OHSU Authors Bibliography
December 2017 – 376 Articles

First person - Brian Jenkins. (2017). *Journal of Cell Science, 130*(24), 4077-4078. doi:10.1242/jcs.213256

First Person is a series of interviews with the first authors of a selection of papers published in Journal of Cell Science, helping early-career researchers promote themselves alongside their papers. Brian Jenkins is the first author on 'Effects of mutating alpha-tubulin lysine 40 on sensory dendrite development', published in Journal of Cell Science. Brian conducted the research in this article while a post-doc in the lab of Jill Wildonger at the University of Wisconsin-Madison, Madison, WI. He is now at the Jungers Center for Neurosciences Research, Oregon Health and Science University, Portland, OR, where his research interests include visualizing all things related to how cells transport RNA, proteins and organelles throughout the cell.

Abdullah, C., Korkaya, H., Iizuka, S., & Courtneidge, S. A. (2017). **SRC increases MYC mRNA expression in ER+ breast cancer via mRNA stabilization and inhibition of p53 function**. *Molecular and Cellular Biology*. doi:10.1128/mcb.00463-17

The transcription factor MYC is important in breast cancer and its mRNA is maintained at a high level even in the absence of gene amplification. The mechanism(s) underlying increased MYC mRNA expression are unknown. Here we demonstrate that MYC mRNA was stabilized upon estrogen stimulation of estrogen receptor-positive breast cancer cells, via SRC-dependent effects on a recently described RNA-binding protein DeltaN-IMP1. We also show that loss of the tumor suppressor p53 increased MYC mRNA levels, even in the absence of estrogen stimulation. However, in cells with wildtype p53, SRC acted to overcome p53-mediated inhibition of estrogen-stimulated cell cycle entry and progression. SRC thus promotes cell proliferation in two ways: stabilizing MYC mRNA and inhibiting p53 function. Since estrogen receptor-positive breast cancers typically express wild-type p53, these studies establish a rationale for p53 status to be predictive for effective SRC inhibitor treatment in this subtype of breast cancer.

Acharya, G., Aplin, J., Brownbill, P., Bulmer, J., Burton, G., Chamley, L., . . . O'Tierney-Ginn, P. (2017). **IFPA meeting 2017 workshop report: Clinical placentology, 3D structure-based modeling of placental function, placental bed, and treating placental dysfunction**. *Placenta*. doi:10.1016/j.placenta.2017.12.011

Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialized topics. At IFPA meeting 2017 there were four themed workshops, all of which are summarized in this report. These workshops discussed new knowledge and technological innovations in the following areas of research: 1) placental bed; 2) 3D structural modeling; 3) clinical placentology; 4) treatment of placental dysfunction.

Achim, V., Bash, J., Mowery, A., Guimaraes, A. R., Li, R., Schindler, J., . . . Clayburgh, D. (2017). **Prognostic Indication of Sarcopenia for Wound Complication After Total Laryngectomy**. *JAMA Otolaryngol Head Neck Surg, 143*(12), 1159-1165. doi:10.1001/jamaoto.2017.0547

Adamyk, K. L. M., Holmes, E., Mayfield, G. R., Moritz, D. J., Scheepers, M., Tenner, B. E., & Wauck, H. C. (2017). **Sorting permutations: Games, genomes, and cycles**. *Discrete Mathematics, Algorithms and Applications, 9*(5). doi:10.1142/S179383091750063X

Permutation sorting, one of the fundamental steps in pre-processing data for the efficient application of other algorithms, has a long history in mathematical research literature and has numerous applications. Two special-purpose sorting operations are considered in this paper: context directed swap, (cds) and context directed reversal, (cdr). These are special cases of sorting operations that were studied in prior work on permutation sorting. Moreover, cds and cdr have been postulated to model molecular sorting events that occur in the genome maintenance program of certain species of single-celled organisms called ciliates. This paper investigates mathematical aspects of these two sorting operations. The main result of this paper is a generalization of previously discovered characterizations of cds-sortability of a permutation. The combinatorial structure underlying this generalization suggests natural combinatorial two-player games. These games are the main mathematical innovation of this paper.

Afifi, L., Sanchez, I. M., Wallace, M. M., Braswell, S. F., Ortega-Loayza, A. G., & Shinkai, K. (2017). **Diagnosis and management of peristomal pyoderma gangrenosum: A systematic review**. *J Am Acad Dermatol*. doi:10.1016/j.jaad.2017.12.049

BACKGROUND: Peristomal pyoderma gangrenosum (PPG) is an uncommon subtype of pyoderma gangrenosum. PPG is a challenging condition to diagnose and treat; no evidence-based guidelines exist. OBJECTIVE: To identify important clinical features of PPG and effective treatments available for its management. METHODS: A systematic literature review of PPG was performed using PubMed, Medline, and Embase databases. RESULTS: We describe 335 patients with PPG from 79 studies. Clinical features include a painful, rapidly progressing ulcer with undermined, violaceous borders with a history of ostomy leakage and local skin irritation or trauma. Systemic steroids are first line therapy; infliximab and adalimumab provide concomitant control of active IBD. Combination local and systemic therapy was commonly utilized. Wound dressings, vehicle selection, and appropriate ostomy devices to minimize leakage, irritation, and pressure-induced ischemia can improve healing. Distinct from classic ulcerative PG, surgical approaches, such as stoma closure and resection of active IBD, have an effective role in PPG management. LIMITATIONS: PPG is a rare disease lacking randomized trials or diagnostic guidelines. Treatment length and follow-up time among studies are variable. CONCLUSION: Key clinical characteristics of PPG are highlighted. Several treatments - including a more prominent role for surgical intervention - may be effective for PPG treatment.

Ahmann, A. J., Capehorn, M., Charpentier, G., Dotta, F., Henkel, E., Lingvay, I., . . . Aroda, V. R. (2017). **Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial**. *Diabetes Care*. doi:10.2337/dc17-0417

OBJECTIVE: To compare the efficacy and safety of once-weekly semaglutide 1.0 mg s.c. with exenatide extended release (ER) 2.0 mg s.c. in subjects with type 2 diabetes. RESEARCH DESIGN AND METHODS: In this phase 3a, open-label, parallel-group, randomized controlled trial, 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomized (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. The primary end point was change from baseline in HbA1c at week 56. RESULTS: Mean HbA1c (8.3% [67.7 mmol/mol] at baseline) was reduced by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER (estimated treatment difference vs. exenatide ER [ETD] -0.62% [95% CI -0.80, -0.44] [-6.78 mmol/mol (95% CI -8.70, -4.86)]; P < 0.0001 for noninferiority and superiority). Mean body weight (95.8 kg at baseline) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD -3.78 kg [95% CI -4.58, -2.98]; P < 0.0001). Significantly more subjects treated with semaglutide (67%) achieved HbA1c <7.0% (<53 mmol/mol) versus those taking exenatide ER (40%). Both treatments had similar safety profiles, but gastrointestinal adverse events were more common in semaglutide-treated subjects (41.8%) than in exenatide ER-treated subjects (33.3%); injection-site reactions were more frequent with exenatide ER (22.0%) than with semaglutide (1.2%). CONCLUSIONS: Semaglutide 1.0 mg was superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight after 56 weeks of treatment; the drugs had comparable safety profiles. These results indicate that semaglutide treatment is highly effective for subjects with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs.

Aisner, D. L., Sholl, L. M., Berry, L., Rossi, M., Chen, H., Fujimoto, J., . . . Kwiatkowski, D. J. (2017). **The Impact of Smoking and TP53 mutations in lung adenocarcinoma patients with targetable mutations - the Lung Cancer Mutation Consortium (LCMC2)**. *Clin Cancer Res*. doi:10.1158/1078-0432.ccr-17-2289

PURPOSE Multiplex genomic profiling is standard of care for patients with advanced lung adenocarcinomas. The Lung Cancer Mutation Consortium (LCMC) is a multi-institutional effort to identify and treat oncogenic driver events in patients with lung adenocarcinomas. PATIENTS AND METHODS Sixteen U.S. institutions enrolled 1367 lung cancer patients in LCMC2; 904 were deemed eligible and had at least one of 14 cancer-related genes profiled using validated methods including genotyping, massively parallel sequencing, and immunohistochemistry. RESULTS The use of targeted therapies in patients with EGFR, ERBB2, or BRAF p.V600E mutations, ALK, ROS1 or RET rearrangements, or MET amplification was associated with a survival increment of 1.5 years compared to those with such mutations not receiving targeted therapy; and 1.0 year compared to those lacking a targetable driver. Importantly, 60 patients with a history of smoking derived similar survival benefit from targeted therapy for alterations in EGFR ALK/ROS1, when compared to 75 never smokers with the same alterations. In addition, co-existing TP53 mutations were associated with shorter survival among patients with EGFR, ALK, or ROS1 alterations. CONCLUSION Patients with adenocarcinoma of the lung and an oncogenic driver mutation treated with effective targeted therapy have a longer survival, regardless of prior smoking history. Molecular testing should be performed on all individuals with lung adenocarcinomas irrespective of clinical characteristics. Routine use of massively parallel sequencing enables detection of both targetable driver alterations and tumor suppressor gene and other alterations that have potential significance for therapy selection and as predictive markers for the efficacy of treatment.

Aksoy, B. A., Dancik, V., Smith, K., Mazerik, J. N., Ji, Z., Gross, B., . . . Clemons, P. A. (2017). **CTD2 Dashboard: a searchable web interface to connect validated results from the Cancer Target Discovery and Development Network**. *Database: The Journal of Biological Databases and Curation, 2017*. doi:10.1093/database/bax054

Database URL: https://ctd2-dashboard.nci.nih.gov/.

Al-Kinani, A. A., Zidan, G., Elsaid, N., Seyfoddin, A., Alani, A. W. G., & Alany, R. G. (2017). **Ophthalmic gels: Past, present and future**. *Adv Drug Deliv Rev*. doi:10.1016/j.addr.2017.12.017

Aqueous gels formulated using hydrophilic polymers (hydrogels) along with those based on stimuli responsive polymers (in situ gelling or gel forming systems) continue to attract increasing interest for various eye health-related applications. They allow the incorporation of a variety of ophthalmic pharmaceuticals to achieve therapeutic levels of drugs and bioactives at target ocular sites. The integration of sophisticated drug delivery technologies such as nanotechnology-based ones with intelligent and environment responsive systems can extend current treatment duration to provide more clinically relevant time courses (weeks and months instead of hours and days) which will inevitably reduce dose frequency, increase patient compliance and improve clinical outcomes. Novel applications and design of contact lenses and intracanalicular delivery devices along with the move towards integrating gels into various drug delivery devices like intraocular pumps, injections and implants has the potential to reduce comorbidities caused by glaucoma, corneal keratopathy, cataract, diabetic retinopathies and age-related macular degeneration. This review describes ophthalmic gelling systems with emphasis on mechanism of gel formation and application in ophthalmology. It provides a critical appraisal of the techniques and methods used in the characterization of ophthalmic preformed gels and in situ gelling systems along with a thorough insight into the safety and biocompatibility of these systems. Newly developed ophthalmic gels, hydrogels, preformed gels and in situ gelling systems including the latest in the area of stimuli responsive gels, molecularly imprinted gels, nanogels, 3D printed hydrogels; 3D printed devices comprising ophthalmic gels are covered. Finally, new

applications of gels in the production of artificial corneas, corneal wound healing and hydrogel contact lenses are described.

Allen, S. E., Limdi, N., Westrick, A. C., Ver Hoef, L. W., Szaflarski, J. P., & Knowlton, R. C. (2017). **Racial disparities in temporal lobe epilepsy**. *Epilepsy Research, 140*, 56-60. doi:10.1016/j.eplepsyres.2017.12.012

OBJECTIVE: This study reports on epilepsy type period prevalence and black-white racial differences in a large patient population in the Southeastern United States. METHODS: For all patients visiting the University of Alabama at Birmingham's seizure monitoring unit between 2000 and 2011 (n=3240), video EEG diagnosis was recorded along with basic demographic information. Descriptive statistics and multivariate logistic regression were used to identify factors associated with temporal lobe epilepsy (TLE) diagnosis. RESULTS: The racial distribution was 77.3% white, and 20.0% black (other races were only 2.3% of the population). Most patients had either TLE (n=630) or PNES (n=1150) compared to other focal (n=424) or generalized epilepsies (n=224). The diagnosis of TLE was significantly greater for blacks than whites (odds ratio [OR]=1.87, 95% confidence interval [CI] 1.47-2.37). The period prevalence measures for the other conclusively diagnosed epilepsies were not significantly different. Women were disproportionately represented in the study population, and black women carried the most statistical weight for the TLE prevalence difference. INTERPRETATION: The nearly two-fold larger period prevalence of TLE among black patients is a striking finding that merits explanation. Although some selection bias exists due to a moderately lower than expected representation of blacks, socioeconomic status or access to care should not be assumed to be the only factors that might be responsible for the prevalence difference. Rather, all clues for distinct pathophysiological racial differences should be explored.

Anderson, D. E., & Johnstone, B. (2017). **Dynamic mechanical compression of chondrocytes for tissue engineering: A critical review**. *Frontiers in Bioengineering and Biotechnology, 5*(DEC). doi:10.3389/fbioe.2017.00076

Articular cartilage functions to transmit and translate loads. In a classical structure-function relationship, the tissue resides in a dynamic mechanical environment that drives the formation of a highly organized tissue architecture suited to its biomechanical role. The dynamic mechanical environment includes multiaxial compressive and shear strains as well as hydrostatic and osmotic pressures. As the mechanical environment is known to modulate cell fate and influence tissue development toward a defined architecture in situ, dynamic mechanical loading has been hypothesized to induce the structure-function relationship during attempts at in vitro regeneration of articular cartilage. Researchers have designed increasingly sophisticated bioreactors with dynamic mechanical regimes, but the response of chondrocytes to dynamic compression and shear loading remains poorly characterized due to wide variation in study design, system variables, and outcome measurements. We assessed the literature pertaining to the use of dynamic compressive bioreactors for in vitro generation of cartilaginous tissue from primary and expanded chondrocytes. We used specific search terms to identify relevant publications from the PubMed database and manually sorted the data. It was very challenging to find consensus between studies because of species, age, cell source, and culture differences, coupled with the many loading regimes and the types of analyses used. Early studies that evaluated the response of primary bovine chondrocytes within hydrogels, and that employed dynamic single-axis compression with physiologic loading parameters, reported consistently favorable responses at the tissue level, with upregulation of biochemical synthesis and biomechanical properties. However, they rarely assessed the cellular response with gene expression or mechanotransduction pathway analyses. Later studies that employed increasingly sophisticated biomaterial-based systems, cells derived from different species, and complex loading regimes, did not necessarily corroborate prior positive results. These studies report positive results with respect to very specific conditions for cellular responses to dynamic load but fail to consistently achieve significant positive changes in relevant tissue engineering parameters, particularly collagen content and stiffness. There is a need for standardized methods and analyses of dynamic mechanical loading systems to guide the field of tissue engineering toward building cartilaginous implants that meet the goal of regenerating articular cartilage. © 2017 Anderson and Johnstone.

Antoniel, M., Jones, K., Antonucci, S., Spolaore, B., Fogolari, F., Petronilli, V., . . . Bernardi, P. (2017). **The unique histidine in OSCP subunit of F-ATP synthase mediates inhibition of the permeability transition pore by acidic pH**. *EMBO Rep*. doi:10.15252/embr.201744705

The permeability transition pore (PTP) is a Ca(2+)-dependent mitochondrial channel whose opening causes a permeability increase in the inner membrane to ions and solutes. The most potent inhibitors are matrix protons, with channel block at pH 6.5. Inhibition is reversible, mediated by histidyl residue(s), and prevented by their carbethoxylation by diethylpyrocarbonate (DPC), but their assignment is unsolved. We show that PTP inhibition by H(+) is mediated by the highly conserved histidyl residue (H112 in the human mature protein) of oligomycin sensitivity conferral protein (OSCP) subunit of mitochondrial F1FO (F)-ATP synthase, which we also show to undergo carbethoxylation after reaction of mitochondria with DPC. Mitochondrial PTP-dependent swelling cannot be inhibited by acidic pH in H112Q and H112Y OSCP mutants, and the corresponding megachannels (the electrophysiological counterpart of the PTP) are insensitive to inhibition by acidic pH in patch-clamp recordings of mitoplasts. Cells harboring the H112Q and H112Y mutations are sensitized to anoxic cell death at acidic pH. These results demonstrate that PTP channel formation and its inhibition by H(+) are mediated by the F-ATP synthase.

Api, A. M., Belsito, D., Bhatia, S., Botelho, D., Browne, D., Bruze, M., . . . Wilcox, D. K. (2017). **RIFM fragrance ingredient safety assessment, dihydro-alpha-terpineol, CAS Registry Number 498-81-7**. *Food Chem Toxicol, 110 Suppl 1*, S253-s262. doi:10.1016/j.fct.2017.05.063

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, .alpha.-methylcyclohexylmethyl acetate, CAS Registry Number 13487-27-9**. *Food Chem Toxicol, 110 Suppl 1*, S242-s252. doi:10.1016/j.fct.2017.05.064

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment diethyl succinate, CAS Registry Number 123-25-1**. *Food Chem Toxicol*. doi:10.1016/j.fct.2017.12.050

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, 4-Hexen-1-ol, (4Z)-, CAS Registry Number 928-91-6**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.038

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment 2,4-dimethylbenzyl acetate, CAS Registry Number 62346-96-7**. *Food Chem Toxicol*. doi:10.1016/j.fct.2017.12.012

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment benzyl 2,2-dimethylpropanoate, CAS Registry Number 2094-69-1**. *Food Chem Toxicol*. doi:10.1016/j.fct.2017.12.048

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment Dimethyl succinate, CAS Registry Number 106-65-0**. *Food Chem Toxicol*. doi:10.1016/j.fct.2017.12.056

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, 2-methylundecanal dimethyl acetal, CAS Registry Number 68141-17-3**. *Food Chem Toxicol*. doi:10.1016/j.fct.2017.12.027

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, 3-Methylbutanal diethyl acetal, CAS Registry Number 3842-03-3**. *Food Chem Toxicol*. doi:10.1016/j.fct.2017.12.049

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, 3-tert-butylcyclohexyl acetate, CAS Registry Number 31846-06-7**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.034

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, (Z)-4-hepten-1-ol, CAS Registry Number 6191-71-5**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.035

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, Amylcyclohexyl acetate (mixed isomers), CAS Registry Number 67874-72-0**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.040

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, cis-5-octen-1-ol CAS Registry Number 64275-73-6**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.037

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, dodecanal dimethyl acetal, CAS Registry Number 14620-52-1**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.033

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, heptanal dimethyl acetal, CAS Registry Number 10032-05-0**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.043

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, l-menthyl lactate, CAS Registry Number 59259-38-0**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.041

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., Jr., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, phenylacetaldehyde diethyl acetal, CAS Registry Number 6314-97-2**. *Food Chem Toxicol, 110 Suppl 1*, S431-s438. doi:10.1016/j.fct.2017.08.039

Api, A. M., Belsito, D., Botelho, D., Browne, D., Bruze, M., Burton, G. A., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, 3-methyl-1-pentanol, CAS Registry Number 589-35-5**. *Food and Chemical Toxicology*. doi:10.1016/j.fct.2017.11.036

Api, A. M., Belsito, D., Botelho, D., Bruze, M., Burton, G. A., Buschmann, J., . . . Wahler, J. (2017). **RIFM fragrance ingredient safety assessment, beta-Guaiene, CAS Registry Number 88-84-6**. *Food Chem Toxicol, 110 Suppl 1*, S9-s15. doi:10.1016/j.fct.2016.11.017

Bacchi, A., Yih, J. A., Platta, J., Knight, J., & Pfeifer, C. S. (2018). **Shrinkage / stress reduction and mechanical properties improvement in restorative composites formulated with thio-urethane oligomers**. *J Mech Behav Biomed Mater, 78*, 235-240. doi:10.1016/j.jmbbm.2017.11.011

Thio-urethane oligomers (TUs) have been shown to favorably modify methacrylate networks to reduce stress and significantly increase fracture toughness. Since those are very desirable features in dental applications, the objective of this work was to characterize restorative composites formulated with the addition of TUs. TUs were synthesized by combining thiols – pentaerythritol tetra-3-mercaptopropionate (PETMP) or trimethylol-tris-3-mercaptopropionate (TMP) – with isocyanates – 1,6-Hexanediol-diissocyante (HDDI) (aliphatic) or 1,3-bis(1-isocyanato-1-methylethyl)benzene (BDI) (aromatic) or dicyclohexylmethane 4,4'-Diisocyanate (HMDI) (cyclic), at 1:2 isocyanate:thiol, leaving pendant thiols. 20 wt% TU were added to BisGMA-TEGDMA (70-30%). To this organic matrix, 70 wt% silanated inorganic fillers were added. Near-IR was used to follow methacrylate conversion and rate of polymerization (Rpmax). Mechanical properties were evaluated in three-point bending (ISO 4049) for flexural strength/modulus (FS/FM) and toughness (T), and notched specimens (ASTM Standard E399-90) for fracture toughness (KIC). Polymerization stress (PS) was measured on the Bioman. Volumetric shrinkage (VS) was measured with the bonded disk technique. Glass transition temperature (Tg) and heterogeneity of network were obtained with dynamic mechanical analysis. The addition of TUs led to an increase in mechanical properties (except for Tg and FS). Fracture toughness ranged from 1.6–1.94 MPa m1/2 for TU-modified groups, an increase of 33–61% in relation to the control (1.21 ± 0.1 MPa m1/2). Toughness showed a two-fold increase in relation to the control: from 0.91 MPa to values ranging from 1.70–1.95 MPa. Flexural modulus was statistically higher for the TU-modified groups. The Tg, as expected, decreased for all TU groups due to the greater flexibility imparted to the network (which also explains the increase in toughness and fracture toughness). Narrower tan-delta peaks suggest more homogeneous networks for the TU-modified materials, though differences were marked only for TMP_AL. Degree of conversion was not affected by the addition of TUs. VS was similar for all groups, with one exception where VS dropped (PETMP-cyclic). Finally, PS showed a reduction of 23–57% for TU-modified groups (6.7 ± 1.3 to 11.9 ± 1.0 MPa) in relation to the control (15.56 ± 1.4 MPa). The addition of thio-

urethane oligomers was able to reduce polymerization stress by up to 57% while increasing fracture toughness by up to 61%. © 2017 Elsevier Ltd

Bagi, Z., Brandner, D. D., Le, P., McNeal, D. W., Gong, X., Dou, H., . . . Back, S. A. (2017). **Vasodilator Dysfunction and Oligodendrocyte Dysmaturation in Aging White Matter**. *Ann Neurol*. doi:10.1002/ana.25129

OBJECTIVE: Microvascular brain injury (mVBI) is a common pathologic correlate of vascular contributions to cognitive impairment and dementia (VCID) that leads to white matter injury (WMI). VCID appears to arise from chronic recurrent white matter ischemia that triggers oxidative stress and an increase in total oligodendrocyte lineage cells. We hypothesized that mVBI involves vasodilator dysfunction of white matter penetrating arterioles and aberrant oligodendrocyte progenitor cell (OPC) responses to WMI. METHODS: We analyzed cases of mVBI with low Alzheimer's disease neuropathologic change in prefrontal cortex WM from rapid autopsies in a population-based cohort where VCID frequently occurs. Arteriolar vasodilator function was quantified by videomicroscopy. OPC maturation was quantified using lineage specific markers. RESULTS: ACh-mediated arteriolar dilation in mVBI was significantly reduced in WM penetrators relative to pial arterioles. Astrogliosis-defined WMI was positively associated with increased OPCs and was negatively associated with decreased mature oligodendrocytes. INTERPRETATION: Selectively impaired vasodilator function of WM penetrating arterioles in mVBI occurs in association with aberrant differentiation of OPCs in WMI, which supports that myelination disturbances in VCID are related to disrupted maturation of myelinating oligodendrocytes. This article is protected by copyright. All rights reserved.

