NDL PCBs also triggers

dendritic spine formation. Nanomolar concentrations of PCB 95, a NDL congener with potent RyR activity, significantly increased spine density and the frequency of miniature EPSCs in primary dissociated rat hippocampal cultures coincident with upregulation of miR132. Inhibition of RyR, CREB, or miR132 as well as expression of a mutant p250GAP cDNA construct that is not suppressed by miR132 blocked PCB 95 effects on spines and miniature EPSCs. PCB 95 also induced spine formation via RyR- and miR132-dependent mechanisms in hippocampal slice cultures. These data demonstrate a novel mechanism of PCB developmental neurotoxicity whereby RyR sensitization modulates spine formation and synaptogenesis via CREB-mediated miR132 upregulation, which in turn suppresses the translation of p250GAP, a negative regulator of synaptogenesis. In light of recent evidence implicating miR132 dysregulation in Rett syndrome and schizophrenia, these findings identify NDL PCBs as potential environmental risk factors for neurodevelopmental disorders.

Li, F., Harmer, P., Liu, Y., Eckstrom, E., Fitzgerald, K., Stock, R., et al. (2013). A randomized controlled trial of patient-reported outcomes with tai chi exercise in parkinson's disease.

*Movement Disorders,*

A previous randomized, controlled trial of tai chi showed improvements in objectively measured balance and other motor-related outcomes in patients with Parkinson's disease. This study evaluated whether patient-reported outcomes could be improved through exercise interventions and whether improvements were associated with clinical outcomes and exercise adherence. In a secondary analysis of the tai chi trial, patient-reported and clinical outcomes and exercise adherence measures were compared between tai chi and resistance training and between tai chi and stretching exercise. Patient-reported outcome measures were perceptions of health-related benefits resulting from participation, assessed by the Parkinson's Disease Questionnaire (PDQ-8) and Vitality Plus Scale (VPS). Clinical outcome measures included motor symptoms, assessed by a modified Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) and a 50-foot speed walk. Information on continuing exercise after the structured interventions were terminated was obtained at a 3-month postintervention follow-up. Tai chi participants reported significantly better improvement in the PDQ-8 (-5.77 points,  $P=0.014$ ) than did resistance training participants and in PDQ-8 (-9.56 points,  $P<0.001$ ) and VPS (2.80 points,  $P=0.003$ ) than

did stretching participants. For tai chi, patient-reported improvement in the PDQ-8 and VPS was significantly correlated with their clinical outcomes of UPDRS-ME and a 50-foot walk, but these correlations were not statistically different from those shown for resistance training or stretching. However, patient-reported outcomes from tai chi training were associated with greater probability of continued exercise behavior than were either clinical outcomes or patient-reported outcomes from resistance training or stretching. Tai chi improved patient-reported perceptions of health-related benefits, which were found to be associated with a greater probability of exercise adherence. The findings indicate the potential of patient perceptions to drive exercise behavior after structured exercise programs are completed and the value of strengthening such perceptions in any behavioral intervention. © 2013 The Authors.

Li, T., Luo, Q., & Jacques, S. L. (2012). Effect of cerebral cortex sulci on near-infrared light propagation during monitoring and treatment. *Biomedical Optics, BIOMED 2012*, Miami, FL. Central sulcus substantially affects NIRS/NIRI spatial sensitivity and LLLT fluence rate in the study of light transport within a high-resolution 3D anatomical head structure, allowing deeper penetration of light than previous models predicted. © 2012.

Li, X., Brazauskas, R., Wang, Z., Al-Seraihy, A., Baker, K. S., Cahn, J. Y., et al. (2014). Avascular necrosis of bone after allogeneic hematopoietic cell transplantation in children and adolescents. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,  
We conducted a nested case-control study within a cohort of 6244 patients to assess risk factors for avascular necrosis (AVN) of bone in children and adolescents after allogeneic transplantation. Eligible patients were  $\geq$  6 months from transplantation. Overall, 160 patients with AVN and 478 control subjects matched by year of transplant, length of follow-up and transplant center were identified. Patients and control subjects were confirmed via central review of radiology, pathology, and/or surgical procedure reports. Median time from transplant to diagnosis of AVN was 14 months. On conditional logistic regression, increasing age at transplant ( $\geq$ 5 years), female gender, and chronic graft-versus-host disease (GVHD) were significantly associated with increased risks of AVN. Compared with patients receiving myeloablative regimens for malignant

diseases, lower risks of AVN were seen in patients with nonmalignant diseases and those who had received reduced-intensity conditioning regimens for malignant diseases. Children at high risk for AVN include those within the age group where rapid bone growth occurs as well as those who experience exposure to myeloablative conditioning regimens and immunosuppression after hematopoietic cell transplantation for the treatment of GVHD. More research is needed to determine whether screening strategies specifically for patients at high risk for developing AVN with early interventions may mitigate the morbidity associated with this complication.

Li, Y., Sun, X. X., Elferich, J., Shinde, U., David, L. L., & Dai, M. S. (2014). Monoubiquitination is critical for Otub1 to suppress UbcH5 and stabilize p53. *The Journal of Biological Chemistry*, Otub1 regulates p53 stability and activity via non-canonical inhibition of the MDM2 cognate ubiquitin (Ub)-conjugating enzyme (E2) UbcH5. However, it is not clear how this activity of Otub1 is regulated in cells. Here we report that Otub1 is monoubiquitinated by UbcH5 in cells and in vitro, primarily at lysine 59 and 109 residues. This monoubiquitination in turn contributes to the activity of Otub1 to suppress UbcH5. The lysine-free Otub1 mutant (Otub1K0) fails to be monoubiquitinated and is unable to suppress the Ub-conjugating activity of UbcH5 in vitro and the MDM2-mediated p53 ubiquitination in cells. Consistently, this mutant is unable to stabilize p53, induce apoptosis, and suppress cell growth. Overexpression of Otub1K0 inhibits DNA-damage induced apoptosis. Adding either Lys 59 or Lys 109 back to the Otub1K0 mutant restored the monoubiquitination of Otub1 and its function to stabilize and activate p53. We further show that UbcH5 preferentially binds to the monoubiquitinated Otub1 via Ub interaction with its backside donor Ub-interacting surface, suggesting that this binding interferes with the self-assembly of Ub-charged UbcH5 (UbcH5~Ub) conjugates, which is critical for the Ub transfer. Thus, our data reveal novel insights into the Otub1 inhibition of E2 wherein monoubiquitination promotes the interaction of Otub1 with and its function to suppress UbcH5.

Lieberman, D. A. (2014). Colon polyp surveillance: Clinical decision tool. *Gastroenterology*, 146(1), 305-306.

Lim, M. M., Elkind, J., Xiong, G., Galante, R., Zhu, J., Zhang, L., et al. (2013). Dietary therapy mitigates persistent wake deficits caused by mild traumatic brain injury. *Science Translational*

*Medicine*, 5(215)

Sleep disorders are highly prevalent in patients with traumatic brain injury (TBI) and can significantly impair cognitive rehabilitation. No proven therapies exist to mitigate the neurocognitive consequences of TBI. We show that mild brain injury in mice causes a persistent inability to maintain wakefulness and decreases orexin neuron activation during wakefulness. We gave mice a dietary supplement of branched-chain amino acids (BCAAs), precursors for de novo glutamate synthesis in the brain. BCAA therapy reinstated activation of orexin neurons and improved wake deficits in mice with mild brain injury. Our data suggest that dietary BCAA intervention, acting in part through orexin, can ameliorate injury-induced sleep disturbances and may facilitate cognitive rehabilitation after brain injury.

Lin, P., Suhler, E. B., & Rosenbaum, J. T. (2014). The future of uveitis treatment. *Ophthalmology*, 121(1), 365-376.

Uveitis is a heterogeneous collection of diseases with polygenic and environmental influences. This heterogeneity presents challenges in trial design and selection of end points. Despite the multitude of causes, therapeutics targeting common inflammatory pathways are effective in treating diverse forms of uveitis. These treatments, including corticosteroids and immunomodulatory agents, although often effective, can have untoward side effects, limiting their utility. The search for drugs with equal or improved efficacy that are safe is therefore paramount. A mechanism-based approach is most likely to yield the future breakthroughs in the treatment of uveitis. We review the literature and provide examples of the nuances of immune regulation and dysregulation that can be targeted for therapeutic benefit. As our understanding of the causes of uveitis grows we will learn how to better apply antibodies designed to block interaction between inflammatory cytokines and their receptors. T-lymphocyte activation can be targeted by blocking co-stimulatory pathways or inhibiting major histocompatibility complex protein interactions. Furthermore, intracellular downstream molecules from cytokine or other pathways can be inhibited using small molecule inhibitors, which have the benefit of being orally bioavailable. An emerging field is the lipid-mediated inflammatory and regulatory pathways. Alternatively, anti-inflammatory cytokines can be provided by administering recombinant protein, and intracellular "brakes" of inflammatory pathways can be introduced potentially by gene

therapy. Novel approaches of delivering a therapeutic substance include, but are not limited to, the use of small interfering RNA, viral and nonviral gene therapy, and microparticle or viscous gel sustained-release drug-delivery platforms. © 2014 by the American Academy of Ophthalmology.

Lin, Y. C., Li, L., Makarova, A. V., Burgers, P. M., Stone, M. P., & Lloyd, R. S. (2014). Molecular basis of aflatoxin-induced mutagenesis - role of the aflatoxin B1-formamidopyrimidine adduct.

*Carcinogenesis,*

Aflatoxin B1 (AFB1) is a known carcinogen associated with early onset hepatocellular carcinoma (HCC) and is thought to contribute to over half a million new HCCs per year. Although some of the fundamental risk factors are established, the molecular basis of AFB1-induced mutagenesis in primate cells has not been rigorously investigated. To gain insights into genome instability that is produced as a result of replicating DNAs containing AFB1 adducts, site-specific mutagenesis assays were used to establish the mutagenic potential of the persistent ring-opened AFB1 adduct, AFB1-formamidopyrimidine (AFB1-FAPY). This lesion was highly mutagenic, yielding replication error frequencies of 97%, with the predominant base substitution being a G to T transversion. This transversion is consistent with previous mutational data derived from aflatoxin-associated HCCs. In vitro translesion synthesis (TLS) assays demonstrated that polymerase (pol) zeta was the most likely candidate polymerase that is responsible for the G to T mutations induced by this adduct.

Lindsay, M., Messing, J. T., Thaller, J., Baldwin, A., Clough, A., Bloom, T., et al. (2013). Survivor feedback on a safety decision aid smartphone application for college-age women in abusive relationships. *Journal of Technology in Human Services, 31*(4), 368-388.

College-age women are at high risk for dating violence and tend to seek services at rates lower than older adults. Young women are more likely to look to their peers or to technology as a forum for accessing safety resources. This study explores a prototype smart phone application ("app") that is a safety decision aid for female survivors of dating violence. The app is intended to assist young women to assess the danger in their abusive relationship, set priorities for safety, and develop a personalized safety plan. Through focus group sessions and individual interviews, 38 female college students in 4 states (Arizona, Maryland, Missouri, and Oregon) who self-identified

as survivors of abusive relationships reviewed and provided feedback on the usefulness, understandability, appropriateness, and comprehensiveness of the app. The focus group sessions and interviews were transcribed and analyzed. Participants were positive about the potential of the app to provide personalized information about abusive dating relationships and appropriate resources in a private, safe, and nonjudgmental manner. Detailed feedback from survivors and recommendations for further development of the app are discussed. © 2013 Copyright Taylor and Francis Group, LLC.

Lisowski, L., Dane, A. P., Chu, K., Zhang, Y., Cunningham, S. C., Wilson, E. M., et al. (2013).

Selection and evaluation of clinically relevant AAV variants in a xenograft liver model. *Nature*, Recombinant adeno-associated viral (rAAV) vectors have shown early promise in clinical trials. The therapeutic transgene cassette can be packaged in different AAV capsid pseudotypes, each having a unique transduction profile. At present, rAAV capsid serotype selection for a specific clinical trial is based on effectiveness in animal models. However, preclinical animal studies are not always predictive of human outcome. Here, in an attempt to further our understanding of these discrepancies, we used a chimaeric human-murine liver model to compare directly the relative efficiency of rAAV transduction in human versus mouse hepatocytes *in vivo*. As predicted from preclinical and clinical studies, rAAV2 vectors functionally transduced mouse and human hepatocytes at equivalent but relatively low levels. However, rAAV8 vectors, which are very effective in many animal models, transduced human hepatocytes rather poorly—approximately 20 times less efficiently than mouse hepatocytes. In light of the limitations of the rAAV vectors currently used in clinical studies, we used the same murine chimaeric liver model to perform serial selection using a human-specific replication-competent viral library composed of DNA-shuffled AAV capsids. One chimaeric capsid composed of five different parental AAV capsids was found to transduce human primary hepatocytes at high efficiency *in vitro* and *in vivo*, and provided species-selected transduction in primary liver, cultured cells and a hepatocellular carcinoma xenograft model. This vector is an ideal clinical candidate and a reagent for gene modification of human xenotransplants in mouse models of human diseases. More importantly, our results suggest that humanized murine models may represent a more precise approach for both selecting and evaluating clinically relevant rAAV serotypes for gene therapeutic applications.

Long, B. R., Robinson, D. C., & Zhong, H. (2014). Subdiffractive microscopy: Techniques, applications, and challenges. *Wiley Interdisciplinary Reviews. Systems Biology and Medicine*,

Cellular processes rely on the precise orchestration of signaling and effector molecules in space and time, yet it remains challenging to gain a comprehensive picture of the molecular organization underlying most basic biological functions. This organization often takes place at length scales below the resolving power of conventional microscopy. In recent years, several 'superresolution' fluorescence microscopic techniques have emerged that can surpass the diffraction limit of conventional microscopy by a factor of 2-20. These methods have been used to reveal previously unknown organization of macromolecular complexes and cytoskeletal structures. The resulting high-resolution view of molecular organization and dynamics is already changing our understanding of cellular processes at the systems level. However, current subdiffractive microscopic techniques are not without limitations; challenges remain to be overcome before these techniques achieve their full potential. Here, we introduce three primary types of subdiffractive microscopic techniques, consider their current limitations and challenges, and discuss recent biological applications. For further resources related to this article, please visit the WIREs website. Conflict of interest: The authors have declared no conflicts of interest for this article.

Majumdar, A., Apfel, U. -, Jiang, Y., Moënne-Loccoz, P., & Lippard, S. J. (2014). Versatile reactivity of a solvent-coordinated diiron(II) compound: Synthesis and dioxygen reactivity of a mixed-valent Fe<sup>II</sup>Fe<sup>III</sup> species. *Inorganic Chemistry*, 53(1), 167-181.

A new, DMF-coordinated, preorganized diiron compound [Fe<sub>2</sub>(N-Et-HPTB)(DMF)<sub>4</sub>](BF<sub>4</sub>)<sub>3</sub> (1) was synthesized, avoiding the formation of [Fe(N-Et-HPTB)](BF<sub>4</sub>)<sub>2</sub> (10) and [Fe<sub>2</sub>(N-Et-HPTB)(μ-MeCONH)](BF<sub>4</sub>)<sub>2</sub> (11), where N-Et-HPTB is the anion of N,N,N',N'-tetrakis[2-(1-ethylbenzimidazolyl)]-2-hydroxy-1, 3-diaminopropane. Compound 1 is a versatile reactant from which nine new compounds have been generated. Transformations include solvent exchange to yield [Fe<sub>2</sub>(N-Et-HPTB)(MeCN)<sub>4</sub>](BF<sub>4</sub>)<sub>3</sub> (2), substitution to afford [Fe<sub>2</sub>(N-Et-HPTB)(μ-RCOO)](BF<sub>4</sub>)<sub>2</sub> (3, R = Ph; 4, RCOO = 4-methyl-2,6-diphenyl benzoate]), one-electron oxidation by (Cp<sub>2</sub>Fe)(BF<sub>4</sub>) to yield a Robin-Day class II mixed-valent diiron(II,III) compound, [Fe<sub>2</sub>(N-Et-HPTB)(μ-PhCOO)(DMF)<sub>2</sub>](BF<sub>4</sub>)<sub>3</sub> (5), two-electron oxidation with tris(4-bromophenyl)aminium

hexachloroantimonate to generate  $[\text{Fe}_2(\text{N-Et-HPTB})\text{Cl}_3(\text{DMF})](\text{BF}_4)_2$  (6), reaction with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl to form  $[\text{Fe}_5(\text{N-Et-HPTB})_2(\mu\text{-OH})_4(\mu\text{-O})(\text{DMF})_2](\text{BF}_4)_4$  (7), and reaction with dioxygen to yield an unstable peroxy compound that decomposes at room temperature to generate  $[\text{Fe}_4(\text{N-Et-HPTB})_2(\mu\text{-O})_3(\text{H}_2\text{O})_2](\text{BF}_4)_8 \cdot 8\text{DMF}$  (8) and  $[\text{Fe}_4(\text{N-Et-HPTB})_2(\mu\text{-O})_4](\text{BF}_4)_2$  (9). Compound 5 loses its bridging benzoate ligand upon further oxidation to form  $[\text{Fe}_2(\text{N-Et-HPTB})(\text{OH})_2(\text{DMF})_2](\text{BF}_4)_3$  (12). Reaction of the diiron(II,III) compound 5 with dioxygen was studied in detail by spectroscopic methods. All compounds (1-12) were characterized by single-crystal X-ray structure determinations. Selected compounds and reaction intermediates were further examined by a combination of elemental analysis, electronic absorption spectroscopy, Mössbauer spectroscopy, EPR spectroscopy, resonance Raman spectroscopy, and cyclic voltammetry. © 2013 American Chemical Society.

Mangla, A., Daya, M. R., & Gupta, S. (2014). Post-resuscitation care for survivors of cardiac arrest. *Indian Heart Journal*,

Cardiac arrest can occur following a myriad of clinical conditions. With advancement of medical science and improvements in Emergency Medical Services systems, the rate of return of spontaneous circulation for patients who suffer an out-of-hospital cardiac arrest (OHCA) continues to increase. Managing these patients is challenging and requires a structured approach including stabilization of cardiopulmonary status, early consideration of neuroprotective strategies, identifying and managing the etiology of arrest and initiating treatment to prevent recurrence. This requires a closely coordinated multidisciplinary team effort. In this article, we will review the initial management of survivors of OHCA, highlighting advances and ongoing controversies. © 2014 Cardiological Society of India.

Marotta, J. J. (2013). Abstinence from or management of gambling in jails and prisons? perspectives of a field worker. *Journal of Gambling Issues*, (28)

Marshall, N. E., Guild, C., Cheng, Y. W., Caughey, A. B., & Halloran, D. R. (2014). Racial disparities in pregnancy outcomes in obese women. *Journal of Maternal-Fetal and Neonatal Medicine*, 27(2), 122-126.

Objective: To estimate the effect of race on perinatal outcomes in obese women. Methods:

Retrospective cohort study of birth records linked to hospital discharge data for all live born singleton infants  $\geq 37$  weeks gestation born to African-American or Caucasian Missouri residents from 2000 to 2006. We excluded major congenital anomalies and women with diabetes or chronic hypertension. Obesity was defined as pre-pregnancy body mass index  $\geq 30$  kg/m<sup>2</sup>. Results: There were 312 412 births meeting study criteria. 27.1% (11 776) of African-American mothers and 19.1% (49 415) of Caucasian mothers were obese. There were no differences in cesarean delivery or preeclampsia between obese African-American and obese Caucasian women. Infants of obese African-American women were significantly less likely to be macrosomic (0.9% vs. 2.2%, adjusted odds ratio [aOR] 0.5, 95% confidence interval [CI] 0.4 0.6) and more likely to be low birth weight (3.4% vs. 1.8%, aOR 1.9, 95% CI 1.7, 2.2) compared to infants of obese Caucasian women. Compared to their normal weight peers, obese Caucasian women had a greater relative risk of developing preeclampsia (aOR 3.1, 95% CI 2.9, 3.2) than obese African-American women (aOR 2.1, 95% CI 1.9, 2.4). Conclusion: Racial disparities impact obesity-related maternal and neonatal complications of pregnancy. © 2014 Informa UK Ltd. All rights reserved: reproduction in whole or part not permitted.