Baker, S., & Thomas, M. (2017). **Pediatric Dental Resident's Education on Children with Special Health Care Needs in the United States**. *J Dent Child (Chic), 84*(3), 120-124.

PURPOSE: To describe pediatric dental residents education as it pertains to children with special healthcare needs (CSHCN). METHODS: A web-based survey was administered to 80 program directors of pediatric dental residencies recognized by the American Academy of Pediatric Dentistry (AAPD). The survey identified demographic data and education and training methods pertaining to CSHCN. RESULTS: Forty surveys (50 percent) were received from programs in all six AAPD regions. Programs that treated 4,500 patients or less/year were statistically less likely to require a specific assessment and were less likely to use written tests to assess competency treating CSHCN. A specific special needs didactic course (88 percent) and journal articles (85 percent) were the most common didactic training methods. The majority of the programs (69 percent) offered more than 20 hours of didactic education. On average 36.3 percent of the patients treated in residencies reported to be CSHCN and each resident clinically treated and average of 13 CSHCN/week. One-third of the respondents planned to increase CSHCN education in the next three years. Almost 70 percent of respondents supported the standardization of a national curriculum regarding CSHCN. CONCLUSIONS: A wide disparity exists among residencies regarding education related to CSHCN. Most pediatric dental residency directors support the national standardization of CSHCN education.

Banach, D. B., Johnston, B. L., Al-Zubeidi, D., Bartlett, A. H., Bleasdale, S. C., Deloney, V. M., . . . Trivedi, K. K. (2017). **Outbreak Response and Incident Management: SHEA Guidance and Resources for Healthcare Epidemiologists in United States Acute-Care Hospitals**. *Infection Control and Hospital Epidemiology, 38*(12), 1393-1419. doi:10.1017/ice.2017.212

Banerjee, K. (2017). **Translating technobabble: All you really need to know about uris, linked data, and FRBR**. *Computers in Libraries, 37*(10), 21-24.

Baynam, G., Bowman, F., Lister, K., Walker, C. E., Pachter, N., Goldblatt, J., . . . Dawkins, H. J. S. (2017). **Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework**. *Advances in Experimental Medicine and Biology, 1031*, 55-94. doi:10.1007/978-3-319-67144-4_4

Public health relies on technologies to produce and analyse data, as well as effectively develop and implement policies and practices. An example is the public health practice of epidemiology, which relies on computational technology to monitor the health status of populations, identify disadvantaged or at risk population groups and thereby inform health policy and priority setting. Critical to achieving health improvements for the underserved population of people living with rare diseases is early diagnosis and best care. In the rare diseases field, the vast majority of diseases are caused by destructive but previously difficult to identify protein-coding gene mutations. The reduction in cost of genetic testing and advances in the clinical use of genome sequencing, data science and imaging are converging to provide more precise understandings of the 'person-time-place' triad. That is: who is affected (people); when the disease is occurring (time); and where the disease is occurring (place). Consequently we are witnessing a paradigm shift in public health policy and practice towards 'precision public health'.Patient and stakeholder engagement has informed the need for a national public health policy framework for rare diseases. The engagement approach in different countries has produced highly comparable outcomes and objectives. Knowledge and experience sharing across the international rare diseases networks and partnerships has informed the development of the Western Australian Rare Diseases Strategic Framework 2015-2018 (RD Framework) and Australian government health briefings on the need for a National plan.The RD Framework is guiding the translation of genomic and other technologies into the Western Australian health system, leading to greater precision in diagnostic pathways and care, and is an example of how a precision public health framework can improve health outcomes for the rare diseases population.Five vignettes are used to illustrate how policy decisions provide the scaffolding for translation of new genomics knowledge, and catalyze transformative change in delivery of clinical services. The vignettes presented here are from an Australian perspective and are not intended to be comprehensive, but rather to provide insights into how a new and emerging 'precision public health' paradigm can improve the experiences of patients living with rare diseases, their caregivers and families.The conclusion is that genomic public health is informed by the individual and family needs, and the population health imperatives of an early and accurate diagnosis; which is the portal to best practice care. Knowledge sharing is critical for public health policy development and improving the lives of people living with rare diseases.

Bengtzen, R. R., Ma, O. J., & Herzka, A. (2017). **Point-of-Care Ultrasound Diagnosis of Proximal Hamstring Rupture**. *J Emerg Med*. doi:10.1016/j.jemermed.2017.11.027

BACKGROUND: Acute proximal hamstring ruptures can be a diagnostic challenge in the emergency department. The revealing sign of large posterior thigh ecchymosis is typically not yet present; the physical examination is limited due to pain, radiographs can be unremarkable, and definitive testing with magnetic resonance imaging is not practical. These avulsions are often misdiagnosed as hamstring strains and treated conservatively. The diagnosis is made after failed treatment, often months after the injury. Surgical repair at that time can be technically challenging and higher risk due to tendon retraction and adhesion of the tendon stump to the sciatic nerve. CASE REPORTS: The first case illustrates an example of how delay in diagnosis can occur in both emergency medicine and outpatient primary care settings. It also shows complications and morbidity potential for patients who warrant and do not receive timely surgical repair. The second case illustrates physical examination findings obtainable during the acute setting, and the use of point-of-care ultrasound (POCUS) in facilitating an expedited diagnosis and treatment plan. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?: Timely diagnosis of hamstring rupture is paramount to optimize patient outcomes for this serious injury. The best results are obtained with surgical repair within 3-6 weeks of injury. POCUS evaluation can aid significantly in the timely diagnosis of this injury. If the POCUS examination raises clinical concern for a proximal hamstring rupture, this may allow for earlier diagnosis and definitive treatment of proximal hamstring rupture.

Berg, M. R., MacAllister, R. P., & Martin, L. D. (2017). **Nonreducible Inguinal Hernia Containing the Uterus and Bilateral Adnexa in a Rhesus Macaque (Macaca mulatta)**. *Comparative Medicine, 67*(6), 537-540.

Inguinal herniation of abdominal viscera is a relatively common condition in both humans and domestic animal species. In captive rhesus macaques (Macaca mulatta), the highest incidence occurs in overweight, aged males. However, inguinal herniation of the uterus with bilateral adnexa is extremely rare in both human and veterinary medicine. Here we report a previously undescribed uterine inguinal herniation with bilateral adnexa in a 3-y-old female rhesus macaque. Although uterine herniation remains a rare condition in rhesus macaques, it should be considered as a differential diagnosis in animals with unilateral subcutaneous enlargements in the inguinal region.

Berry, M. H., Holt, A., Levitz, J., Broichhagen, J., Gaub, B. M., Visel, M., . . . Isacoff, E. Y. (2017). **Restoration of patterned vision with an engineered photoactivatable G protein-coupled receptor**. *Nat Commun, 8*(1), 1862. doi:10.1038/s41467-017-01990-7

Retinitis pigmentosa results in blindness due to degeneration of photoreceptors, but spares other retinal cells, leading to the hope that expression of light-activated signaling proteins in the surviving cells could restore vision. We used a retinal G protein-coupled receptor, mGluR2, which we chemically engineered to respond to light. In retinal ganglion cells (RGCs) of blind rd1 mice, photoswitch-charged mGluR2 ("SNAG-mGluR2") evoked robust OFF responses to light, but not in wild-type retinas, revealing selectivity for RGCs that have lost photoreceptor input. SNAG-mGluR2 enabled animals to discriminate parallel from perpendicular lines and parallel lines at varying spacing. Simultaneous viral delivery of the inhibitory SNAG-mGluR2 and excitatory light-activated ionotropic glutamate receptor LiGluR yielded a distribution of expression ratios, restoration of ON, OFF and ON-OFF light responses and improved visual acuity. Thus, SNAG-mGluR2 restores patterned vision and combinatorial light response diversity provides a new logic for enhanced-acuity retinal prosthetics.

Beswick, D. M., Kaushik, A., Beinart, D., McGarry, S., Yew, M. K., Kennedy, B. F., & Maria, P. L. S. (2017). **Biomedical device innovation methodology: applications in biophotonics**. *J Biomed Opt, 23*(2), 1-7. doi:10.1117/1.jbo.23.2.021102

The process of medical device innovation involves an iterative method that focuses on designing innovative, device-oriented solutions that address unmet clinical needs. This process has been applied to the field of biophotonics with many notable successes. Device innovation begins with identifying an unmet clinical need and evaluating this need through a variety of lenses, including currently existing solutions for the need, stakeholders who are interested in the need, and the market that will support an innovative solution. Only once the clinical need is understood in detail can the invention process begin. The ideation phase often involves multiple levels of brainstorming and prototyping with the aim of addressing technical and clinical questions early and in a cost-efficient manner. Once potential solutions are found, they are tested against a number of known translational factors, including intellectual property, regulatory, and reimbursement landscapes. Only when the solution matches the clinical need, the next phase of building a "to market" strategy should begin. Most aspects of the innovation process can be conducted relatively quickly and without significant capital expense. This white paper focuses on key points of the medical device innovation method and how the field of biophotonics has been applied within this framework to generate clinical and commercial success.

Bharadwaj, A. S., Stempel, A. J., Olivas, A., Franzese, S. E., Ashander, L. M., Ma, Y., . . . Smith, J. R. (2017). **Molecular Signals Involved in Human B Cell Migration into the Retina: In Vitro Investigation of ICAM-1, VCAM-1, and CXCL13**. *Ocul Immunol Inflamm, 25*(6), 811-819. doi:10.1080/09273948.2016.1180401

PURPOSE: B cells participate in diverse retinal immunopathologies. Endothelial adhesion molecules and chemokines direct leukocyte trafficking. We examined the involvement of three molecular signals in retinal transendothelial migration of human B cells: ICAM-1, VCAM-1, and CXCL13. METHODS: Peripheral blood B cells were isolated by negative selection. Migration was studied in transwells populated with human retinal endothelial monolayers, using antibody to block ICAM-1 or VCAM-1. Retinal expression of CXCL13 was investigated. RESULTS: B cells crossed retinal endothelium. ICAM-1 blockade significantly reduced migration when results for all subjects were combined, and for a majority when results were analyzed by individual. This effect was irrespective of the presence or absence of CXCL13, although CXCL13 increased migration. CXCL13 was detected in neural retina and retinal pigment epithelium. Endothelial cells of some retinal vessels presented CXCL13 protein. CONCLUSION: ICAM-1 blockade may be an effective treatment in some patients with retinal diseases that involve B cells.

Bhavsar, K. V., Jia, Y., Wang, J., Patel, R. C., Lauer, A. K., Huang, D., & Bailey, S. T. (2017). **Projection-resolved optical coherence tomography angiography exhibiting early flow prior to clinically observed retinal angiomatous proliferation**. *Am J Ophthalmol Case Rep, 8*, 53-57. doi:10.1016/j.ajoc.2017.10.001

Purpose: The purpose of this study is to analyze early retinal angiomatous proliferation (RAP) utilizing a novel imaging modality, Projection-Resolved Optical Coherence Tomography Angiography (PR-OCTA). Observations: Five months prior to the diagnosis of a RAP lesion, cross-sectional PR-OCTA demonstrated flow in the outer retina contiguous with the deep retinal capillary plexus (DCP) and adjacent to a small pigment epithelial detachment. After development of a clinically visible RAP lesion, cross-sectional PR-OCTA demonstrated the RAP lesion connecting DCP and sub-retinal pigment epithelial neovascularization. Conclusions & importance: This is the first report of PR-OCTA demonstrating abnormal flow in the outer retina prior to the development of a clinically detectable RAP lesion. PR-OCTA may be useful for surveillance and to help further characterize and stage RAP lesions.

Bhojwani, D., Burke, M. J., Horton, T., Ziegler, D. S., Sulis, M. L., Schultz, K. R., . . . Chang, B. H. (2017). **Investigating the biology of relapsed acute leukemia: Proceedings of the Therapeutic Advances for Childhood Leukemia & Lymphoma (TACL) Consortium Biology Working Group**. *Pediatric Hematology and Oncology*, 1-10. doi:10.1080/08880018.2017.1395937

During the 2016 Therapeutic Advances for Childhood Leukemia & Lymphoma (TACL) Consortium investigators' meeting (Los Angeles, CA), a Biology Working Group was established to support the consortium's mission of developing innovative therapies for currently incurable childhood leukemias and lymphomas. The charge of the Biology Working Group was to address how TACL could advance biological investigations of pediatric relapsed/refractory hematologic malignancies while undertaking forward-looking therapeutic trials. To this end, the TACL Biology Committee was established to provide the scientific platform needed to further develop preclinical and translational studies that will advance the understanding and treatment of relapsed and refractory disease. The Biology Committee will focus on ensuring state-of-the-art studies that address biological components of early phase clinical trials, and developing a central biology bank of materials from these early phase trials for interrogations into the mechanisms of disease resistance.

Bircher, J. S., & Dukhovny, D. (2017). **Response to Malla et al**. *Journal of Perinatology*. doi:10.1038/s41372-017-0021-7

Bishop, C. V., Mishler, E. C., Takahashi, D. L., Reiter, T. E., Bond, K. R., True, C. A., . . . Stouffer, R. L. (2018). **Chronic hyperandrogenemia in the presence and absence of a western-style diet impairs ovarian and uterine structure/function in young adult rhesus monkeys**. *Human Reproduction, 33*(1), 128-139. doi:10.1093/humrep/dex338

STUDY QUESTION: Does chronic hyperandrogenemia beginning at menarche, in the absence and presence of a western-style diet (WSD), alter ovarian and uterine structure-function in young adult rhesus monkeys? SUMMARY ANSWER: Phenotypic alterations in ovarian and uterine structure/function were induced by exogenous testosterone (T), and compounded in the presence of a WSD (T+WSD). WHAT IS KNOWN ALREADY: Hyperandrogenemia is a well-established component of PCOS and is observed in adolescent girls, indicating a potential pubertal onset of disease symptoms. Obesity is often associated with hyperandrogenemia and it is hypothesized that metabolic dysfunction exacerbates PCOS symptoms. STUDY DESIGN, SIZE, DURATION: Macaque females (n = 40) near the onset of menarche (~2.5 years of age) were assigned to a 2 by 2 factorial cohort design. Effects on reproductive characteristics were evaluated after 3 years of treatment. PARTICIPANTS/MATERIALS, SETTING, METHODS: Rhesus macaques (Macaca mulatta) were fed either a normal balanced diet (n = 20) or a WSD (n = 20). Additionally, implants containing cholesterol (n = 20) or T (n = 20) were implanted subcutaneously to elevate serum T approximately 5-fold. This resulted in treatment groups of controls (C), T, WSD and T+WSD (n = 10/group). Vaginal swabbing was performed daily to detect menses. After 3 years of treatment, daily serum samples from one menstrual cycle were assayed for hormone levels. Ovarian structure was evaluated in the early follicular phase by 3D/4D ultrasound. Uterine endometrial size and ovarian/luteal vascular function was also evaluated in subgroups (n = 6/group) in the late follicular and mid-luteal phases by 3D/4D ultrasound and contrast-enhanced ultrasound, respectively. Expression of steroid hormone receptors and markers of decidualization and endometrial receptivity were assessed in endometrial biopsies at mid-luteal phase. MAIN RESULTS AND THE ROLE OF CHANCE: Approximately 90% of menstrual cycles appeared ovulatory with no differences in frequency or duration between groups. Serum estradiol (E2) levels during the early follicular phase were greatest in the T alone group, but reduced in T+WSD ($P < 0.02$). Serum LH was elevated in the T group ($P < 0.04$); however, there were no differences among groups in FSH levels ($P > 0.13$). Ovarian size at menses tended to be greater in the WSD groups ($P < 0.07$) and antral follicles >/=1 mm were more numerous in the T+WSD group ($P < 0.05$). Also, females in T and T+WSD groups displayed polycystic ovarian morphology (PCOM) at greater frequency than C or WSD groups ($P < 0.01$). Progesterone (P4) levels during the luteal phase were reduced in the T+WSD group compared to C and T groups ($P < 0.05$). Blood volume (BV) and vascular flow (VF) within the corpus luteum was reduced in all treatment groups compared to C ($P < 0.01$, $P = 0.03$), with the WSD alone group displaying the slowest BV and VF ($P < 0.05$). C and WSD groups displayed endometrial glands at mid-luteal phase with low estrogen receptor 1 (ESR1) and progesterone receptor (PGR) mRNA and immunohistochemical staining in the functionalis zone, but appreciable PGR in the stroma. In contrast, T and T+WSD treatment resulted in glands with less secretory morphology, high ESR1 expression in the glandular epithelium and low PGR in the stroma. Endometrial levels of TIMP3 and MMP26 mRNA and immunostaining were also decreased in the T and T+WSD groups, whereas AR expression was unchanged. LARGE SCALE DATA: None. LIMITATIONS, REASONS FOR CAUTION: Females are young adults, so effects could change as they reach prime reproductive age. The T level generated for hyperandrogenemia may be somewhat greater than the 3-4-fold increase observed in adolescent girls, but markedly less than those observed in male monkeys or adolescent boys. WIDER IMPLICATIONS OF THE FINDINGS: Alterations to ovarian and uterine structure-function observed in T and, in particular, T+WSD-treated female macaques are consistent with some of the features observed in women diagnosed with polycystic ovary syndrome (PCOS), and suggest impaired fertility. STUDY FUNDING/COMPETING INTEREST(S): Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD) of the National Institutes of Health (NIH) under Award Number P50HD071836 (to RLS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional funding was provided by Office of the Director, NIH under Award Number P51OD011092 (Support for National Primate Research Center). Authors declare no competing interests.

Bloom, J. D., & Novosad, D. (2017). **The Forensic Mental Health Services Census of Forensic Populations in State Facilities**. *J Am Acad Psychiatry Law, 45*(4), 447-451.

This article focuses on the development of a Forensic Mental Health Services Census (FMHSC), proposed to differentiate between five different patient populations institutionalized in state facilities. The FMHSC would

comprise patients who are civilly committed for mental illness or sexual dangerousness, those found incompetent to stand trial, those committed after a verdict of not guilty by reason of insanity, and those voluntarily committed. The census would be performed by state mental health authorities for each of these populations within the particular jurisdiction and then would be reported to a national coordinating organization. These data are important because of the large number of persons involved and the significant resources devoted to the management and treatment of each involuntary group. The census is necessary for clinical, research, and policy purposes, to provide more rational management of these populations, both within and across jurisdictions.

Boespflug, E. L., & Iliff, J. J. (2017). **The Emerging Relationship Between Interstitial Fluid-Cerebrospinal Fluid Exchange, Amyloid-beta, and Sleep**. *Biol Psychiatry*. doi:10.1016/j.biopsych.2017.11.031

Amyloid-beta (Abeta) plaques are a key histopathological hallmark of Alzheimer's disease (AD), and soluble Abeta species are believed to play an important role in the clinical development of this disease. Emerging biomarker data demonstrate that Abeta plaque deposition begins decades before the onset of clinical symptoms, suggesting that understanding the biological determinants of the earliest steps in the development of AD pathology may provide key opportunities for AD treatment and prevention. Although a clinical association between sleep disruption and AD has long been appreciated, emerging clinical studies and insights from the basic neurosciences have shed important new light on how sleep and Abeta homeostasis may be connected in the setting of AD. Abeta, like many interstitial solutes, is cleared in part through the exchange of brain interstitial fluid and cerebrospinal fluid along a brain-wide network of perivascular pathways recently termed the glymphatic system. Glymphatic function is primarily a feature of the sleeping brain, rather than the waking brain, and is slowed in the aging and posttraumatic brain. These changes may underlie the diurnal fluctuations in interstitial and cerebrospinal fluid Abeta levels observed in both the rodent and the human. These and other emerging studies suggest that age-related sleep disruption may be one key factor that renders the aging brain vulnerable to Abeta deposition and the development of AD. If this is true, sleep may represent a key modifiable risk factor or therapeutic target in the preclinical phases of AD.

Bourne, D., Plinke, W., Hooker, E. R., & Nielson, C. M. (2017). **Cannabis use and bone mineral density: NHANES 2007-2010**. *Arch Osteoporos, 12*(1), 29. doi:10.1007/s11657-017-0320-9

Cannabis use is rising in the USA. Its relationship to cannabinoid signaling in bone cells implies its use could affect bone mineral density (BMD) in the population. In a national survey of people ages 20-59, we found no association between self-reported cannabis use and BMD of the hip or spine. INTRODUCTION: Cannabis is the most widely used illegal drug in the USA, and its recreational use has recently been approved in several US states. Cannabinoids play a role in bone homeostasis. We aimed to determine the association between cannabis use and BMD in US adults. METHODS: In the National Health and Nutrition Examination Survey 2007-2010, 4743 participants between 20 and 59 years old, history of cannabis use was categorized into never, former (previous use, but not in last 30 days), light (1-4 days of use in last 30 days), and heavy (>/=5 days of use in last 30 days). Multivariable linear regression was used to test the association between cannabis use and DXA BMD of the proximal femur and lumbar spine with adjustment for age, sex, BMI, and race/ethnicity among other BMD determinants. RESULTS: Sixty percent of the population reported ever using cannabis; 47% were former users, 5% were light users, and 7% were heavy users. Heavy cannabis users were more likely to be male, have a lower BMI, increased daily alcohol intake, increased tobacco pack-years, and were more likely to have used other illegal drugs (cocaine, heroin, or methamphetamines). No association between cannabis and BMD was observed for any level of use (p >/= 0.28). CONCLUSIONS: A history of cannabis use, although highly prevalent and related to other risk factors for low BMD, was not independently associated with BMD in this cross-sectional study of American men and women.

Bradshaw, W. E., Burkhart, J., Colbourne, J. K., Borowczak, R., Lopez, J., Denlinger, D. L., . . . Holzapfel, C. M. (2017). **Evolutionary transition from blood feeding to obligate nonbiting in a mosquito**. *Proc Natl Acad Sci U S A*. doi:10.1073/pnas.1717502115

The spread of blood-borne pathogens by mosquitoes relies on their taking a blood meal; if there is no bite, there is no disease transmission. Although many species of mosquitoes never take a blood meal, identifying genes that distinguish blood feeding from obligate nonbiting is hampered by the fact that these different lifestyles occur in separate, genetically incompatible species. There is, however, one unique extant species with populations that share a common genetic background but blood feed in one region and are obligate nonbiters in the rest of their range: Wyeomyia smithii Contemporary blood-feeding and obligate nonbiting populations represent end points of divergence between fully interfertile southern and northern populations. This divergence has undoubtedly resulted in genetic changes that are unrelated to blood feeding, and the challenge is to winnow out the unrelated genetic factors to identify those related specifically to the evolutionary transition from blood feeding to obligate nonbiting. Herein, we determine differential gene expression resulting from directional selection on blood feeding within a polymorphic population to isolate genetic differences between blood feeding and obligate nonbiting. We show that the evolution of nonbiting has resulted in a greatly reduced metabolic investment compared with biting populations, a greater reliance on opportunistic metabolic pathways, and greater reliance on visual rather than olfactory sensory input. W. smithii provides a unique starting point to determine if there are universal nonbiting genes in mosquitoes that could be manipulated as a means to control vector-borne disease.

Brammer, J. E., Chihara, D., Poon, L. M., Caimi, P., de Lima, M., Ledesma, C., . . . Oki, Y. (2018). **Management of Advanced and Relapsed/Refractory Extranodal Natural Killer T-Cell Lymphoma: An Analysis of Stem Cell Transplantation and Chemotherapy Outcomes**. *Clinical Lymphoma, Myeloma & Leukemia, 18*(1), e41-e50. doi:10.1016/j.clml.2017.10.001

BACKGROUND: Extra-Nodal natural killer/T-cell lymphoma (ENKL) is a rare lymphoma representing approximately 5-10% of T-cell non-Hodgkin lymphomas diagnosed in the United States each year. Patients with advanced stage III/IV ENKL and relapsed refractory ENKL have a poor prognosis even despite aggressive therapy and stem cell transplantation (SCT). We conducted a review of the management of 37 patients with advanced-stage and relapsed/refractory ENKL in a predominantly non-Asian cohort evaluating both chemotherapy and SCT outcomes. PATIENTS AND METHODS: We evaluated clinical outcomes in all patients treated for advanced stage III/IV or relapsed/refractory ENKL at MD Anderson cancer center between 2000-2014. Next, we collected stem cell transplant data from four transplant institutions to further evaluate outcomes of both allogeneic (allo-SCT) and autologous (auto-SCT) stem cell transplantation in ENKL. RESULTS: OS and PFS were 73% and 45% at one year, and 30% and 19% at 3-years, respectively. SMILE chemotherapy was more effective in maintaining a CR compared to CHOP (83% vs 17%). Only achievement of CR was prognostic for OS (HR 0.245, p=0.002) and PFS (HR 0.072, p) CONCLUSION: Our results suggest that achievement of a CR is imperative in patients with advanced ENKL, and is desirable for any patient for whom auto-SCT is utilized. SMILE-based chemotherapy appeared effective in attaining a CR, and was also an effective salvage regimen. For patients attaining a first CR, auto-SCT should be strongly considered, but should definitely be utilized in patients attaining CR2. For patients with refractory disease, allo-SCT can be considered in a selected group of patients.

Bridges, K. J., & Raslan, A. M. (2017). **Utility of intracranial pressure monitoring for diagnosis of Idiopathic Intracranial Hypertension in the absence of papilledema**. *World Neurosurgery*. doi:10.1016/j.wneu.2017.12.036

BACKGROUND: Idiopathic intracranial hypertension (IIH) is characterized by headaches, visual obscurations, and papilledema, while diagnosis involves lumbar puncture (LP) with an elevated opening pressure (OP) >/= 20cm H20. When papilledema is absent, diagnosis becomes less clear. Some physicians have argued that absence of papilledema rules out IIH, while others maintain that elevated OP is sufficient for diagnosis.

METHODS: The authors performed a single institution 4-year retrospective analysis of patients who underwent invasive intracranial pressure (ICP) monitoring for presumed IIH. RESULTS: A total of 22 patients were reviewed and 13 had classic symptoms of IIH, documented elevated OP and absence of papilledema, 5/13 (38%) patients had proven intracranial hypertension using invasive ICP monitoring, while 8/13 (62%) had normal ICP. CONCLUSIONS: Using current diagnostic algorithms of clinical presentation and elevated OP, over half of patients without papilledema in our series would be falsely diagnosed with IIH, which could result in unnecessary medical and surgical intervention. Thus, elevated OP as determined by LP is insufficient to diagnosis IIH. On the other hand, the absence of papilledema does not rule out intracranial hypertension.

Brignon, W. R., Pike, M. M., Ebbesson, L. O. E., Schaller, H. A., Peterson, J. T., & Schreck, C. B. (2017). **Rearing environment influences boldness and prey acquisition behavior, and brain and lens development of bull trout**. *Environmental Biology of Fishes*, 1-19. doi:10.1007/s10641-017-0705-z

Animals reared in barren captive environments exhibit different developmental trajectories and behaviors than wild counterparts. Hence, the captive phenotypes may influence the success of reintroduction and recovery programs for threatened and endangered species. We collected wild bull trout embryos from the Metolius River Basin, Oregon and reared them in differing environments to better understand how captivity affects the bull trout Salvelinus confluentus phenotype. We compared the boldness and prey acquisition behaviors and development of the brain and eye lens of bull trout reared in conventional barren and more structurally complex captive environments with that of wild fish. Wild fish and captive reared fish from complex habitats exhibited a greater level of boldness and prey acquisition ability, than fish reared in conventional captive environments. In addition, the eye lens of conventionally reared bull trout was larger than complex reared captive fish or same age wild fish. Interestingly, we detected wild fish had a smaller relative cerebellum than either captive reared treatment. Our results suggest that rearing fish in more complex captive environments can create a more wild-like phenotype than conventional rearing practices. A better understanding of the effects of captivity on the development and behavior of bull trout can inform rearing and reintroduction programs though prediction of the performance of released individuals.

Britton, D., Roeske, A., Ennis, S. K., Benditt, J. O., Quinn, C., & Graville, D. (2017). **Utility of Pulse Oximetry to Detect Aspiration: An Evidence-Based Systematic Review**. *Dysphagia*. doi:10.1007/s00455-017-9868-1

Pulse oximetry is a commonly used means to measure peripheral capillary oxyhemoglobin saturation (SpO2). Potential use of pulse oximetry to detect aspiration is attractive to clinicians, as it is readily available, quick, and noninvasive. However, research regarding validity has been mixed. This systematic review examining evidence on the use of pulse oximetry to detect a decrease in SpO2 indicating aspiration during swallowing is undertaken to further inform clinical practice in dysphagia assessment. A multi-engine electronic search was conducted on 8/25/16 and updated on 4/8/17 in accordance with standards published by the Preferred Reporting for Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA). Inclusion criteria included use of pulse oximetry to detect aspiration with simultaneous confirmation of aspiration via a gold standard instrumental study. Keywords included dysphagia or aspiration AND pulse oximetry. Articles meeting criteria were reviewed by two blinded co-investigators. The search yielded 294 articles, from which 19 were judged pertinent and reviewed in full. Ten met the inclusion criteria and all were rated at Level III-2 on the Australian Diagnostic Levels of Evidence. Study findings were mixed with sensitivity ranging from 10 to 87%. Potentially confounding variables were observed in all studies reviewed, and commonly involved defining "desaturation" within a standard measurement error range (~ 2%), mixed populations, mixed viscosities/textures observed during swallowing, and lack of comparison group. The majority of studies failed to demonstrate an association between observed aspiration and oxygen desaturation. Current evidence does not support the use of pulse oximetry to detect aspiration.

Brockmeyer, D. L., Sivakumar, W., Mazur, M. D., Sayama, C. M., Goldstein, H. E., Lew, S. M., . . . Riva-Cambrin, J. K. (2017). **Identifying Factors Predictive of Atlantoaxial Fusion Failure in Pediatric Patients: Lessons Learned From A Retrospective Pediatric Craniocervical Society Study**. *Spine (Phila Pa 1976)*. doi:10.1097/brs.0000000000002495

STUDY DESIGN: Multicenter retrospective cohort study with multivariate analysis. OBJECTIVE: To determine factors predictive of posterior atlantoaxial fusion failure in pediatric patients. SUMMARY OF BACKGROUND DATA: Fusion rates for pediatric posterior atlantoaxial arthrodesis have been reported to be high in single-center studies; however, factors predictive of surgical non-union have not been identified by a multicenter study. METHODS: Clinical and surgical details for all patients who underwent posterior atlantoaxial fusion at seven pediatric spine centers from 1995 to 2014 were retrospectively recorded. The primary outcome was surgical failure, defined as either instrumentation failure or fusion failure seen on either plain x-ray or CT scan. Multiple logistic regression analysis was undertaken to identify clinical and technical factors predictive of surgical failure. RESULTS: One hundred thirty-one patients met the inclusion criteria and were included in the analysis. Successful fusion was seen in 117 (89%) of the patients. Of the 14 (11%) patients with failed fusion, the cause was instrumentation failure in 3 patients (2%) and graft failure in 11 (8%). Multivariate analysis identified Down syndrome as the single factor predictive of fusion failure (OR 14.6, 95% CI [3.7-64.0]). CONCLUSIONS: This retrospective analysis of a multicenter cohort demonstrates that although posterior pediatric atlantoaxial fusion success rates are generally high, Down syndrome is a risk factor that significantly predicts the possibility of surgical failure. LEVEL OF EVIDENCE: 3.

Brown, C. E., Back, A. L., Ford, D. W., Kross, E. K., Downey, L., Shannon, S. E., . . . Engelberg, R. A. (2018). **Self-Assessment Scores Improve After Simulation-Based Palliative Care Communication Skill Workshops**. *American Journal of Hospice and Palliative Medicine, 35*(1), 45-51. doi:10.1177/1049909116681972

Background: We conducted a randomized trial of a simulation-based multisession workshop to improve palliative care communication skills (Codetalk). Standardized patient assessments demonstrated improved communication skills for trainees receiving the intervention; however, patient and family assessments failed to demonstrate improvement. This article reports findings from trainees' self-assessments. Aim: To examine whether Codetalk resulted in improved self-assessed communication competence by trainees. Design: Trainees were recruited from the University of Washington and the Medical University of South Carolina. Internal medicine residents, medicine subspecialty fellows, nurse practitioner students, or community-based advanced practice nurses were randomized to Codetalk, a simulation-based workshop, or usual education. The outcome measure was self-assessed competence discussing palliative care needs with patients and was assessed at the start and end of the academic year. We used robust linear regression models to predict self-assessed competency, both as a latent construct and as individual indicators, including randomization status and baseline self-assessed competency. Results: We randomized 472 trainees to the intervention (n = 232) or usual education (n = 240). The intervention was associated with an improvement in trainee's overall self-assessment of competence in communication skills (P <.001). The intervention was also associated with an improvement in trainee self-assessments of 3 of the 4 skill-specific indicators—expressing empathy, discussing spiritual issues, and eliciting goals of care. Conclusion: Simulation-based communication training was associated with improved self-assessed competency in overall and specific communication skills in this randomized trial. Further research is needed to fully understand the importance and limitations of self-assessed competence in relation to other outcomes of improved communication skill. © 2016, © The Author(s) 2016.

Brown, W. J., Wilkerson, A. K., Boyd, S. J., Dewey, D., Mesa, F., & Bunnell, B. E. (2017). **A review of sleep disturbance in children and adolescents with anxiety**. *J Sleep Res*. doi:10.1111/jsr.12635

The present review examines the relations between sleep disturbance and anxiety in children and adolescents. The review begins with a detailed discussion of normative developmental trends in sleep, and the relation between sleep quality and emotion dysregulation in children. The extant literature on sleep disturbance in

clinically anxious children with a focus on subjective versus objective measures of sleep is then summarized in detail. Finally, a review of the reciprocal relationship between sleep and emotion regulation is provided. The available research suggests that sleep disturbance is quite prevalent in children with anxiety disorders, although the directionality of the association between sleep disturbance and anxiety in children remains unclear. Despite this limitation, a reciprocal relationship between sleep quality and anxiety appears to be well established. Research using objective measures of sleep quality (e.g. polysomnography, sleep actigraphy, sleep bruxism) is warranted to better understand this relation. Further, complicating factors such as the environment in which sleep quality is measured, the developmental stage of participants, varying severity of anxiety and the timeframe during which assessment takes place should all be considered when examining sleep disturbance in this population.

Burwitz, B. J., Wettengel, J. M., Muck-Hausl, M. A., Ringelhan, M., Ko, C., Festag, M. M., . . . Sacha, J. B. (2017). **Hepatocytic expression of human sodium-taurocholate cotransporting polypeptide enables hepatitis B virus infection of macaques**. *Nat Commun, 8*(1), 2146. doi:10.1038/s41467-017-01953-y

Hepatitis B virus (HBV) is a major global health concern, and the development of curative therapeutics is urgently needed. Such efforts are impeded by the lack of a physiologically relevant, pre-clinical animal model of HBV infection. Here, we report that expression of the HBV entry receptor, human sodium-taurocholate cotransporting polypeptide (hNTCP), on macaque primary hepatocytes facilitates HBV infection in vitro, where all replicative intermediates including covalently closed circular DNA (cccDNA) are present. Furthermore, viral vector-mediated expression of hNTCP on hepatocytes in vivo renders rhesus macaques permissive to HBV infection. These in vivo macaque HBV infections are characterized by longitudinal HBV DNA in serum, and detection of HBV DNA, RNA, and HBV core antigen (HBcAg) in hepatocytes. Together, these results show that expressing hNTCP on macaque hepatocytes renders them susceptible to HBV infection, thereby establishing a physiologically relevant model of HBV infection to study immune clearance and test therapeutic and curative approaches.

Butler, M., Drum, E., Evans, F. M., Fitzgerald, T., Fraser, J., Holterman, A. X., . . . Yudkowitz, F. S. (2017). **Guidelines and checklists for short-term missions in global pediatric surgery: Recommendations from the American Academy of Pediatrics Delivery of Surgical Care Global Health Subcommittee, American Pediatric Surgical Association Global Pediatric Surgery Committee, Society for Pediatric Anesthesia Committee on International Education and Service, and American Pediatric Surgical Nurses Association, Inc. Global Health Special Interest Group**. *J Pediatr Surg*. doi:10.1016/j.jpedsurg.2017.11.037

INTRODUCTION: Pediatric surgeons, anesthesia providers, and nurses from North America and other high-income countries (HICs) are increasingly engaged in resource-limited areas, with short-term missions (STMs) as the most common form of involvement. However, consensus recommendations currently do not exist for STMs in pediatric general surgery and associated perioperative care. METHODS: The American Academy of Pediatrics (AAP) Delivery of Surgical Care Subcommittee and American Pediatric Surgical Association (APSA) Global Pediatric Surgery Committee, with the American Pediatric Surgical Nurses Association, Inc. (APSNA) Global Health Special Interest Group, and the Society for Pediatric Anesthesia (SPA) Committee on International Education and Service generated consensus recommendations for STMs based on extensive experience with STMs. RESULTS: Three distinct, but related areas were identified: 1) Broad goals of surgical partnerships between HICs- and low and middle-income countries (LMICs). A previous set of guidelines published by the Global Paediatric Surgery Network Collaborative (GPSN), was endorsed by all groups; 2) Guidelines for the conduct of STMs were developed, including planning, in-country perioperative patient care, post-trip follow-up, and sustainability; 3) travel and safety considerations critical to STM success were enumerated. CONCLUSION: A diverse group of stakeholders developed these guidelines for STMs in LMICs. These guidelines may be a useful tool to ensure safe, responsible, and ethical STMs given increasing engagement of HIC providers in this work. LEVEL OF EVIDENCE: 5.

Caicedo, A., & Rosenfeld, R. (2017). **Challenges and future for the delivery of growth hormone therapy**. *Growth Hormone and IGF Research*. doi:10.1016/j.ghir.2017.12.008

Growth hormone (GH) has multiple roles in sustaining human development and homeostasis. Its pulsatile secretion stimulates growth and contributes to an equilibrium in a process tightly regulated and coordinated by many organs. GH deficiency is a medical condition affecting all ages, with not only significant consequences in the health of the patient but also impact on the quality of life. This review gathers the different strategies used today with a glance at future technologies to treat GH deficiency. We present key aspects for consideration when developing new methods to deliver GH, mimicking or replacing its pulsatile activity. Today and in the future, the fusion of biochemistry, biology and nanotechnology will provide hybrid devices using microfluidic systems. But, until new technologies for GH delivery will become available, current methods must be reinforced in conjunction with the development of better communication strategies between the health system and patients. Treating GH deficiency represents a multidisciplinary effort for which this review provides a glance at potential future directions for this therapy.

Carlin, D. E., Paull, E. O., Graim, K., Wong, C. K., Bivol, A., Ryabinin, P., . . . Stuart, J. M. (2017). **Prophetic Granger Causality to infer gene regulatory networks**. *PLoS ONE, 12*(12), e0170340. doi:10.1371/journal.pone.0170340

We introduce a novel method called Prophetic Granger Causality (PGC) for inferring gene regulatory networks (GRNs) from protein-level time series data. The method uses an L1-penalized regression adaptation of Granger Causality to model protein levels as a function of time, stimuli, and other perturbations. When combined with a data-independent network prior, the framework outperformed all other methods submitted to the HPN-DREAM 8 breast cancer network inference challenge. Our investigations reveal that PGC provides complementary information to other approaches, raising the performance of ensemble learners, while on its own achieves moderate performance. Thus, PGC serves as a valuable new tool in the bioinformatics toolkit for analyzing temporal datasets. We investigate the general and cell-specific interactions predicted by our method and find several novel interactions, demonstrating the utility of the approach in charting new tumor wiring.

Casanueva, F., Gerecci, D., & Cardemil, F. (2017). **Hemitransdomal versus Dome-Binding Suture**. *Facial Plastic Surgery*. doi:10.1055/s-0036-1598014

The dome-binding suture (DBS) and hemitransdomal suture (HTS) are suture techniques used to narrow and define the nasal tip. The DBS can create a pinched, unnatural appearance, while the HTS puts the lateral crus in a more favorable orientation. This allows a natural contour between the nasal tip and alar lobule while maintaining alar margin support. Objective measurement of the rotational axis of the lateral crus between the DBS and the HTS has not been reported in the literature. To determine whether the DBS or HTS technique results in a more favorable rotational axis of the lateral crus as measured by the alar surface septal angle (ASSA). Open rhinoplasty with cephalic trim and placement of a DBS or HTS was performed in 6 cadaveric heads, for a total of 12 lower lateral cartilages at the VirtuOHSU Simulation and Surgical Training Center at Oregon Health and Science University (OHSU). ASSA measurements were taken at baseline and after placement of either a DBS or HTS. A total of 36 ASSA measurements were obtained. The median baseline ASSA prior to suture placement was 142 degrees (interquartile range [IQR]: 131.5-145 degrees), following DBS placement was 141 degrees (IQR: 33-150.5 degrees), and following HTS placement was 112 degrees (IQR: 108-117 degrees). There was no statistically significant difference of ASSA measurements between baseline and DBS placement ($p = 0.24$), but there was a statistically significant difference between baseline and HTS ($p < 0.0001$) and between DBS and HTS ($p < 0.0001$). The HTS technique creates a more favorable rotational axis of the lateral crus as compared with the DBS, as measured by the ASSA. This study provides objective data to support the use of the HTS for nasal tip contouring.

Cascio, M. J., & Jen, K. Y. (2018). **Cocaine/levamisole-associated autoimmune syndrome: a disease of neutrophil-mediated autoimmunity**. *Current Opinion in Hematology, 25*(1), 29-36. doi:10.1097/moh.0000000000000393

PURPOSE OF REVIEW: Levamisole was previously used for its immunomodulatory properties to treat rheumatoid arthritis and some cancers. However, because of serious side-effects, it was taken off the market in the United States. Recently, levamisole has reemerged as a popular cocaine adulterant. Some individuals who consume levamisole-adulterated cocaine can develop a life-threatening autoimmune syndrome. In this review, the medical consequences of levamisole exposure and postulated mechanisms by which levamisole induces these adverse effects are discussed. RECENT FINDINGS: Although agranulocytosis and cutaneous vasculitis are the major findings in patients who develop cocaine/levamisole-associated autoimmune syndrome (CLAAS), more recent experience indicates that other organ systems can be involved as well. Current studies point to neutrophil activation and neutrophil extracellular trap formation with subsequent antineutrophil cytoplasmic antibody-mediated tissue injury as a possible mechanism of CLAAS. SUMMARY: In the past decade, the detrimental effects of levamisole have reemerged because of its popularity as a cocaine adulterant. Although infrequent, some individuals develop a systemic autoimmune syndrome characterized by immune-mediated agranulocytosis and antineutrophil cytoplasmic antibody-mediated vasculitis. Mechanistically, neutrophil antigens appear to be a major player in inducing CLAAS. Prompt cessation of levamisole exposure is key to treatment, although relapses are frequent because of the addictive effects of cocaine and the high prevalence of levamisole within the cocaine supply.

Casulo, C., Friedberg, J. W., Ahn, K. W., Flowers, C., DiGilio, A., Smith, S. M., . . . Hamadani, M. (2017). **Autologous Transplantation in Follicular Lymphoma with Early Therapy Failure: a NLCS and CIBMTR Analysis**. *Biol Blood Marrow Transplant*. doi:10.1016/j.bbmt.2017.12.771

Patients with follicular lymphoma (FL) experiencing early therapy failure (ETF) within two years of frontline chemoimmunotherapy have poor overall survival (OS). We analyzed data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National LymphoCare Study (NLCS) to determine whether autologous hematopoietic cell transplant (autoHCT) can improve outcomes in this high-risk FL subgroup.ETF was defined as failure to achieve at least partial response after frontline chemoimmunotherapy or lymphoma progression within two years of frontline chemoimmunotherapy. We identified two groups: the non-autoHCT cohort (patients from the NLCS with ETF not undergoing autoHCT); and the autoHCT cohort (CIBMTR patients with ETF undergoing autoHCT). All patients received rituximab-based chemotherapy as frontline treatment. 174 non-autoHCT patients and 175 autoHCT patients were identified and analyzed. There was no difference in five year OS between the two groups (60% vs 67% respectively; p=0.16). A planned subgroup analysis showed that patients with ETF receiving autoHCT soon after treatment failure (</=1year of ETF; n=123) had higher five year OS than those without autoHCT (73% vs 60%, p=0.05). On multivariate analysis, early use of autoHCT was associated with significantly reduced mortality (HR=0.63, 95%CI:0.42-0.94, p=0.02). Patients with FL experiencing ETF after frontline chemoimmunotherapy lack optimal therapy. We demonstrate improved OS when receiving autoHCT within one year of treatment failure. Results from this unique collaboration between the NLCS and CIBMTR support consideration of early consolidation with autoHCT in select FL patients experiencing ETF.

Caughey, A. B. (2017). **Prepregnancy obesity and severe maternal morbidity: What can be done?** *JAMA - Journal of the American Medical Association, 318*(18), 1765-1766. doi:10.1001/jama.2017.16189

Cefalu, W. T., Kaul, S., Gerstein, H. C., Holman, R. R., Zinman, B., Skyler, J. S., . . . Riddle, M. C. (2018). **Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum**. *Diabetes Care, 41*(1), 14-31. doi:10.2337/dci17-0057

In December 2008, the U.S. Food and Drug Administration issued guidance to the pharmaceutical industry setting new expectations for the development of antidiabetes drugs for type 2 diabetes. This guidance expanded the scope and cost of research necessary for approval of such drugs by mandating long-term cardiovascular outcomes trials (CVOTs) for safety. Since 2008, 9 CVOTs have been reported, 13 are under way, and 4 have been terminated. Reassuringly, each of the completed trials demonstrated the noninferiority of their respective drugs to placebo for their primary cardiovascular (CV) composite end point. Notably, four additionally provided evidence of CV benefit in the form of significant decreases in the primary CV composite end point, two suggested reductions in CV death, and three suggested reductions in all-cause mortality. Although these trials have yielded much valuable information, whether that information justifies the investment of time and resources is controversial. In June 2016, a Diabetes Care Editors' Expert Forum convened to review the processes and challenges of CVOTs, discuss the benefits and limitations of their current designs, and weigh the merits of modifications that might improve the efficiency and clinical value of future trials. Discussion and analysis continued with the CVOT trial results released in June 2017 at the American Diabetes Association's Scientific Sessions and in September 2017 at the European Association for the Study of Diabetes scientific meeting. This article summarizes the discussion and findings to date.

Chandler, C. H., Chari, S., Kowalski, A., Choi, L., Tack, D., DeNieu, M., . . . Dworkin, I. (2017). **How well do you know your mutation? Complex effects of genetic background on expressivity, complementation, and ordering of allelic effects**. *PLoS Genetics, 13*(11). doi:10.1371/journal.pgen.1007075

For a given gene, different mutations influence organismal phenotypes to varying degrees. However, the expressivity of these variants not only depends on the DNA lesion associated with the mutation, but also on factors including the genetic background and rearing environment. The degree to which these factors influence related alleles, genes, or pathways similarly, and whether similar developmental mechanisms underlie variation in the expressivity of a single allele across conditions and among alleles is poorly understood. Besides their fundamental biological significance, these questions have important implications for the interpretation of functional genetic analyses, for example, if these factors alter the ordering of allelic series or patterns of complementation. We examined the impact of genetic background and rearing environment for a series of mutations spanning the range of phenotypic effects for both the scalloped and vestigial genes, which influence wing development in Drosophila melanogaster. Genetic background and rearing environment influenced the phenotypic outcome of mutations, including intra-genic interactions, particularly for mutations of moderate expressivity. We examined whether cellular correlates (such as cell proliferation during development) of these phenotypic effects matched the observed phenotypic outcome. While cell proliferation decreased with mutations of increasingly severe effects, surprisingly it did not co-vary strongly with the degree of background dependence. We discuss these findings and propose a phenomenological model to aid in understanding the biology of genes, and how this influences our interpretation of allelic effects in genetic analysis.