Martin, G. M., Chen, P. C., Devaraneni, P., & Shyng, S. L. (2013). Pharmacological rescue of trafficking-impaired ATP-sensitive potassium channels. *Frontiers in Physiology*, 4, 386.

ATP-sensitive potassium (KATP) channels link cell metabolism to membrane excitability and are involved in a wide range of physiological processes including hormone secretion, control of vascular tone, and protection of cardiac and neuronal cells against ischemic injuries. In pancreatic beta-cells, KATP channels play a key role in glucose-stimulated insulin secretion, and gain or loss of channel function results in neonatal diabetes or congenital hyperinsulinism, respectively. The beta-cell KATP channel is formed by co-assembly of four Kir6.2 inwardly rectifying potassium channel subunits encoded by KCNJ11 and four sulfonylurea receptor 1 subunits encoded by ABCC8. Many mutations in ABCC8 or KCNJ11 cause loss of channel function, thus, congenital hyperinsulinism by hampering channel biogenesis and hence trafficking to the cell surface. The trafficking defects caused by a subset of these mutations can be corrected by sulfonylureas, KATP channel antagonists that have long been used to treat type 2 diabetes. More recently, carbamazepine, an anticonvulsant that is thought to target primarily voltage-gated

sodium channels has been shown to correct KATP channel trafficking defects. This article reviews studies to date aimed at understanding the mechanisms by which mutations impair channel biogenesis and trafficking and the mechanisms by which pharmacological ligands overcome channel trafficking defects. Insight into channel structure-function relationships and therapeutic implications from these studies are discussed.

Mason, G. E., Aung, L., Gall, S., Meyers, P. A., Butler, R., Krüg, S., et al. (2013). Quality of life following amputation or limb preservation in patients with lower extremity bone sarcoma. *Frontiers in Oncology*, 3 AUG

**Purpose:** Although functional differences have been described between patients with lower extremity bone sarcoma with amputation and limb-preservation surgery, differences have not clearly been shown between the two groups related to quality of life. The purpose of the study was to determine if there is a difference in overall quality of life in lower extremity bone sarcoma survivors related to whether they had an amputation or a limb-preservation procedure while identifying psychological differences for further evaluation. The main hypothesis was that sparing a person's limb, as opposed to amputating it, would result in a better quality of life. Patients and **Methods:** Eighty-two long-term survivors of lower extremity bone sarcoma were studied to make a comparison of the overall quality of life, pain assessment, and psychological evaluations in limb preservation and amputation patients. Forty-eight patients with limb preservation and thirty-four patients with amputations were enrolled in the study. Validated psychometric measures including the Quality of Life Questionnaire (QLQ), the Minnesota Multiphasic Personality Inventory, and visual analog scales were utilized. **Results:** The overall quality of life of patients with limb preservation was significantly higher than patients with amputation ( $p$ -value < 0.01). Significant differences were noted in the categories of material well-being, job satisfiers, and occupational relations. **Conclusion:** The overall quality of life of patients with limb-preservation appears to be better than for those patients with amputation based on the QLQ in patients surviving lower extremity bone sarcoma. Further analysis needs to verify the results and focus on the categories that significantly affect the overall quality of life. © 2013 Mason, Aung, Gall, Meyers, Butler, Krüg, Kim, Healey and Gorlick.

Matin, S. F., Shariat, S. F., Milowsky, M. I., Hansel, D. E., Kassouf, W., Koppie, T., et al. (2014).

Highlights from the first symposium on upper tract urothelial carcinoma. *Urologic Oncology*,

OBJECTIVES: Upper tract urothelial carcinoma (UTUC) is a rare disease in Western countries and garners little focused attention in urologic and oncologic circles. We report highlights from the first symposium on UTUC. METHODS: All participants were asked to provide a summary of their presentation to be included as part of these proceedings. Submitted summaries were synthesized into this document. All contributors reviewed and provided input on the final draft. RESULTS: Five highlights are included in this report, including landmark research that not only reveals the likely cause of Balkan endemic nephropathy and associated UTUC but also links it directly to UTUC in Taiwan. Because of the ubiquitous use of Aristolochia plants in these herbal remedies, a public health problem of considerable magnitude is anticipated in Asian countries. Gene expression signatures reveal some differential expression in bladder carcinoma, such as CLCA2 and GABRE. Few urinary markers have proven utility for the diagnosis and follow-up of UTUC, and no tissue or blood-based markers are currently undergoing clinical application. Novel endoscopic therapies provide some hope of improving tissue sampling, diagnosis, and kidney-sparing therapeutics, but the greatest potential lies in improving clinical (preoperative) risk stratification, which is critically limited in this disease. Biomarkers, currently untested, hold promise in identifying patients most likely to benefit from perioperative chemotherapy and at high risk from cisplatin-induced nephrotoxicity. CONCLUSIONS: Despite its rarity in the West, UTUC is reaching potentially epidemic proportions in the East because of exposure to carcinogenic herbal remedies. Critical trials are needed to improve our understanding and treatment of UTUC. Because of the broad range of comorbid conditions in patients suffering from this disease, it is the consensus of the participants that future clinical trials should be practical in design and applicable to a broad range of patients, diverging from the current dogma of narrow patient selection criteria in clinical trials. Practical designs would maximize accrual for a still uncommon disease, and their findings would be applicable to a larger proportion of patients than current narrowly selected designs.

Matsumura, H., Hayashi, T., Chakraborty, S., Lu, Y., & Moenne-Loccoz, P. (2014). The production of nitrous oxide by the Heme/Nonheme diiron center of engineered myoglobins (FeMbs) proceeds through a trans-iron-nitrosyl dimer. *Journal of the American Chemical Society*,

Denitrifying NO reductases are transmembrane protein complexes that are evolutionarily related to heme/copper terminal oxidases. They utilize a heme/nonheme diiron center to reduce two NO molecules to N<sub>2</sub>O. Engineering a nonheme FeB site within the heme distal pocket of sperm whale myoglobin has offered well-defined diiron clusters for the investigation of the mechanism of NO reduction in these unique active sites. In this study, we use FTIR spectroscopy to monitor the production of N<sub>2</sub>O in solution and to show that the presence of a distal FeBII is not sufficient to produce the expected product. However, the addition of a glutamate side chain peripheral to the diiron site allows for 50% of a productive single-turnover reaction. Unproductive reactions are characterized by resonance Raman spectroscopy as dinitrosyl complexes, where one NO molecule is bound to the heme iron to form a five-coordinate low-spin {FeNO}<sub>2</sub> species with  $\nu(\text{FeNO})_{\text{heme}}$  and  $\nu(\text{NO})_{\text{heme}}$  at 522 and 1660 cm<sup>-1</sup>, and a second NO molecule is bound to the nonheme FeB site with a  $\nu(\text{NO})_{\text{FeB}}$  at 1755 cm<sup>-1</sup>. Stopped-flow UV-vis absorption coupled with rapid-freeze-quench resonance Raman spectroscopy provide a detailed map of the reaction coordinates leading to the unproductive iron-nitrosyl dimer. Unexpectedly, NO binding to FeB is kinetically favored and occurs prior to the binding of a second NO to the heme iron, leading to a (six-coordinate low-spin heme-nitrosyl/FeB-nitrosyl) transient dinitrosyl complex with characteristic  $\nu(\text{FeNO})_{\text{heme}}$  at 570 +/- 2 cm<sup>-1</sup> and  $\nu(\text{NO})_{\text{FeB}}$  at 1755 cm<sup>-1</sup>. Without the addition of a peripheral glutamate, the dinitrosyl complex is converted to a dead-end product after the dissociation of the proximal histidine of the heme iron, but the added peripheral glutamate side chain in FeBMb2 lowers the rate of dissociation of the proximal histidine which in turn allows the (six-coordinate low-spin heme-nitrosyl/FeB-nitrosyl) transient dinitrosyl complex to decay with production of N<sub>2</sub>O at a rate of 0.7 s<sup>-1</sup> at 4 degrees C. Taken together, our results support the proposed trans mechanism of NO reduction in NORs.

Maxson, J. E., Luty, S. B., Macmaniman, J., Abel, M. L., Druker, B. J., & Tyner, J. W. (2014). Ligand-independence of the colony stimulating factor 3 receptor (CSF3R) T618I mutation results from loss of O-linked glycosylation and increased receptor dimerization. *The Journal of Biological Chemistry*,  
Mutations in the CSF3 (GCSF) receptor, CSF3R have recently been found in a large percentage of patients with chronic neutrophilic leukemia (CNL) and more rarely in other types of leukemia.

These CSF3R mutations fall into two distinct categories: membrane proximal mutations and truncation mutations. Although both classes of mutation have exhibited the capacity for cellular transformation, several aspects of this transformation including the kinetics, requirement for ligand, and dysregulation of downstream signaling pathways have all been shown to be discrepant between the mutation types, suggesting distinct mechanisms of activation. CSF3R truncation mutations induce overexpression and ligand hypersensitivity of the receptor, likely due to removal of motifs necessary for endocytosis and degradation. In contrast, little is known about the mechanism of activation of membrane proximal mutations, which are much more commonly observed in CNL. In contrast to CSF3R truncation mutations, membrane proximal mutations do not exhibit overexpression and are capable of signaling in the absence of ligand. We show that the T615 and T618 sites of membrane proximal mutations are part of an O-linked glycosylation cluster. Mutation at these sites prevents O- glycosylation of CSF3R, and increases receptor dimerization. This increased dimerization explains the ligand-independent activation of CSF3R membrane proximal mutations. Cytokine receptor activation through loss of O- glycosylation represents a novel avenue of aberrant signaling. Finally, combination of the CSF3R membrane proximal and truncation mutations, as has been reported in some patients, leads to enhanced cellular transformation when compared to either mutation alone, underscoring their distinct mechanisms of action.

McClendon, E., Chen, K., Gong, X., Sharifnia, E., Hagen, M., Cai, V., et al. (2014). Prenatal cerebral ischemia triggers dysmaturation of caudate projection neurons. *Annals of Neurology*, Objective: Recently we reported that the neocortex displays impaired growth after transient cerebral hypoxia-ischemia (HI) at preterm gestation that is unrelated to neuronal death but is associated with decreased dendritic arbor complexity of cortical projection neurons. We hypothesized that these morphological changes constituted part of a more widespread neuronal dysmaturation response to HI in the caudate nucleus (CN), which contributes to motor and cognitive disability in preterm survivors. Methods: Ex vivo magnetic resonance imaging (MRI), immunohistochemistry and Golgi staining defined CN growth, cell death, proliferation and dendritic maturation in preterm fetal sheep four weeks after HI. Patch-clamping recording was used to analyze glutamatergic synaptic currents in CN neurons. Results: MRI-defined growth of

the CN was reduced after ischemia compared to controls. However, no significant acute or delayed neuronal death was seen in the CN or white matter. Neither was there significant loss of calbindin-positive medium spiny projection neurons (MSNs) or CN interneurons expressing somatostatin, calretinin, parvalbumin, or tyrosine hydroxylase. Morphologically, ischemic MSNs showed a markedly immature dendritic arbor, with fewer dendritic branches, nodes, endings and spines. The magnitude and kinetics of synaptic currents, and the relative contribution of glutamate receptor subtypes in the CN were significantly altered. Interpretation: The marked MSN dendritic and functional abnormalities after preterm cerebral HI, despite the marked resistance of immature CN neurons to cell death, are consistent with widespread susceptibility of projection neurons to HI-induced dysmaturation. These global disturbances in dendritic maturation and glutamatergic synaptic transmission suggest a new mechanism for long-term motor and behavioral disabilities in preterm survivors via widespread disruption of neuronal connectivity. ANN NEUROL 2013. (c) 2013 American Neurological Association.

Mehrotra, R., Agarwal, A., Bargman, J. M., Himmelfarb, J., Johansen, K. L., Watnick, S., et al. (2014).

Dialysis therapies: A national dialogue. *Clinical Journal of the American Society of Nephrology : CJASN*,

The National Institute of Diabetes, Digestive, and Kidney Diseases-supported Kidney Research National Dialogue asked the scientific community to formulate and prioritize research objectives that would improve our understanding of kidney function and disease. Kidney Research National Dialogue participants identified the need to improve outcomes in ESRD by decreasing mortality and morbidity and enhancing quality of life as high priority areas in kidney research. To reach these goals, we must identify retained toxins in kidney disease, accelerate technologic advances in dialysate composition and devices to remove these toxins, advance vascular access, and identify measures that decrease the burden of disease in maintenance dialysis patients. Together, these research objectives provide a path forward for improving patient-centered outcomes in ESRD.

Messer, W. B., de Alwis, R., Yount, B. L., Royal, S. R., Huynh, J. P., Smith, S. A., et al. (2014).

Dengue virus envelope protein domain I/II hinge determines long-lived serotype-specific dengue

immunity. *Proceedings of the National Academy of Sciences of the United States of America*, The four dengue virus (DENV) serotypes, DENV-1, -2, -3, and -4, are endemic throughout tropical and subtropical regions of the world, with an estimated 390 million acute infections annually. Infection confers long-term protective immunity against the infecting serotype, but secondary infection with a different serotype carries a greater risk of potentially fatal severe dengue disease, including dengue hemorrhagic fever and dengue shock syndrome. The single most effective measure to control this threat to global health is a tetravalent DENV vaccine. To date, attempts to develop a protective vaccine have progressed slowly, partly because the targets of type-specific human neutralizing antibodies (NAbs), which are critical for long-term protection, remain poorly defined, impeding our understanding of natural immunity and hindering effective vaccine development. Here, we show that the envelope glycoprotein domain I/II hinge of DENV-3 and DENV-4 is the primary target of the long-term type-specific NAb response in humans. Transplantation of a DENV-4 hinge into a recombinant DENV-3 virus showed that the hinge determines the serotype-specific neutralizing potency of primary human and nonhuman primate DENV immune sera and that the hinge region both induces NAbs and is targeted by protective NAbs in rhesus macaques. These results suggest that the success of live dengue vaccines may depend on their ability to stimulate NAbs that target the envelope glycoprotein domain I/II hinge region. More broadly, this study shows that complex conformational antibody epitopes can be transplanted between live viruses, opening up similar possibilities for improving the breadth and specificity of vaccines for influenza, HIV, hepatitis C virus, and other clinically important viral pathogens.

Meyer, J. M., Perlewitz, K. S., Hayden, J. B., Doung, Y. -, Hung, A. Y., Vetto, J. T., et al. (2013).

Phase i trial of preoperative chemoradiation plus sorafenib for high-risk extremity soft tissue sarcomas with dynamic contrast-enhanced MRI correlates. *Clinical Cancer Research*, 19(24), 6902-6911.

Purpose: We conducted a phase I trial of the addition of sorafenib to a chemoradiotherapy regimen in patients with high-risk (intermediate/high grade, >5 cm) extremity soft tissue sarcoma undergoing limb salvage surgery. We conducted a correlative study of quantitative dynamic contrast-enhanced MRI (DCE-MRI) to assess response to treatment. Experimental

Design: Patients were treated at increasing dose levels of sorafenib (200 mg daily, 400 mg daily, 400 mg twice daily) initiated 14 days before three preoperative and three postoperative cycles of epirubicin/ifosfamide. Radiation (28 Gy) was administered during cycle 2 with epirubicin omitted. The primary objective was to determine the maximum tolerated dose (MTD) of sorafenib. DCE-MRI was conducted at baseline, after 2 weeks of sorafenib, and before surgery. The imaging data were subjected to quantitative pharmacokinetic analyses. Results: Eighteen subjects were enrolled, of which 16 were evaluable. The MTD of sorafenib was 400 mg daily. Common grade 3-4 adverse events included neutropenia (94%), hypophosphatemia (75%), anemia (69%), thrombocytopenia (50%), and neutropenic fever/infection (50%). Of note, 38% developed wound complications requiring surgical intervention. The rate of  $\geq 95\%$  histopathologic tumor necrosis was 44%. Changes in DCE-MRI biomarker DKtrans  $\Delta$ Ktrans after 2 weeks of sorafenib correlated with histologic response ( $R^2 = 0.67$ ,  $P = 0.012$ ) at surgery. Conclusion: The addition of sorafenib to preoperative chemoradiotherapy is feasible and warrants further investigation in a larger trial. DCE-MRI detected changes in tumor perfusion after 2 weeks of sorafenib and may be a minimally invasive tool for rapid assessment of drug effect in soft tissue sarcoma. © 2013 American Association for Cancer Research.

Milano, C. E., Hardman, J. A., Plesiu, A., Rdesinski, R. E., & Biagioli, F. E. (2014). Simulated electronic health record (sim-EHR) curriculum: Teaching EHR skills and use of the EHR for disease management and prevention. *Academic Medicine : Journal of the Association of American Medical Colleges*,

Electronic health records (EHRs) can improve many aspects of patient care, yet few formal EHR curricula exist to teach optimal use to students and other trainees. The Simulated EHR (Sim-EHR) curriculum was introduced in January 2011 at Oregon Health & Science University (OHSU) to provide learners with a safe hands-on environment in which to apply evidence-based guidelines while learning EHR skills. Using an EHR training platform identical to the OHSU EHR system, learners review and correct a simulated medical chart for a complex virtual patient with chronic diseases and years of fragmented care. They write orders and prescriptions, create an evidence-based plan of care for indicated disease prevention and management, and review their work in a small-group setting. Third-year students complete the Sim-EHR curriculum as part of the

required family medicine clerkship; their chart work is assessed using a rubric tied to the curriculum's general and specific objectives. As of January 2014, 406 third-year OHSU medical students, on campus or at remote clerkship sites, and 21 OHSU internal medicine interns had completed simulated charts. In this article, the authors describe the development and implementation of the Sim-EHR curriculum, with a focus on use of the curriculum in the family medicine clerkship. They also share preliminary findings and lessons learned. They suggest that the Sim-EHR curriculum is an effective, interactive method for providing learners with EHR skills education while demonstrating how a well-organized chart helps ensure safe, efficient, and quality patient care.

Mohammadi, S. H., & Kain, A. (2013). Transmutative voice conversion. *2013 38th IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2013, Vancouver, BC*. pp. 6920-6924.

There are two types of voice conversion (VC) systems: generative and transmutative. A generative VC system typically uses a compact parametrization of speech and maps input to output parameters directly; however, the relative low dimensionality of the underlying speech model reduces quality. On the other hand, a transmutative VC system modifies high-dimensional features of a high-fidelity speech model, leaving critical details unmodified. Two versions of transmutative VC approach are implemented and compared to a generative VC approach. The results show that the implemented transmutative VC is significantly better compared to generative VC in terms of quality. The difference between the two VC methods regarding recognition scores are insignificant. © 2013 IEEE.

Moreira, D. M., Aronson, W. J., Terris, M. K., Kane, C. J., Amling, C. L., Cooperberg, M. R., et al. (2014). Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: Results from the SEARCH database. *Cancer, 120*(2), 197-204.

**BACKGROUND** The current study was conducted to analyze the association between cigarette smoking and metastasis (the primary outcome) as well as time to biochemical disease recurrence (BCR), metastasis, castration-resistant prostate cancer (CRPC), and prostate cancer-specific and

overall mortality (secondary outcomes) after radical prostatectomy among men from the Shared Equal Access Regional Cancer Hospital cohort. METHODS A retrospective analysis was performed of 1450 subjects for whom smoking status was available from preoperative notes. Analysis of baseline characteristics by smoking status was performed using the chi-square and rank sum tests. The association between smoking status and time to the event was analyzed using Kaplan-Meier plots, the log-rank test, and Cox and competing risk models. RESULTS A total of 549 men (33%) men were active smokers and 1121 (67%) were nonsmokers at the time of surgery. Current smokers were younger and had a lower body mass index, higher prostate-specific antigen level, and more extracapsular extension and seminal vesicle invasion (all  $P < .05$ ). A total of 509 patients, 26 patients, 30 patients, 18 patients, and 217 patients, respectively, experienced BCR, metastasis, CRPC, prostate cancer-related death, and any-cause death over a median follow-up of 62 months, 75 months, 61 months, 78 months, and 78 months, respectively. After adjusting for preoperative features, active smoking was found to be associated with an increased risk of BCR (hazards ratio [HR], 1.25;  $P = .024$ ), metastasis (HR, 2.64;  $P = .026$ ), CRPC (HR, 2.62;  $P = .021$ ), and overall mortality (HR, 2.14;  $P < .001$ ). Similar results were noted after further adjustment for postoperative features, with the exception of BCR (HR, 1.10;  $P = .335$ ), metastasis (HR, 2.51;  $P = .044$ ), CRPC (HR, 2.67;  $P = .015$ ), and death (HR, 2.03;  $P < .001$ ). CONCLUSIONS Among patients undergoing radical prostatectomy, cigarette smoking was associated with an increased risk of metastasis. In addition, smoking was associated with a higher risk of BCR, CRPC, and overall mortality. If confirmed, these data suggest that smoking is a modifiable risk factor in patients with aggressive prostate cancer. © 2013 American Cancer Society.