Chang, J. S., Sorensen, J. L., Masson, C. L., Shopshire, M. S., Hoffman, K., McCarty, D., & Iguchi, M. (2017). **Structural factors affecting Asians and Pacific Islanders in community-based substance use treatment: Treatment provider perspectives**. *Journal of Ethnicity in Substance Abuse, 16*(4), 479-494. doi:10.1080/15332640.2017.1395384

Asians and Pacific Islanders (API) have large disparities in utilization of substance use treatment compared to other racial groups. In this study, we analyzed factors that shape API experiences accessing and engaging in community-based treatment from the perspective of treatment providers. We conducted semi-structured interviews with 40 treatment providers who work with API clients in treatment programs in San Francisco and Los Angeles. We analyzed the transcribed interview data in ATLAS.ti using a content analysis approach. There were three main findings. First, treatment providers found the API category itself is too broad and heterogeneous to meaningfully explain substance use patterns. Second, beyond race/ethnicity, structural factors such as poverty, neighborhood, housing, and age had an impact on API substance use. Third, factors

such as family, immigration status, religion, language, stigma played complex roles in API treatment experiences, contingent on how client, programs, and providers attended to differences in these categories.

Chang, R., Fox, E. E., Greene, T. J., Swartz, M. D., DeSantis, S. M., Stein, D. M., . . . Holcomb, J. B. (2017). **Abnormalities of laboratory coagulation tests versus clinically evident coagulopathic bleeding: results from the prehospital resuscitation on helicopters study (PROHS)**. *Surgery*. doi:10.1016/j.surg.2017.10.050

BACKGROUND: Laboratory-based evidence of coagulopathy (LC) is observed in 25-35% of trauma patients, but clinically-evident coagulopathy (CC) is not well described. METHODS: Prospective observational study of adult trauma patients transported by helicopter from the scene to nine Level 1 trauma centers in 2015. Patients meeting predefined highest-risk criteria were divided into CC+ (predefined as surgeon-confirmed bleeding from uninjured sites or injured sites not controllable by sutures) or CC-. We used a mixed-effects, Poisson regression with robust error variance to test the hypothesis that abnormalities on rapid thrombelastography (r-TEG) and international normalized ratio (INR) were independently associated with CC+. RESULTS: Of 1,019 highest-risk patients, CC+ (n=41, 4%) were more severely injured (median ISS 32 vs 17), had evidence of LC on r-TEG and INR, received more transfused blood products at 4 hours (37 vs 0 units), and had greater 30-day mortality (59% vs 12%) than CC- (n=978, 96%). The overall incidence of LC was 39%. 30-day mortality was 22% vs 9% in those with and without LC. In two separate models, r-TEG K-time >2.5 min (RR 1.3, 95% CI 1.1-1.7), r-TEG mA <55 mm (RR 2.5, 95% CI 2.0-3.2), platelet count <150 x 10(9)/L (RR 1.2, 95% CI 1.1-1.3), and INR >1.5 (RR 5.4, 95% CI 1.8-16.3) were independently associated with CC+. A combined regression model was not generated because too few patients underwent both r-TEG and INR. CONCLUSION: CC was rare compared to LC. CC was associated with poor outcomes and impairment of both clotting factor and platelet-mediated coagulation components. (Surgery 2017;160:XXX-XXX.).

Chen, A. I., Leonard, J. T., Okada, C. Y., Gay, N. D., Chansky, K., Fan, G., . . . Maziarz, R. T. (2017). **Outcomes of DA-EPOCH-R induction plus autologous transplant consolidation for double hit lymphoma**. *Leukemia and Lymphoma*, 1-6. doi:10.1080/10428194.2017.1406085

High-grade B cell lymphoma with MYC and BCL2 rearrangements (double hit) has a poor prognosis with standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). We report here a treatment algorithm of DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) followed by BEAM (carmustine, etoposide, cytarabine, melphalan) autologous transplant in 36 cases of previously untreated double hit lymphoma (DHL) from 2010 to 2015. A high risk International Prognostic Index (IPI) was present in 42% of cases. At median follow-up of 38 months, the 2-year progression free survival (PFS) and overall survival (OS) were 69% (95% CI 54-84%) and 71% (95% CI 56-86%). Eight cases were refractory to induction with 1-year OS 20%, and no factors were predictive for primary refractory disease. Of 28 responders, 17 proceeded to transplant while 11 were observed, primarily due to age and co-morbidities. By 24-week landmark analysis after diagnosis, the 2-year PFS and OS were both 94% (95% CI 83-100%) vs 79% (95% CI 52-100%) for transplant vs observation (p = .59 for both PFS and OS). There was no significant benefit to consolidative transplant in our series, and primary refractory DHL needs novel approaches.

Chen, E. Y., & Prasad, V. (2017). **Crossover is not associated with faster trial accrual**. *Annals of Oncology*. doi:10.1093/annonc/mdx793

Chen, G., Lu, H. D., Tanigawa, H., & Roe, A. W. (2017). **Solving visual correspondence between the two eyes via domain-based population encoding in nonhuman primates**. *Proc Natl Acad Sci U S A, 114*(49), 13024-13029. doi:10.1073/pnas.1614452114

Stereoscopic vision depends on correct matching of corresponding features between the two eyes. It is unclear where the brain solves this binocular correspondence problem. Although our visual system is able to make correct global matches, there are many possible false matches between any two images. Here, we use optical imaging data of binocular disparity response in the visual cortex of awake and anesthetized monkeys to demonstrate that the second visual cortical area (V2) is the first cortical stage that correctly discards false matches and robustly encodes correct matches. Our findings indicate that a key transformation for achieving depth perception lies in early stages of extrastriate visual cortex and is achieved by population coding.

Chiarotto, A., Boers, M., Deyo, R. A., Buchbinder, R., Corbin, T. P., Costa, L. O. P., . . . Ostelo, R. W. (2017). **Core outcome measurement instruments for clinical trials in non-specific low back pain**. *Pain*. doi:10.1097/j.pain.0000000000001117

To standardize outcome reporting in clinical trials of patients with non-specific low back pain (LBP), an international multidisciplinary panel recommended physical functioning, pain intensity, and health-related quality of life (HRQoL) as core outcome domains. Given the lack of consensus on measurement instruments for these three domains in patients with LBP, this study aimed to generate such consensus. The measurement properties of 17 patient-reported outcome measures for physical functioning, three for pain intensity, and five for HRQoL were appraised in three systematic reviews following COSMIN methodology. Researchers, clinicians and patients (n = 207) were invited in a two-round Delphi survey to generate consensus (>/= 67% agreement among participants) on which instruments to endorse. Response rates were 44% and 41%, respectively. In Round 1, consensus was achieved on the Oswestry Disability Index version 2.1a (ODI 2.1a) for physical functioning (78% agreement) and the Numeric Rating Scale (NRS) for pain intensity (75% agreement). No consensus was achieved on any HRQoL instrument, although the Short Form 12 (SF12) approached the consensus threshold (64% agreement). In Round 2, consensus was reached on a NRS version with a 1-week recall period (96% agreement). Various participants requested one free-to-use instrument per domain. Considering all issues together, recommendations on core instruments were formulated: ODI 2.1a or 24-item Roland-Morris Disability Questionnaire for physical functioning, NRS for pain intensity, SF12 or 10-item PROMIS Global Health form for HRQoL. Further studies need to fill the evidence gaps on the measurement properties of these and other instruments.

Child, S. J., Hickson, S. E., Bayer, A., Malouli, D., Fruh, K., & Geballe, A. P. (2017). **Antagonism of the protein kinase R pathway in human cells by rhesus cytomegalovirus**. *J Virol*. doi:10.1128/jvi.01793-17

While cytomegalovirus (CMV) infections are often limited in host range by lengthy coevolution with a singular host species, a few CMVs are known to deviate from this rule. For example, rhesus macaque CMV (RhCMV), a model for human CMV (HCMV) pathogenesis and vaccine development, can replicate in human cells, as well as in rhesus cells. Both HCMV and RhCMV encode species-specific antagonists of the broadly acting host cell restriction factor protein kinase R (PKR). Although the RhCMV antagonist of PKR, rTRS1, has very limited activity against human PKR, here we show it is essential for RhCMV replication in human cells because it prevents human PKR from phosphorylating the translation initiation factor eIF2alpha, thereby allowing continued translation and viral replication. Although rTRS1 is necessary for RhCMV replication, it is not sufficient to rescue replication of HCMV lacking its own PKR antagonists in human fibroblasts. However, overexpression of rTRS1 in human fibroblasts enabled HCMV expressing rTRS1 to replicate, indicating that elevated levels or early expression of a weak antagonist can counteract a resistant restriction factor like human PKR. Exploring potential mechanisms that might allow RhCMV to replicate in human cells revealed that RhCMV makes no less double-stranded RNA than HCMV. Rather, in human cells, RhCMV expresses rTRS1 at levels 2-3 times higher than those of the HCMV-encoded PKR antagonists during HCMV infection. These data suggest that even a modest increase in expression of this weak PKR antagonist is sufficient to enable RhCMV replication in human cells.IMPORTANCE Rhesus macaque cytomegalovirus (RhCMV) offers a valuable model for studying congenital human cytomegalovirus (HCMV) pathogenesis and vaccine development. Therefore, it is critical to understand variations in how each virus infects and affects its host species to be able to apply insights gained from the RhCMV model to HCMV. While HCMV is only capable of

infecting cells from humans and very closely related species, RhCMV displays a wider host range, including human as well as rhesus cells. RhCMV expresses an antagonist of a broadly acting antiviral factor present in all mammalian cells, and its ability to counter both the rhesus and human versions of this host factor is a key component of RhCMV's ability to cross species barriers. Here we examine the molecular mechanisms that allow this RhCMV antagonist to function against a human restriction factor.

Chiu, A. W., & Hinson, H. E. (2017). **Future Directions for Hypothermia following Severe Traumatic Brian Injury**. *Semin Respir Crit Care Med, 38*(6), 768-774. doi:10.1055/s-0037-1607989

Traumatic brain injury (TBI) is a serious health care problem on both individual and public health levels. As a major cause of death and disability in the United States, it is associated with a significant economic and public health burden. Although the evidence to support the use of induced hypothermia on neurologic outcome after cardiac arrest is well established, its use in treating TBI remains controversial. Hypothermia has the potential to mitigate some of the destructive processes that occur as part of secondary brain injury after TBI. Hypothermia can be helpful in lowering intracranial pressure, for example, but its influence on functional outcome is unclear. There is insufficient evidence to support the broad use of prophylactic hypothermia for neuroprotection after TBI. Investigators are beginning to more carefully select patients for temperature modulating therapies, in a more personalized approach. Examples include targeting immunomodulation and scaling hypothermia to achieve metabolic targets. This review will summarize the clinical evidence for the use of hypothermia to limit secondary brain injury following acute TBI.

Chou, R., Korthuis, P. T., McCarty, D., Coffin, P. O., Griffin, J. C., Davis-O'Reilly, C., . . . Daya, M. (2017). **Management of Suspected Opioid Overdose With Naloxone in Out-of-Hospital Settings: A Systematic Review**. *Ann Intern Med, 167*(12), 867-875. doi:10.7326/m17-2224

Background: Naloxone is effective for reversing opioid overdose, but optimal strategies for out-of-hospital use are uncertain. Purpose: To synthesize evidence on 1) the effects of naloxone route of administration and dosing for suspected opioid overdose in out-of-hospital settings on mortality, reversal of overdose, and harms, and 2) the need for transport to a health care facility after reversal of overdose with naloxone. Data Sources: Ovid MEDLINE (1946 through September 2017), PsycINFO, Cochrane Central Register of Controlled Trials, CINAHL, U.S. Food and Drug Administration (FDA) materials, and reference lists. Study Selection: English-language cohort studies and randomized trials that compared different doses of naloxone, administration routes, or transport versus nontransport after reversal of overdose with naloxone. Main outcomes were mortality, reversal of overdose, recurrence of overdose, and harms. Data Extraction: Dual extraction and quality assessment of individual studies; consensus assessment of overall strength of evidence (SOE). Data Synthesis: Of 13 eligible studies, 3 randomized controlled trials and 4 cohort studies compared different administration routes. At the same dose (2 mg), 1 trial found similar efficacy between higher-concentration intranasal naloxone (2 mg/mL) and intramuscular naloxone, and 1 trial found that lower-concentration intranasal naloxone (2 mg/5 mL) was less effective than intramuscular naloxone but was associated with decreased risk for agitation (low SOE). Evidence was insufficient to evaluate other comparisons of route of administration. Six uncontrolled studies reported low rates of death and serious adverse events (0% to 1.25%) in nontransported patients after successful naloxone treatment. Limitation: There were few studies, all had methodological limitations, and none evaluated FDA-approved autoinjectors or highly concentrated intranasal formulations. Conclusion: Higher-concentration intranasal naloxone (2 mg/mL) seems to have efficacy similar to that of intramuscular naloxone for reversal of opioid overdose, with no difference in adverse events. Nontransport after reversal of overdose with naloxone seems to be associated with a low rate of serious harms, but no study evaluated risks of transport versus nontransport. Primary Funding Source: Agency for Healthcare Research and Quality. (PROSPERO: CRD42016053891).

Christy, A., Murchison, C., & Wilson, J. L. (2017). **Quick Brain Magnetic Resonance Imaging With Diffusion-Weighted Imaging as a First Imaging Modality in Pediatric Stroke**. *Pediatric Neurology*. doi:10.1016/j.pediatrneurol.2017.09.020

Background: Diagnostic delay hinders management of pediatric arterial ischemic stroke. Quick brain MRI with diffusion-weighted imaging sequences may provide a rapid diagnosis without the ionizing radiation of a computed tomography (CT) scan. Methods: This was a single center retrospective chart review of children one month to 18 years old with acute arterial ischemic stroke hospitalized between January 2010 and January 2017. We evaluated sensitivity and the time to diagnostic study based on the first imaging study (CT or quick brain MRI with diffusion-weighted imaging). Results: Twenty-five patients were included. Eleven patients (44%) were initially assessed with CT, 10 (40%) with quick brain MRI with diffusion-weighted imaging, and four (16%) with a full MRI. Compared with children undergoing CT, children with quick brain MRI with diffusion-weighted imaging as first study were younger (5.8 vs 14.1 years, P < 0.001) and were more likely to be hospitalized at stroke onset (70% vs 18.2%, P = 0.03). Quick brain MRI with diffusion-weighted imaging was more sensitive for ischemia than CT (100% vs. 27.3%). The median time from presentation to diagnostic imaging was 4.3 hours, with no differences between CT and quick brain MRI with diffusion-weighted imaging groups, although the quick brain MRI with diffusion-weighted imaging group had a shorter median time from first imaging to diagnostic imaging (P = 0.002). There were no significant missed findings on quick brain MRI with diffusion-weighted imaging. Conclusions: Quick brain MRI with diffusion-weighted imaging was more sensitive than CT for detecting ischemia and may be considered as the first study for some children presenting with suspected arterial ischemic stroke.

Chua, V. S., Esquivel, J. Z., Paul, A. S., Techathamnukool, T., Fajardo, C. F., Jain, N., . . . Iyer, R. (2017). **Visual IoT: Ultra-Low-Power Processing Architectures and Implications**. *IEEE Micro, 37*(6), 52-61. doi:10.1109/MM.2017.4241343

Visual IoT is a rapidly growing usage based on rich visual sensing, processing, and analytics. One approach for addressing visual IoT challenges is to move some computation closer to the edge device where data is captured. This article begins with a description of three key implications in ultra-low-power visual edge processing: the data footprint is constrained due to SRAM power, the available power-efficient computation is limited, and the ability to process large-scale data is challenging. To explore suitable approaches, the authors review three case studies: small-scale visual recognition for digits and characters, medium-scale visual recognition for hand gestures, and large-scale visual processing requiring video summarization. They show that co-designing algorithms and architectures for ultra-low-power processing in edge devices helps address the key challenges.

Ciporen, J., Gillham, H., Noles, M., Dillman, D., Baskerville, M., Haley, C., . . . Lucke-Wold, B. P. (2018). **Crisis Management Simulation: Establishing a Dual Neurosurgery and Anesthesia Training Experience**. *J Neurosurg Anesthesiol, 30*(1), 65-70. doi:10.1097/ana.0000000000000401

BACKGROUND: Simulation training has been shown to be an effective teaching tool. Learner management of an intraoperative crisis such as a major cerebrovascular bleed requires effective teamwork, communication, and implementation of key skill sets at appropriate time points. This study establishes a first of a kind simulation experience in a neurosurgery/anesthesia resident (learners) team working together to manage an intraoperative crisis. METHODS: Using a cadaveric cavernous carotid injury perfusion model, 7 neurosurgery and 6 anesthesia learners, were trained on appropriate vascular injury management using an endonasal endoscopic technique. Learners were evaluated on communication skills, crisis management algorithms, and implementation of appropriate skill sets at the right time. A preanatomic and postanatomic examination and postsimulation survey was administered to neurosurgery learners. Anesthesia learners provided posttraining evaluation through a tailored realism and teaching survey. RESULTS: Neurosurgery learners' anatomic examination score improved from presimulation (33.89%) to postsimulation (86.11%). No significant difference between learner specialties was observed for situation awareness, decision making,

communications and teamwork, or leadership evaluations. Learners reported the simulation realistic, beneficial, and highly instructive. CONCLUSIONS: Realistic, first of kind, clinical simulation scenarios were presented to a neurosurgery/anesthesia resident team who worked together to manage an intraoperative crisis. Learners were effectively trained on crisis management, the importance of communication, and how to develop algorithms for future implementation in difficult scenarios. Learners were highly satisfied with the simulation training experience and requested that it be integrated more consistently into their residency training programs.

Clauw, D. J., D'Arcy, Y., Gebke, K., Semel, D., Pauer, L., & Jones, K. D. (2018). **Normalizing fibromyalgia as a chronic illness**. *Postgrad Med, 130*(1), 9-18. doi:10.1080/00325481.2018.1411743

Fibromyalgia (FM) is a complex chronic disease that affects 3-10% of the general adult population and is principally characterized by widespread pain, and is often associated with disrupted sleep, fatigue, and comorbidities, among other symptoms. There are many gaps in our knowledge of FM, such that, compared with other chronic illnesses including diabetes, rheumatoid arthritis, and asthma, it is far behind in terms of provider understanding and therapeutic approaches. The experience that healthcare professionals (HCPs) historically gained in developing approaches to manage and treat patients with these chronic illnesses may help show how they can address similar problems in patients with FM. In this review, we examine some of the issues around the management and treatment of FM, and discuss how HCPs can implement appropriate strategies for the benefit of patients with FM. These issues include understanding that FM is a legitimate condition, the benefits of prompt diagnosis, use of non-drug and pharmacotherapies, patient and HCP education, watchful waiting, and assessing patients by FM domain so as not to focus exclusively on one symptom to the detriment of others. Developing successful approaches is of particular importance for HCPs in the primary care setting who are in the ideal position to provide long-term care for patients with FM. In this way, FM may be normalized as a chronic illness to the benefit of both patients and HCPs.

Coghlan, R. F., Oberdorf, J. A., Sienko, S., Aiona, M. D., Boston, B. A., Connelly, K. J., . . . Horton, W. A. (2017). **A degradation fragment of type X collagen is a real-time marker for bone growth velocity**. *Sci Transl Med, 9*(419). doi:10.1126/scitranslmed.aan4669

Despite its importance as a key parameter of child health and development, growth velocity is difficult to determine in real time because skeletal growth is slow and clinical tools to accurately detect very small increments of growth do not exist. We report discovery of a marker for skeletal growth in infants and children. The intact trimeric noncollagenous 1 (NC1) domain of type X collagen, the marker we designated as CXM for Collagen X Marker, is a degradation by-product of endochondral ossification that is released into the circulation in proportion to overall growth plate activity. This marker corresponds to the rate of linear bone growth at time of measurement. Serum concentrations of CXM plotted against age show a pattern similar to well-established height growth velocity curves and correlate with height growth velocity calculated from incremental height measurements in this study. The CXM marker is stable once collected and can be accurately assayed in serum, plasma, and dried blood spots. CXM testing may be useful for monitoring growth in the pediatric population, especially responses of infants and children with genetic and acquired growth disorders to interventions that target the underlying growth disturbances. The utility of CXM may potentially extend to managing other conditions such as fracture healing, scoliosis, arthritis, or cancer.

Cohen, T., Roberts, K., Gururaj, A. E., Chen, X., Pournejati, S., Alter, G., . . . Xu, H. (2017). **A publicly available benchmark for biomedical dataset retrieval: the reference standard for the 2016 bioCADDIE dataset retrieval challenge**. *Database: The Journal of Biological Databases and Curation, 2017*. doi:10.1093/database/bax061

Database URL: https://biocaddie.org/benchmark-data.

Collins, S. L., Chantraine, F., Morgan, T. K., & Jauniaux, E. (2017). **Abnormally adherent and invasive placenta: A spectrum disorder in need of a name**. *Ultrasound in Obstetrics and Gynecology*. doi:10.1002/uog.18982

There is little doubt that the worldwide Cesarean delivery epidemic has led to an increased incidence of abnormally adherent and invasive placentation. The significant impact that this disorder has on maternal morbidity and mortality has led to a flurry of publications in the literature concerning all aspects of the condition. These papers have arisen from many sources, notably pathologists, epidemiologists, obstetricians and radiologists.

Cooper-Vince, C. E., Kakuhikire, B., Vorechovska, D., McDonough, A. Q., Perkins, J., Venkataramani, A. S., . . . Tsai, A. C. (2017). **Household water insecurity, missed schooling, and the mediating role of caregiver depression in rural Uganda**. *Glob Ment Health (Camb), 4*, e15. doi:10.1017/gmh.2017.14

Background: School attendance rates in sub-Saharan Africa are among the lowest worldwide, placing children at heightened risk for poor educational and economic outcomes. One understudied risk factor for missed schooling is household water insecurity, which is linked to depression among women and may increase children's water-fetching burden at the expense of educational activities, particularly among children of depressed caregivers. In this study conducted in rural Uganda, we assessed the association between household water insecurity and child school participation and the mediating pathways behind these associations. Method: We conducted a population-based, cross-sectional study of female household heads (N = 257) and their children ages 5-17 (N = 551) in the rural regions surrounding the town of Mbarara, in southwestern Uganda. We used multivariable linear regressions to estimate the association between water insecurity and missed schooling. We then assessed the extent to which the association was mediated by caregiver depression. Results: Among children, water insecurity had a statistically significant association with the number of missed school days (a standard deviation increase in water insecurity resulted in 0.30 more missed school days in the last week). The estimated association was partially mediated by caregiver depression. When stratified by sex, this mediating pathway remained significant for boys, but not among girls. Conclusions: Water insecurity is a risk factor for missed schooling among children in rural Uganda. Caregiver depression partially mediated this relationship. Also addressing caregiver mental health in water insecure families may more fully address the needs of sub-Saharan African families and promote educational participation among youth.