Moreira, D. M., Cooperberg, M. R., Howard, L. E., Aronson, W. J., Kane, C. J., Terris, M. K., et al. (2014). Predicting bone scan positivity after biochemical recurrence following radical prostatectomy in both hormone-naïve men and patients receiving androgen-deprivation therapy: Results from the SEARCH database. *Prostate Cancer and Prostatic Diseases*,  
Background: To evaluate the factors associated with positive bone scans after biochemical recurrence (BCR) following radical prostatectomy in both hormone-naïve subjects and subjects after androgen-deprivation therapy (ADT). Methods: Retrospective analysis of 380 bone scans of

301 hormone-naive subjects and 214 bone scans of 137 subjects after ADT following BCR from the Shared Equal Access Regional Cancer Hospital database. Generalized estimating equations and local regression plots were used to evaluate bone scan positivity by patients' demographics, pathological features, PSA levels and kinetics. Results: Among hormone-naive subjects and subjects on ADT, bone scan positivity was seen in 24 (6%) and 65 (30%) subjects, respectively. In hormone-naive subjects, the higher prescan PSA, higher PSA velocity (PSAV) and shorter PSA doubling time (PSADT) were significantly associated with positive scans ( $P=0.008$ ,  $P<0.001$  and  $P<0.001$ , respectively). In subjects after ADT, the prescan PSA, PSAV and PSADT were significantly associated with positive scans ( $P=0.011$ ,  $P<0.001$  and  $P=0.002$ , respectively). Regression plots showed increased scan positivity with increasing PSA levels and shortening PSADT (all  $P<0.001$ ) for both hormone-naive subjects and subjects after ADT. For a given PSA level and PSADT, subjects on ADT had higher bone scan positivity. Conclusions: In both hormone-naive subjects and subjects after ADT, more aggressive and advanced disease identified by higher PSA levels, higher PSAV and shorter PSADT were associated with higher bone scan positivity. For the same PSA level and PSADT, subjects after ADT had higher bone scan positivity than hormone-naive subjects. Therefore, PSA levels and kinetics may be used as selection criteria for bone scan in these patients. Prostate Cancer and Prostatic Disease advance online publication, 14 January 2014; doi:10.1038/pcan.2013.59.

Mullegama, S. V., Rosenfeld, J. A., Orellana, C., Van Bon, B. W. M., Halbach, S., Repnikova, E. A., et al. (2014). Reciprocal deletion and duplication at 2q23.1 indicates a role for MBD5 in autism spectrum disorder. *European Journal of Human Genetics*, 22(1), 57-63.

Copy number variations associated with abnormal gene dosage have an important role in the genetic etiology of many neurodevelopmental disorders, including intellectual disability (ID) and autism. We hypothesize that the chromosome 2q23.1 region encompassing MBD5 is a dosage-dependent region, wherein deletion or duplication results in altered gene dosage. We previously established the 2q23.1 microdeletion syndrome and report herein 23 individuals with 2q23.1 duplications, thus establishing a complementary duplication syndrome. The observed phenotype includes ID, language impairments, infantile hypotonia and gross motor delay, behavioral problems, autistic features, dysmorphic facial features (pinnae anomalies, arched eyebrows,

prominent nose, small chin, thin upper lip), and minor digital anomalies (fifth finger clinodactyly and large broad first toe). The microduplication size varies among all cases and ranges from 68 kb to 53.7 Mb, encompassing a region that includes MBD5, an important factor in methylation patterning and epigenetic regulation. We previously reported that haploinsufficiency of MBD5 is the primary causal factor in 2q23.1 microdeletion syndrome and that mutations in MBD5 are associated with autism. In this study, we demonstrate that MBD5 is the only gene in common among all duplication cases and that overexpression of MBD5 is likely responsible for the core clinical features present in 2q23.1 microduplication syndrome. Phenotypic analyses suggest that 2q23.1 duplication results in a slightly less severe phenotype than the reciprocal deletion. The features associated with a deletion, mutation or duplication of MBD5 and the gene expression changes observed support MBD5 as a dosage-sensitive gene critical for normal development. © 2014 Macmillan Publishers Limited.

Musser, E. D., Hawkey, E., Kachan-Liu, S. S., Lees, P., Roulet, J. B., Goddard, K., et al. (2014).

Shared familial transmission of autism spectrum and attention-deficit/hyperactivity disorders.

*Journal of Child Psychology and Psychiatry, and Allied Disciplines,*

BACKGROUND: To determine whether familial transmission is shared between autism spectrum disorders and attention-deficit/hyperactivity disorder, we assessed the prevalence, rates of comorbidity, and familial transmission of both disorders in a large population-based sample of children during a recent 7 year period. METHODS: Study participants included all children born to parents with the Kaiser Permanente Northwest (KPNW) Health Plan between 1 January 1998 and 31 December 2004 (n = 35,073). Children and mothers with physician-identified autism spectrum disorders (ASD) and/or attention-deficit/hyperactivity disorder (ADHD) were identified via electronic medical records maintained for all KPNW members. RESULTS: Among children aged 6-12 years, prevalence was 2.0% for ADHD and 0.8% for ASD; within those groups, 0.2% of the full sample (19% of the ASD sample and 9.6% of the ADHD sample) had co-occurring ASD and ADHD, when all children were included. When mothers had a diagnosis of ADHD, first born offspring were at 6-fold risk of ADHD alone (OR = 5.02, p < .0001) and at 2.5-fold risk of ASD alone (OR = 2.52, p < .01). Results were not accounted for by maternal age, child gestational

age, child gender, and child race. CONCLUSIONS: Autism spectrum disorders shares familial transmission with ADHD. ADHD and ASD have a partially overlapping diathesis.

Nakajima, E., Hammond, K. B., Shearer, T. R., & Azuma, M. (2014). Activation of the mitochondrial caspase pathway and subsequent calpain activation in monkey RPE cells cultured under zinc depletion. *Eye (Basingstoke)*, 28(1), 85-92.

Purpose Decreased 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. Methods RPE 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. Results TPEN 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. Conclusions Relative zinc deficiency in RPE cells causes activation of cytosolic calpain and mitochondrial caspase pathways without ER stress. © 2014 Macmillan Publishers Limited All rights reserved.

Nakamoto, B. K., Shikuma, C. M., Ogata-Arakaki, D., Umaki, T., Neuwelt, E. A., Shiramizu, B. T., et al. (2013). Feasibility and potential role of ferumoxytol-enhanced neuroimaging in HIV-associated neurocognitive disorder. *Journal of Neurovirology*, 19(6), 601-605.

We assessed ferumoxytol-enhanced brain MRI to identify monocyte/macrophage accumulation in HIV-associated neurocognitive disorder (HAND). Four HIV-infected subjects with undetectable HIV RNA levels on antiretroviral therapy, HIV DNA level in CD14+ cells  $\geq 10$  copies/10<sup>6</sup> cells, and cognitive impairment underwent ferumoxytol-enhanced brain MRI. On post-ferumoxytol susceptibility-weighted images, all HIV-infected subjects demonstrated a diffuse "tram track" appearance in the perivascular regions of cortical and deep white matter vessels suggesting ferumoxytol uptake in monocytes/ macrophages. This finding was not present in an HIV-

seronegative control. While ferumoxytol may have potential as an imaging biomarker for monocyte/macrophage accumulation in patients with HAND, future study is needed. © 2013 Journal of NeuroVirology, Inc.

Narayanan, K., Reinier, K., Uy-Evanado, A., Teodorescu, C., Chugh, H., Marijon, E., et al. (2013).

Frequency and determinants of implantable cardioverter defibrillator deployment among primary prevention candidates with subsequent sudden cardiac arrest in the community. *Circulation*, 128(16), 1733-1738.

**BACKGROUND:** The prevalence rates and influencing factors for deployment of primary prevention implantable cardioverter defibrillators (ICDs) among subjects who eventually experience sudden cardiac arrest in the general population have not been evaluated. **METHODS AND RESULTS:** Cases of adult sudden cardiac arrest with echocardiographic evaluation before the event were identified from the ongoing Oregon Sudden Unexpected Death Study (population approximately 1 million). Eligibility for primary ICD implantation was determined from medical records based on established guidelines. The frequency of prior primary ICD implantation in eligible subjects was evaluated, and ICD nonrecipients were characterized. Of 2093 cases (2003-2012), 448 had appropriate pre- sudden cardiac arrest left ventricular ejection fraction information available. Of these, 92 (20.5%) were eligible for primary ICD implantation, 304 (67.9%) were ineligible because of left ventricular ejection fraction >35%, and the remainder (52, 11.6%) had left ventricular ejection fraction  $\leq$ 80 years (versus 0% among recipients,  $P=0.11$ ). Additionally, a subgroup (26%) had either a clinical history of dementia or were undergoing chronic dialysis. **CONCLUSIONS:** Only one fifth of the sudden cardiac arrest cases in the community were eligible for a primary prevention ICD before the event, but among these, a small proportion (13%) were actually implanted. Although older age and comorbidity may explain nondeployment in a subgroup of these cases, other determinants such as socioeconomic factors, health insurance, patient preference, and clinical practice patterns warrant further detailed investigation.

Newell, L. F., Deans, R. J., & Maziarz, R. T. (2014). Adult adherent stromal cells in the management of graft-versus-host disease. *Expert Opinion on Biological Therapy*, 14(2), 231-246.

Introduction: Early reports demonstrated the safety of adherent mesenchymal stromal cell (MSC) infusions in the hematopoietic stem cell transplantation (HCT) setting, as well as clinical efficacy for treatment of steroid refractory acute graft-versus-host disease (GVHD); however, two large, Phase III randomized, placebo-controlled trials of MSC for initial therapy or steroid refractory GVHD failed to meet their primary endpoints of durable complete response. Subset analyses demonstrated efficacy in selected patient populations, contributing to recent approvals of MSC for pediatric patients in Canada and New Zealand. Areas covered: In this review, we discuss the biologic and immunomodulatory properties of MSC and potential mechanisms involved. We review the results of prior clinical trials incorporating MSC for GVHD treatment or prophylaxis, the recent approvals in Canada and New Zealand, as well as future directions in the field. Expert opinion: The role of MSC infusions, in the prophylaxis and/or treatment of GVHD after HCT, continues to be under active investigation. Whether, and how, to incorporate MSC infusions is unclear, and ongoing questions include the source tissue type and culture methods, the timing and dosage of MSC product infusions, as well as the optimal clinical trial design and endpoints for assessment of clinical response.

Nicolaidis, C., Mejia, A., Perez, M., Alvarado, A., Celaya-Alston, R., Quintero, Y., et al. (2013).

Proyecto interconexiones: A pilot test of a community-based depression care program for latina violence survivors. *Progress in Community Health Partnerships: Research, Education, and Action*, 7(4), 395-401.

Background: Latina intimate partner violence (IPV) survivors often face great barriers to depression care. We sought to use a community-based participatory research (CBPR) approach to create and evaluate a community-based depression care program for Latina IPV survivors.

Methods: We created a multifaceted, culturally tailored intervention, based on principles of chronic illness management. A promotora provided case management services and led 12 weekly group sessions. Participants completed surveys at baseline and 6 months and participated in open-ended exit interviews. Results: Ten Spanish-speaking Latina women participated in the intervention. The program had excellent attendance, with 100% of women attending at least 10 group sessions, and high satisfaction. We found a large decrease in depression severity (Patient Health Questionnaire [PHQ]-9, 17.3-7.2;  $p = .001$ ), as well as improvements in depression self-

efficacy, self-esteem, and stress. Conclusion: This study offers promising preliminary data to support the use of community-based approaches to reducing depression disparities in Latina IPV survivors. © 2013 The Johns Hopkins University Press.

Onishi, E., Biagioli, F., & Safraneck, S. (2014). Methylphenidate for management of fatigue in the palliative care setting. *American Family Physician, 89*(2), 124-127.

Orloff, M. J., Orloff, M. S., Orloff, S. L., Orloff, L. A., Daily, P. O., Girard, B., et al. (2014). Unshuntable extrahepatic portal hypertension revisited: 43 years' experience with radical esophagogastrectomy treatment of bleeding esophagogastric varices. *American Journal of Surgery, 207*(1), 46-52.

Background In 1994, the authors reported their experience with radical esophagogastrectomy for bleeding esophagogastric varices due to unshuntable extra-hepatic portal hypertension. Since then, the series has expanded from 22 to 44 patients. The aim of this study was to assess the validity of the previous observations and conclusions in the largest series with the longest follow-up. Methods From 1968 to 2005, 44 patients with unshuntable extra-hepatic portal hypertension were treated by total gastrectomy and resection of the distal two thirds of the esophagus. Before referral, the patients experienced 4 to 24 episodes of variceal bleeding requiring a mean 130 U of blood transfusion, 15 hospital admissions, and 6 previous unsuccessful operations. Results Transient postoperative complications occurred in 50% of patients. The survival rate is 100%, with no recurrence of variceal bleeding during 7 to 43 years of follow-up. Liver function and biopsy results have been normal. Quality of life has been excellent or good in 91%. Eighty-six percent have resumed employment or full-time housekeeping. Conclusions In unshuntable extra-hepatic portal hypertension, radical esophagogastrectomy is the only consistently effective treatment of variceal hemorrhage. Prompt use of this lifesaving procedure is warranted. © 2014 Elsevier Inc. All rights reserved.

Overton, L. C., & Heinrich, M. C. (2014). Regorafenib for treatment of advanced gastrointestinal stromal tumors. *Expert Opinion on Pharmacotherapy,*

Introduction: Gastrointestinal stromal tumors (GISTs) are abdominal sarcomas which are extremely refractory to chemotherapy treatment. The treatment of GISTs has been revolutionized

by use of KIT/platelet-derived growth factor receptor-alpha (PDGFRA) kinase inhibitors. Unfortunately, most tumors develop resistance to front-line (imatinib) or second-line (sunitinib) therapy. Regorafenib, a KIT/PDGFRA/vascular endothelial growth factor receptor (VEGFR) oral kinase inhibitor, has been shown to improve progression-free survival in the third- or fourth-line setting. Areas covered: This review covers the preclinical and clinical studies of regorafenib for treatment of GIST. A literature search on regorafenib was carried out using the PubMed database up to October 2013. Expert opinion: Currently, imatinib and sunitinib represent the only proven first- and second-line therapies, respectively, for advanced GISTs. Based on the results of a Phase III study, regorafenib is now established as the only proven third-line therapy. Regorafenib activity in this setting is believed to be due to its activity against oncogenic forms of KIT/PDGFRA. Although side effects are common with this agent, they can be effectively managed with a combination of supportive care, dose interruptions/reductions. The toxicity profile is similar to other oral kinase inhibitors with anti-VEGFR activity. Regorafenib is mainly metabolized by CYP3A4, and concomitant use of strong inducers/inhibitors of this enzyme should be avoided.

Parker, M., Bellec, J., McFarland, T. J., Scripps, V., Appukuttan, B., Hartzell, M., et al. (2014).

Suppression of neovascularisation of donor corneas by transduction with equine infectious anemia virus-based lentiviral vectors expressing endostatin and angiostatin. *Human Gene Therapy*, Corneal transplantation is the oldest and one of the most successful transplant procedures with a success rate in many studies in excess of 90%. The high success rate is mainly due to the relatively immune-privileged status of the eye and the fact that the cornea is largely avascular. However, the success rate in patients with failed grafts is much lower such that regrafting is frequently the top indication for corneal transplantation in many centres. Neovascularisation is the most important risk factor for rejection, as it allows access of the immune system to the donor tissue, compromising immune privilege of the graft/eye. We have developed a process to modify donor corneal tissue to prevent rejection by a single exposure to a gene therapy vector prior to surgery (EncorStat(R)). The vector used is based on clinically-relevant EIAV-derived lentiviral platform and contains genes for two potentially angiostatic genes, endostatin and angiostatin. We show that incubation of rabbit, primate and human corneal tissue with EIAV vector mediates strong, stable expression in the corneal endothelium. We have optimised this

process to maximize transduction and, once this is complete, maximize the removal of free vector prior to transplant. Rabbit corneas treated with two different anti-angiogenic expression vectors (EIAV-EndoAngio and to a lesser extent EIAV-Endo:k5) significantly suppressed neovascularisation in a rabbit model of corneal rejection. As a result, corneal opacity, oedema and inflammatory infiltrates were reduced in these corneas. This study demonstrates that angiogenesis is a suitable target to prevent corneal rejection, and provides the first proof-of-concept data for the development of EncorStat(R), an ex vivo gene therapy treatment to prevent corneal rejection.

Patel, S. A., Magnuson, J. S., Holsinger, F. C., Karni, R. J., Richmon, J. D., Gross, N. D., et al. (2013).

Robotic surgery for primary head and neck squamous cell carcinoma of unknown site. *JAMA Otolaryngology-- Head & Neck Surgery*, 139(11), 1203-1211.

**IMPORTANCE:** Identification of the primary site in head and neck squamous cell carcinoma (HNSCC) is crucial because it improves the patient's prognosis and minimizes morbidity from treatment. **OBJECTIVES:** To determine the efficacy of transoral robotic surgery (TORS) in identifying unknown primary sites of head and neck squamous cell carcinoma. **DESIGN, SETTING, AND PARTICIPANTS:** Retrospective, multi-institutional case series from January 1, 2010, to February 28, 2013, in which data were pooled from the following 6 institutions: University of Washington Medical Center, The University of Texas MD Anderson Cancer Center, University of Alabama-Birmingham Hospital, The University of Texas Medical School at Houston, Johns Hopkins Hospital, and Oregon Health Sciences University. All patients diagnosed as having HNSCC of an unknown primary site who underwent TORS to identify the primary site were included in the study. We excluded those with recurrent disease, a history of radiation therapy to the head and neck, or evidence of a primary tumor site based on previous biopsy results. **MAIN OUTCOME AND MEASURE:** Identification of the primary tumor site. **RESULTS:** Forty-seven patients were eligible for the study. The tumor site was identified by TORS in 34 of 47 patients (72.3%). The primary site was located in the base of tongue for 20 patients (58.8%) and the palatine tonsil for 13 patients (38.2%), with 1 patient having a primary site in both the base of tongue and the palatine tonsil. Suspicious physical examination findings were present in 23 of 47 patients (48.9%), with positive and negative predictive values of 56.5% and 25.0%, respectively. Of

those who underwent any imaging, 16 patients had suspicious findings, with positive and negative predictive values of 50.0% and 16.7%, respectively. In 18 of 47 patients (38.3%), both preoperative radiographic and physical examination failed to suggest a primary site. Of these 18 patients, 13 (72.2%) were identified after undergoing TORS. CONCLUSIONS AND RELEVANCE: We demonstrate that TORS is a useful approach to identify and treat the primary site in patients with HNSCC who present with an unknown primary site.

Pavelin, J., Reynolds, N., Chiweshe, S., Wu, G., Tiribassi, R., & Grey, F. (2013). Systematic MicroRNA analysis identifies ATP6V0C as an essential host factor for human cytomegalovirus replication. *PLoS Pathogens*, 9(12), e1003820.