Copelan, A. Z., Kapoor, B. S., AbuRahma, A. F., Cain, T. R., Caplin, D. M., Farsad, K., . . . Lorenz, J. M. (2017). **ACR Appropriateness Criteria® Iliac Artery Occlusive Disease**. *Journal of the American College of Radiology, 14*(11), S530-S539. doi:10.1016/j.jacr.2017.08.039

Iliac artery occlusive disease can present as a sudden-onset acute thrombotic or thromboembolic event or as a chronic progressive atherosclerotic process that presents as claudication progressing to rest pain. Depending on the clinical presentation, the diagnosis is usually confirmed through Doppler vascular ultrasound, CT angiography, or MR angiography; the choice of imaging is usually based on modality availability and the presence of patient comorbidities such as chronic kidney disease. The Trans-Atlantic Inter-Society Consensus II classification system is commonly used to describe the extent of the peripheral vascular disease. Depending on the pathophysiology, clinical presentation, and radiologic extent of the disease process, therapeutic options for acute thrombotic cases can include supportive care, anticoagulation, thrombolytic therapy, surgical or catheter-directed mechanical thrombectomy, and surgical bypass. Therapeutic options for atherosclerotic disease include supportive measures such as behavior modification, a supervised exercise program, adjunctive treatment with anticoagulation and antiplatelet medications, angioplasty, stent placement, stent-graft placement, surgical or catheter-directed endarterectomy or plaque excision, and surgical bypass. This document describes the appropriateness of imaging in this patient population, treatment procedures for specific clinical scenarios, and the likely prognosis for these patients. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision

include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment. © 2017 American College of Radiology

Corbitt, H., Maslen, C., Prakash, S., Morris, S. A., & Silberbach, M. (2017). **Allometric considerations when assessing aortic aneurysms in Turner syndrome: Implications for activity recommendations and medical decision-making**. *Am J Med Genet A*. doi:10.1002/ajmg.a.38584

In Turner syndrome, the potential to form thoracic aortic aneurysms requires routine patient monitoring. However, the short stature that typically occurs complicates the assessment of severity and risk because the relationship of body size to aortic dimensions is different in Turner syndrome compared to the general population. Three allometric formula have been proposed to adjust aortic dimensions, all employing body surface area: aortic size index, Turner syndrome-specific Z-scores, and Z-scores based on a general pediatric and young adult population. In order to understand the differences between these formula we evaluated the relationship between age and aortic size index and compared Turner syndrome-specific Z-scores and pediatric/young adult based Z-scores in a group of girls and women with Turner syndrome. Our results suggest that the aortic size index is highly age-dependent for those under 15 years; and that Turner-specific Z-scores are significantly lower than Z-scores referenced to the general population. Higher Z-scores derived from the general reference population could result in stigmatization, inappropriate restriction from sports, and increasing the risk of unneeded medical or operative treatments. We propose that when estimating aortic dissection risk clinicians use Turner syndrome-specific Z-score for those under fifteen years of age.

Costantino, G., Falavigna, G., Solbiati, M., Casagranda, I., Sun, B. C., Grossman, S. A., . . . Ippoliti, R. (2017). **Neural networks as a tool to predict syncope risk in the Emergency Department**. *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology, 19*(11), 1891-1895. doi:10.1093/europace/euw336

The optimal disposition approach to patients presenting to an Emergency Department (ED) with syncope is unclear. Many low-risk patients with syncope are unnecessarily admitted to hospital. This may increase risk associated with hospitalization (including medication errors and hospital-acquired infections), and to an excessive use of resources.1 On the other hand, patients inappropriately discharged from the ED may experience serious adverse events or even death that may have been preventable with hospital-based interventions.2-4 This can partially explain the high heterogeneity in practice and hospitalization rate observed from multiple reports obtained from different countries.4,5 Despite many attempts to optimize ED syncope management, such as the use of structured management pathways and ED syncope observation units, a rigorous and effective approach remains elusive.6,7 Several syncope prediction tools have been developed to guide clinician decision-making in the ED.8-12 However, none has proved superior to clinical practice.5,6,13 Artificial neural networks (ANNs) are complex non-linear models inspired by the working of biological neural networks (i.e. the central nervous system). They are used to estimate complex functions (i.e. non-linear) that require a large number of inputs. Artificial neural networks are presented as systems of layers (multilayer) composed of neurons (also called perceptrons) which exchange messages between each other by synapsis (weights). The synapses have numeric weights that can be tuned based on experience, making neural nets adaptive to inputs and capable of learning. 14 As one of the major problems in syncope risk stratification is that syncope itself can be the final common presentation of several conditions which are very heterogeneous in terms of prognosis, the absence of linearity in such a context could make the application of ANNs appealing.15 The use of ANNs has already shown promising results in emergency medicine. For example, ANNs have been developed to reduce computed tomography imaging for suspected craniocervical junction injury in major head trauma patients.16 Artificial neural networks have also been used to predict risk ofmyocardial infarction in patients with chest pain.17 The aim of our study was to investigate the effectiveness of ANNs as a short-term risk stratification tool for syncope patients in the ED. © The Author 2016.

Coultas, D. B., Jackson, B. E., Russo, R., Peoples, J., Singh, K. P., Sloan, J., . . . Bae, S. (2017). **Home-Based Physical Activity Coaching, Physical Activity, and Healthcare Utilization in COPD: COPD-SMART Secondary Outcomes**. *Ann Am Thorac Soc*. doi:10.1513/AnnalsATS.201704-308OC

RATIONALE: Physical inactivity among patients with chronic obstructive pulmonary disease (COPD) is associated with exacerbations requiring high-cost healthcare utilization including urgent, emergent, and hospital care. OBJECTIVE: To examine the effectiveness of a behavioral lifestyle physical activity intervention combined with COPD self-management education to prevent high-cost healthcare utilization. METHODS: This was an analysis of secondary outcomes of the Chronic Obstructive Pulmonary Disease Self-Management Activation Research Trial, a two-arm randomized trial of stable adult outpatients with COPD recruited from primary care and pulmonary clinics. Following a six-week self-management education run-in period, participants were randomized to usual care or to a telephone-delivered home-based health coaching intervention over 20 weeks. Secondary outcomes of physical activity and healthcare utilization were determined by self-report at 6-, 12-, and 18-months after randomization. Associations between treatment allocation arm and these secondary outcomes were examined using log-binomial and Poisson regression models. RESULTS: A total of 325 outpatients with stable COPD were enrolled in the trial. The average age of 70.3 years (standard deviation 9.5), and 50.5% were female; 156 were randomized to usual care and 149 to the intervention. A greater proportion of participants reported being persistently active over the 18-month follow-up period in the intervention group (73.6%) compared to the usual care group (57.8%) (mean difference=15.8%, 95% confidence interval [CI] 4.0%-27.7%)). This association varied by severity of FEV1 impairment (p for interaction = 0.09). Those in the intervention group with moderate impairment(FEV1=50%-70% predicted), more frequently reported being persistently active compared to the usual care (86.0% vs. 65.1%, mean difference=20.9%, 95% CI 5.7%-36.1%). Patients with severe and very severe FEV1 impairment (FEV1 < 50% predicted) in the intervention group also reported being persistently active more frequently compared to usual care (63.3% vs. 50.8%, mean difference=12.6%, 95% CI -4.7-29.8). The intervention was associated with a lower rate of lung-related utilization (adjusted rate ratio = 0.38 [95% CI 0.23-0.63]) only among participants with severe spirometric impairment. CONCLUSION: Our results demonstrate that a feasible and generalizable home-based coaching intervention may decrease sedentary behavior and increase physical activity levels. In those with severe COPD, this intervention may reduce lung disease-related healthcare utilization. Clinical trial registered with Clinicaltrials.gov (NCT01108991).

Courcoulas, A. P., King, W. C., Belle, S. H., Berk, P., Flum, D. R., Garcia, L., . . . Yanovski, S. Z. (2017). **Seven-Year Weight Trajectories and Health Outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) Study**. *JAMA Surg*. doi:10.1001/jamasurg.2017.5025

Importance: More information is needed about the durability of weight loss and health improvements after bariatric surgical procedures. Objective: To examine long-term weight change and health status following Roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB). Design, Setting, and Participants: The Longitudinal Assessment of Bariatric Surgery (LABS) study is a multicenter observational cohort study at 10 US hospitals in 6 geographically diverse clinical centers. Adults undergoing bariatric surgical procedures as part of clinical care between 2006 and 2009 were recruited and followed up until January 31, 2015. Participants completed presurgery, 6-month, and annual research assessments for up to 7 years. Main Outcome and Measures: Percentage of weight change from baseline, diabetes, dyslipidemia, and hypertension, determined by physical measures, laboratory testing, and medication use. Results: Of 2348 participants, 1738 underwent RYGB (74%) and 610 underwent LAGB (26%). For RYBG, the median age was 45 years (range, 19-75 years), the median body mass index (calculated as weight in kilograms divided by height in meters squared) was 47 (range, 34-81), 1389 participants (80%) were women, and 257 participants (15%) were nonwhite. For LAGB, the median age was 48 years (range, 18-78), the body mass index was 44 (range, 33-87), 465 participants (76%) were women, and 63 participants (10%) were nonwhite. Follow-up weights were obtained in 1300 of 1569 (83%) eligible for a year-7 visit. Seven years following RYGB, mean weight loss was 38.2 kg (95% CI, 36.9-39.5), or 28.4% (95% CI, 27.6-29.2) of baseline weight; between years 3 and 7 mean

weight regain was 3.9% (95% CI, 3.4-4.4) of baseline weight. Seven years after LAGB, mean weight loss was 18.8 kg (95% CI, 16.3-21.3) or 14.9% (95% CI, 13.1-16.7), with 1.4% (95% CI, 0.4-2.4) regain. Six distinct weight change trajectory patterns for RYGB and 7 for LAGB were identified. Most participants followed trajectories in which weight regain from 3 to 7 years was small relative to year-3 weight loss, but patterns were variable. Compared with baseline, dyslipidemia prevalence was lower 7 years following both procedures; diabetes and hypertension prevalence were lower following RYGB only. Among those with diabetes at baseline (488 of 1723 with RYGB [28%]; 175 of 604 with LAGB [29%]), the proportion in remission at 1, 3, 5, and 7 years were 71.2% (95% CI, 67.0-75.4), 69.4% (95% CI, 65.0-73.8), 64.6% (95% CI, 60.0-69.2), and 60.2% (95% CI, 54.7-65.6), respectively, for RYGB and 30.7% (95% CI, 22.8-38.7), 29.3% (95% CI, 21.6-37.1), 29.2% (95% CI, 21.0-37.4), and 20.3% (95% CI, 9.7-30.9) for LAGB. The incidence of diabetes at all follow-up assessments was less than 1.5% for RYGB. Bariatric reoperations occurred in 14 RYGB and 160 LAGB participants. Conclusions and Relevance: Following bariatric surgery, different weight loss patterns were observed, but most participants maintained much of their weight loss with variable fluctuations over the long term. There was some decline in diabetes remission over time, but the incidence of new cases is low following RYGB. Trial Registration: clinicaltrials.gov Identifier: NCT00465829.

Cousijn, J., Luijten, M., & Feldstein Ewing, S. W. (2018). **Adolescent resilience to addiction: a social plasticity hypothesis**. *The Lancet Child and Adolescent Health, 2*(1), 69-78. doi:10.1016/S2352-4642(17)30148-7

The prevalence of substance use disorders is highest during adolescence; however, many adolescents experience a natural resolution of their substance use by early adulthood, without any formal intervention. Something appears to be unique and adaptive about the adolescent brain. In this Review, we examine the roles of the social environment and neurocognitive development in adolescents' natural resilience to substance use disorders. At present, little is known about the neurocognitive mechanisms that underlie this adaptive phenomenon, since neurodevelopmental studies have mainly focused on the risk side of the substance use equation: escalation of substance use. To provide a framework for future studies, we put forth a social plasticity model that includes developmentally limited enhanced social attunement (ie, the need to harmonise with the social environment), affective processing, and brain plasticity, which underlie adolescents' capacity to learn from and adapt to their constantly evolving social environments. © 2018 Elsevier Ltd

Crabtree, B., Bootman, J. L., Boyle, C. J., Chase, P., Piascik, P., & Maine, L. L. (2017). **Aligning the AACP Strategic Engagement Agenda with Key Federal Priorities in Health: Report of the 2016-17 Argus Commission**. *American Journal of Pharmaceutical Education, 81*(8), S15. doi:10.5688/ajpeS15

The Argus Commission identified three major federal priorities related to health care, including the precision medicine initiative, the Cancer Moonshot and the opioid abuse epidemic. Current activities at the federal level were summarized and an analysis of activities within the profession, and academic pharmacy specifically, was prepared. The implications for pharmacy education, research and practice are compelling in all three areas. Recommendations, suggestions and two policy statements aim to optimize the attention to these priorities by the academy. Further, aligning the AACP Strategic Engagement agenda with the opportunities and threats acknowledged in the analysis is essential.

Curtis, J. R., Winthrop, K., O'Brien, C., Ndlovu, M. N., de Longueville, M., & Haraoui, B. (2017). **Use of a baseline risk score to identify the risk of serious infectious events in patients with rheumatoid arthritis during certolizumab pegol treatment**. *Arthritis Res Ther, 19*(1), 276. doi:10.1186/s13075-017-1466-y

BACKGROUND: The risk of serious infectious events (SIEs) is increased in patients with rheumatoid arthritis (RA). The aim of this study was to develop an age-adjusted comorbidity index (AACI) to predict, using baseline characteristics, the SIE risk in patients with RA treated with certolizumab pegol (CZP). METHODS: Data of CZP-treated patients with RA were pooled from the RAPID1/RAPID2 randomized controlled trials (RCT CZP)

and their open-label extensions (All CZP). Predictors of the first SIE were examined using multivariate Cox models. The AACI was developed by assigning specific weights to patient age and comorbidities on the basis of relative SIE risk. SIE rates were predicted using AACI score and baseline glucocorticoid use, and they were compared with observed rates. The percentage of patients in each SIE risk group achieving low disease activity (LDA)/remission was examined at 1 year of treatment. RESULTS: Among 1224 RCT CZP patients, 40 reported >/= 1 SIE (incidence rate [IR] 5.09/100 patient-years [PY]), and 201 of 1506 All CZP patients reported >/= 1 SIE (IR 3.66/100 PY). Age >/= 70 years, diabetes mellitus, and chronic obstructive pulmonary disease/asthma made the greatest contributions to AACI score. SIE rates predicted using AACI and glucocorticoid use at baseline showed good agreement with observed SIE rates across low-risk and high-risk groups. At 1 year, more high-risk All CZP patients than low-risk All CZP patients reported SIEs (IR 8.4/100 PY vs. IR 3.4/100 PY). Rates of LDA/remission were similar between groups. CONCLUSIONS: AACI and glucocorticoid use were strong baseline predictors of SIE risk in CZP-treated patients with RA. Predicted SIE risk was not associated with patients' likelihood of clinical response. This SIE risk score may provide a valuable tool for clinicians when considering the risk of infection in individual patients with RA. TRIAL REGISTRATION: ClinicalTrials.gov, NCT00152386 (registered 7 September 2005); NCT00160602 (registered 8 September 2005); NCT00175877 (registered 9 September 2005); and NCT00160641 (registered 8 September 2005).

Cuzon Carlson, V. C., Grant, K. A., & Lovinger, D. M. (2017). **Synaptic adaptations to chronic ethanol intake in male rhesus monkey dorsal striatum depend on age of drinking onset**. *Neuropharmacology, 131*, 128-142. doi:10.1016/j.neuropharm.2017.12.010

One in 12 adults suffer with alcohol use disorder (AUD). Studies suggest the younger the age in which alcohol consumption begins the higher the probability of being diagnosed with AUD. Binge/excessive alcohol drinking involves a transition from flexible to inflexible behavior likely involving the dorsal striatum (caudate and putamen nuclei). A major focus of this study was to examine the effect of age of drinking onset on subsequent chronic, voluntary ethanol intake and dorsal striatal circuitry. Data from rhesus monkeys (n=45) that started drinking as adolescents, young adults or mature adults confirms an age-related risk for heavy drinking. Striatal neuroadaptations were examined using whole-cell patch clamp electrophysiology to record AMPA receptor-mediated miniature excitatory postsynaptic currents (mEPSCs) and GABAA receptor-mediated miniature inhibitory postsynaptic currents (mIPSCs) from medium-sized spiny projection neurons located in the caudate or putamen nuclei. In controls, greater GABAergic transmission (mIPSC frequency and amplitude) was observed in the putamen compared to the caudate. With advancing age, in the absence of ethanol, an increase in mIPSC frequency concomitant with changes in mIPSC amplitude was observed in both regions. Chronic ethanol drinking decreased mIPSC frequency in the putamen regardless of age of onset. In the caudate, an ethanol drinking-induced increase in mIPSC frequency was only observed in monkeys that began drinking as young adults. Glutamatergic transmission did not differ between the dorsal striatal subregions in controls. With chronic ethanol drinking there was a decrease in the postsynaptic characteristics of rise time and area of mEPSCs in the putamen but an increase in mEPSC frequency in the caudate. Together, the observed changes in striatal physiology indicate a combined disinhibition due to youth and ethanol leading to abnormally strong activation of the putamen that could contribute to the increased risk for problem drinking in younger drinkers.

Davidson Peiris, E., & Wusirika, R. (2017). **A Case Report of Compound Heterozygous CYP24A1 Mutations Leading to Nephrolithiasis Successfully Treated with Ketoconazole**. *Case Reports in Nephrology and Dialysis*, 167-171. doi:10.1159/000485243

CYP24A1 is an enzyme that inactivates vitamin D. Loss-of-function mutations in this enzyme are rare but have been linked with idiopathic infantile hypercalcemia as well as adult-onset nephrocalcinosis and nephrolithiasis. Genetic testing for this mutation should be considered in the presence of calciuria, elevated serum calcium, elevated 1,25-dihydroxyvitamin D, and suppressed parathyroid hormone. We present a case with these lab findings as well as an elevated 25-hydroxyvitamin D/24,25-dihydroxyvitamin D ratio in whom compound

heterozygous CYP24A1 mutations were found. His hypercalciuria resolved and 1,25-vitamin D level improved with ketoconazole treatment. We suggest that it is clinically important to identify patients with this phenotype as testing and treatment options are available which could reduce progression to chronic kidney disease in this population. © 2017 The Author(s). Published by S. Karger AG, Basel

DeBoard, Z. M., Paisley, M., & Thomas, D. D. (2017). **Self-Appraised Readiness of Senior and Graduating General Surgery Residents to Perform Thoracic Surgery**. *J Surg Educ*. doi:10.1016/j.jsurg.2017.11.010

OBJECTIVE: General surgeons perform up to 50% of noncardiac thoracic surgery (TS). Although data show consistent TS case volume during general surgery (GS) residency it is unknown whether this operative trend will persist given potentially limited subspecialty exposure. We sought to determine if certain aspects of residency programs and resident characteristics were associated with trainees' perceived comfort in performing certain basic TS procedures. DESIGN: An anonymous survey was distributed to GS residents regarding program characteristics, presence of a TS residency, and intent to pursue thoracic surgical training, and estimated case volumes of individual procedures. Comfort levels for performing video-assisted thoracoscopic surgical (VATS) procedures, open lobectomy, elective thoracotomy, and sternotomy were attained through a 5-point Likert-type scale. SETTING: This survey was administered at 50 training programs with responses recorded via an online form. PARTICIPANTS: Fourth- and fifth-year GS residents in the United States. RESULTS: Of 272 respondents 58% were fourth-year residents, 62% of residents trained at university-affiliated programs, and 64% reported a TS residency program at their institution and 16% stated intent to pursue TS. Fifth-year residents performed significantly more cases than fourth-year residents despite no difference in median comfort levels. Residents intending to pursue TS performed significantly more cases and were more comfortable performing a thoracotomy, sternotomy, VATS wedge resection/biopsy, and VATS decortication/pleurodesis ($p = 0.044$, <0.001, 0.045, 0.025). No characteristics were associated with comfort performing a lobectomy via thoracoscopic or open (thoracotomy) approaches. CONCLUSION: Most senior or graduating GS residents state they are comfortable performing certain thoracic procedures with those pursuing additional thoracic surgical training more comfortable overall. No characteristics were associated with comfort performing a lobectomy. These findings may advise residency curriculum design to ensure continued thoracic surgical exposure and recommend against non-fellowship trained surgeons performing a pulmonary lobectomy.

Deck, L. M., Hunsaker, L. A., Vander Jagt, T. A., Whalen, L. J., Royer, R. E., & Vander Jagt, D. L. (2018). **Activation of anti-oxidant Nrf2 signaling by enone analogues of curcumin**. *European Journal of Medicinal Chemistry, 143*, 854-865. doi:10.1016/j.ejmech.2017.11.048

Inflammation and oxidative stress are common in many chronic diseases. Targeting signaling pathways that contribute to these conditions may have therapeutic potential. The transcription factor Nrf2 is a major regulator of phase II detoxification and anti-oxidant genes as well as anti-inflammatory and neuroprotective genes. Nrf2 is widespread in the CNS and is recognized as an important regulator of brain inflammation. The natural product curcumin exhibits numerous biological activities including ability to induce the expression of Nrf2-dependent phase II and anti-oxidant enzymes. Curcumin has been examined in a number of clinical studies with limited success, mainly owing to limited bioavailability and rapid metabolism. Enone analogues of curcumin were examined with an Nrf2 reporter assay to identify Nrf2 activators. Analogues were separated into groups with a 7-carbon dienone spacer, as found in curcumin; a 5-carbon enone spacer with and without a ring; and a 3-carbon enone spacer. Activators of Nrf2 were found in all three groups, many of which were more active than curcumin. Dose-response studies demonstrated that a range of substituents on the aromatic rings of these enones influenced not only the sensitivity to activation, reflected in EC50 values, but also the extent of activation, which suggests that multiple mechanisms are involved in the activation of Nrf2 by these analogues. © 2017

Del Brutto, O. H., O'Neal, S. E., Dorny, P., & Garcia, H. H. (2017). **Spontaneously Arrested Transmission of Cysticercosis in a Highly Endemic Village with a Very Low Migration Rate**. *Am J Trop Med Hyg*. doi:10.4269/ajtmh.17-0723

Taenia solium cysticercosis is difficult to eliminate without interventions or societal development. Atahualpa is a rural Ecuadorian village with documented low migration rate, where domestic pig raising is common and human cysticercosis is endemic. To assess neurocysticercosis (NCC) prevalence, 1,273 villagers aged >/= 20 years underwent neuroimaging studies, which showed calcified lesions in 121 (9.5%) individuals, but no active disease. Likewise, positive reactions, apparently nonspecific, were found in only 3/200 subjects by the use of a monoclonal antibody-based enzyme-linked immunosorbent assay to detect T. solium antigens in urine. Only 2/418 pigs reacted to three antibody bands on serum western blot and none to more than three bands. This is the first time that spontaneously arrested T. solium transmission is documented in a known endemic village. Understanding why active transmission stopped could provide insights on potential targets for control interventions. Atahualpa could provide an optimal scenario for longitudinal studies on the consequences of calcified NCC.

Deodhar, A. (2018). **Spondyloarthropathies: TNF inhibitors and structural damage in ankylosing spondylitis**. *Nature Reviews: Rheumatology, 14*(1), 5-6. doi:10.1038/nrrheum.2017.197

Deodhar, A., Reveille, J. D., Harrison, D. D., Kim, L., Lo, K. H., Leu, J. H., & Hsia, E. C. (2017). **Safety and Efficacy of Golimumab Administered Intravenously in Adults with Ankylosing Spondylitis: Results through Week 28 of the GO-ALIVE Study**. *J Rheumatol*. doi:10.3899/jrheum.170487

OBJECTIVE: To evaluate the safety and efficacy of intravenous golimumab (GOL) in patients with active ankylosing spondylitis (AS). METHODS: In a phase III, randomized, double-blind, placebo (PBO)-controlled trial, 208 patients were randomized (1:1) to intravenous (IV) infusions of GOL 2 mg/kg (n = 105) at weeks 0, 4, 12, and every 8 weeks, or PBO (n = 103) at weeks 0, 4, and 12, with crossover to GOL at Week 16. The primary endpoint was >/= 20% improvement from baseline in the Assessment of Spondyloarthritis International Society Criteria (ASAS20) at Week 16. Secondary endpoints included ASAS40, >/= 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50), and change in the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16. Safety was monitored through Week 28. RESULTS: Significantly greater proportions of GOL-treated patients had ASAS20 response at Week 2 (37.1% vs 19.4%; p = 0.005) and at Week 16 (73.3% vs 26.2%; p < 0.001). At Week 16, 41.0% of those receiving GOL achieved BASDAI50 compared with 14.6% of those taking PBO (p < 0.001), and the GOL group had greater mean improvement in BASFI (-2.4 vs -0.5; p < 0.001). Through Week 16, 23.3% of patients in the PBO group and 32.4% of patients in the GOL group had >/= 1 adverse event (AE); infections being the commonest type of AE. Through Week 28, two GOL-treated patients had a serious AE. CONCLUSION: GOL 2 mg/kg administered IV at weeks 0, 4, and every 8 weeks significantly reduced the signs and symptoms of AS in adults. AE were consistent with other antitumor necrosis factor therapies, with no new safety signals (Clinicaltrials.gov: NCT02186873).

DeVine, T., Sears, R. C., & Dai, M. S. (2017). **The ubiquitin-specific protease USP36 is a conserved histone H2B deubiquitinase**. *Biochemical and Biophysical Research Communications*. doi:10.1016/j.bbrc.2017.12.107

Histone H2B monoubiquitination plays a critical role in the regulation of gene transcription. Deregulation of H2B monoubiquitination contributes to human pathologies, such as cancer. Here we report that human USP36 is a novel H2Bub1 deubiquitinase. We show that USP36 interacts with H2B and deubiquitinates H2Bub1 in cells and in vitro. Overexpression of USP36 markedly reduced the levels of H2Bub1 in cells. Using the p21 gene as a model, we demonstrate that depletion of USP36 increases H2Bub1 at the p21 locus, primarily within its gene body. Consistently, knockdown of USP36 induced the expression of p21 and inhibits cell proliferation.

Together, our results reveal USP36 as a novel H2B deubiquitinase and shed light on its additional functions in regulating gene expression.

Dewland, T. A., Soliman, E. Z., Yamal, J. M., Davis, B. R., Alonso, A., Albert, C. M., . . . Marcus, G. M. (2017). **Pharmacologic Prevention of Incident Atrial Fibrillation: Long-Term Results From the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)**. *Circ Arrhythm Electrophysiol, 10*(12). doi:10.1161/circep.117.005463

BACKGROUND: Although atrial fibrillation (AF) guidelines indicate that pharmacological blockade of the renin-angiotensin system may be considered for primary AF prevention in hypertensive patients, previous studies have yielded conflicting results. We sought to determine whether randomization to lisinopril reduces incident AF or atrial flutter (AFL) compared with chlorthalidone in a large clinical trial cohort with extended post-trial surveillance. METHODS AND RESULTS: We performed a secondary analysis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a randomized, double-blind, active-controlled clinical trial that enrolled hypertensive individuals >/=55 years of age with at least one other cardiovascular risk factor. Participants were randomly assigned to receive amlodipine, lisinopril, or chlorthalidone. Individuals with elevated fasting low-density lipoprotein cholesterol levels were also randomized to pravastatin versus usual care. The primary outcome was the development of either AF or AFL as diagnosed by serial study ECGs or by Medicare claims data. Among 14 837 participants without prevalent AF or AFL, 2514 developed AF/AFL during a mean 7.5+/-3.2 years of follow-up. Compared with chlorthalidone, randomization to either lisinopril (hazard ratio, 1.04; 95% confidence interval, 0.94-1.15; P=0.46) or amlodipine (hazard ratio, 0.93; 95% confidence interval, 0.84-1.03; P=0.16) was not associated with a significant reduction in incident AF/AFL. CONCLUSIONS: Compared with chlorthalidone, treatment with lisinopril is not associated with a meaningful reduction in incident AF or AFL among older adults with a history of hypertension. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000542.

Dimitrova, A. (2017). **Introducing a Standardized Acupuncture Protocol for Peripheral Neuropathy: A Case Series**. *Med Acupunct, 29*(6), 352-365. doi:10.1089/acu.2017.1242

Background: Peripheral neuropathy (PN) is defined as damage to the peripheral nervous system caused by a primary lesion or dysfunction. Multiple recent trials have suggested that acupuncture is beneficial for treating neuropathic pain. One challenge in acupuncture research is the lack of standardization of point selection, number of needles used, needle-retention time, needling depth, amount of needle manipulation, and use of moxibustion and electroacupuncture (EA). Objectives: This article presents a standardized acupuncture protocol for the treatment of PN that incorporates structural acupuncture principles based on proximity to peripheral nerves and on traditional approaches to the treatment of neuropathic pain. Materials and Methods: Ten consecutive patients diagnosed with large- or small-fiber neuropathy of various etiologies were treated with a standardized protocol, based on anatomical correlations of peripheral nerves and acupuncture points. Manual acupuncture was applied to left LR 4, LU 5; bilateral LI 11, KI 27, ST 36, GB 34, SP 6, SP 9, LI 4, TE 5, and BaFeng (except for the space between the first and second digits of the toes; LR 3 was used for that space). EA was applied to bilateral KI 3-1 and bilateral ST 41-LR 3. Patients underwent at least six acupuncture sessions, although the total number of sessions varied. Outcomes were measured using a visual analogue scale (VAS) and clinical signs and symptoms. Results: All 10 patients indicated improvement on the VAS and in clinical presentation. Conclusions: This standardized protocol appears to be effective for the treatment of neuropathy of various causes, including large- and small-fiber involvement. Further studies with larger sample sizes and randomized comparisons against sham acupuncture and other acupuncture regimens will be helpful to determine if this protocol could be established as a guideline for approaching peripheral neuropathy.

Donovan, L. M., Rise, P. J., Carson, S. S., Feemster, L. C., Griffith, M. F., Kapur, V. K., . . . Au, D. H. (2017). **Sleep Disturbance in Smokers with Preserved Pulmonary Function and with Chronic Obstructive Pulmonary Disease**. *Ann Am Thorac Soc, 14*(12), 1836-1843. doi:10.1513/AnnalsATS.201706-453OC

RATIONALE: Sleep disturbance frequently affects patients with chronic obstructive pulmonary disease (COPD), and is associated with reduced quality of life and poorer outcomes. Data indicate that smokers with preserved pulmonary function have clinical symptoms similar to those meeting spirometric criteria for COPD, but little is known about the driving factors for sleep disturbance in this population of emerging interest. OBJECTIVES: To compare the magnitude and correlates of sleep disturbance between smokers with preserved pulmonary function and those with airflow obstruction. METHODS: Using cross-sectional data from the COPD Outcomes-Based Network for Clinical Effectiveness and Research Translation multicenter registry, we identified participants clinically identified as having COPD with a smoking history of at least 20 pack-years and either preserved pulmonary function or airflow obstruction. We quantified sleep disturbance by T-score measured in the sleep disturbance domain of the Patient-Reported Outcomes Information System questionnaire, and defined a minimum important difference as a T-score difference of two points. We performed univariate and multivariable linear regression to evaluate correlates within each group. RESULTS: We identified 100 smokers with preserved pulmonary function and 476 with airflow obstruction. The sleep disturbance T-score was 4.1 points greater among individuals with preserved pulmonary function (95% confidence interval [CI], 2.0-6.3). In adjusted analyses, depression symptom T-score was associated with sleep disturbance in both groups (airflow obstruction: beta, 0.61 points; 95% CI, 0.27-0.94; preserved pulmonary function: beta, 0.25 points; 95% CI, 0.12-0.38). Of note, lower percent predicted FEV1 was associated with greater sleep disturbance among those with preserved pulmonary function (beta, -0.19 points; 95% CI, -0.31 to -0.07), whereas higher FEV1 was associated with greater sleep disturbance among individuals with airflow obstruction (beta, 0.06 points; 95% CI, 0.01-0.10). CONCLUSIONS: Among smokers with clinically identified COPD, the severity of sleep disturbance is greater among those with preserved pulmonary function compared with those with airflow obstruction. Nonrespiratory symptoms, such as depression, were associated with sleep disturbance in both groups, whereas the relationship of sleep disturbance with FEV1 differed.

Donovan-Maiye, R. M., Langmead, C. J., & Zuckerman, D. M. (2017). **Systematic Testing of Belief-Propagation Estimates for Absolute Free Energies in Atomistic Peptides and Proteins**. *Journal of Chemical Theory and Computation*. doi:10.1021/acs.jctc.7b00775

Motivated by the extremely high computing costs associated with estimates of free energies for biological systems using molecular simulations, we further the exploration of existing "belief propagation" (BP) algorithms for fixed-backbone peptide and protein systems. The precalculation of pairwise interactions among discretized libraries of side-chain conformations, along with representation of protein side chains as nodes in a graphical model, enables direct application of the BP approach, which requires only approximately 1 s of single-processor run time after the precalculation stage. We use a "loopy BP" algorithm, which can be seen as an approximate generalization of the transfer-matrix approach to highly connected (i.e., loopy) graphs, and it has previously been applied to protein calculations. We examine the application of loopy BP to several peptides as well as the binding site of the T4 lysozyme L99A mutant. The present study reports on (i) the comparison of the approximate BP results with estimates from unbiased estimators based on the Amber99SB force field; (ii) investigation of the effects of varying library size on BP predictions; and (iii) a theoretical discussion of the discretization effects that can arise in BP calculations. The data suggest that, despite their approximate nature, BP free-energy estimates are highly accurate-indeed, they never fall outside confidence intervals from unbiased estimators for the systems where independent results could be obtained. Furthermore, we find that libraries of sufficiently fine discretization (which diminish library-size sensitivity) can be obtained with standard computing resources in most cases. Altogether, the extremely low computing times and accurate results suggest the BP approach warrants further study.

Doron, B., Handu, M., & Kurre, P. (2017). **Concise Review: Adaptation of the Bone Marrow Stroma in Hematopoietic Malignancies: Current Concepts and Models**. *Stem Cells*. doi:10.1002/stem.2761

The bone marrow stroma maintains hematopoiesis and coordinately regulates regenerative responses through dynamic interactions with hematopoietic stem and progenitor cells. Recent studies indicate that stromal components in the bone marrow of leukemia patients undergo a process of successive adaptation that in turn exerts dramatic effects on the hematopoietic stem cell compartment and promotes leukemic drug resistance. Therefore, functional changes in discrete marrow stromal populations can be considered an aspect of leukemia biogenesis in that they create an aberrant, self-reinforcing microenvironment. In this review, we will describe the current understanding of the remodeling of the hematopoietic stem cell niche following invasion by leukemia cells. We place emphasis on existing evidence of how mesenchymal stem cells and their progeny facilitate neoplastic growth and describe available models and analytical techniques to understand the conversion of the niche toward disease persistence. Stem Cells 2017.

Dreicer, J. J., Mailankody, S., Fahkrejahani, F., & Prasad, V. (2017). **Clinically meaningful benefit: real world use compared against the American and European guidelines**. *Blood Cancer J, 7*(12), 645. doi:10.1038/s41408-017-0009-8

Dugas, C., Simard, M. N., Fombonne, E., & Couture, M. (2018). **Comparison of Two Tools to Assess Sensory Features in Children With Autism Spectrum Disorder**. *American Journal of Occupational Therapy, 72*(1), 7201195010p7201195011-7201195010p7201195019. doi:10.5014/ajot.2018.024604

OBJECTIVE: This article documents the convergent validity of the Sensory Profile (SP) and the Sensory Processing Measure (SPM)-Home Form for children with autism spectrum disorder (ASD). METHO: . Parents of 34 children with ASD between ages 5 and 8 yr filled out both measures. Through correlations, chi(2) tests, and levels of agreement between classifications, the results for the SP and the SPM-Home Form were compared. RESULTS: The raw scores were correlated for some sensory domains (hearing, vision, touch, and proprioception) and for social functioning. The classifications showed a significant level of agreement for most scales (kappas = .247-.589, p </= .05) and for the total scores (kappa = .324, p </= .01). CONCLUSION: This study provides further evidence of convergent validity between both tools. The SPM-Home Form identifies more children with ASD who present with sensory features for every domain measured by both tools.

Duke, J. W., Gladstone, I. M., Sheel, A. W., & Lovering, A. T. (2017). **Premature birth affects the degree of airway dysanapsis and mechanical ventilatory constraints**. *Experimental Physiology*. doi:10.1113/ep086588

NEW FINDINGS: What is the central question of this study? Adult survivors of preterm birth without (PRE) and with bronchopulmonary dysplasia (BPD) have airflow obstruction at rest and significant mechanical ventilatory constraints during exercise compared with those born at full term (CON). Do PRE/BPD have smaller airways, indexed via the dysanapsis ratio, than CON? What is the main finding and its importance? The dysanapsis ratio was significantly smaller in BPD and PRE compared with CON, with BPD having the smallest dysanapsis ratio. These data suggest that airflow obstruction in PRE and BPD might be because of smaller airways than CON. Adult survivors of very preterm birth (</=32 weeks gestational age) without (PRE) and with bronchopulmonary dysplasia (BPD) have obstructive lung disease as evidenced by reduced expiratory airflow at rest and have significant mechanical ventilatory constraints during exercise. Airflow obstruction, in any conditions, could be attributable to several factors, including small airways. PRE and/or BPD could have smaller airways than their counterparts born at full term (CON) owing to a greater degree of dysanaptic airway development during the pre- and/or postnatal period. Thus, the purpose of the present study was to compare the dysanapsis ratio (DR), as an index of airway size, between PRE, BPD and CON. To do so, we calculated DR in PRE (n = 21), BPD (n = 14) and CON (n = 34) individuals and examined flow-volume loops

at rest and during submaximal exercise. The DR, using multiple estimates of static recoil pressure, was significantly smaller in PRE and BPD (0.16 +/- 0.05 and 0.10 +/- 0.03 a.u.) compared with CON (0.22 +/- 0.04 a.u.; both P < 0.001) and smallest in BPD (P < 0.001). The DR was significantly correlated with peak expiratory airflow at rest (r = 0.42; P < 0.001) and the extent of expiratory flow limitation during exercise (r = 0.60; P < 0.001). Our findings suggest that PRE/BPD might have anatomically smaller airways than CON, which might help to explain their lower expiratory airflow rate at rest and during exercise and further our understanding of the consequences of preterm birth and neonatal O2 therapy.

Edelman, A., Trussell, J., Aiken, A. R. A., Portman, D. J., Chiodo, J. A., 3rd, & Garner, E. I. O. (2017). **The emerging role of obesity in short-acting hormonal contraceptive effectiveness**. *Contraception*. doi:10.1016/j.contraception.2017.12.012

Elliott, A. B., Holley, A. L., Ross, A. C., Soleta, A. O., & Koh, J. L. (2017). **A prospective study comparing perioperative anxiety and posthospital behavior in children with autism spectrum disorder vs typically developing children undergoing outpatient surgery**. *Paediatric Anaesthesia*. doi:10.1111/pan.13298

BACKGROUND: Research describing the experience of youth with autism spectrum disorders in the perioperative setting is limited. This study compared youth with autism spectrum disorder to typically developing children in the perioperative setting and examined group differences in: child anxiety, parent anxiety, premedication patterns, induction compliance, and changes in behavior postprocedure. METHODS: Participants were 60 youth (32 with autism spectrum disorder, 28 typically developing) of ages 2-19 years undergoing outpatient surgery and their parents. Parents and research assistants rated children's anxiety at 3 time points (waiting room, preoperative holding, separation), and parents rated their own anxiety in the waiting room and at separation. The anesthesiologist rated induction compliance. Postprocedure behavior change was assessed via phone survey 1 and 7 days postprocedure. Analyses examined group differences in anxiety, medication patterns, and behavior. RESULTS: Children with autism spectrum disorder had higher research assistant reported anxiety than typically developing youth in the holding room only. There were no group differences in parent report of their own anxiety or their child's anxiety across time points. Compared to typically developing youth, children with autism spectrum disorder were more likely to receive a premedication (including nonstandard premedication), and had poorer induction compliance. Groups did not differ on posthospital behavior change 1 or 7 days postsurgery. CONCLUSION: Findings revealed ratings of anxiety in youth with and without autism spectrum disorder facing surgery varied by reporter and setting, highlighting the importance of using multiple reporters in research of youth with autism spectrum disorder in the perioperative period. Furthermore, while results showed group differences in premedication patterns and induction compliance, groups did not differ in level of negative behavior change after surgery. Future research can examine how individual differences in youth with autism impact anxiety in the perioperative setting and degree of behavior change postprocedure.

Ellison, D. H., & Felker, G. M. (2017). **Diuretic treatment in heart failure**. *New England Journal of Medicine, 377*(20), 1964-1975. doi:10.1056/NEJMra1703100

Faria, E. S. A. L., Fanger, C., Nguyen, L., Howerton, D., & Pfeifer, C. S. (2017). **Impact of Material Shade and Distance from Light Curing Unit Tip on the Depth of Polymerization of Composites**. *Braz Dent J, 28*(5), 632-637. doi:10.1590/0103-6440201701727

This study aimed to evaluate the effect of the composite shade and distance from the light-curing unit (LCU) tip on the irradiance reaching the bottom of composite disks and on the depth of polymerization. Composites of three shades (opaque - OXDC, bleach - BXL, and A2) were inserted into molds with 3-mm of thickness

positioned over a spectrometer and photo-activated with the LCU (Bluephase) tip placed at 0 or 1 cm from the composite surface. The mean irradiance reaching the bottom of composite was recorded during the entire photo-activation (30 s). Specimens (2 x 2 x 4 mm) were polymerized and used to map the degree of conversion achieved in different depths from irradiated surface. Specimens were sectioned into slices that were positioned over the platform of the infra-red microscope connected to the spectrometer to map the conversion. The conversion was measured in eight different depths every 500-microm. Increasing the distance of LCU tip reduced the irradiance only for A2. Interposing OXDC disks resulted in lowest values of irradiance and A2 the highest one. A tendency to decrease the conversion was observed towards the bottom of specimens for all experimental conditions, and the slope was more accentuated for OXDC. Differences among shades and distances from LCU tip were evident only beyond 1.5-2.0 mm of depth. In conclusion, both composite shade and distance from LCU tip might affect the light-transmission and depth of polymerization, while the effect of last was more pronounced.

Faria-E-Silva, A. L., Covell, D. A., Jr., Ferracane, J. L., & Pfeifer, C. S. (2017). **Effectiveness of high irradiance for short-time exposures on polymerization of composite under metal brackets**. *Angle Orthodontist, 87*(6), 834-840. doi:10.2319/051817-338.1

Objective: To evaluate the effect of different curing modes available in a dental light-curing unit on degree of conversion (DC) of a composite photoactivated under a metal orthodontic bracket. Materials and Methods: The average irradiance and total energy delivered by three curing modes (standard, high, and extra power) of a multiwave LED unit (Valo Cordless, Ultradent Products, South Jordan, Utah) were measured using the longest time available for each mode (20, 4, and 3 seconds, respectively). Brackets (n =3/group) were bonded to molar epoxy resin replicas using each curing mode. Mesiodistal sections, 0.5 mm thick, were assessed using an infrared spectrometer microscope. Spectra of composite beneath the brackets were sequentially collected using the mapping tool in near-infrared (NIR)-transmittance mode. Composite conversion was mapped between the mesial and distal edges of the bracket base using 400-lm steps for a total of 10 measurements per specimen. Data from irradiance and total energy were analyzed by one-way ANOVA, while data of DC were analyzed with two-way repeated measures ANOVA (α=0.05). Results: The highest DC values were observed for standard power (mean 56%, P <.05), while no difference was observed between high (50%) and extra power (49%) modes. Regarding the site of measurement, higher DC was observed close to the bracket edges (52%, P <.05). Conclusions: The use of high irradiance for a short time slightly reduced the DC. The small magnitude of reduction suggests that use of a high irradiance protocol is a clinically valid approach when bonding metal brackets.

Farkouh-Karoleski, C., Najaf, T., Wynn, J., Aspelund, G., Chung, W. K., Stolar, C. J., . . . Needelman, H. (2017). **A definition of gentle ventilation in congenital diaphragmatic hernia: A survey of neonatologists and pediatric surgeons**. *Journal of Perinatal Medicine, 45*(9), 1031-1038. doi:10.1515/jpm-2016-0271

Ventilation practices have changed significantly since the initial reports in the mid 1980 of successful use of permissive hypercapnia and spontaneous ventilation [often called gentle ventilation (GV)] in infants with congenital diaphragmatic hernia (CDH). However, there has been little standardization of these practices or of the physiologic limits that define GV. We sought to ascertain among Diaphragmatic Hernia Research and Exploration; Advancing Molecular Science (DHREAMS) centers' GV practices in the neonatal management of CDH. Pediatric surgeons and neonatologists from DHREAMS centers completed an online survey on GV practices in infants with CDH. The survey gathered data on how individuals defined GV including ventilator settings, blood gas parameters and other factors of respiratory management. A total of 87 respondents, from 12 DHREAMS centers completed the survey for an individual response rate of 53% and a 92% center response rate. Approximately 99% of the respondents defined GV as accepting higher carbon dioxide (PCO2) and 60% of the respondents also defined GV as accepting a lower pH. There was less consensus about the use of sedation and neuromuscular blocking agents in GV, both within and across the centers. Acceptable pH and PCO2 levels are broader than the goal ranges. Despite a lack of formal standardization, the results

suggest that GV practice is consistently defined as the use of permissive hypercapnia with mild respiratory acidosis and less consistently with the use of sedation and neuromuscular blocking agents. GV is the reported practice of surveyed neonatologists and pediatric surgeons in the respiratory management of infants with CDH.

Farrell, A. S., Joly, M. M., Allen-Petersen, B. L., Worth, P. J., Lanciault, C., Sauer, D., . . . Sears, R. C. (2017). **MYC regulates ductal-neuroendocrine lineage plasticity in pancreatic ductal adenocarcinoma associated with poor outcome and chemoresistance**. *Nature Communications, 8*(1). doi:10.1038/s41467-017-01967-6

Intratumoral phenotypic heterogeneity has been described in many tumor types, where it can contribute to drug resistance and disease recurrence. We analyzed ductal and neuroendocrine markers in pancreatic ductal adenocarcinoma, revealing heterogeneous expression of the neuroendocrine marker Synaptophysin within ductal lesions. Higher percentages of Cytokeratin-Synaptophysin dual positive tumor cells correlate with shortened disease-free survival. We observe similar lineage marker heterogeneity in mouse models of pancreatic ductal adenocarcinoma, where lineage tracing indicates that Cytokeratin-Synaptophysin dual positive cells arise from the exocrine compartment. Mechanistically, MYC binding is enriched at neuroendocrine genes in mouse tumor cells and loss of MYC reduces ductal-neuroendocrine lineage heterogeneity, while deregulated MYC expression in KRAS mutant mice increases this phenotype. Neuroendocrine marker expression is associated with chemoresistance and reducing MYC levels decreases gemcitabine-induced neuroendocrine marker expression and increases chemosensitivity. Altogether, we demonstrate that MYC facilitates ductal-neuroendocrine lineage plasticity in pancreatic ductal adenocarcinoma, contributing to poor survival and chemoresistance.