Recent advances in microRNA target identification have greatly increased the number of putative targets of viral microRNAs. However, it is still unclear whether all targets identified are biologically relevant. Here, we use a combined approach of RISC immunoprecipitation and focused siRNA screening to identify targets of HCMV encoded human cytomegalovirus that play an important role in the biology of the virus. Using both a laboratory and clinical strain of human cytomegalovirus, we identify over 200 putative targets of human cytomegalovirus microRNAs following infection of fibroblast cells. By comparing RISC-IP profiles of miRNA knockout viruses, we have resolved specific interactions between human cytomegalovirus miRNAs and the top candidate target transcripts and validated regulation by western blot analysis and luciferase assay. Crucially we demonstrate that miRNA target genes play important roles in the biology of human cytomegalovirus as siRNA knockdown results in marked effects on virus replication. The most striking phenotype followed knockdown of the top target ATP6V0C, which is required for endosomal acidification. siRNA knockdown of ATP6V0C resulted in almost complete loss of infectious virus production, suggesting that an HCMV microRNA targets a crucial cellular factor required for virus replication. This study greatly increases the number of identified targets of human cytomegalovirus microRNAs and demonstrates the effective use of combined miRNA target identification and focused siRNA screening for identifying novel host virus interactions.

Piepkorn, M. W., Barnhill, R. L., Elder, D. E., Knezevich, S. R., Carney, P. A., Reisch, L. M., et al. (2014). The MPATH-dx reporting schema for melanocytic proliferations and melanoma. *Journal of*

*the American Academy of Dermatology, 70(1), 131-141.*

**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. © 2013 by the American Academy of Dermatology, Inc.

Pissani, F., Malherbe, D. C., Schuman, J. T., Robins, H., Park, B. S., Krebs, S. J., et al. (2014).

Improvement of antibody responses by HIV envelope DNA and protein co-immunization. *Vaccine, 32(4), 507-513.*

**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. © 2013 Elsevier Ltd.

Platt, E. J., Gomes, M. M., & Kabat, D. (2014). Reversible and efficient activation of HIV-1 cell entry by a tyrosine sulfated peptide dissects endocytic entry and inhibitor mechanisms. *Journal of Virology*,

HIV-1 membranes contain gp120-gp41 trimers. Binding of gp120 to CD4 and a coreceptor (CCR5 or CXCR4) reduces constraint on metastable gp41, enabling a series of conformational changes that cause membrane fusion. An analytic difficulty occurs because these steps occur slowly and asynchronously within cohorts of adsorbed virions. We previously isolated HIV-1JRCSF variants that efficiently use CCR5 mutants severely damaged in the tyrosine sulfated amino terminus or extracellular loop two. Surprisingly, both independent adaptations included gp120 mutations S298N, F313L, and N403S, supporting other evidence that they function by weakening gp120's grip on gp41 rather than by altering gp120 binding to specific CCR5 sites. Although several natural HIV-1 isolates reportedly use CCR5(Delta18) lacking the amino terminus when the soluble tyrosine sulfated peptide is present, we show that HIV-1JRCSF(Ad) with the adaptive mutations functions approximately 100-times more efficiently and that coreceptor activation is reversible, enabling synchronous efficient entry control in physiological conditions. This system revealed that three-stranded gp41 folding intermediates susceptible to the inhibitor enfuvirtide form slowly and

asynchronously on cell surface virions but resolve rapidly, with virions generally forming only one target. Adsorbed virions asynchronously and transiently become competent for entry at 37°C but are inactivated if the CCR5 peptide is absent during their window of opportunity. This competency is conferred by endocytosis, which results in inactivation if the peptide is absent. For both wild-type and adapted HIV-1s, early gp41 refolding steps obligatorily occur on cell surfaces, whereas final step(s) are endosomal. This system powerfully dissects HIV-1 entry and inhibitor mechanisms. Importance statement We present a powerful means to reversibly and efficiently activate or terminate HIV-1 entry by adding or removing a tyrosine sulfated CCR5 peptide from culture medium. This system uses stable cell clones and a variant of HIV-1JRCSF with three adaptive mutations. It enabled us to show that CCR5 coreceptor activation is rapidly reversible and to dissect aspects of entry that had previously been relatively intractable. Our analyses elucidate enfuvirtide (T-20) function and suggest that HIV-1 virions form only one nonredundant membrane fusion complex on cell surfaces. Additionally, we obtained novel and conclusive evidence that HIV-1 entry occurs in an assembly line manner, with some steps obligatorily occurring on cell surfaces and with final membrane fusion occurring in endosomes. Our results were confirmed for wild-type HIV-1. Thus, our paper provides major methodological and mechanistic insights about HIV-1 infection.

Pokidysheva, E., Boudko, S., Vranka, J., Zientek, K., Maddox, K., Moser, M., et al. (2014). Biological role of prolyl 3-hydroxylation in type IV collagen. *Proceedings of the National Academy of Sciences of the United States of America*, 111(1), 161-166.

Collagens constitute nearly 30% of all proteins in our body. Type IV collagen is a major and crucial component of basement membranes. Collagen chains undergo several posttranslational modifications that are indispensable for proper collagen function. One of these modifications, prolyl 3-hydroxylation, is accomplished by a family of prolyl 3-hydroxylases (P3H1, P3H2, and P3H3). The present study shows that P3H2-null mice are embryonic-lethal by embryonic day 8.5. The mechanism of the unexpectedly early lethality involves the interaction of non-3-hydroxylated embryonic type IV collagen with the maternal platelet-specific glycoprotein VI (GPVI). This interaction results in maternal platelet aggregation, thrombosis of the maternal blood, and death of the embryo. The phenotype is completely rescued by producing double KO of P3H2 and GPVI.

Double nulls are viable and fertile. Under normal conditions, subendothelial collagens bear the GPVI-binding sites that initiate platelet aggregation upon blood exposure during injuries. In type IV collagen, these sites are normally 3-hydroxylated. Thus, prolyl 3-hydroxylation of type IV collagen has an important function preventing maternal platelet aggregation in response to the early developing embryo. A unique link between blood coagulation and the ECM is established. The newly described mechanism may elucidate some unexplained fetal losses in humans, where thrombosis is often observed at the maternal/fetal interface. Moreover, epigenetic silencing of P3H2 in breast cancers implies that the interaction between GPVI and non-3-hydroxylated type IV collagen might also play a role in the progression of malignant tumors and metastasis.

Portfors, C. V., & Roberts, P. D. (2014). Mismatch of structural and functional tonotopy for natural sounds in the auditory midbrain. *Neuroscience*, 258, 192-203.

Neurons in the auditory system are spatially organized in their responses to pure tones, and this tonotopy is expected to predict neuronal responses to more complex sounds such as vocalizations. We presented vocalizations with low-, medium- and high-frequency content to determine if selectivity of neurons in the inferior colliculus (IC) of mice respects the tonotopic spatial structure. Tonotopy in the IC predicts that neurons located in dorsal regions should only respond to low-frequency vocalizations and only neurons located in ventral regions should respond to high-frequency vocalizations. We found that responses to vocalizations were independent of location, and many neurons in the dorsal, low-frequency region of IC responded to high-frequency vocalizations. To test whether this was due to dorsal neurons having broad frequency tuning curves, we convolved each neuron's frequency tuning curve with each vocalization, and found that the tuning curves were not good predictors of the actual neural responses to the vocalizations. We then used a nonlinear model of signal transduction in the cochlea that generates distortion products to predict neural responses to the vocalizations. We found that these predictions more closely matched the actual neural responses. Our findings suggest that the cochlea distorts the frequency representation in vocalizations and some neurons use this distorted representation to encode the vocalizations. © 2013 IBRO.

Qu, Z., Krishnamurthy, V., Haller, C. A., Dorr, B. M., Marzec, U. M., Hurst, S., et al. (2014).

Immobilization of actively thromboresistant assemblies on sterile blood-contacting surfaces. *Advanced Healthcare Materials*, 3(1), 30-35.

Rapid one-step modification of thrombomodulin with alkylamine derivatives such as azide, biotin, and PEG is achieved using an evolved sortase (eSrtA) mutant. The feasibility of a point-of-care scheme is demonstrated herein to site-specifically immobilize azido-thrombomodulin on sterilized commercial ePTFE vascular grafts, which exhibit superior thromboresistance compared with commercial heparin-coated grafts in a primate model of acute graft thrombosis. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Quackenbush, J. F., Cassidy, P. B., Pfeffer, L. M., Boucher, K. M., Hawkes, J. E., Pfeffer, S. R., et al.

(2014). In Thurin M., &Marincola F.M.(Eds.), *Isolation of circulating microRNAs from microvesicles found in human plasma*

Intact miRNAs can be isolated from the circulation in significant quantities despite the presence of extremely high levels of RNase activity. The remarkable stability of circulating miRNAs makes them excellent candidates for biomarkers in diagnostic applications as well as therapeutic targets in a variety of disease states including melanoma. Circulating RNA molecules are resistant to degradation by RNases because they are encapsulated in membrane-bound microvesicles. We describe a convenient method for the use of ExoQuick, a proprietary resin developed by Systems Biosciences (Mountain View, CA), whereby microvesicles can be purified under gentle conditions using readily available laboratory equipment. This protocol allows for isolation all microvesicles, regardless of their origin, and provides a convenient method for identifying potential cancer-specific biomarkers from biological fluids including serum and plasma. © Springer Science+Business Media New York 2014.

Quinones, A. R., Richardson, J., Freeman, M., Fu, R., O'Neil, M. E., Motu'apuaka, M., et al. (2014).

Educational group visits for the management of chronic health conditions: A systematic review. *Patient Education and Counseling*,

OBJECTIVE: Review the effectiveness of group visits (appointments of multiple patients) on quality of life, function, self-efficacy, utilization, and biophysical outcomes in randomized

controlled trials of patients with chronic conditions. METHODS: We searched MEDLINE(R), Cochrane, CINAHL, and PsycINFO to January 2013 for English-language trials of educational group visits led by non-prescribing facilitators (e.g., peer educators). RESULTS: We report on 80 arthritis/falls (n=22), asthma/COPD (n=10), CHF/hypertension (n=12), diabetes (n=29), multiple conditions (n=4), and pain (n=4) studies. We found moderate evidence of improved short-term self-efficacy in patients with arthritis (10 studies) and diabetes (10 studies). We found no consistent evidence of improved quality of life; however a moderately strong body of evidence suggests peer-led community-based programs might improve quality of life and utilization in patients with multiple chronic conditions. Meta-analyses found short- (14 studies; mean change HbA1c=-0.27, CI=-0.44, 0.11) and long-term (10 studies; mean change HbA1c=-0.23, CI=-0.44, -0.02) glycemic improvement. CONCLUSIONS: Group visits may improve self-efficacy and glycemic control. There was little consistent evidence of improved quality of life, functional status, or utilization. PRACTICE IMPLICATIONS: Group visits represent a reasonable alternative for educating patients with chronic illness, though varied participation/retention suggests they should not be the sole alternative.

Ramiro, S., Gaujoux-Viala, C., Nam, J. L., Smolen, J. S., Buch, M., Gossec, L., et al. (2014). Safety of synthetic and biological DMARDs: A systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Annals of the Rheumatic Diseases*,

Objectives: To update the evidence for the safety of synthetic disease-modifying antirheumatic drugs (sDMARDs), glucocorticoids (GC) and biological DMARDs (bDMARDs) in patients with rheumatoid arthritis (RA) to inform the European League Against Rheumatism (EULAR) recommendations for the management of RA. Methods: Systematic literature review (SLR) of observational studies (including registries). Interventions were any bDMARD (anakinra, infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, golimumab or certolizumab pegol) or sDMARD (methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, gold/auranofin, azathioprine, chlorambucil, chloroquine, cyclosporin, cyclophosphamide, mycophenolate, minocycline, penicillamine, tacrolimus or tofacitinib) and a comparator was required. Information on GCs was collected from the included studies. All safety outcomes were

included. Results: Forty-nine observational studies addressing diverse safety outcomes of therapy with bDMARDs met eligibility criteria. Substantial heterogeneity precluded meta-analysis of any of the outcomes. Patients on tumour necrosis factor inhibitors (TNFi) compared to patients on conventional sDMARDs had a higher risk of serious infections (adjusted HR (aHR) 1.1-1.8), a higher risk of tuberculosis, and an increased risk of infection by herpes zoster cannot be excluded. Patients on TNFi did not have an increased risk for malignancies in general, lymphoma or non-melanoma skin cancer, but the risk of melanoma may be slightly increased (aHR 1.5). From the studies identified on conventional sDMARDs, no new safety signals were found. Conclusions: The findings from this SLR confirm the known safety pattern of sDMARDs and bDMARDs for the treatment of RA. © 2014 BMJ Publishing Group Ltd & European League Against Rheumatism.

Raymond, J. K., Duke, D. C., Shimomaeda, L., & Harris, M. A. (2013). Looking forward to transition: Perspectives on transition from pediatric to adult diabetes care. *Diabetes Management (London, England)*, 3(4), 10.2217/dmt.13.27.

AIM: This study aimed to prospectively investigate transition beliefs, knowledge and needs of pediatric patients with diabetes and their parents. PATIENTS & METHODS: Parallel youth and parent questionnaires evaluating the transition process were distributed over a 6-month time period. Respondents included 123 pediatric patients with diabetes (11-19 years old) and their parents. RESULTS: Few families had discussed the transition of diabetes care (approximately 25%). Most had not established a transition plan (approximately 90%). Youth and parents agreed that seeing the doctor alone, discussions about transition and transition itself should occur at 17-18 years of age. CONCLUSION: Youth with diabetes and their parents are not prepared for transition to adult care. Transition discussions should begin at an earlier age. Additional research is needed to learn how and when to begin these discussions.

Reddy, P. H. (2014). Inhibitors of mitochondrial fission as a therapeutic strategy for diseases with oxidative stress and mitochondrial dysfunction. *Journal of Alzheimer's Disease : JAD*, Mitochondria are essential cytoplasmic organelles, critical for cell survival and death. Recent mitochondrial research revealed that mitochondrial dynamics-the balance of fission and fusion in

normal mitochondrial dynamics-is an important cellular mechanism in eukaryotic cell and is involved in the maintenance of mitochondrial morphology, structure, number, distribution, and function. Research into mitochondria and cell function has revealed that mitochondrial dynamics is impaired in a large number of aging and neurodegenerative diseases, and in several inherited mitochondrial diseases, and that this impairment involves excessive mitochondrial fission, resulting in mitochondrial structural changes and dysfunction, and cell damage. Attempts have been made to develop molecules to reduce mitochondrial fission while maintaining normal mitochondrial fusion and function in those diseases that involve excessive mitochondrial fission. This review article discusses mechanisms of mitochondrial fission in normal and diseased states of mammalian cells and discusses research aimed at developing therapies, such as Mdivi, Dynasore and P110, to prevent or to inhibit excessive mitochondrial fission.

Reece, T. B., Welke, K. F., O'Brien, S., Grau-Sepulveda, M. V., Grover, F. L., & Gammie, J. S. (2014). Rethinking the ross procedure in adults. *Annals of Thoracic Surgery*, 97(1), 175-181.

Background Although questionable durability has tempered enthusiasm for the Ross procedure in the last decade, the perioperative risks of the Ross procedure relative to conventional aortic valve replacement are not well described. The goal of this study is to describe both the perioperative outcomes and utilization trends of the Ross procedure in adults in The Society of Thoracic Surgeons Adult Cardiac Surgery Database. Methods The Society of Thoracic Surgeons Adult Cardiac Surgery Database was used to review all Ross procedures performed between 1994 and 2010. The utilization of the procedure in the database was assessed. Then the preoperative comorbidities, patient demographics, and risk factors were reviewed, as were intraoperative and perioperative outcomes. Results Of 648,541 aortic valve replacements during the study period, 3,054 (0.47%) were identified as Ross procedures. Utilization of the procedures as a percent of total aortic valve replacements peaked in 1998 at 1.2%, followed by a steady decline to 0.09% by 2010. More than a quarter of all Ross operations were performed at six sites. Using propensity-matching analyses, Ross patients experienced significantly more perioperative complications including reexploration (9.4% versus 5.8%;  $p < 0.01$ ), renal failure (2.6% versus 0.8%;  $p < 0.001$ ), and operative mortality (2.7% versus 0.9%;  $p = 0.001$ ). Conclusions These data suggest that the Ross procedure is associated with greater perioperative morbidity and

mortality risks compared with conventional aortic valve replacement. Recognition of these risks along with durability concerns have resulted in a dramatic decline in the number of Ross procedures performed in North America in the last decade. © 2014 by The Society of Thoracic Surgeons.

Reiss, L. A., Ito, R. A., Eggleston, J. L., & Wozny, D. R. (2014). Abnormal binaural spectral integration in cochlear implant users. *Journal of the Association for Research in Otolaryngology : JARO*, Bimodal stimulation, or stimulation of a cochlear implant (CI) together with a contralateral hearing aid (HA), can improve speech perception in noise. However, this benefit is variable, and some individuals even experience interference with bimodal stimulation. One contributing factor to this variability may be differences in binaural spectral integration (BSI) due to abnormal auditory experience. CI programming introduces interaural pitch mismatches, in which the frequencies allocated to the electrodes (and contralateral HA) differ from the electrically stimulated cochlear frequencies. Previous studies have shown that some, but not all, CI users adapt pitch perception to reduce this mismatch. The purpose of this study was to determine whether broadened BSI may also reduce the perception of mismatch. Interaural pitch mismatches and dichotic pitch fusion ranges were measured in 21 bimodal CI users. Seventeen subjects with wide fusion ranges also conducted a task to pitch match various fused electrode-tone pairs. All subjects showed abnormally wide dichotic fusion frequency ranges of 1-4 octaves. The fusion range size was weakly correlated with the interaural pitch mismatch, suggesting a link between broad binaural pitch fusion and large interaural pitch mismatch. Dichotic pitch averaging was also observed, in which a new binaural pitch resulted from the fusion of the original monaural pitches, even when the pitches differed by as much as 3-4 octaves. These findings suggest that abnormal BSI, indicated by broadened fusion ranges and spectral averaging between ears, may account for speech perception interference and nonoptimal integration observed with bimodal compared with monaural hearing device use.

Rennie, M. Y., Sled, J. G., & Adamson, S. L. (2014). Effects of genes and environment on the fetoplacental arterial microcirculation in mice revealed by micro-computed tomography imaging. *Microcirculation*, 21(1), 48-57.

The fetoplacental arterial tree is critical for efficient distribution of arterial blood to capillaries throughout the placental exchange region; yet, little is known about the factors and mechanisms that control its development. Advances in micro-CT imaging and analysis, and available mutant mouse strains, are facilitating rapid progress. Indeed, micro-CT studies show that genetic differences between the CD1 and C57Bl/6 mouse strains, and between Gcm1 heterozygotes and wild-type littermates alter the developmental trajectory of the fetoplacental arterial tree as do environmental factors including maternal exposure to toxins in cigarette smoke and malarial infection. Relative to other vascular beds, the fetoplacental arterial tree is particularly tractable because veins can more easily be excluded when infusing the contrast agent and because of the placenta's small size, which means that the whole organ can be imaged (maintaining connectivity) and that the tree is simpler (fewer branching generations). Despite these differences, measured parameters were found to be similar to arterial trees in other adult rodent organs. Thus, micro-CT analysis provides a means for advancing of our understanding of the mechanisms controlling development of the fetoplacental arterial tree. Results will likely have relevance to other arterial vasculatures as well. © 2013 John Wiley & Sons Ltd.

Reynolds, M., Bonham, L., Gueck, M., Hammond, K., Lowery, J., Redel, C., et al. (2014). Are temporal artery temperatures accurate enough to replace rectal temperature measurement in pediatric ED patients? *Journal of Emergency Nursing*, 40(1), 46-50.

Objective: This study examined the accuracy of temporal artery and axillary temperatures compared with rectal temperatures in pediatric ED patients younger than 4 years. Methods: A method-comparison study design was used to examine the agreement between a temporal artery or axillary thermometer and a nondisposable, rectal electronic thermometer, which is the clinical reference standard for temperature measurement in children. Temperatures were taken with each device in a convenience sample of stable, pediatric ED patients who were younger than 4 years. Bias and precision were calculated to quantify the differences between the 2 devices, as well as the percentage of temporal artery and axillary temperatures that were  $>\pm 1.0^{\circ}\text{C}$  and  $>\pm 1.5^{\circ}\text{C}$  higher or lower than the rectal temperature. Results: A total of 52 pediatric ED patients were studied over a 10-month period. Bias and precision for the temporal artery and axillary devices were  $-0.46^{\circ}\text{C} \pm 0.50^{\circ}\text{C}$  and  $-0.93^{\circ}\text{C} \pm 0.49^{\circ}\text{C}$ , respectively. The percentage of temporal

artery and axillary temperatures that were  $>\pm 1.0^{\circ}\text{C}$  and/or  $>\pm 1.5^{\circ}\text{C}$  above or below the clinical reference temperature were 15% and 6%, respectively, for the temporal artery thermometer and 39% and 14%, respectively, for the axillary thermometer. Discussion: Bias and precision values for the temporal artery, but not the axillary temperature, were within the acceptable range set by experts to use as a noninvasive substitute for core body temperature measurements. If properly used by ED staff, temporal artery thermometers could be used to obtain temperature in pediatric patients younger than 4 years, thus avoiding physical and psychological discomfort for the child and parent associated with obtaining rectal thermometers.