Feczko, E., Balba, N., Miranda-Dominguez, O., Cordova, M., Karalunas, S. L., Irwin, L., . . . Fair, D. A. (2017). **Subtyping cognitive profiles in Autism Spectrum Disorder using a random forest algorithm**. *Neuroimage*. doi:10.1016/j.neuroimage.2017.12.044

DSM-5 Autism Spectrum Disorder (ASD) comprises a set of neurodevelopmental disorders characterized by deficits in social communication and interaction and repetitive behaviors or restricted interests, and may both affect and be affected by multiple cognitive mechanisms. This study attempts to identify and characterize cognitive subtypes within the ASD population using a random forest (RF) machine learning classification model. We trained our model on measures from seven tasks that reflect multiple levels of information processing. 47 ASD diagnosed and 58 typically developing (TD) children between the ages of 9 and 13 participated in this study. Our RF model was 72.7% accurate, with 80.7% specificity and 63.1% sensitivity. Using the RF model, we measured the proximity of each subject to every other subject, generating a distance matrix between participants. This matrix was then used in a community detection algorithm to identify subgroups within the ASD and TD groups, revealing 3 ASD and 4 TD putative subgroups with unique behavioral profiles. We then examined differences in functional brain systems between diagnostic groups and putative subgroups using resting-state functional connectivity magnetic resonance imaging (rsfcMRI). Chi-square tests revealed a significantly greater number of between group differences ($p<.05$) within the cingulo-opercular, visual, and default systems as well as differences in inter-system connections in the somato-motor, dorsal attention, and subcortical systems. Many of these differences were primarily driven by specific subgroups suggesting that our method could potentially parse the variation in brain mechanisms affected by ASD.

Ferdaus, M. Z., Miller, L. N., Agbor, L. N., Saritas, T., Singer, J. D., Sigmund, C. D., & McCormick, J. A. (2017). **Mutant Cullin 3 causes familial hyperkalemic hypertension via dominant effects**. *JCI Insight, 2*(24). doi:10.1172/jci.insight.96700

Mutations in the ubiquitin ligase scaffold protein Cullin 3 (CUL3) cause the disease familial hyperkalemic hypertension (FHHt). In the kidney, mutant CUL3 (CUL3-Delta9) increases abundance of With-No-Lysine [K] Kinase 4 (WNK4), with excessive activation of the downstream Sterile 20 (STE20)/SPS-1-related proline/alanine-rich

kinase (SPAK) increasing phosphorylation of the Na+-Cl- cotransporter (NCC). CUL3-Delta9 promotes its own degradation via autoubiquitination, leading to the hypothesis that Cul3 haploinsufficiency causes FHHt. To directly test this, we generated Cul3 heterozygous mice (CUL3-Het), and Cul3 heterozygotes also expressing CUL3-Delta9 (CUL3-Het/Delta9), using an inducible renal epithelial-specific system. Endogenous CUL3 was reduced to 50% in both models, and consistent with autoubiquitination, CUL3-Delta9 protein was undetectable in CUL3-Het/Delta9 kidneys unless primary renal epithelia cells were cultured. Abundances of WNK4 and phosphorylated NCC did not differ between control and CUL3-Het mice, but they were elevated in CUL3-Het/Delta9 mice, which also displayed higher plasma [K+] and blood pressure. Abundance of phosphorylated Na+-K+-2Cl- cotransporter (NKCC2) was also increased, which may contribute to the severity of CUL3-Delta9-mediated FHHt. WNK4 and SPAK localized to puncta in NCC-positive segments but not in NKCC2-positive segments, suggesting differential effects of CUL3-Delta9. These results indicate that Cul3 haploinsufficiency does not cause FHHt, but dominant effects of CUL3-Delta9 are required.

Ferguson, L. B., Ozburn, A. R., Ponomarev, I., Metten, P., Reilly, M., Crabbe, J. C., . . . Mayfield, R. D. (2017). **Genome-Wide Expression Profiles Drive Discovery of Novel Compounds that Reduce Binge Drinking in Mice**. *Neuropsychopharmacology*. doi:10.1038/npp.2017.301

Transcriptome-based drug discovery has identified new treatments for some complex diseases, but has not been applied to alcohol use disorder (AUD) or other psychiatric diseases, where there is a critical need for improved pharmacotherapies. High Drinking in the Dark (HDID-1) mice are a genetic model of AUD risk that have been selectively bred (from the HS/Npt line) to achieve intoxicating blood alcohol levels (BALs) after binge-like drinking. We compared brain gene expression of HDID-1 and HS/Npt mice to determine a molecular signature for genetic risk for high intensity, binge-like drinking. Using multiple computational methods, we queried LINCS-L1000 (Library of Integrated Cellular Signatures), a database containing gene expression signatures of thousands of compounds, to predict candidate drugs with the greatest potential to decrease alcohol consumption. Our analyses predicted novel compounds for testing, many with anti-inflammatory properties, providing further support for a neuroimmune mechanism of excessive alcohol drinking. We validated the top 2 candidates in vivo as a proof-of-concept. Terreic acid (a Bruton's tyrosine kinase inhibitor) and pergolide (a dopamine and serotonin receptor agonist) robustly reduced alcohol intake and BALs in HDID-1 mice, providing the first evidence for transcriptome-based drug discovery to target an addiction trait. Effective drug treatments for many psychiatric diseases are lacking, and the emerging tools and approaches outlined here offer researchers studying complex diseases renewed opportunities to discover new or repurpose existing compounds and expedite treatment options.Neuropsychopharmacology accepted article preview online, 18 December 2017. doi:10.1038/npp.2017.301.

Finn, D. A., & Jimenez, V. A. (2017). **Dynamic Adaptation in Neurosteroid Networks in Response to Alcohol**. *Handbook of Experimental Pharmacology*. doi:10.1007/164_2017_82

The term neurosteroid refers to rapid membrane actions of steroid hormones and their derivatives that can modulate physiological functions and behavior via their interactions with ligand-gated ion channels. This chapter will highlight recent advances pertaining to the modulatory effects of a select group of neurosteroids that are primarily potent positive allosteric modulators of gamma-aminobutyric acidA receptors (GABAARs). Nanomolar concentrations of neurosteroids, which occur in vivo, potentiate phasic and tonic forms of GABAAR-mediated inhibition, indicating that both synaptic and extrasynaptic GABAARs possess sensitivity to neurosteroids and contribute to the overall ability of neurosteroids to modulate central nervous system excitability. Common effects of alcohol and neurosteroids at GABAARs have stimulated research on the ability of neurosteroids to modulate alcohol's acute and chronic effects. Background on neurosteroid pharmacology and biosynthetic enzymes will be provided as it relates to experimental findings. Data will be summarized on alcohol and neurosteroid interactions across neuroanatomical regions and models of intoxication, consumption, dependence, and withdrawal. Evidence supports independent regulation of neurosteroid synthesis between periphery and brain as well as across brain regions following acute alcohol administration and during withdrawal. Local mechanisms for fine-tuning neuronal excitability via

manipulation of neurosteroid synthesis exert predicted behavioral and electrophysiological responses on GABAAR-mediated inhibition. Collectively, targeting neurosteroidogenesis may be a beneficial treatment strategy for alcohol use disorders.

Foster, B. A., Fu, E., Bendiks, N., Gaspard, C. S., & Sharifi, M. (2017). **Capacity-oriented approaches to developing childhood obesity interventions: a systematic review**. *Clin Obes*. doi:10.1111/cob.12234

Capacity-oriented approaches to health interventions seek to empower the target population or community to manage the health issue themselves using resources they can control. Positive deviance, resilience and asset-based approaches are three such methods of developing and implementing health interventions. This study aimed to review the efficacy of interventions explicitly applying these methods in addressing childhood obesity using adiposity as the primary outcome, measured by standardized body mass index. The search strategy was developed and implemented across four electronic databases. Of the 181 records identified and screened, 11 studies were identified as using a capacity-oriented approach overall. Asset-based approaches (n = 8 studies) consisted of 47 880 participants, positive deviance (n = 2 studies) consisted of 781 participants, and resilience-based interventions (n = 1 study) consisted of 35 participants. The asset-based approaches were mixed, with three of the eight studies showing a significant reduction in adiposity, while the other five did not find a difference. The positive deviance and resilience-based studies showed signs of efficacy in reducing adiposity. There was significant design heterogeneity across studies, and varied interpretations and definitions of the approaches were used. Further work should attempt to achieve some consensus on the use of these approaches to facilitate comparison and advance the science of capacity-oriented interventions for childhood obesity.

Frandsen, E. L., Burchill, L. J., Khan, A. M., & Broberg, C. S. (2018). **Ascending aortic size in aortic coarctation depends on aortic valve morphology: Understanding the bicuspid valve phenotype**. *International Journal of Cardiology, 250*, 106-109. doi:10.1016/j.ijcard.2017.07.017

Background In roughly half of patients with coarctation of the aorta (CoA), the aorta may be enlarged. It is uncertain whether enlargement is independent of aortic valve morphology. We sought to compare aortic size in CoA with a tricuspid valve (TAV) to those with bicuspid aortic valve (BAV). Methods Sixty-eight CoA patients and 20 healthy controls with prior cardiac magnetic resonance (CMR) imaging were included. CMR was retrospectively reanalyzed to measure aortic root and mid-ascending aorta. The maximum aortic diameter was compared between CoA with TAV, CoA with BAV, and control groups. Results CoA with TAV patients (n = 27) had smaller aortic root diameters than CoA with BAV (n = 41) (32 ± 4.9 vs. 37 ± 5.8 mm, p = 0.001), despite being older (40 vs. 32 years, p = 0.01). Similarly, TAV CoA patients had a smaller mid-ascending aortic diameter (28 ± 4.5 vs. 33 ± 6.9 mm, p = 0.019) than BAV patients. TAV CoA was similar to controls in all metrics. Twenty-four patients (35%) with CoA had dilated aortas (> 37 mm), of which 79% had BAV. A history of hypertension did not predict larger aortic root or mid-ascending aortic dimensions. Conclusions In patients with CoA, TAV is associated with smaller aortic size compared to those with BAV, and similar to healthy controls. Aortic size in CoA is independent of hypertension. Therefore, aortopathy associated with BAV is likely a reflection of the BAV phenotype rather than CoA or its physiologic effects. This distinction may have implications for the frequency and types of monitoring and treatment of CoA patients. © 2017 Elsevier B.V.

Frank, J., & Fett, N. (2017). **Azathioprine Hypersensitivity Syndrome**. *J Rheumatol, 44*(12), 1876-1877. doi:10.3899/jrheum.170066

Gall, B., Pryke, K., Abraham, J., Mizuno, N., Botto, S., Sali, T. M., . . . DeFilippis, V. (2017). **Emerging Alphaviruses are Sensitive to Cellular States Induced by a Novel Small Molecule Agonist of the STING Pathway**. *J Virol*. doi:10.1128/jvi.01913-17

The type I interferon (IFN) system represents an essential innate immune response that renders cells resistant to virus growth via the molecular actions of IFN-induced effector proteins. IFN-mediated cellular states inhibit growth of numerous and diverse virus types including those of known pathogenicity as well as potentially emerging agents. As such, targeted pharmacologic activation of the IFN response may represent a novel therapeutic strategy to prevent infection or spread of clinically impactful viruses. In light of this we employed a high-throughput screen to identify small cell-permeable molecules capable of activating IFN-dependent signaling processes. Here we report the identification and characterization of N-(Methylcarbamoyl)-2-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-2-pheny lacetamide (referred to as C11), a novel compound capable of inducing IFN secretion from human cells. Using reverse genetics-based loss of function assays we show that C11 activates the type I IFN response in a manner that requires the adaptor protein STING but not alternative adaptors MAVS and TRIF. Importantly, treatment of cells with C11 generated a cellular state that potently blocked replication of multiple emerging Alphavirus types including Chikungunya, Ross River, Venezuelan Equine Encephalitis, Mayaro, and O'nyong'nyong viruses. The antiviral effects of C11 were subsequently abrogated in cells lacking STING or the type I IFN receptor indicating that they are mediated, at least predominantly, by way of STING-mediated IFN secretion and subsequent autocrine/paracrine signaling. This work also allowed characterization of differential antiviral roles of innate immune signaling adaptors and IFN-mediated responses and identified MAVS as crucial to cellular resistance to Alphavirus infection.IMPORTANCE: Due to the increase in emerging arthropod-borne viruses like Chikungunya that lack FDA-approved therapeutics and vaccines, it is important to better understand signaling pathways that lead to clearance of virus. Here we show that C11 treatment makes human cells refractory to replication of a number of these viruses, and supports its value in understanding the immune response and viral pathogenesis required to establish host infection. We also show C11 depends on signaling through STING to produce antiviral type I interferon, which further supports its potential as a therapeutic drug or research tool.

Garvey, B. T., Moyano, L. M., Ayvar, V., Rodriguez, S., Gilman, R. H., Gonzalez, A. E., . . . For The Cysticercosis Working Group In, P. (2017). **Neurocysticercosis among People Living Nearby Pigs Heavily Infected with Cysticercosis in Rural Endemic Peru**. *Am J Trop Med Hyg*. doi:10.4269/ajtmh.17-0443

Neurocysticercosis causes substantial neurologic morbidity in endemic regions around the world. In this cross-sectional study, we describe the frequency of neurocysticercosis among a presumed high-risk group of people in an endemic community in northern Peru. Participants who screened positive on a nine-question seizure survey were evaluated clinically to diagnose epilepsy using International League Against Epilepsy criteria. Those with epilepsy were offered a noncontrast computerized tomography (CT) of the head. We also tested sera from all participants using an enzyme-linked immunoelectrotransfer blot (EITB) LLGP to detect anti-cysticercus antibodies and enzyme-linked immunosorbent assay (ELISA) B60/B158 to detect cysticercosis antigens. Participants with strongly positive ELISA (ratio >/= 3) were offered a noncontrast magnetic resonance imaging (MRI) of the brain. We diagnosed 16 cases of epilepsy among 527 people screened (lifetime prevalence 30 per 1,000). Twelve with epilepsy accepted CT scan and five (41.7%) had parenchymal calcifications. None had viable cysts. Of the 514 who provided a blood sample, 241 (46.9%) were seropositive by EITB and 12 (2.9%) were strongly positive by ELISA (ratio >/= 3). Eleven accepted MRI and eight (72.3%) had neurocysticercosis, including five with extraparenchymal cysts, five with parenchymal vesicular cysts, and two with parenchymal granulomas. These findings show that clinically relevant forms of neurocysticercosis and epilepsy can be found by applying screening interventions in communities endemic to Taenia solium. Longitudinal controlled studies are needed to better understand which subgroups are at highest risk and which are most likely to have improved prognosis as a result of screening.

Gay, N. D., Kozin, E., Okada, C., Danilov, A. V., & Spurgeon, S. (2017). **Obinutuzumab monotherapy in previously untreated chronic lymphocytic leukemia**. *Leukemia and Lymphoma*, 1-3. doi:10.1080/10428194.2017.1410890

Gerson, R., Havens, J., Marr, M., Storfer-Isser, A., Lee, M., Marcos, C. R., . . . Horwitz, S. M. (2017). **Utilization patterns at a specialized children's comprehensive psychiatric emergency program**. *Psychiatric Services, 68*(11), 1104-1111. doi:10.1176/appi.ps.201600436

Objective: Most youths experiencing a psychiatric crisis present to emergency departments (EDs) that lack the specialized staff to evaluate them, so youths are often discharged without appropriate mental health assessment or treatment. To better understand the needs of this population, this study described clinical details and disposition associated with visits for psychiatric emergencies to a specialized ED staffed 24/7 by child psychiatrists. Methods: Through retrospective chart review, 1,180 visits to the ED during its first year of operation were reviewed for clinical characteristics, prior service utilization, and demographic characteristics. Bivariate analyses (chi-square test and Wilcoxon rank sum test) compared differences in disposition (evaluate and release, brief stabilization, and inpatient psychiatric admission) associated with characteristics of the children's first visit (N=885). Measures with bivariate association of p,.10 were further assessed by using multinomial logistic regression analyses. Results: For most visits (59%), children were evaluated and released, 13% were briefly stabilized, and 28% were admitted for psychiatric treatment. Youths with mood or psychotic disorders were more likely to be admitted, as were those with current suicidality or aggression. Many youths who presented with aggression were also identified as having suicidality or self-harm. Conclusions: Clinical factors, especially suicidality, predicted psychiatric admission. Admission rates for youths with suicidality were significantly higher in this study than previously reported, suggesting the availability of child psychiatrists in this ED allowed greater ascertainment of suicide risk (and thus hospitalization to mitigate that risk) than occurs in EDs without such staffing.

Geryk, L. L., Roberts, C. A., & Carpenter, D. M. (2017). **A systematic review of school-based interventions that include inhaler technique education**. *Respiratory Medicine, 132*, 21-30. doi:10.1016/j.rmed.2017.09.001

BACKGROUND: Proper use of inhaled medication is essential for the successful treatment of childhood asthma; yet, improper inhaler technique among school-aged children is common. There are many schoolbased asthma education programs, but the extent to which these programs teach inhaler technique is unknown. METHODS: We systematically reviewed the literature to identify schoolbased asthma interventions that included inhaler technique instruction. We searched several databases, including PubMed, for relevant articles. Studies were included if they were asthma interventions of any type (programs, curriculums, education) conducted at kindergarten through twelfth grade schools that taught inhaler technique and included inhaler technique as an outcome measure. Of the 285 citations identified, the final nine studies (selected from 71 full-text articles) met the inclusion criteria. RESULTS: Findings from this systematic review identified a very small number of school-based interventions that evaluated improvements in students' inhaler technique. Two of the nine studies (22%) used a validated measure of inhaler technique. Inhaler technique instruction varied in length, from 15 min to 1 h and nurses implemented inhaler technique instruction in six of the nine (67%) interventions. Existing studies offer mixed evidence for sustained technique improvements up to a 12-month follow-up period. CONCLUSIONS: Evidence suggests that students benefit from school-based inhaler technique education; however, inconsistencies in how technique was measured limit our ability to draw firm conclusions regarding the effectiveness of inhaler technique education on student outcomes. Future studies are needed to identify the most appropriate and feasible inhaler technique education components for use in comprehensive asthma self management interventions.

Gibbs Pickens, C. M., Kramer, M. R., Howards, P. P., Badell, M. L., Caughey, A. B., & Hogue, C. J. (2018). **Term Elective Induction of Labor and Pregnancy Outcomes Among Obese Women and Their Offspring**. *Obstet Gynecol, 131*(1), 12-22. doi:10.1097/aog.0000000000002408

OBJECTIVE: To evaluate whether elective induction of labor between 39 through 41 weeks of gestation, as compared with expectant management, is associated with reduced cesarean delivery and other adverse outcomes among obese women and their offspring. METHODS: We conducted a retrospective cohort study using the 2007-2011 California Linked Patient Discharge Data-Birth Cohort File of 165,975 singleton, cephalic, nonanomalous deliveries to obese women. For each gestational week (39-41), we used multivariable logistic regression models, stratified by parity, to assess whether elective induction of labor or expectant management was associated with lower odds of cesarean delivery and other adverse outcomes. RESULTS: At 39 and 40 weeks of gestation, cesarean delivery was less common in obese nulliparous women who were electively induced compared with those who were expectantly managed (at 39 weeks of gestation, frequencies were 35.9% vs 41.0%, respectively [P<.05]; adjusted odds ratio [OR] 0.82, 95% CI 0.77-0.88). Severe maternal morbidity was less frequent among electively induced obese nulliparous patients (at 39 weeks of gestation, 5.6% vs 7.6% [P<.05]; adjusted OR 0.75, 95% CI 0.65-0.87). Neonatal intensive care unit admission was less common among electively induced obese nulliparous women (at 39 weeks of gestation, 7.9% vs 10.1% [P<.05]; adjusted OR 0.79, 95% CI 0.70-0.89). Patterns were similar among obese parous women at 39 weeks of gestation (crude frequencies and adjusted ORs [95% CIs] were as follows: for cesarean delivery, 7.0% vs 8.7% [P<.05] and 0.79 [0.73-0.86]; for severe maternal morbidity, 3.3% vs 4.0% [P<.05] and 0.83 [0.74-0.94]; for neonatal intensive care unit admission: 5.3% vs 7.4% [P<.05] and 0.75 [0.68-0.82]). Similarly, elective induction at 40 weeks of gestation was associated with reduced odds of cesarean delivery, maternal morbidity, and neonatal intensive care unit admission among both obese nulliparous and parous patients. CONCLUSION: Elective labor induction after 39 weeks of gestation was associated with reduced maternal and neonatal morbidity among obese women. Further prospective investigation is necessary.

Gill, T., Asquith, M., Brooks, S. R., Rosenbaum, J. T., & Colbert, R. A. (2017). **Effects of HLA-B27 on Gut Microbiota in Experimental Spondyloarthritis Implicate an Ecological Model of Dysbiosis**. *Arthritis Rheumatol*. doi:10.1002/art.40405

OBJECTIVES: We investigated whether HLA-B27-mediated experimental spondyloarthritis (SpA) is associated with a common gut microbial signature to identify potential drivers of pathogenesis. METHODS: Effects of HLA-B27 on three genetic backgrounds, Dark Agouti (DA), Lewis, and Fischer were compared, using wild-type littermates and HLA-B7 transgenic Lewis rats as controls. At 2, 3-4, and 6-8 months of age, cecal and colonic tissue or contents were analyzed by histology for inflammation, RNA-Seq for gene expression differences, and 16S rRNA gene sequencing for microbiota differences. RESULTS: HLA-B27 transgenic Lewis and Fischer rats develop gut inflammation, while DA rats are resistant to effects of HLA-B27, and HLA-B7 transgenic rats remain unaffected. Immune dysregulation in affected Lewis and Fischer rats is similar and dominated by activation of IL-23/IL-17, IFN, TNF, and IL-1 cytokines and pathways in colon and cecum, while DA rats exhibit low-level cytokine dysregulation without inflammation. Gut microbial changes in HLA-B27 transgenic rats are strikingly divergent on the three different backgrounds, including different patterns of dysbiosis in HLA-B27 transgenic Lewis and Fischer strains with some overlap. Interestingly, DA rats lack segmented filamentous bacteria (SFB) that promote CD4+ Th17 T-cell development, which may explain their resistance to disease. CONCLUSION: Effects of HLA-B27 on gut microbiota and dysbiosis in SpA are highly dependent on host genetic background and/or environment despite convergence of dysregulated immune pathways. These results indicate an ecological model of dysbiosis where the effects of multiple microbes contribute to the aberrant immune response, rather than a single or small number of microbes driving pathogenesis. This article is protected by copyright. All rights reserved.

Golden, S. E., Thomas, C. R., Jr., Deffebach, M. E., Sukumar, M. S., Schipper, P. H., Tieu, B. H., . . . Slatore, C. G. (2017). **"It wasn't as bad as I thought it would be": a qualitative study of early stage non-small cell lung cancer patients after treatment**. *BMC Research Notes, 10*(1), 642. doi:10.1186/s13104-017-2956-3

OBJECTIVE: While surgical resection is recommended for most patients with early stage lung cancer, stereotactic body radiotherapy (SBRT) is being increasingly utilized. Provider-patient communication regarding risks/benefits of each approach may be a modifiable factor leading to improved patient-centered outcomes. Our objective was to determine a framework and recommended strategies on how to best communicate with patients with early stage non-small cell lung cancer (NSCLC) in the post-treatment setting. We qualitatively evaluated the experiences of 11 patients with early clinical stage NSCLC after treatment, with a focus on treatment experience, knowledge obtained, communication, and recommendations. We used conventional content analysis and a patient-centered communication theoretical model to guide our understanding. RESULTS: Five patients received surgery and six received SBRT. Both treatments were generally well-tolerated. Few participants reported communication deficits around receiving follow-up information, although several had remaining questions about their treatment outcome (mainly those who underwent SBRT). They described feeling anxious regarding their first surveillance CT scan and clinician visit. Overall, participants remained satisfied with care because of implicit trust in their clinicians rather than explicit communication. Communication gaps remain but may be addressed by a trusting relationship with the clinician. Patients recommend clinicians give thorough explanations and personalize when possible.