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Reznik, N., Lajoinie, G., Shpak, O., Gelderblom, E. C., Williams, R., de Jong, N., et al. (2014). On the acoustic properties of vaporized submicron perfluorocarbon droplets. *Ultrasound in Medicine & Biology*,

The acoustic characteristics of microbubbles created from vaporized submicron perfluorocarbon droplets with fluorosurfactant coating are examined. Utilizing ultra-high-speed optical imaging, the acoustic response of individual microbubbles to low-intensity diagnostic ultrasound was observed on clinically relevant time scales of hundreds of milliseconds after vaporization. It was found that the vaporized droplets oscillate non-linearly and exhibit a resonant bubble size shift and increased damping relative to uncoated gas bubbles due to the presence of coating material. Unlike the commercially available lipid-coated ultrasound contrast agents, which may exhibit compression-only behavior, vaporized droplets may exhibit expansion-dominated oscillations. It was further observed that the non-linearity of the acoustic response of the bubbles was comparable to that of SonoVue microbubbles. These results suggest that vaporized submicron perfluorocarbon droplets possess the acoustic characteristics necessary for their potential use as ultrasound contrast agents in clinical practice.

Riddle, A., Maire, J., Cai, V., Nguyen, T., Gong, X., Hansen, K., et al. (2013). Hemodynamic and metabolic correlates of perinatal white matter injury severity. *PLoS One*, 8(12), e82940.

BACKGROUND AND PURPOSE: Although the spectrum of perinatal white matter injury (WMI) in preterm infants is shifting from cystic encephalomalacia to milder forms of WMI, the factors that

contribute to this changing spectrum are unclear. We hypothesized that the variability in WMI quantified by immunohistochemical markers of inflammation could be correlated with the severity of impaired blood oxygen, glucose and lactate. METHODS: We employed a preterm fetal sheep model of in utero moderate hypoxemia and global severe but not complete cerebral ischemia that reproduces the spectrum of human WMI. Since there is small but measurable residual brain blood flow during occlusion, we sought to determine if the metabolic state of the residual arterial blood was associated with severity of WMI. Near the conclusion of hypoxia-ischemia, we recorded cephalic arterial blood pressure, blood oxygen, glucose and lactate levels. To define the spectrum of WMI, an ordinal WMI rating scale was compared against an unbiased quantitative image analysis protocol that provided continuous histo-pathological outcome measures for astrogliosis and microgliosis derived from the entire white matter. RESULTS: A spectrum of WMI was observed that ranged from diffuse non-necrotic lesions to more severe injury that comprised discrete foci of microscopic or macroscopic necrosis. Residual arterial pressure, oxygen content and blood glucose displayed a significant inverse association with WMI and lactate concentrations were directly related. Elevated glucose levels were the most significantly associated with less severe WMI. CONCLUSIONS: Our results suggest that under conditions of hypoxemia and severe cephalic hypotension, WMI severity measured using unbiased immunohistochemical measurements correlated with several physiologic parameters, including glucose, which may be a useful marker of fetal response to hypoxia or provide protection against energy failure and more severe WMI.

Riddle, M. C. (2013). Learning about new therapies: Phase 3 clinical studies-and beyond. *Diabetes Care*, 36(9), 2453-2455.

Riddle, M. C., & Gerstein, H. (2013). Comments and responses: Response to comment on: The ORIGIN trial investigators. characteristics associated with maintenance of mean A1C <6.5% in people with dysglycemia in the ORIGIN trial. *diabetes care* 2013; 36:2915-2922. *Diabetes Care*, 36(10)

Rotwein, P. (2013). In memoriam: William H. daughaday, MD (1918-2013). *Endocrine Reviews*, 34(6), 764-765.

Rotwein, P. (2014). Editorial: The fall of mechanogrowth factor? *Molecular Endocrinology (Baltimore, Md.)*, 28(2), 155-156.

Sadanandam, A., Wang, X., de Sousa E Melo, F., Gray, J. W., Vermeulen, L., Hanahan, D., et al.

(2014). Reconciliation of classification systems defining molecular subtypes of colorectal cancer: Interrelationships and clinical implications. *Cell Cycle (Georgetown, Tex.)*, 13(3)

Recently we published two independent studies describing novel gene expression-based classifications of colorectal cancer (CRC). Notably, each study stratified CRC into a different number of subtypes: one reported 3 subtypes, whereas the second highlighted 5. Given that each ascribed clinical significance, distinctive biology, and therapeutic prognosis to the different subtypes, we sought to reconcile this apparent incongruity in subtype stratification of CRC, and to interrelate the results. To do so, we each evaluated the other's data sets and analytical methods and discovered that the subtypes and their classifiers are, in fact, clearly related to each other; indeed, the 5 subtype outcomes can be coalesced into the same three. In addition to presenting this clarification, we briefly discuss how both classification methods can be viewed within the broader literature on CRC subtypes, and potentially applied.

Sandborn, W. J., Feagan, B. G., Marano, C., Zhang, H., Strauss, R., Johanss, J., et al. (2014).

Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*, 146(1), 85-95.

Background & Aims Little is known about the efficacy of golimumab, a fully human monoclonal antibody to tumor necrosis factor (TNF) - $\alpha$ , for treatment of ulcerative colitis (UC). We evaluated subcutaneous golimumab induction therapy in TNF- $\alpha$  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  $\geq 2$ ; 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,  $P \leq .0001$ ). Rates of clinical remission and mucosal healing and mean changes in IBDQ scores were significantly greater in both golimumab groups vs the placebo group ( $P \leq .0014$ , 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. © 2014 by the AGA Institute.

Sandborn, W. J., Feagan, B. G., Marano, C., Zhang, H., Strauss, R., Johanns, J., et al. (2014).

Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*, 146(1), 96-109.e1.

Background & Aims Subcutaneous golimumab, a fully human monoclonal antibody to tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), was evaluated as maintenance therapy in TNF $\alpha$  antagonist-naive adults with moderate-to-severe active ulcerative colitis, despite conventional therapy, who responded to golimumab induction therapy. Methods We performed a phase 3, double-blind trial of patients who completed golimumab induction trials (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment, eg, PURSUIT). Patients who responded to induction therapy with golimumab ( $n = 464$ ) were assigned randomly to groups given placebo or injections of 50 or 100 mg golimumab every 4 weeks through week 52. Patients who responded to placebo in the induction study continued to receive placebo. Nonresponders in the induction study received 100 mg golimumab. The primary end point was clinical response maintained through week 54; secondary end points included clinical remission and mucosal healing at both weeks 30 and 54. Results Clinical response was maintained through week 54 in 47.0% of patients receiving 50 mg golimumab, 49.7% of patients receiving 100 mg golimumab, and 31.2% of patients receiving placebo ( $P = .010$  and  $P < .001$ , respectively). At weeks 30 and 54, a higher percentage

of patients who received 100 mg golimumab were in clinical remission and had mucosal healing (27.8% and 42.4%) than patients given placebo (15.6% and 26.6%;  $P = .004$  and  $P = .002$ , respectively) or 50 mg golimumab (23.2% and 41.7%, respectively). Percentages of serious adverse events were 7.7%, 8.4%, and 14.3% among patients given placebo, 50 mg, or 100 mg golimumab, respectively; percentages of serious infections were 1.9%, 3.2%, and 3.2%, respectively. Among all patients given golimumab in the study, 3 died (from sepsis, tuberculosis, and cardiac failure, all in patients who received 100 mg golimumab) and 4 developed active tuberculosis. Conclusions Golimumab (50 mg or 100 mg) maintained clinical response through week 54 in patients who responded to induction therapy with golimumab and had moderate-to-severe active ulcerative colitis; patients who received 100 mg golimumab had clinical remission and mucosal healing at weeks 30 and 54. Safety was consistent with that reported for other TNF $\alpha$  antagonists and golimumab in other approved indications. ClinicalTrials.gov number: NCT00488631. © 2014 by the AGA Institute.

Saultz, J. (2014). Around the kitchen table. *Family Medicine*, 46(1), 61-63.

Schmidt, T. A., Zive, D., Fromme, E. K., Cook, J. N., & Tolle, S. W. (2014). Physician orders for life-sustaining treatment (POLST): Lessons learned from analysis of the oregon POLST registry. *Resuscitation*,

BACKGROUND: Physician Orders for Life-Sustaining Treatment (POLST) has become a common means of documenting patient treatment preferences. In addition to orders either for Attempt Resuscitation or Do Not Attempt Resuscitation, for patients not in cardiopulmonary arrest, POLST provides three levels of treatment: Full Treatment, Limited Interventions, and Comfort Measures Only. Oregon has an electronic registry for POLST forms completed in the state. We used registry data to examine the different combinations of treatment orders. METHODS AND RESULTS: We analyzed data from forms signed and entered into the Oregon POLST Registry in 2012. The analysis included 31,294 POLST forms. The mean Registrant age was 76.7 years. 21,396 (68.4%) had Do Not Attempt Resuscitation (DNR) orders and 9900 (31.6%) had orders for "Attempt Resuscitation". The 6 order combinations were: Do Not Resuscitate (DNR)/Comfort Measures Only 10,769 (34.4%), DNR/Limited Interventions 9306 (29.7%), DNR/Full Treatment

1211 (3.9%), Attempt Cardiopulmonary Resuscitation (CPR)/Comfort Measures Only 11 (0.04%), Attempt CPR/Limited Interventions 2281 (7.3%), and Attempt CPR/Full Treatment 7473 (23.9%).

CONCLUSIONS: The most common order combinations were DNR/Comfort Measures Only, DNR/Limited Interventions and Attempt Resuscitation/Full Treatment. These three makes sense to health professionals. However, other order combinations that require interpretation at the time of a crisis were completed for about 10% of Registrants. These combinations need further investigation.

Scott, G. D., Blum, E. D., Fryer, A. D., & Jacoby, D. B. (2014). Tissue optical clearing, 3D imaging, and computer morphometry in whole mouse lungs and human airways. *American Journal of Respiratory Cell and Molecular Biology*,

In whole adult mouse lung, full identification of airways nerves (or other cellular/sub-cellular objects) has not been possible due to patchy distribution and micron-scale size. Here we describe a method using tissue clearing in order to acquire the first complete image of three-dimensional innervation in the lung. We then created a method to pair analysis of nerve (or any other co-labeled epitope) images with identification of 3D tissue compartments and airway morphometry by using fluorescent casting and morphometry software (which we designed and are making available as open-source). We then tested our method to quantify a sparse heterogeneous nerve population by examining visceral pleural nerves. Finally, we demonstrate the utility of our method in human tissue to image full thickness innervation in irregular three-dimensional tissue compartments and to quantify sparse objects (intrinsic airway ganglia). Overall, this method can uniquely pair the advantages of whole tissue imaging and cellular/sub-cellular fluorescence microscopy.

Senders, A., Hanes, D., Bourdette, D., Whitham, R., & Shinto, L. (2014). Reducing survey burden: Feasibility and validity of PROMIS measures in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*,

BACKGROUND: Patient-reported outcomes are important for clinical research and care, yet administering and scoring the questionnaires requires considerable effort and time. The Patient Reported Outcomes Measurement Information System (PROMIS) could considerably reduce

administrative obstacles and lessen survey burden for participants. OBJECTIVE: Assess the feasibility and validity of PROMIS, compared to commonly-used legacy measures for multiple sclerosis (MS). METHODS: In this cross-sectional survey, 133 participants with confirmed MS completed legacy surveys and PROMIS Computerized Adaptive Tests (CATs) for depression, anxiety, pain, fatigue and physical function. We conducted a multi-trait, multi-method analysis and verified results with confirmatory factor analysis. RESULTS: The correlations between PROMIS and the corresponding legacy measures were large (0.67 to 0.87). The multi-trait, multi-method criteria were generally well met, providing good evidence of the validity of PROMIS measures. PROMIS surveys asked fewer questions and required substantially less time to complete than the legacy scales. CONCLUSIONS: Our results provide evidence of the construct validity of PROMIS for use with MS patients. Several aspects of the PROMIS CATs made them an important resource, including: (a) less time was required to complete them; (b) missing data was reduced; and (c) the automatic scoring referenced the general population. Our findings support the use of PROMIS in MS research and may have broader implications for clinical care, as well.

Shah, R. C., Kamphuis, P. J., Leurgans, S., Swinkels, S. H., Sadowsky, C. H., Bongers, A., et al. (2013). The S-connect study: Results from a randomized, controlled trial of souvenaid in mild-to-moderate alzheimer's disease. *Alzheimer's Research and Therapy*, 5(6)

Introduction. Souvenaid® containing Fortasyn® Connect is a medical food designed to support synapse synthesis in persons with Alzheimer's disease (AD). Fortasyn Connect includes precursors (uridine monophosphate; choline; phospholipids; eicosapentaenoic acid; docosahexaenoic acid) and cofactors (vitamins E, C, B12, and B6; folic acid; selenium) for the formation of neuronal membranes. Whether Souvenaid slows cognitive decline in treated persons with mild-to-moderate AD has not been addressed. Methods. In a 24-week, double-masked clinical trial at 48 clinical centers, 527 participants taking AD medications [52% women, mean age 76.7 years (Standard Deviation, SD = 8.2), and mean Mini-Mental State Examination score 19.5 (SD = 3.1, range 14-24)] were randomized 1:1 to daily, 125-mL (125 kcal), oral intake of the active product (Souvenaid) or an iso-caloric control. The primary outcome of cognition was assessed by the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog). Compliance was calculated from daily diary recordings of product intake. Statistical analyses were

performed using mixed models for repeated measures. Results: Cognitive performance as assessed by ADAS-cog showed decline over time in both control and active study groups, with no significant difference between study groups (difference = 0.37 points, Standard Error, SE = 0.57,  $p = 0.513$ ). No group differences in adverse event rates were found and no clinically relevant differences in blood safety parameters were noted. Overall compliance was high (94.1% [active] and 94.5% [control]), which was confirmed by significant changes in blood (nutritional) biomarkers. Conclusions: Add-on intake of Souvenaid during 24 weeks did not slow cognitive decline in persons treated for mild-to-moderate AD. Souvenaid was well tolerated in combination with standard care AD medications. Trial registration. Dutch Trial Register number: NTR1683. © 2013 Shah et al.; licensee BioMed Central Ltd.

Sharma, V., Zargaroff, S., Sheth, K. R., Le, B. V., Dupree, J. M., Sandlow, J. I., et al. (2014). Relating economic conditions to vasectomy and vasectomy reversal frequencies: A multi-institutional study. *The Journal of Urology*,

INTRODUCTION AND OBJECTIVES: It has been theorized that utilization of permanent contraceptive methods may vary with economic conditions. Here we evaluate the relationship between vasectomy/vasectomy reversal frequencies at several large referral centers with national economic indicators over a period of two recessions spanning 2001 to 2011. METHODS: An IRB approved retrospective chart review was conducted to identify the number of vasectomies/vasectomy reversals per month at several large referral centers from January 2001 to July 2011. The incidences of these procedures were pooled, correlated with national economic data, and analyzed in a multivariate-linear regression model. RESULTS: There were 4599 vasectomies and 1549 vasectomy reversals performed at our institutions during the study period. The number of vasectomies performed per month was positively correlated to the unemployment rate ( $r = +0.556$ ,  $P < 0.001$ ) and personal income per capita ( $r = +0.276$ ,  $P = 0.002$ ). The number of vasectomy reversals performed per month was negatively correlated with the unemployment rate ( $r = -0.399$ ,  $P < 0.001$ ) and personal income per capita ( $r = -0.305$ ,  $P < 0.001$ ). Neither vasectomy nor vasectomy reversal frequencies significantly correlated with the inflation rate or the S&P 500. Regression models confirmed that the unemployment rate explained more of the variance in vasectomy/vasectomy reversal frequencies than other

indicators. CONCLUSIONS: We noted a correlation between the number of vasectomies/vasectomy reversals performed at our institutions and national economic indicators, with the strongest association with unemployment rate. This points to the importance of financial pressures on family planning decisions.

Shindo, M. L., Caruana, S., Kandil, E., McCaffrey, J. C., Orloff, L., Porterfield, J. R., et al. (2014).

Management of invasive well-differentiated thyroid cancer an american head and neck society consensus statement. *Head & Neck*,

Background: Invasive differentiated thyroid cancer (DTC) is relatively frequent, yet there is a paucity of specific guidelines devoted to its management. The Endocrine Committee of the American Head and Neck Society (AHNS) convened a panel to provide clinical consensus statements based on review of the literature, synthesized with the expert opinion of the group.

Methods: An expert panel, selected from membership of the AHNS constructed the manuscript and recommendations for management of DTC with invasion of recurrent laryngeal nerve, trachea, esophagus, larynx and major vessels based on current best evidence. A Modified Delphi survey was then constructed by another expert panelist utilizing 9 anchor points, 1= strongly disagree to 9 = strongly agree. Results of the survey were utilized to determine which statements achieved consensus, near-consensus, or non-consensus. Results: After endorsement by the AHNS Endocrine Committee and Quality of Care Committee, it received final approval from the AHNS Council. *Head Neck*, 2014.

Shoja, M. M., Oyesiku, N. M., Griessenauer, C. J., Radcliff, V., Loukas, M., Chern, J. J., et al. (2014).

Anastomoses between lower cranial and upper cervical nerves: A comprehensive review with potential significance during skull base and neck operations, part I: Trigeminal, facial, and vestibulocochlear nerves. *Clinical Anatomy*, 27(1), 118-130.

Descriptions of the anatomy of the neural communications among the cranial nerves and their branches is lacking in the literature. Knowledge of the possible neural interconnections found among these nerves may prove useful to surgeons who operate in these regions to avoid inadvertent traction or transection. We review the literature regarding the anatomy, function, and clinical implications of the complex neural networks formed by interconnections among the lower

cranial and upper cervical nerves. A review of germane anatomic and clinical literature was performed. The review is organized in two parts. Part I concerns the anastomoses between the trigeminal, facial, and vestibulocochlear nerves or their branches with any other nerve trunk or branch in the vicinity. Part II concerns the anastomoses among the glossopharyngeal, vagus, accessory and hypoglossal nerves and their branches or among these nerves and the first four cervical spinal nerves; the contribution of the autonomic nervous system to these neural plexuses is also briefly reviewed. Part I is presented in this article. An extensive anastomotic network exists among the lower cranial nerves. Knowledge of such neural intercommunications is important in diagnosing and treating patients with pathology of the skull base. *Clin. Anat.* 27:118-130, 2014. © 2013 Wiley Periodicals.

Shum, J., Markiewicz, M. R., Park, E., Bui, T., Lubek, J., Bryan Bell, R., et al. (2014). Low prealbumin level is a risk factor for microvascular free flap failure. *Journal of Oral and Maxillofacial Surgery*, 72(1), 169-177.

**Purpose** The purposes of this study were 1) to estimate and compare the 1-month survival rates of patients with acute malnutrition (low prealbumin level) and patients who are not malnourished (normal prealbumin level) and 2) to identify risk factors associated with microvascular free flap failure. **Materials and Methods** To address the research purposes, we designed a retrospective cohort study and enrolled a sample composed of patients who underwent head and neck microvascular reconstruction and had prealbumin levels measured in the perioperative period. The primary predictor variable was nutritional status (low vs normal prealbumin level). The primary outcome variable was flap survival. One-month survival rates were estimated by use of Kaplan-Meier survival analyses. Risk factors for free flap failure were identified by use of multivariate marginal Cox proportional hazards modeling. **Results** The sample was composed of 162 patients who underwent microvascular free tissue transfer during the study enrollment period. The 1-month survival estimates for patients who were and were not malnourished were 76.5% (95% confidence interval [CI], 48.8% to 90.5%) and 95.2% (95% CI, 90.1% to 97.7%), respectively ( $P = .002$ ). In the adjusted Cox hazards proportions model, acute malnutrition was associated with a 4-fold increased risk of failure ( $P = .04$ ) in comparison with those patients with a normal nutritional status. **Conclusions** Acute malnutrition in patients undergoing microvascular

free flap reconstruction in the head and neck region was associated with an increased risk for free flap failure. © 2014 Published by Elsevier Inc on behalf of the American Association of Oral and Maxillofacial Surgeons. All rights reserved.

Sibley, C. T. (2013). "Spins and loops: Linking myocardial T time to invasively measured hemodynamics". *Journal of the American College of Cardiology*,

Sibley, C. T. (2014). Characterization of ventricular myocardium in atrial fibrillation: Looking where the light is best. *JACC.Cardiovascular Imaging*, 7(1), 12-13.

Singh, R. H., Rohr, F., Frazier, D., Cunningham, A., Mofidi, S., Ogata, B., et al. (2014).

Recommendations for the nutrition management of phenylalanine hydroxylase deficiency.

*Genetics in Medicine : Official Journal of the American College of Medical Genetics*,

The effectiveness of a phenylalanine-restricted diet to improve the outcome of individuals with phenylalanine hydroxylase deficiency (OMIM no. 261600) has been recognized since the first patients were treated 60 years ago. However, the treatment regime is complex, costly, and often difficult to maintain for the long term. Improvements and refinements in the diet for phenylalanine hydroxylase deficiency have been made over the years, and adjunctive therapies have proven to be successful for certain patients. Yet evidence-based guidelines for managing phenylalanine hydroxylase deficiency, optimizing outcomes, and addressing all available therapies are lacking. Thus, recommendations for nutrition management were developed using evidence from peer-reviewed publications, gray literature, and consensus surveys. The areas investigated included choice of appropriate medical foods, integration of adjunctive therapies, treatment during pregnancy, monitoring of nutritional and clinical markers, prevention of nutrient deficiencies, providing of access to care, and compliance strategies. This process has not only provided assessment and refinement of current nutrition management and monitoring recommendations but also charted a direction for future studies. This document serves as a companion to the concurrently published American College of Medical Genetics and Genomics guideline for the medical treatment of phenylalanine hydroxylase deficiency. *Genet Med* advance online publication 2 January 2014 *Genetics in Medicine* (2014); doi:10.1038/gim.2013.179.

Smith, L. B., Leo, M. C., Anderson, C., Wright, T. J., Weymann, K. B., & Wood, L. J. (2014). The role of IL-1beta and TNF-alpha signaling in the genesis of cancer treatment related symptoms (CTRS): A study using cytokine receptor-deficient mice. *Brain, Behavior, and Immunity*, Cytotoxic chemotherapeutic agents often induce a cluster of cancer treatment related symptoms (CTRS). The purpose of this study was to develop a mouse model of CTRS to examine the role of IL-1beta and TNF-alpha signaling in the genesis of these symptoms. CTRS (change in wheel running activity, food intake, and body weight from baseline) were examined in wild type (WT) mice or mice lacking the TNF-alpha p55 (type 1) receptor (TNFR1<sup>-/-</sup>) and/or IL-1beta type 1 receptor (IL-1R1<sup>-/-</sup>) injected with four doses of cyclophosphamide/Adriamycin/5-fluorouracil (CAF) at 20-day intervals. Inflammatory cytokines in blood and tissues were measured using multiplex immunoassays and quantitative RT-PCR. ANOVA was used to examine differences between genotype and/or treatment group. Kaplan-Meier analysis was used to estimate survival rate. CAF rapidly increased IL-1beta and TNF-alpha signaling in WT mice. CAF induced acute CTRS immediately following drug injection which returned to baseline prior to the next CAF dose. Persistent CTRS were evident 3weeks after the 4th CAF dose. Acute but not persistent CTRS were associated with increased levels of IL-7, IL-9, KC, MCP-1, GCSF, and IP-10. This CAF induced inflammatory response was blunted in IL-1R1 deficient mice and absent in IL-1R1/TNFR1-deficient mice. IL-1R1<sup>-/-</sup> mice showed an identical pattern of CTRS to their WT counterparts. The assessment of CTRS in IL-1R1/TNF-R1-deficient mice was precluded by severe toxicity. Our data suggest that an important function of the IL-1beta and TNF-alpha driven inflammatory cascade is to promote recovery following exposure to cytotoxic agents.

Snider, B. R., & Kain, A. (2013). Automatic classification of breathing sounds during sleep. *2013 38th IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2013*, Vancouver, BC. pp. 699-703.

Sleep-disordered breathing (SDB) is a highly prevalent condition associated with many adverse health problems. As the current means of diagnosis (polysomnography) is obtrusive and ill-suited for mass screening of the population, we explore a non-contact, automatic approach that uses acoustics-based methods. We present a method for automatically classifying breathing sounds produced during sleep. We compare the performance of several acoustic feature representations

for detecting diagnostically-relevant sleep breathing events to predict overall SDB severity. Our subject-independent method tracks rest in the breathing cycle with 84-87% accuracy, and predicts SDB severity at a level similar to polysomnography. © 2013 IEEE.

Sobanko, J. F., Vanderbeek, G. E., White, K. P., White Jr, C. R., & Bar, A. A. (2013). What is your diagnosis? *Cutis*, 92(6), 285-287.

An 88-year-old woman with Alzheimer disease and a history of numerous basal cell carcinomas presented to our clinic with a rapidly growing nodule on the right arm of 2 weeks' duration. No antecedent lesion was present at that site. The nodule was asymptomatic, and a review of systems did not reveal constitutional symptoms. Physical examination revealed a 3×2-cm, oval, dome-shaped, burgundy-colored nodule with a smooth shiny surface adjacent to the right antecubital fossa. A round, 0.5-cm, crateriform ulceration was present at the right pole of the nodule. © Cutis 2013.

Sonnenberg, A. (2014). Modeling lengthy work-ups in gastrointestinal bleeding. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*,

Multiple procedures and medical devices are being utilized in a complex interplay to diagnose and treat gastrointestinal bleeding. The aim of the study is to develop a mathematical model that helps estimating the average number of procedures to be expected in the general management of gastrointestinal bleeding. The modeling process serves as an example of how mathematical analysis in general can be used to answer unresolved clinical questions, lead to a better understanding of the underlying influences in a disease process, and provide a starting point for future clinical trials. The analysis uses a Markov chain to model the transition probabilities amongst consecutive interventions utilized to find and treat a bleeding site. The results show that starting a work-up of gastrointestinal bleeding with an EGD will lead on average to 2.69 procedures per patient. Of these expected procedures, 1.46 will be EGDs, 0.69 colonoscopies, 0.25 video capsule endoscopies, 0.14 double-balloon enteroscopies, and 0.14 procedures from interventional radiology. Management chains initiated with a colonoscopy result in similar outcomes. Among 10,000 simulated individual patients, the number of procedures varies

between 1 and 16 consecutive procedures, with 95% of all patients undergoing 6 procedures or less. The outcomes of the model suggest that the published success rates of endoscopic and radiographic procedures are overly optimistic. The results also point at the need to generate clinical data through future studies that more reliably account for treatment failures and the interchange among various complementary diagnostic modalities.

Sonnenberg, A. (2014). Time trends of US hospitalization for esophageal disease. *Journal of Clinical Gastroenterology*,

BACKGROUND AND AIMS:: The occurrence of reflux disease seems to be rising in the United States. The aim of the present study was to follow the time trends of hospitalization for gastroesophageal reflux disease (GERD) and other esophageal disease during the past 4 decades. METHODS:: US hospital utilization data were available for individual years from 1970 to 2010 through the National Hospital Discharge Survey. Esophageal diagnoses were stratified by their ninth revision of the International Classification of Diseases codes. Annual hospitalizations were expressed as rates per 100,000 living US population. RESULTS:: GERD was by far the most common esophageal disorder resulting in hospitalization. However, in only 5% of instances did GERD-related diagnoses constitute the primary cause of hospitalization. Between 1970 and 2010 the rates of GERD-related hospitalizations increased in an exponential manner almost 10-fold. This rise affected both sex and all age groups alike. A 3-fold rise was noted in hospitalizations for esophageal adenocarcinoma. Other esophageal diagnoses, such as achalasia, dyskinesia, or stricture were characterized by falling or stable trends. CONCLUSIONS:: US hospitalization data show a continued exponential rise in the occurrence of GERD without any signs of leveling off. These trends are likely to represent ongoing changes in the underlying incidence and prevalence of the disease.

Soule, I. (2014). Cultural competence in health care: An emerging theory. *ANS. Advances in Nursing Science*, 37(1), 48-60.

This study examined the current state of cultural competence in health care using a qualitative descriptive design. Interviews were conducted with 20 multidisciplinary experts in culture and cultural competence from the United States and abroad. Findings identified 3 themes; awareness,

engagement, and application that crossed 4 domains of cultural competence; intrapersonal, interpersonal, system/organization, and global.

Spain, R. I., Mancini, M., Horak, F. B., & Bourdette, D. (2013). Body-worn sensors capture variability, but not decline, of gait and balance measures in multiple sclerosis over 18 months. *Gait & Posture*,

Gait and balance deficits are a frequent complaint in MS but poorly captured by stopwatch-timed tests or rating scales. Body-worn accelerometers and gyroscopes are able to detect gait and balance abnormalities in people with MS who have normal walking speeds. Few longitudinal studies exist using this technology to study the evolution of mobility deficits. The purpose of this study was to determine if body-worn sensors detected any decline in gait and balance measures in people with MS over time. Twenty-seven people with MS (13 mildly disabled, self-rated expanded disability status scale 0-3.5; 14 moderately disabled, SR-EDSS 4.0-5.5) who had normal walking speeds and 18 matched control subjects underwent gait and balance testing using body-worn sensors every 6 months for 18 months. While no parameter worsened over time, the moderately disabled MS cohort performed more poorly than the mildly disabled MS cohort who, in turn, was worse than control subjects for both objective and subjective walking and balance measures. Furthermore, the moderately disabled MS cohort demonstrated greater variation in between-visit performance than did the less disabled MS cohort or controls (Bonferroni-corrected  $p < 0.05$ ). Variability may be a key indicator of worsening gait and balance disability in MS.

Spain, R. I., Mancini, M., Horak, F. B., & Bourdette, D. (2014). Body-worn sensors capture variability, but not decline, of gait and balance measures in multiple sclerosis over 18 months. *Gait and Posture*,

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Stagg, S. M., Noble, A. J., Spilman, M., & Chapman, M. S. (2013). ResLog plots as an empirical metric of the quality of cryo-EM reconstructions. *Journal of Structural Biology*,  
Compared to the field of X-ray crystallography, the field of single particle three-dimensional electron microscopy has few reliable metrics for assessing the quality of 3D reconstructions. New metrics are needed that can determine whether a given 3D reconstruction accurately reflects the structure of the particles from which it was derived or instead depicts a plausible though incorrect structure due to coarse misalignment of particles. Here an empirical procedure is presented for differentiating between a reconstruction with well-aligned particles and a reconstruction with grossly misclassified particles. For a given dataset, 3D reconstructions are computed from subsets of particles with decreasing numbers of particles contributing to the reconstruction. A plot of inverse resolution vs. the logarithm of the number of particles (a "ResLog" plot) provides metrics for the reliability of the reconstruction and the overall quality of the dataset and processing. Specifically, the y-intercept of a regression line provides a measure of the relative accuracy of the particle alignment and classification, and the slope is an indicator of the overall data quality including the imaging conditions and processing steps. ResLog plots can also be used to optimize conditions for data collection and reconstruction parameters. Although resolution estimates can vary by method of calculation, ResLog-derived parameters are consistent whether calculated by Fourier shell correlation or Fourier neighbor correlation, or a new coordinate-based metric that serves as a yardstick for structures where atomic coordinates are available. ResLog

plots could become part of a standard set of parameters to be included in 3D reconstruction reports.

Steiger, J. R., Thielman, E. J., & Henry, J. A. (2013). Tinnitus loudness tracking: A "type v bekesy" pattern does not exist for pseudotinnitus. *Journal of the American Academy of Audiology, 24*(10), 920-926.

Background: Evaluation tools are lacking for the identification of patients exhibiting pseudotinnitus. It was hypothesized that tinnitus loudness traces might show a separation between continuous and pulsed tones for participants exhibiting pseudotinnitus, that is, the "type V" pattern shown for threshold tracking among participants exhibiting pseudohypacusis. It was further hypothesized that tinnitus loudness tracking might reveal unreliable tinnitus loudness matches among participants exhibiting pseudotinnitus due to their lack of an internal tinnitus standard. Purpose: To determine whether a tinnitus loudness tracking pattern exists for participants exhibiting pseudotinnitus. Research Design: Nonrandomized posttest-only control design. The experimental group participants were those without tinnitus, and the control group participants were those with tinnitus. Study Sample: There were 86 participants, including 45 with tinnitus and 41 without tinnitus. The participants' hearing varied from normal to severe hearing losses by pure-tone average at 1000, 2000, and 4000 Hz. Intervention: Participants without tinnitus were asked to act as if they had tinnitus and to complete tinnitus loudness matching as if they were trying to convince the test (or computer) that they had tinnitus. Data Analysis: t-tests Results: There were no statistically significant differences between individuals with tinnitus and participants acting out pseudotinnitus for any of six measures: (1) continuous tone tinnitus loudness tracking; (2) pulsed tone tinnitus loudness tracking; (3) differences between continuous and pulsed tone tinnitus loudness tracking; (4) continuous tone excursion width; (5) pulsed tone excursion width; and (6) differences between continuous and pulsed tone excursion width. Conclusions: Tinnitus loudness tracking does not appear to hold promise as a clinical tool for the identification of participants exhibiting pseudotinnitus.

Su, W., Hopkins, S., Nesser, N. K., Sopher, B., Silvestroni, A., Ammanuel, S., et al. (2014). The p53 transcription factor modulates microglia behavior through microRNA-dependent regulation of c-

maf. *Journal of Immunology*, 192(1), 358-366.

Neuroinflammation occurs in acute and chronic CNS injury, including stroke, traumatic brain injury, and neurodegenerative diseases. Microglia are specialized resident myeloid cells that mediate CNS innate immune responses. Disease-relevant stimuli, such as reactive oxygen species (ROS), can influence microglia activation. Previously, we observed that p53, a ROS-responsive transcription factor, modulates microglia behaviors in vitro and in vivo, promoting proinflammatory functions and suppressing downregulation of the inflammatory response and tissue repair. In this article we describe a novel mechanism by which p53 modulates the functional differentiation of microglia both in vitro and in vivo. Adult microglia from p53-deficient mice have increased expression of the antiinflammatory transcription factor c-Maf. To determine how p53 negatively regulates c-Maf, we examined the impact of p53 on known c-Maf regulators. MiR-155 is a microRNA that targets c-Maf. We observed that cytokine-induced expression of miR-155 was suppressed in p53-deficient microglia. Furthermore, Twist2, a transcriptional activator of c-Maf, is increased in p53-deficient microglia. We identified recognition sites in the 3' untranslated region of Twist2 mRNA that are predicted to interact with two p53-dependent microRNAs: miR-34a and miR-145. In this article, we demonstrate that miR-34a and -145 are regulated by p53 and negatively regulate Twist2 and c-Maf expression in microglia and the RAW macrophage cell line. Taken together, these findings support the hypothesis that p53 activation induced by local ROS or accumulated DNA damage influences microglia functions and that one specific molecular target of p53 in microglia is c-Maf. Copyright © 2013 by The American Association of Immunologists, Inc.

Sullivan, D. R., Ganzini, L., Duckart, J. P., Lopez-Chavez, A., Deffebach, M. E., Thielke, S. M., et al. (2014). Treatment receipt and outcomes among lung cancer patients with depression. *Clinical Oncology*, 26(1), 25-31.

Aims: Among lung cancer patients, depression has been associated with increased mortality, although the mechanisms are unknown. We evaluated the association of depression with mortality and receipt of cancer therapies among depressed veterans with lung cancer. Materials and methods: A retrospective, cohort study of lung cancer patients in the Veterans Affairs-Northwest Health Network from 1995 to 2010. Depression was defined by ICD-9 coding within 24

months before lung cancer diagnosis. Multivariable Cox proportional analysis and logistic regression were used. Results: In total, 3869 lung cancer patients were evaluated; 14% had a diagnosis of depression. A diagnosis of depression was associated with increased mortality among all stage lung cancer patients (hazard ratio=1.14, 95% confidence interval: 1.03-1.27, P=0.01). Among early-stage (I and II) non-small cell lung cancer (NSCLC) patients, the hazard ratio was 1.37 (95% confidence interval: 1.12-1.68, P=0.003). There was no association of depression diagnosis with surgery (odds ratio=0.83, 95% confidence interval: 0.56-1.22, P=0.34) among early-stage NSCLC patients. A depression diagnosis was not associated with mortality (hazard ratio=1.02, 95% confidence interval: 0.89-1.16, P=0.78) or chemotherapy (odds ratio=1.07, 95% confidence interval: 0.83-1.39, P=0.59) or radiation (odds ratio=1.04, 95% confidence interval: 0.81-1.34, P=0.75) receipt among advanced-stage (III and IV) NSCLC patients. Increased utilisation of health services for depression was associated with increased mortality among depressed patients. Conclusions: Depression is associated with increased mortality in lung cancer patients and this association is higher among those with increased measures of depression care utilisation. Differences in lung cancer treatment receipt are probably not responsible for the observed mortality differences between depressed and non-depressed patients. Clinicians should recognise the significant effect of depression on lung cancer survival. © 2013 The Royal College of Radiologists.

Swank, M. L., Caughey, A. B., Farinelli, C. K., Main, E. K., Melsop, K. A., Gilbert, W. M., et al. (2014).

The impact of change in pregnancy body mass index on the development of gestational hypertensive disorders. *Journal of Perinatology : Official Journal of the California Perinatal Association*,

Objective: To examine the impact of change in body mass index (BMI) during pregnancy on the incidence of gestational hypertension/preeclampsia. Study Design: This is a retrospective cohort study using linked California birth certificate and discharge diagnosis data from the year 2007. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated for the outcome of gestational hypertension/preeclampsia, as a function of a categorical change in pregnancy BMI: BMI loss (10). The impact of change in pregnancy BMI was evaluated for the entire cohort and then as a function of prepregnancy BMI category. Women with no change in pregnancy BMI

served as the reference group. Result: The study population consisted of 436 414 women with singleton gestations. Overall, women with excessive BMI change had a nearly twofold increased odds of gestational hypertension/preeclampsia (aOR=1.94; 95% CI=1.72 to 2.20). By prepregnancy BMI class, overweight and obese women who had a moderate change in pregnancy BMI also had increased odds of developing gestational hypertension/preeclampsia with aOR ranging from 1.73 to 1.97. Conclusion: Regardless of prepregnancy BMI category, women with excessive BMI change have a higher chance of developing gestational hypertension/preeclampsia. Overweight and obese women with moderate BMI change may also be at increased risk. Journal of Perinatology advance online publication, 2 January 2014; doi:10.1038/jp.2013.168.

Tabaee, A., Chen, L., Smith, T. L., Hwang, P. H., Schaberg, M., Raithatha, R., et al. (2014). Academic rhinology: A survey of residency programs and rhinology faculty in the united states.

*International Forum of Allergy and Rhinology,*

Background: Rhinology has rapidly evolved as a subspecialty over the past decade. The professional activities of rhinology faculty in otolaryngology residency programs is an important defining feature of this process but remains incompletely understood. Methods: An examination of faculty profiles of otolaryngology residency programs in the United States was performed to examine the professional activities of rhinologists. An anonymous, web-based survey of rhinology faculty was also performed to query professional activities and career satisfaction. Results: Nine percent of chairmen and 12% of residency program directors were rhinologists. The number of full-time rhinology faculty members varied significantly among departments (mean 1; range, 0-4). Rhinology faculty members were noted to have a high number of scientific publications over the past 5 years (mean 15 per faculty), a high level of membership to the American Rhinologic Society (90%) and modest levels of membership to other societies. As reported by the 45 respondents who successfully completed the survey, higher percentages of professional time was devoted to clinical medicine when compared with administrative and research activities.

Inflammatory sinusitis represented the most common clinical condition treated, and there was variability with respect to other disorders and procedures. Career satisfaction scores were highest for medical and surgical care, teaching activities, financial and emotional well being, and overall career to date. Lower satisfaction scores were noted for research and administrative activities

and for balance of personal life with work. Conclusion: This study further defines the professional, clinical, and surgical activities of academic rhinologists. Continued analysis of the subspecialization of rhinology is required. © 2014 ARS-AAOA, LLC.

Tanner, C. A. (2014). Remembering RHEBA: A tribute to dr. rheba de tornyay, editor emeritus 1926-2013. *Journal of Nursing Education*, 53(1), 3-4.

Thomas, K. A., Roy, N., Troxell, M., & Oh, K. Y. (2014). Osteosarcoma of the breast. *The Breast Journal*,

Thomas, S. H., Brown, K. M., Oliver, Z. J., Spaite, D. W., Lawner, B. J., Sahni, R., et al. (2014). An evidence-based guideline for the air medical transportation of prehospital trauma patients. *Prehospital Emergency Care*, 18(SUPPL.1), 35-44.

Background. Decisions about the transportation of trauma patients by helicopter are often not well informed by research assessing the risks, benefits, and costs of such transport. Objective. The objective of this evidence-based guideline (EBG) is to recommend a strategy for the selection of prehospital trauma patients who would benefit most from aeromedical transportation. Methods. A multidisciplinary panel was recruited consisting of experts in trauma, EBG development, and emergency medical services (EMS) outcomes research. Representatives of the Federal Interagency Committee on Emergency Medical Services (FICEMS), the National Highway Traffic Safety Administration (NHTSA) (funding agency), and the Children's National Medical Center (investigative team) also contributed to the process. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to guide question formulation, evidence retrieval, appraisal/synthesis, and formulate recommendations. The process followed the National Evidence-Based Guideline Model Process, which has been approved by the Federal Interagency Committee on EMS and the National EMS Advisory Council. Results. Two strong and three weak recommendations emerged from the process, all supported only by low or very low quality evidence. The panel strongly recommended that the 2011 CDC Guideline for the Field Triage of Injured Patients be used as the initial step in the triage process, and that ground emergency medical services (GEMS) be used for patients not meeting CDC anatomic, physiologic, and situational high-acuity criteria. The panel issued a weak

recommendation to use helicopter emergency medical services (HEMS) for higher-acuity patients if there is a time-savings versus GEMS, or if an appropriate hospital is not accessible by GEMS due to systemic/logistical factors. The panel strongly recommended that online medical direction should not be required for activating HEMS. Special consideration was given to the potential need for local adaptation. Conclusions. Systematic and transparent methodology was used to develop an evidence-based guideline for the transportation of prehospital trauma patients. The recommendations provide specific guidance regarding the activation of GEMS and HEMS for patients of varying acuity. Future research is required to strengthen the data and recommendations, define optimal approaches for guideline implementation, and determine the impact of implementation on safety and outcomes including cost. © 2014 National Association of EMS Physicians.

Tipps, M. E., Raybuck, J. D., & Lattal, K. M. (2014). Substance abuse, memory, and post-traumatic stress disorder. *Neurobiology of Learning and Memory*,

A large body of literature demonstrates the effects of abused substances on memory. These effects differ depending on the drug, the pattern of delivery (acute or chronic), and the drug state at the time of learning or assessment. Substance use disorders involving these drugs are often comorbid with anxiety disorders, such as post-traumatic stress disorder (PTSD). When the cognitive effects of these drugs are considered in the context of the treatment of these disorders, it becomes clear that these drugs may play a deleterious role in the development, maintenance, and treatment of PTSD. In this review, we examine the literature evaluating the cognitive effects of three commonly abused drugs: nicotine, cocaine, and alcohol. These three drugs operate through both common and distinct neurobiological mechanisms and alter learning and memory in multiple ways. We consider how the cognitive and affective effects of these drugs interact with the acquisition, consolidation, and extinction of learned fear, and we discuss the potential impediments that substance abuse creates for the treatment of PTSD. © 2013 Elsevier Inc. All rights reserved.

Traer, E., Javidi-Sharifi, N., Agarwal, A., Dunlap, J., English, I., Martinez, J., et al. (2014). Ponatinib overcomes FGF2-mediated resistance in CML patients without kinase domain mutations. *Blood*,

Development of resistance to kinase inhibitors remains a clinical challenge. Kinase domain mutations are a common mechanism of resistance in chronic myeloid leukemia (CML), yet the mechanism of resistance in the absence of mutations remains unclear. We tested proteins from the bone marrow microenvironment and found that FGF2 promotes resistance to imatinib in vitro. FGF2 was uniquely capable of promoting growth in both short- and long-term assays through the FGFR3/RAS/c-RAF/MAPK pathway. Resistance could be overcome with ponatinib, a multi-kinase inhibitor that targets BCR-ABL and FGFR. Clinically, we identified CML patients without kinase domain mutations who were resistant to multiple ABL kinase inhibitors, and responded to ponatinib treatment. In comparison to CML patients with kinase domain mutations, these patients had increased FGF2 in their bone marrow when analyzed by immunohistochemistry. Moreover, FGF2 in the marrow decreased concurrently with response to ponatinib, further suggesting that FGF2-mediated resistance is interrupted by FGFR inhibition. These results illustrate the clinical importance of ligand-induced resistance to kinase inhibitors and support an approach of developing rational inhibitor combinations to circumvent resistance.

Troxell, M. L. (2014). Reversed MUC1/EMA polarity in both mucinous and micropapillary breast carcinoma. *Human Pathology*, 45(2), 432-434.

Tubbs, R. S., Benninger, B., Loukas, M., & Cohen-Gadol, A. A. (2014). Cranial roots of the accessory nerve exist in the majority of adult humans. *Clinical Anatomy*, 27(1), 102-107.

The inclusion of a cranial root as a component of the accessory nerve is controversial with at least one recent study claiming that intracranial rootlets do not exist in humans. In response to this debate, the present study aimed to clarify this anatomy in a large cadaveric sample. In this study, 43 adult cadavers (86 sides) were dissected via a posterior approach to the craniocervical junction. Observations were made for the presence or absence of cranial roots of the accessory nerve, and when present, their lengths and diameters were measured. Relationships of these rootlets were documented. A cranial root of the accessory nerve was identified in 76% of sides. When identified, 1-6 cranial rootlets (mean 4.5) of the accessory nerve were observed. They ranged in diameter from 0.1 to 1.1 mm (mean 0.7 mm). The length of these nerves ranged from 8 to 24 mm with a mean of 17 mm. In general, the more superior rootlets were shorter and the

more inferior rootlets were longer. Although there was a slight tendency for the cranial roots to be more numerous and larger on right sides and in males, this did not reach statistical significance. We believe this to be the largest study to date documenting the presence of a cranial root of the accessory nerve. Based on our findings, a cranial root exists in the majority of specimens. Neurosurgical procedures or high quality imaging of this area should enable the physician to see these structures. *Clin. Anat.* 27:102-107, 2014. © 2012 Wiley Periodicals, Inc. Copyright © 2012 Wiley Periodicals, Inc., a Wiley company.

Tuz, K., Bachmann-Gagescu, R., O'Day, D. R., Hua, K., Isabella, C. R., Phelps, I. G., et al. (2014). Mutations in CSPP1 cause primary cilia abnormalities and joubert syndrome with or without jeune asphyxiating thoracic dystrophy. *American Journal of Human Genetics*, 94(1), 62-72.

Joubert syndrome (JBTS) is a recessive ciliopathy in which a subset of affected individuals also have the skeletal dysplasia Jeune asphyxiating thoracic dystrophy (JATD). Here, we have identified biallelic truncating CSPP1 (centrosome and spindle pole associated protein 1) mutations in 19 JBTS-affected individuals, four of whom also have features of JATD. CSPP1 mutations explain ~5% of JBTS in our cohort, and despite truncating mutations in all affected individuals, the range of phenotypic severity is broad. Morpholino knockdown of cspp1 in zebrafish caused phenotypes reported in other zebrafish models of JBTS (curved body shape, pronephric cysts, and cerebellar abnormalities) and reduced ciliary localization of Arl13b, further supporting loss of CSPP1 function as a cause of JBTS. Fibroblasts from affected individuals with CSPP1 mutations showed reduced numbers of primary cilia and/or short primary cilia, as well as reduced axonemal localization of ciliary proteins ARL13B and adenylyl cyclase III. In summary, CSPP1 mutations are a major cause of the Joubert-Jeune phenotype in humans; however, the mechanism by which these mutations lead to both JBTS and JATD remains unknown. © 2014 The American Society of Human Genetics.

Ventres, W. (2014). Chronic kidney disease among agricultural workers in central america. *American Journal of Public Health*,

I read the editorial by Wesseling et al.<sup>1</sup> on Chronic Kidney Disease (CKD) in Central America with interest, for I too live in the region. As a US family physician and anthropologist working in El

Salvador—a knowledgeable observer of recent debates on the topic—I offer the following observations for readers of the Journal regarding the authors' analyses: As Wesseling et al. mention (but do not cite), other articles challenge their own conclusions<sup>2,3</sup>; Powerful ideological and commercial concerns have aligned themselves on opposite sides of the scientific debate as to the etiology of CKD in the area; Because of these polarized positions, professional discussion on the relative merits of respective hypotheses is strained; Given the intricacies of the above situation and the lack of truly confirmatory evidence one way or another, it is too soon to suggest that one etiologic hypothesis take priority over others<sup>4</sup>; and, Because of multiple economic, social, and historical reasons, the work conditions of agricultural laborers in Central America are harsh. Whether triggered by repeat episodes of heat stress and dehydration or agrochemical exposure (or any other hypotheses), the incidence of CKD in the area can likely be reduced by occupational, environmental, and health-related reforms that make this work more humane. (Am J Public Health. Published online ahead of print January 16, 2014: e1. doi:10.2105/AJPH.2013.301756).

Ventres, W., & Dharamsi, S. (2013). Beyond religion and spirituality: Faith in the study and practice of medicine. *Perspectives in Biology and Medicine*, 56(3), 352-361.

Discussions about faith in medicine traditionally have been linked to religion and spirituality. Faith, however, is also that sense of trust or confidence one has in someone or something. As such, it is a concept integral to medical education and practice. This essay explores several dimensions of faith that play significant roles in medicine. It reviews why developing an awareness of faith is important for medical students and practitioners alike, and concludes by suggesting it is by seeking such faith in the profession that medical students and physicians can nurture their personal and professional growth. © 2013 by The Johns Hopkins University Press.

Verghese, S. C., Goloviznina, N. A., Skinner, A. M., Lipps, H. J., & Kurre, P. (2014). S/MAR sequence confers long-term mitotic stability on non-integrating lentiviral vector episomes without selection. *Nucleic Acids Research*,

Insertional oncogene activation and aberrant splicing have proved to be major setbacks for retroviral stem cell gene therapy. Integrase-deficient human immunodeficiency virus-1-derived

vectors provide a potentially safer approach, but their circular genomes are rapidly lost during cell division. Here we describe a novel lentiviral vector (LV) that incorporates human ss-interferon scaffold/matrix-associated region sequences to provide an origin of replication for long-term mitotic maintenance of the episomal LTR circles. The resulting 'anchoring' non-integrating lentiviral vector (aniLV) achieved initial transduction rates comparable with integrating vector followed by progressive establishment of long-term episomal expression in a subset of cells. Analysis of aniLV-transduced single cell-derived clones maintained without selective pressure for >100 rounds of cell division showed sustained transgene expression from episomes and provided molecular evidence for long-term episome maintenance. To evaluate aniLV performance in primary cells, we transduced lineage-depleted murine hematopoietic progenitor cells, observing GFP expression in clonogenic progenitor colonies and peripheral blood leukocyte chimerism following transplantation into conditioned hosts. In aggregate, our studies suggest that scaffold/matrix-associated region elements can serve as molecular anchors for non-integrating lentivector episomes, providing sustained gene expression through successive rounds of cell division and progenitor differentiation in vitro and in vivo.

Wakeland, W., Nielsen, A., Schmidt, T. D., McCarty, D., Webster, L. R., Fitzgerald, J., et al. (2013).

Modeling the impact of simulated educational interventions on the use and abuse of pharmaceutical opioids in the united states: A report on initial efforts. *Health Education and Behavior*, 40(1 SUPPL.), 74S-86S.

Three educational interventions were simulated in a system dynamics model of the medical use, trafficking, and nonmedical use of pharmaceutical opioids. The study relied on secondary data obtained in the literature for the period of 1995 to 2008 as well as expert panel recommendations regarding model parameters and structure. The behavior of the resulting systems-level model was tested for fit against reference behavior data. After the base model was tested, logic to represent three educational interventions was added and the impact of each intervention on simulated overdose deaths was evaluated over a 7-year evaluation period, 2008 to 2015. Principal findings were that a prescriber education intervention not only reduced total overdose deaths in the model but also reduced the total number of persons who receive opioid analgesic therapy, medical user education not only reduced overdose deaths among medical users but also

resulted in increased deaths from nonmedical use, and a "popularity" intervention sharply reduced overdose deaths among nonmedical users while having no effect on medical use. System dynamics modeling shows promise for evaluating potential interventions to ameliorate the adverse outcomes associated with the complex system surrounding the use of opioid analgesics to treat pain. © 2013 Society for Public Health Education.

Wallia, A., Colleran, K., Purnell, J. Q., Gross, C., & Molitch, M. E. (2013). Improvement in insulin sensitivity during mifepristone treatment of cushing syndrome: Early and late effects. *Diabetes Care*, 36(9), e147-e148.

Walsh, E. S., Peterson, J. J., Judkins, D. Z., & Expert Panel on Health Care Disparities Among Individuals With Disabilities. (2014). Searching for disability in electronic databases of published literature. *Disability and Health Journal*, 7(1), 114-118.

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, K., Lin, M. T., Adelman, J. P., & Maylie, J. (2014). Distinct  $Ca^{2+}$  sources in dendritic spines of hippocampal CA1 neurons couple to SK and Kv4 channels. *Neuron*, 81(2), 379-387.

Small conductance  $Ca^{2+}$ -activated  $K^{+}$  (SK) channels and voltage-gated A-type Kv4 channels

shape dendritic excitatory postsynaptic potentials (EPSPs) in hippocampal CA1 pyramidal neurons. Synaptically evoked Ca(2+) influx through N-methyl-D-aspartate receptors (NMDARs) activates spine SK channels, reducing EPSPs and the associated spine head Ca(2+) transient. However, results using glutamate uncaging implicated Ca(2+) influx through SNX-482-sensitive (SNX-sensitive) Cav2.3 (R-type) Ca(2+) channels as the Ca(2+) source for SK channel activation. The present findings show that, using Schaffer collateral stimulation, the effects of SNX and apamin are not mutually exclusive and SNX increases EPSPs independent of SK channel activity. Dialysis with 1,2-bis(o-aminophenoxy)ethane-N'N'N'-tetraacetic acid (BAPTA), application of 4-Aminopyridine (4-AP), expression of a Kv4.2 dominant negative subunit, and dialysis with a KChIPs antibody occluded the SNX-induced increase of EPSPs. The results suggest two distinct Ca(2+) signaling pathways within dendritic spines that link Ca(2+) influx through NMDARs to SK channels and Ca(2+) influx through R-type Ca(2+) channels to Kv4.2-containing channels.

Wang, Z., Xiong, W., Tebo, B. M., & Giammar, D. E. (2014). Oxidative UO<sub>2</sub> dissolution induced by soluble Mn(III). *Environmental Science and Technology*, 48(1), 289-298.

The stability of UO<sub>2</sub> is critical to the success of reductive bioremediation of uranium. When reducing conditions are no longer maintained, Mn redox cycling may catalytically mediate the oxidation of UO<sub>2</sub> and remobilization of uranium. Ligand-stabilized soluble Mn(III) was recently recognized as an important redox-active intermediate in Mn biogeochemical cycling. This study evaluated the kinetics of oxidative UO<sub>2</sub> dissolution by soluble Mn(III) stabilized by pyrophosphate (PP) and desferrioxamine B (DFOB). The Mn(III)-PP complex was a potent oxidant that induced rapid UO<sub>2</sub> dissolution at a rate higher than that by a comparable concentration of dissolved O<sub>2</sub>. However, the Mn(III)-DFOB complex was not able to induce oxidative dissolution of UO<sub>2</sub>. The ability of Mn(III) complexes to oxidize UO<sub>2</sub> was probably determined by whether the coordination of Mn(III) with ligands allowed the attachment of the complexes to the UO<sub>2</sub> surface to facilitate electron transfer. Systematic investigation into the kinetics of UO<sub>2</sub> oxidative dissolution by the Mn(III)-PP complex suggested that Mn(III) could directly oxidize UO<sub>2</sub> without involving particulate Mn species (e.g., MnO<sub>2</sub>). The expected 2:1 reaction stoichiometry between Mn(III) and UO<sub>2</sub> was observed. The reactivity of soluble Mn(III) in oxidizing UO<sub>2</sub> was higher at lower

ratios of pyrophosphate to Mn(III) and lower pH, which is probably related to differences in the ligand-to-metal ratio and/or protonation states of the Mn(III)-pyrophosphate complexes. Disproportionation of Mn(III)-PP occurred at pH 9.0, and the oxidation of UO<sub>2</sub> was then driven by both MnO<sub>2</sub> and soluble Mn(III). Kinetic models were derived that provided excellent fits of the experimental results. © 2013 American Chemical Society.

Washington, K., & Corless, C. L. (2011). *Practical gastrointestinal oncology correlative science*  
Springer Berlin Heidelberg.

Gastrointestinal (GI) cancers, like other human malignancies, are characterized by the accumulation of a variety of genetic alterations, including mutations that lead to inactivation of tumor suppressor genes or activation of oncogenes. These genetic and epigenetic changes can be used to classify tumors on the molecular level, and form the basis for development of new prognostic and predictive markers. While a number of molecular prognostic factors in GI cancers have been recognized or postulated (Table 3.1), few have been validated in large data sets to date and their utilization is not yet considered a standard of care. The essential prognostic factors for carcinomas across all GI sites remain the anatomic stage as classified, using TNM categories, lymphovascular invasion, and achievement of margin-negative surgical resection in potentially curable neoplasms. However, with the development of therapies targeted to specific molecular pathways involved in tumorigenesis, characterization of molecular alterations in individual GI malignancies has become important for prediction of response to therapy and thus may be used in some situations to guide selection of treatment options. Currently, the two most prominent examples are colorectal carcinoma and gastrointestinal stromal tumors (GISTs), for which molecular testing for prediction of response to therapy has become widely applied in certain clinical settings, such as KRAS mutational testing prior to treatment with cetuximab in high stage colorectal carcinoma. © 2011 Springer-Verlag Berlin Heidelberg.

Wester, J. L., Pittman, A. L., Lindau, R. H., & Wax, M. K. (2014). AlloDerm with split-thickness skin graft for coverage of the forearm free flap donor site. *Otolaryngology - Head and Neck Surgery (United States)*, 150(1), 47-52.

Objective. Major causes of donor site morbidity after free flap harvest are lack of split-thickness

skin graft (STSG) take and tendon exposure. Long-term cosmesis remains poor. AlloDerm has shown cosmetically better donor site healing, albeit prolonged healing. We sought to evaluate the use of STSG with AlloDerm compared with STSG alone. Study Design. Case series with chart review. Setting. Academic tertiary care medical center. Methods and Subjects. Institutional review board-approved study. Microvascular database queried from 2002 to 2012. Subjects with forearm free flaps and either AlloDerm + STSG or STSG alone for donor site reconstruction were included. Morbidity outcomes were compared. Results. Eighty patients (50 male, 30 female) received AlloDerm + STSG at the donor site. Major and minor donor site complications were 15.0% and 18.8% in the AlloDerm + STSG group compared with 10.2% and 16.9% in the STSG-only group ( $P = .30$  and  $P = .72$ ), respectively. Complete STSG loss (5.0% vs 3.0%,  $P = .48$ ), tendon exposure (5.0% vs 5.4%,  $P = 1.0$ ), functional impairment (2.5% vs 1.8%,  $P = .66$ ), infection (8.8% vs 9.6%,  $P = 1.0$ ), hematoma/ seroma (5.0% vs 3.6%,  $P = .73$ ), and paresthesia (1.3% vs 3.6%,  $P = .43$ ) were not significant. No patients required a second STSG after loss in the AlloDerm + STSG group compared with 60% ( $P = .17$ ). Cosmetic results were superior in the AlloDerm + STSG group as rated by the surgeon (3.5 vs 2.6,  $P = .03$ ) and patients (3.7 vs 2.9,  $P = .05$ ) on a scale of 1 to 5. Conclusion. Our results suggest that the use of AlloDerm with STSG can provide thicker coverage of the forearm defect, with minimal donor site morbidity and superior cosmetic results compared with STSG alone. © American Academy of Otolaryngology - Head and Neck Surgery Foundation 2013.

Wild, M., Kühlmann, B., Stauffenberg, A., Jungbluth, P., Hakimi, M., Rapp, W., et al. (2014). Does age affect the response of pelvis and spine to simulated leg length discrepancies? A rasterstereographic pilot study. *European Spine Journal*, , 1-8.

Purpose : The purpose of this study was to investigate age differences in the response of the spine and pelvis to simulated leg length inequalities (LLIs). Methods : A total of 107 subjects, separated into three age groups (group 1: 20-39 years, group 2: 40-59 years, group 3: >60 years), were used to evaluate for any age effects in the response to LLIs. LLIs of +10, +20, and +30 mm were simulated with a simulation platform on both sides, and the respective changes of pelvic position (pelvic obliquity, pelvic torsion) and spinal posture (lateral deviation, surface rotation, kyphotic, and lordotic angles) were measured with a rasterstereographic

system. Results : In all three age groups an increase in LLI led to significant changes in the pelvic position as measured by the parameters of pelvic obliquity and torsion. No significant differences in the response of the pelvis to the LLIs were found between the age groups. In all age groups an increase in surface rotation and lateral deviation of the spine with increasing LLIs was found. However, none of these parameters responded significantly different between the three age groups. Conclusions : Under static conditions, LLIs lead to significant changes of the pelvic position and spinal posture. Despite all known age-related changes, no significant differences of the measured pelvic and spinal parameters in elderly patients as a response to the simulated LLIs occurred. © 2014 Springer-Verlag Berlin Heidelberg.

Wilson, G. J., Woods, M., Springer, C. S., Bastawrous, S., Bhargava, P., & Maki, J. H. (2013). Human whole-blood  $^1\text{H}_2\text{O}$  longitudinal relaxation with normal and high-relaxivity contrast reagents: Influence of trans-cell-membrane water exchange. *Magnetic Resonance in Medicine*, Purpose: Accurate characterization of contrast reagent (CR) longitudinal relaxivity in whole blood is required to predict arterial signal intensity in contrast-enhanced MR angiography (CE-MRA). This study measured the longitudinal relaxation rate constants ( $R_1$ ) over a concentration range for non-protein-binding and protein-binding CRs in ex vivo whole blood and plasma at 1.5 and 3.0 Tesla (T) under physiologic arterial conditions. Methods: Relaxivities of gadoteridol, gadobutrol, gadobenate, and gadofosveset were measured for  $[\text{CR}]$  from 0 to 18 mM  $[\text{mmol}(\text{CR})/\text{L}(\text{blood})]$ : the latter being the upper limit of what may be expected in CE-MRA. Results: In plasma, the  $^1\text{H}_2\text{O}$   $R_1$   $[\text{CR}]$ -dependence was nonlinear for gadobenate and gadofosveset secondary to CR interactions with the serum macromolecule albumin, and was well described by an analytical expression for effective 1:1 binding stoichiometry. In whole blood, the  $^1\text{H}_2\text{O}$   $R_1$   $[\text{CR}]$ -dependence was markedly non-linear for all CRs, and was well-predicted by an expression for equilibrium exchange of water molecules between plasma and intracellular spaces using a priori parameter values only. Conclusion: In whole blood,  $^1\text{H}_2\text{O}$   $R_1$  exhibits a nonlinear relationship with  $[\text{CR}]$  over 0 to 18 mM CR. The nonlinearity is well described by exchange of water between erythrocyte and plasma compartments, and is particularly evident for high relaxivity CRs. © 2013 Wiley Periodicals, Inc.

Winters-Stone, K. M., Lauder milk, M., Woo, K., Brown, J. C., & Schmitz, K. H. (2014). Influence of weight training on skeletal health of breast cancer survivors with or at risk for breast cancer-related lymphedema. *Journal of Cancer Survivorship : Research and Practice*,

PURPOSE: This study aimed to determine whether the Physical Activity and Lymphedema (PAL) trial weight training program for breast cancer survivors at risk of or with breast cancer-related lymphedema provided skeletal benefits. METHODS: Of the 295 participants in the randomized controlled PAL trial, 258 (weight training; N = 128; control, N = 130) had complete measures of bone mineral density (BMD (in grams per square centimeter)) of the proximal femur and lumbar spine and were also categorized by T scores. Women in the weight training group performed slowly progressive weight training 2 days/week for 12 months compared to women in the control group who maintained their usual physical activities. RESULTS: There were no significant differences in the rate of BMD change at any skeletal site between weight training and control groups, regardless of menopausal status. Distribution of bone health categories was not significantly different between groups at baseline, but became different at 12 months ( $p < 0.03$ ) among postmenopausal women due to an increase in the percentage of controls who became osteopenic (35 to 44 %) compared to stable bone health in weight lifters. CONCLUSIONS: The PAL weight training program that increased muscle strength without exacerbating or causing lymphedema among breast cancer survivors was not as efficacious at improving skeletal health. The skeletal loads produced from the PAL program may be insufficient to notably shift BMD, but may have a subtle osteogenic effect. IMPLICATIONS FOR CANCER SURVIVORS: The safety and efficacy of rigorous weight training programs for improving skeletal health in women at risk for or with breast cancer-related lymphedema remain to be determined.

Wiszniewska, J., Bi, W., Shaw, C., Stankiewicz, P., Kang, S. -. L., Pursley, A. N., et al. (2014). Combined array CGH plus SNP genome analyses in a single assay for optimized clinical testing. *European Journal of Human Genetics*, 22(1), 79-87.

In clinical diagnostics, both array comparative genomic hybridization (array CGH) and single nucleotide polymorphism (SNP) genotyping have proven to be powerful genomic technologies utilized for the evaluation of developmental delay, multiple congenital anomalies, and neuropsychiatric disorders. Differences in the ability to resolve genomic changes between these

arrays may constitute an implementation challenge for clinicians: which platform (SNP vs array CGH) might best detect the underlying genetic cause for the disease in the patient? While only SNP arrays enable the detection of copy number neutral regions of absence of heterozygosity (AOH), they have limited ability to detect single-exon copy number variants (CNVs) due to the distribution of SNPs across the genome. To provide comprehensive clinical testing for both CNVs and copy-neutral AOH, we enhanced our custom-designed high-resolution oligonucleotide array that has exon-targeted coverage of 1860 genes with 60 000 SNP probes, referred to as Chromosomal Microarray Analysis-Comprehensive (CMA-COMP). Of the 3240 cases evaluated by this array, clinically significant CNVs were detected in 445 cases including 21 cases with exonic events. In addition, 162 cases (5.0%) showed at least one AOH region >10 Mb. We demonstrate that even though this array has a lower density of SNP probes than other commercially available SNP arrays, it reliably detected AOH events >10 Mb as well as exonic CNVs beyond the detection limitations of SNP genotyping. Thus, combining SNP probes and exon-targeted array CGH into one platform provides clinically useful genetic screening in an efficient manner. © 2014 Macmillan Publishers Limited.

Wong, E. B., Akilimali, N. A., Govender, P., Sullivan, Z. A., Cosgrove, C., Pillay, M., et al. (2013). Low levels of peripheral CD161++CD8+ mucosal associated invariant T (MAIT) cells are found in HIV and HIV/TB co-infection. *PLoS One*, 8(12), e83474.

**BACKGROUND:** High expression of CD161 on CD8+ T cells is associated with a population of cells thought to play a role in mucosal immunity. We wished to investigate this subset in an HIV and Mycobacterium tuberculosis (MTB) endemic African setting. **METHODS:** A flow cytometric approach was used to assess the frequency and phenotype of CD161++CD8+ T cells. 80 individuals were recruited for cross-sectional analysis: controls (n = 18), latent MTB infection (LTBI) only (n = 16), pulmonary tuberculosis (TB) only (n = 8), HIV only (n = 13), HIV and LTBI co-infection (n = 15) and HIV and TB co-infection (n = 10). The impact of acute HIV infection was assessed in 5 individuals recruited within 3 weeks of infection. The frequency of CD161++CD8+ T cells was assessed prior to and during antiretroviral therapy (ART) in 14 HIV-positive patients. **RESULTS:** CD161++CD8+ T cells expressed high levels of the HIV co-receptor CCR5, the tissue-homing marker CCR6, and the Mucosal-Associated Invariant T (MAIT) cell TCR

Valpha7.2. Acute and chronic HIV were associated with lower frequencies of CD161++CD8+ T cells, which did not correlate with CD4 count or HIV viral load. ART was not associated with an increase in CD161++CD8+ T cell frequency. There was a trend towards lower levels of CD161++CD8+ T cells in HIV-negative individuals with active and latent TB. In those co-infected with HIV and TB, CD161++CD8+ T cells were found at low levels similar to those seen in HIV mono-infection. CONCLUSIONS: The frequencies and phenotype of CD161++CD8+ T cells in this South African cohort are comparable to those published in European and US cohorts. Low-levels of this population were associated with acute and chronic HIV infection. Lower levels of the tissue-trophic CD161++ CD8+ T cell population may contribute to weakened mucosal immune defense, making HIV-infected subjects more susceptible to pulmonary and gastrointestinal infections and detrimentally impacting on host defense against TB.

Wozniak, C. J., Stehlik, J., Baird, B. C., McKellar, S. H., Song, H. K., Drakos, S. G., et al. (2014).

Ventricular assist devices or inotropic agents in status 1A patients? survival analysis of the united network of organ sharing database. *The Annals of Thoracic Surgery*,

BACKGROUND: Improved outcomes as well as lack of donor hearts have increased the use of ventricular assist devices (VADs), rather than inotropic support, for bridging to transplantation. Recognizing that organ allocation in the highest status patients remains controversial, we sought to compare outcomes of patients with VADs and those receiving advanced medical therapy.

METHODS: The United Network of Organ Sharing (UNOS) database was used to compare survival on the waiting list and posttransplantation survival in status 1A heart transplantation patients receiving VADs or high-dose/dual inotropic therapy or an intraaortic balloon pump( IABP), or both. Adjusted survival was calculated using Cox's proportional hazard model. RESULTS:

Adjusted 1-year posttransplantation mortality was higher among patients with VADs compared with patients receiving inotropic agents alone (hazard ratio [HR], 1.48;  $p < 0.05$ ). Survival remained better for patients receiving inotropic agents alone in the post-2008 era (HR, 1.36;  $p = 0.03$ ) and among those with isolated left-sided support (HR, 1.33;  $p = 0.008$ ). When patients who received IABPs were added and analyzed after 2008, the left ventricular assist device (LVAD) group had similar survival (HR, 1.2;  $p = 0.3$ ). Survival on the waiting list, however, was superior among patients with LVADs (HR, 0.56;  $p < 0.05$ ). In a therapy transition analysis, failure of

inotropic agents and the need for LVAD support was a consistent marker for significantly worse mortality (HR, 1.7;  $p < 0.05$ ). CONCLUSIONS: Although posttransplantation survival is better for patients who are bridged to transplantation with inotropic treatment only, the cost of failure of inotropic agents is significant, with a nearly doubled mortality for those who later require VAD support. Survival on the waiting list appears to be improved among patients receiving VAD support. Careful selection of the appropriate bridging strategy continues to be a significant clinical challenge.

Wysham, N. G., Mularski, R. A., Schmidt, D. M., Nord, S. C., Louis, D. L., Shuster, E., et al. (2013).

Long-term persistence of quality improvements for an intensive care unit communication initiative using the VALUE strategy. *Journal of Critical Care*,

PURPOSE: Communication in the intensive care unit (ICU) is an important component of quality ICU care. In this report, we evaluate the long-term effects of a quality improvement (QI) initiative, based on the VALUE communication strategy, designed to improve communication with family members of critically ill patients. MATERIALS AND METHODS: We implemented a multifaceted intervention to improve communication in the ICU and measured processes of care. Quality improvement components included posted VALUE placards, templated progress note inclusive of communication documentation, and a daily rounding checklist prompt. We evaluated care for all patients cared for by the intensivists during three separate 3 week periods, pre, post, and 3 years following the initial intervention. RESULTS: Care delivery was assessed in 38 patients and their families in the pre-intervention sample, 27 in the post-intervention period, and 41 in follow-up. Process measures of communication showed improvement across the evaluation periods, for example, daily updates increased from pre 62% to post 76% to current 84% of opportunities. CONCLUSIONS: Our evaluation of this quality improvement project suggests persistence and continued improvements in the delivery of measured aspects of ICU family communication. Maintenance with point-of-care-tools may account for some of the persistence and continued improvements.

Yokota, N., Zarpellon, A., Chakrabarty, S., Bogdanov, V. Y., Gruber, A., Castellino, F. J., et al. (2014).

Contributions of thrombin targets to tissue factor-dependent metastasis in hyperthrombotic mice.

*Journal of Thrombosis and Haemostasis*, 12(1), 71-81.

Background: Tumor cell tissue factor (TF)-initiated coagulation supports hematogenous metastasis by fibrin formation, platelet activation and monocyte/macrophage recruitment. Recent studies identified host anticoagulant mechanisms as a major impediment to successful hematogenous tumor cell metastasis. Objective: Here we address mechanisms that contribute to enhanced metastasis in hyperthrombotic mice with functional thrombomodulin deficiency (TMPro mice). Methods: Pharmacological and genetic approaches were combined to characterize relevant thrombin targets in a mouse model of experimental hematogenous metastasis. Results: TF-dependent, but contact pathway-independent, syngeneic breast cancer metastasis was associated with marked platelet hyperreactivity and formation of leukocyte-platelet aggregates in immune-competent TMPro mice. Blockade of CD11b or genetic deletion of platelet glycoprotein Iba excluded contributions of these receptors to enhanced platelet-dependent metastasis in hyperthrombotic mice. Mice with very low levels of the endothelial protein C receptor (EPCR) did not phenocopy the enhanced metastasis seen in TMPro mice. Genetic deletion of the thrombin receptor PAR1 or endothelial thrombin signaling targets alone did not diminish enhanced metastasis in TMPro mice. Combined deficiency of PAR1 on tumor cells and the host reduced metastasis in TMPro mice. Conclusions: Metastasis in the hyperthrombotic TMPro mouse model is mediated by platelet hyperreactivity and contributions of PAR1 signaling on tumor and host cells.

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Yuen, K. C., Koltowska-Haggstrom, M., Cook, D. M., Fox, J. L., Jonsson, P. J., Geffner, M. E., et al. (2014). Primary treatment regimen and diabetes insipidus as predictors of health outcomes in adults with childhood-onset craniopharyngioma. *The Journal of Clinical Endocrinology and Metabolism*, , jc20133631.

Context: Craniopharyngiomas are often associated with significant morbidity due to their location and treatment effects. Little is known of the effects of primary treatment regimen and diabetes insipidus (DI), a clinical surrogate of hypothalamic obesity, on health outcomes in adults with childhood-onset craniopharyngioma (COCP). Objective: The objective of the study was to examine health outcomes of adults with COCP based on primary treatment regimens and the presence of DI. Design: This study included a retrospective KIMS (Pfizer International Metabolic

Database) data analysis of 180 adults with COCP according to the primary treatment regimen [one surgery (1Surg) vs complex treatment regimen (CTrR) of more than 1Surg and/or radiotherapy] and the presence of DI. Results: The majority of COCP patients underwent transcranial surgery (77%) without receiving radiotherapy (84%). Compared with the 1Surg group, more CTrR patients developed visual field defects and ophthalmoplegia (all  $P < .01$ ). Compared with patients without DI, those with DI had higher rates of anterior pituitary hormone deficits, body mass index, and fat mass (all  $P < .01$ ). By contrast, fasting glucose, hemoglobin A1c, lipid panel, and quality of life were comparable among 1Surg vs CTrR patients, and patients with vs without DI. Regardless of primary treatment received, the presence of DI in either group was associated with higher rates of anterior pituitary hormone deficits and obesity. Conclusion: CTrR and DI predicted health outcomes differently. CTrR predisposed to the development of visual dysfunction, whereas DI was associated with higher rates of anterior pituitary dysfunction and weight gain. Higher body mass index and fat mass in patients with DI further implicate the role of hypothalamic damage as an important causal factor of obesity in these patients.

Zhu, M., Streiff, C., Panosian, J., Roundhill, D., Lapin, M., Tutschek, B., et al. (2014). Evaluation of stroke volume and ventricular mass in a fetal heart model: A novel four-dimensional echocardiographic analysis. *Echocardiography (Mount Kisco, N.Y.)*,  
AIMS: This study aimed to assess the feasibility and accuracy of nongated four-dimensional echocardiography (4DE) for determining left ventricular (LV) stroke volume (SV) and mass in a fetal heart-sized LV model. METHODS: A balloon was inserted into the LV of 20 fresh rabbit hearts and attached to a calibrated pulsatile pump. Ten hearts retaining the right ventricle were imaged in Group A. Ten hearts without the right ventricles (RVs) attached were imaged in Group B. Nongated 4D volumes were obtained using a Philips iU-22 system with an X6-1 matrix probe at SVs ranging from 1 to 5 mL at increments of 1 mL. At each SV, the volume displacement of the heart was measured at end-systole and end-diastole. Mass was determined by displacement at the conclusion of the experiment. RESULTS: The images were analyzed offline by manually tracing endocardial and epicardial boundaries of stacked contours. An excellent correlation in SV and mass between echo-derived values and displacement values was demonstrated and accompanied by high coefficients of determination ( $R^2$ ) in both groups (SV: Group A:  $R^2 =$

0.9461, Group B:  $R^2 = 0.9811$ ; Mass: Group A:  $R^2 = 0.9223$ , Group B:  $R^2 = 0.9602$ ; all  $P < 0.001$ ). Bland-Altman analyses showed a slight overestimation in both groups for both SV and LV mass. CONCLUSIONS: Nongated 4DE was demonstrated to be feasible and that it could accurately define SV and ventricular mass for a fetal heart-sized LV model.

Zuloaga, D. G., Johnson, L. A., Agam, M., & Raber, J. (2014). Sex differences in activation of the hypothalamic-pituitary-adrenal axis by methamphetamine. *Journal of Neurochemistry*,  
Dysregulation of hypothalamic-pituitary-adrenal (HPA) axis activation is associated with changes in addiction-related behaviors. In this study we tested whether sex differences in the acute effects of methamphetamine (MA) exposure involve differential activation of the HPA axis. Male and female mice were injected with MA (1mg/kg) or saline for comparison of plasma corticosterone and analysis of the immediate early gene c-Fos in brain. There was a prolonged elevation in corticosterone levels in female compared to male mice. C-Fos was elevated in both sexes following MA in HPA axis-associated regions, including the hypothalamic paraventricular nucleus (PVN), central amygdala, cingulate, and CA3 hippocampal region. MA increased the number of c-Fos and c-Fos/glucocorticoid receptor (GR) dual-labeled cells to a greater extent in males than females in the cingulate and CA3 regions. MA also increased the number of c-fos/vasopressin dual-labeled cells in the PVN as well as the number and percentage of c-Fos/GR dual-labeled cells in the PVN and central amygdala, although no sex differences in dual-labeling were found in these regions. Thus, sex differences in MA-induced plasma corticosterone levels and activation of distinct brain regions and proteins involved in HPA axis regulation may contribute to sex differences in acute effects of MA on the brain. This article is protected by copyright. All rights reserved.