Goldman, J. G., Andrews, H., Amara, A., Naito, A., Alcalay, R. N., Shaw, L. M., . . . Kang, U. J. (2017). **Cerebrospinal fluid, plasma, and saliva in the BioFIND study: Relationships among biomarkers and Parkinson's disease Features**. *Movement Disorders*. doi:10.1002/mds.27232

OBJECTIVE: Examine relationships among neurodegenerative biomarkers and PD motor and nonmotor symptoms. BACKGROUND: CSF alpha-synuclein is decreased in PD versus healthy controls, but whether plasma and saliva alpha-synuclein differentiate these groups is controversial. Correlations of alpha-synuclein among biofluids (CSF, plasma, saliva) or biomarkers (eg, beta-amyloid, tau [total, phosphorylated]) are not fully understood. The relationships of these biomarkers with PD clinical features remain unclear. METHODS: BioFIND, a cross-sectional, observational study, examines clinical and biomarker characteristics in moderate-advanced PD and matched healthy controls. We compared alpha-synuclein concentrations across diagnosis, biofluids, and CSF biomarkers. Correlations of CSF biomarkers and MDS-UPDRS, motor phenotype, MoCA, and rapid eye movement sleep behavior disorder questionnaire scores in PD were examined. RESULTS: CSF alpha-synuclein was lower in PD versus controls ($P = .01$), controlling for age, gender, and education. Plasma and saliva alpha-synuclein did not differ between PD and controls, and alpha-synuclein did not significantly correlate among biofluids. CSF beta-amyloid1-42 was lower in PD versus controls ($P < .01$), and correlated weakly with MoCA recall scores ($r = 0.23$, $P = .02$). CSF alpha-synuclein was lower in the postural instability/gait difficulty phenotype than other motor phenotypes ($P < .01$). No CSF biomarkers predicted or correlated with total motor or rapid eye movement sleep behavior disorder scores. CSF alpha-synuclein correlated with beta-amyloid1-42 , total-tau, and phosphorylated-tau ($r = 0.41, 0.81, 0.43$, respectively; $Ps < .001$). CONCLUSION: Lower CSF alpha-synuclein is associated with diagnosis and motor phenotype in moderate-advanced PD. Plasma and saliva alpha-synuclein neither correlate with CSF alpha-synuclein, nor distinguish PD from controls. CSF beta-amyloid1-42 remains a potential biomarker for cognitive impairment in PD. (c) 2017 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Goodworth, A. D., & Peterka, R. J. (2017). **Identifying mechanisms of stance control: a single stimulus multiple output model-fit approach**. *Journal of Neuroscience Methods*. doi:10.1016/j.jneumeth.2017.12.015

BACKGROUND: Posture control models are instrumental to interpret experimental data and test hypotheses. However, as models have increased in complexity to include multi-segmental dynamics, discrepancy has arisen amongst researchers regarding the accuracy and limitations of identifying neural control parameters using a single stimulus. NEW METHOD: The current study examines this topic using simulations with a parameterized model-fit approach. We first determine if the model-fit approach can identify parameters in the theoretical situation with no noise. Then, we measure variability and bias of parameter estimates when

realistic noise is included. We also address how the accuracy is influenced by the frequency bandwidth of the stimulus, signal-to-noise of the data, and fitting procedures. RESULTS: We found perfect identification of parameters in the theoretical model without noise. With realistic noise, bias errors were 4.4% and 7.6% for fits that included frequencies 0.02-1.2Hz and 0.02-0.4Hz, respectively. Fits between 0.02-1.2Hz also had the lowest variability in parameter estimates compared to other bandwidths. Parameters with the lowest variability tended to have the largest influence on body sways. Results also demonstrated the importance of closely examining model fits because of limitations in fitting algorithms. COMPARISON WITH EXISTING METHOD: The single-input model-fit approach may be a simpler and more practical method for identifying neural control mechanisms compared to a multi-stimulus alternative. CONCLUSIONS: This study provides timely theoretical and practical considerations applicable to the design and analysis of experiments contributing to the identification of mechanisms underlying stance control of a multi-segment body.

Gosselin, J. L., Zabel, R. W., Anderson, J. J., Faulkner, J. R., Baptista, A. M., & Sandford, B. P. (2017). **Conservation planning for freshwater-marine carryover effects on Chinook salmon survival**. *Ecology and Evolution*. doi:10.1002/ece3.3663

Experiences of migratory species in one habitat may affect their survival in the next habitat, in what is known as carryover effects. These effects are especially relevant for understanding how freshwater experience affects survival in anadromous fishes. Here, we study the carryover effects of juvenile salmon passage through a hydropower system (Snake and Columbia rivers, northwestern United States). To reduce the direct effect of hydrosystem passage on juveniles, some fishes are transported through the hydrosystem in barges, while the others are allowed to migrate in-river. Although hydrosystem survival of transported fishes is greater than that of their run-of-river counterparts, their relative juvenile-to-adult survival (hereafter survival) can be less. We tested for carryover effects using generalized linear mixed effects models of survival with over 1 million tagged Chinook salmon, Oncorhynchus tshawytscha (Walbaum) (Salmonidae), migrating in 1999-2013. Carryover effects were identified with rear-type (wild vs. hatchery), passage-type (run-of-river vs. transported), and freshwater and marine covariates. Importantly, the Pacific Decadal Oscillation (PDO) index characterizing cool/warm (i.e., productive/nonproductive) ocean phases had a strong influence on the relative survival of rear- and passage-types. Specifically, transportation benefited wild Chinook salmon more in cool PDO years, while hatchery counterparts benefited more in warm PDO years. Transportation was detrimental for wild Chinook salmon migrating early in the season, but beneficial for later season migrants. Hatchery counterparts benefited from transportation throughout the season. Altogether, wild fish could benefit from transportation approximately 2 weeks earlier during cool PDO years, with still a benefit to hatchery counterparts. Furthermore, we found some support for hypotheses related to higher survival with increased river flow, high predation in the estuary and plume areas, and faster migration and development-related increased survival with temperature. Thus, pre- and within-season information on local- and broad-scale conditions across habitats can be useful for planning and implementing real-time conservation programs. © 2017.

Grabel, Z. J., Hart, R. A., Clark, A. P., Park, S. H., Shaffrey, C. I., Scheer, J. K., . . . Daniels, A. H. (2018). **Adult Spinal Deformity Knowledge in Orthopedic Spine Surgeons: Impact of Fellowship Training, Experience, and Practice Characteristics**. *Spine Deform, 6*(1), 60-66. doi:10.1016/j.jspd.2017.06.003

STUDY DESIGN: Survey study. OBJECTIVE: The purpose of this paper was to assess the level of adult spine deformity (ASD) knowledge among orthopedic spine surgeons and identify areas for improvement in spine surgery training. SUMMARY OF BACKGROUND DATA: ASD is increasingly encountered in spine surgery practice. While ASD knowledge among neurosurgeons has been evaluated, ASD knowledge among orthopedic spine surgeons has not previously been reported. METHODS: A survey of orthopedic spine surgeon members of North American Spine Society (NASS) was conducted to assess level of spine surgery training, practice experience, and spinal deformity knowledge base. The survey used was previously completed by a group of neurologic surgeons with published results. The survey used 11 questions developed and agreed upon by experienced spinal deformity surgeons. RESULTS: Complete responses were received from 413 orthopedic

spine surgeons. The overall correct-answer rate was 69.0%. Surgeons in practice for less than 10 years had a higher correct-answer rate compared to those who have practiced for 10 years or more (74% vs. 67%; p = .000003). Surgeons with 75% or more of their practice dedicated to spine had a higher overall correct rate compared to surgeons whose practice is less than 75% spine (71% vs. 63%; p = .000029). Completion of spine fellowship was associated with a higher overall correct-answer rate compared to respondents who did not complete a spine fellowship (71% vs. 59%; p < .00001). CONCLUSIONS: Completion of spine fellowship and having a dedicated spine surgery practice were significantly associated with improved performance on this ASD knowledge survey. Unlike neurosurgeons, orthopedic spine surgeons who have practiced for less than 10 years performed better than those who have practiced for more than 10 years. Ongoing emphasis on spine deformity education should be emphasized to improve adult spinal deformity knowledge base.

Gradidge, E. A., Bakar, A., Tellez, D., Ruppe, M., Tallent, S., Bird, G., . . . Nishisaki, A. (2017). **Effect of Location on Tracheal Intubation Safety in Cardiac Disease-Are Cardiac ICUs Safer?** *Pediatr Crit Care Med*. doi:10.1097/pcc.0000000000001422

OBJECTIVES: Evaluate differences in tracheal intubation-associated events and process variances (i.e., multiple intubation attempts and oxygen desaturation) between pediatric cardiac ICUs and noncardiac PICUs in children with underlying cardiac disease. DESIGN: Retrospective cohort study using a multicenter tracheal intubation quality improvement database (National Emergency Airway Registry for Children). SETTING: Thirty-six PICUs (five cardiac ICUs, 31 noncardiac ICUs) from July 2012 to March 2016. PATIENTS: Children with medical or surgical cardiac disease who underwent intubation in an ICU. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Our primary outcome was the rate of any adverse tracheal intubation-associated event. Secondary outcomes were severe tracheal intubation-associated events, multiple tracheal intubation attempt rates, and oxygen desaturation. There were 1,502 tracheal intubations in children with underlying cardiac disease (751 in cardiac ICUs, 751 in noncardiac ICUs) reported. Cardiac ICUs and noncardiac ICUs had similar proportions of patients with surgical cardiac disease. Patients undergoing intubation in cardiac ICUs were younger (median age, 1 mo [interquartile range, 0-6 mo]) compared with noncardiac ICUs (median 3 mo [interquartile range, 1-11 mo]; p < 0.001). Tracheal intubation-associated event rates were not different between cardiac ICUs and noncardiac ICUs (16% vs 19%; adjusted odds ratio, 0.74; 95% CI, 0.54-1.02; p = 0.069). However, in a sensitivity analysis comparing cardiac ICUs with mixed ICUs (i.e., ICUs caring for children with either general pediatric or cardiac diseases), cardiac ICUs had decreased odds of adverse events (adjusted odds ratio, 0.71; 95% CI, 0.52-0.97; p = 0.033). Rates of severe tracheal intubation-associated events and multiple attempts were similar. Desaturations occurred more often during intubation in cardiac ICUs (adjusted odds ratio, 1.61; 95% CI, 1.04-1.15; p = 0.002). CONCLUSIONS: In children with underlying cardiac disease, rates of adverse tracheal intubation-associated events were not lower in cardiac ICUs as compared to noncardiac ICUs, even after adjusting for differences in patient characteristics and care models.

Grandi, V. H., Berger, S. B., Fugolin, A. P. P., Gonini-Junior, A., Lopes, M. B., Consani, S., & Guiraldo, R. D. (2017). **Microtensile Bond Strength and Microhardness of Composite Resin Restorations Using a Sonic-Resin Placement System**. *Braz Dent J, 28*(5), 618-623. doi:10.1590/0103-6440201701469

The aim of this study was to evaluate the efficacy of applying sonic energy on microtensile bond strength and microhardness after the restoration process. A total of 40 human third molars were extracted. Class II cavities were prepared and restored with composite SonicFill or Filtek Z350 XT with and without the application of sonic energy. After the teeth were stored in water for 24 h, the teeth were sectioned into sticks (1.0 mm2) and subjected to tensile testing. For a depth Knoop hardness test, the samples were cut and indentations were made sequentially from the surface of the samples to the bottom of the samples in three intervals of 1 mm each. The samples were then subjected to a load of 50 g for 10 s. The results from the tensile (factors: placement system and composite) and hardness (factors: placement system, composite and depth) tests were subjected to the Kolmogorov-Smirnov normality test, followed by analysis of variance and Tukey's test (5% significance). For the placement system factor, higher bond strength was observed for the cavities that

were restored with sonic energy ($p < 0.001$). For depth Knoop hardness, the hardness at 1 mm depth was significantly greater than that at 3 mm depth just for the restorations with Filtek Z350 XT composite without the application of sonic energy. Therefore, the use of sonic energy during the restorative process improved bonding, yet it did not markedly affect the depth hardness for both composites.

Gregg, J. L. (2017). **The Promises And Pitfalls Of Treating Addiction**. *Health Aff (Millwood), 36*(12), 2204-2206. doi:10.1377/hlthaff.2017.0632

Treatment of addiction in primary care should increase, but it will fail without the proper supports for providers in place.

Guevara-Aguirre, J., Teran, E., & Rosenfeld, R. (2017). **Meeting Reports: The 2017-USFQ Biennial Meeting on Growth Hormone and IGF1 Research**. *Pediatric Endocrinology Reviews, 15*(2), 173-184. doi:10.17458/per.vol15.2017.gtr.mr.2017usfqbiennialmeeting

Gummin, D. D., Mowry, J. B., Spyker, D. A., Brooks, D. E., Fraser, M. O., & Banner, W. (2017). **2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report**. *Clinical Toxicology (Philadelphia, Pa.), 55*(10), 1072-1252. doi:10.1080/15563650.2017.1388087

INTRODUCTION: This is the 34th Annual Report of the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS). As of 1 January 2016, 55 of the nation's poison centers (PCs) uploaded case data automatically to NPDS. The upload interval was 9.50 [7.33, 14.6] (median [25%, 75%]) min, facilitating a near real-time national exposure and information database and surveillance system. METHODS: We analyzed the case data tabulating specific indices from NPDS. The methodology was similar to that of previous years. Where changes were introduced, the differences are identified. Cases with medical outcomes of death were evaluated by a team of medical and clinical toxicologist reviewers using an ordinal scale of 1-6 to assess the Relative Contribution to Fatality (RCF) of the exposure. RESULTS: In 2016, 2,710,042 closed encounters were logged by NPDS: 2,159,032 human exposures, 54,019 animal exposures, 490,215 information cases, 6687 human confirmed non-exposures, and 89 animal confirmed non-exposures. US PCs also made 2,718,022 follow-up calls in 2016. Total encounters showed a 2.94% decline from 2015, while health care facility (HCF) human exposure cases increased by 3.63% from 2015. All information calls decreased by 12.5% but HCF information calls increased 0.454%, and while medication identification requests (Drug ID) decreased 29.6%, human exposure cases were essentially flat, decreasing by 0.431%. Human exposures with less serious outcomes have decreased 2.59% per year since 2008 while those with more serious outcomes (moderate, major or death) have increased by 4.39% per year since 2000. The top five substance classes most frequently involved in all human exposures were analgesics (11.2%), household cleaning substances (7.54%), cosmetics/personal care products (7.20%), sedatives/hypnotics/antipsychotics (5.84%), and antidepressants (4.74%). As a class, sedative/hypnotics/antipsychotics exposures increased most rapidly, by 10.7% per year (2088 cases/year), over the last 15 years for cases showing more serious outcomes. The top five most common exposures in children age 5 years or less were cosmetics/personal care products (13.3%), household cleaning substances (11.1%), analgesics (9.21%), foreign bodies/toys/miscellaneous (6.48%), and topical preparations (5.07%). Drug identification requests comprised 28.1% of all information calls. NPDS documented 1977 human exposures resulting in death; 1492 (75.5%) of these were judged as related (RCF of 1 - undoubtedly responsible, 2 - probably responsible, or 3 - contributory). CONCLUSIONS: These data support the continued value of PC expertise and need for specialized medical toxicology information to manage more serious exposures, despite a decrease in cases involving less serious exposures. Unintentional and intentional exposures continue to be a significant cause of morbidity and mortality in the US. The near real-time, always current status of NPDS represents a national public health resource for collecting and monitoring US exposure cases and information calls. The continuing

mission of NPDS is to provide a nationwide infrastructure for surveillance for all types of exposures (e.g. foreign body, infectious, venomous, chemical agent, or commercial product), and the identification and tracking of significant public health events. NPDS is a model system for the real-time surveillance of national and global public health.

Haberer, J. E., Ngure, K., Muwonge, T., Mugo, N., Katabira, E., Heffron, R., . . . Partners Mobile Adherence to Pr, E. P. T. (2017). **Brief Report: Context Matters: PrEP Adherence is Associated With Sexual Behavior Among HIV Serodiscordant Couples in East Africa**. *Journal of acquired immune deficiency syndromes (1999), 76*(5), 488-492. doi:10.1097/QAI.0000000000001548

BACKGROUND: Short message service (SMS) surveys are a promising tool for understanding whether preexposure prophylaxis (PrEP) adherence aligns with risk for HIV acquisition-a concept known as prevention-effective adherence. METHODS: The Partners Demonstration Project was an open-label study of integrated PrEP and antiretroviral therapy (ART) delivery among high-risk HIV serodiscordant couples in East Africa. HIV-uninfected partners were offered PrEP until their HIV-infected partner had taken ART for ≥6 months. At 2 study sites, HIV-uninfected partners were offered enrollment into the Partners Mobile Adherence to PrEP (PMAP) substudy based on ongoing PrEP use, personal cell phone ownership, and ability to use SMS. SMS surveys asked about PrEP adherence and sexual activity in the previous 24 hours; these surveys were sent daily for the 7 days before and 7 days after routine study visits in the Partners Demonstration Project. RESULTS: The PMAP substudy enrolled 373 HIV-uninfected partners; 69% were men and mean age was 31 years. Participants completed 17,030 of 23,056 SMS surveys sent (74%) with a mean of 47 surveys per participant over 9.8 months of follow-up. While HIV-infected partner use of ART was <6 months, mean reported PrEP adherence was 92% on surveys concurrently reporting sex within the serodiscordant partnership, and 84% on surveys reporting no sex ($P < 0.001$). DISCUSSION: SMS surveys provided daily assessment of concurrent PrEP adherence and sexual behavior. Higher PrEP adherence was temporally associated with increased risk for HIV acquisition.

Haisley, K. R., Drexel, S. E., Watters, J. M., Hunter, J. G., & Mullins, R. J. (2017). **Major Barbara Stimson: A Historical Perspective on the American Board of Surgery Through the Accomplishments of the First Woman to Achieve Board Certification**. *Annals of Surgery*. doi:10.1097/sla.0000000000002636

: Dr. Barbara Bartlett Stimson, AB, MD, MedScD, FACS (1898-1986) was a pioneering orthopedic surgeon from a prominent American family who, in 1940, became the first woman certified by the American Board of Surgery (ABS, certificate number 860). It would be another 7 years and approximately 2500 candidates before the next female surgeon would be certified. A member of the third class to admit women to Columbia Medical School and the second female surgical resident to complete training at Columbia-Presbyterian Medical Center, Dr. Stimson was a confident and exceptionally accomplished trailblazer for women in surgery. In this biographical sketch based upon documents from the ABS, and the archives of Vassar College and the College of Physicians and Surgeons at Columbia-Presbyterian Medical Center, Dr. Stimson's motivations, attitudes, and unique accomplishments emerge as testimony to the exceptional career of this driven, self-possessed woman. Stimson was undaunted by the sex-based conventions of her time, and achieved a notable career as a surgeon in the profession she loved; first honing her skills at a busy urban fracture service in New York, then serving with distinction in the Royal Army Medical Corps during World War II, and finally returning to the states to become a respected leader in her field. Her life story and unprecedented ABS certification affirm her conviction that proven skill and ability can be used as a means of overcoming unfounded biases, and helped pave the way for future generations of board certified female surgeons in the United States.

Hammarlund, E., Thomas, A., Amanna, I. J., Holden, L. A., Slayden, O. D., Park, B., . . . Slifka, M. K. (2017). **Plasma cell survival in the absence of B cell memory**. *Nature Communications, 8*(1). doi:10.1038/s41467-017-01901-w

Pre-existing serum antibodies play an important role in vaccine-mediated protection against infection but the underlying mechanisms of immune memory are unclear. Clinical studies indicate that antigen-specific antibody responses can be maintained for many years, leading to theories that reactivation/differentiation of memory B cells into plasma cells is required to sustain long-term antibody production. Here, we present a decade-long study in which we demonstrate site-specific survival of bone marrow-derived plasma cells and durable antibody responses to multiple virus and vaccine antigens in rhesus macaques for years after sustained memory B cell depletion. Moreover, BrdU+ cells with plasma cell morphology can be detected for 10 years after vaccination/BrdU administration, indicating that plasma cells may persist for a prolonged period of time in the absence of cell division. On the basis of these results, long-lived plasma cells represent a key cell population responsible for long-term antibody production and serological memory. © 2017 The Author(s).

Han, L., Patil, E., Kidula, N., Lyn Gaffield, M., & Steyn, P. S. (2017). **From Research to Policy: The WHO Experience With Developing Guidelines on the Potential Risk of HIV Acquisition and Progestogen-Only Contraception Use**. *Glob Health Sci Pract, 5*(4), 540-546. doi:10.9745/ghsp-d-17-00278

Harris, S. K., Mitchell, E. L., Lasarev, M. R., Attia, F., Hunter, J. G., & Sheppard, B. C. (2017). **Effect of a hospital-associated urinary tract infection reduction policy on general surgery patients**. *Am J Surg*. doi:10.1016/j.amjsurg.2017.11.025

BACKGROUND: Hospital-associated UTI rates in surgery patients have not improved despite recommendations for reducing indwelling catheter days. METHODS: We performed a retrospective review of institutional NSQIP general surgery patient data, 2006-2015. During this time, a UTI-reduction policy was implemented. Demographics, HA-UTI incidence, CA-UTI incidence, indwelling catheter days, straight catheterization rates, and mortality were examined. RESULTS: Females had significantly higher risk of HA-UTI. There was no significant change in HA-UTI (X12=0.02, p=.878) or indwelling catheter days (5.18+/-1.12 days v 3.73+/-0.39 days, p=.23). Straight catheterizations among those with HA-UTI increased (0.04+/-0.04 v 0.32+/-0.12, p=.029). There was no change in CA-UTI (1.38 v 1.11 CAUTI/1000 patient hospital-days P=.555) or in initial indwelling catheter days of patients with CA-UTI (7.2 SD 8.89 v 47.0 SD 7.04 days P=.961) after policy implementation. CONCLUSIONS: The reduction policy increased the number of straight catheterizations for patients developing HA-UTI, but did not reduce the number of initial indwelling catheter days, HA-UTI rates, or CA-UTI rates.

Harris, S. K., Wilson, D. G., Jung, E., Azarbal, A. F., Landry, G. J., Liem, T. K., . . . Mitchell, E. L. (2017). **Interhospital vascular surgery transfers to a tertiary care hospital**. *Journal of Vascular Surgery*. doi:10.1016/j.jvs.2017.09.044

OBJECTIVE: Interhospital transfers (IHTs) to tertiary care centers are linked to lower operative mortality in vascular surgery patients. However, IHT incurs great health care costs, and some transfers may be unnecessary or futile. In this study, we characterize the patterns of IHT at a tertiary care center to examine appropriateness of transfer for vascular surgery care. METHODS: A retrospective review was performed of all IHT requests made to our institution from July 2014 to October 2015. Interhospital physician communication and reasons for not accepting transfers were reviewed. Diagnosis, intervention, referring hospital size, and mortality were examined. Follow-up for all patients was reviewed. RESULTS: We reviewed 235 IHT requests for vascular surgical care involving 210 patients during 15 months; 33% of requested transfers did not occur, most commonly after communication with the physician resulting in reassurance (35%), clinic referral (30%), or further local workup obviating need for transfer (11%); 67% of requests were accepted. Accepted transfers generally carried life- or limb-threatening diagnoses (70%). Next most common transfer reasons were infection or nonhealing wounds (7%) and nonurgent postoperative complications (7%). Of accepted transfers, 72% resulted in operative or endovascular intervention; 20% were performed <8 hours of arrival,

12% <24 hours of arrival, and 68% during hospital admission (average of 3 days); 28% of accepted patients received no intervention. Small hospitals (<100 beds) were more likely than large hospitals (>300 beds) to transfer patients not requiring intervention (47% vs 18%; P = .005) and for infection or nonhealing wounds (30% vs 10%; P = .013). Based on referring hospital size, there was no difference in IHTs requiring emergent, urgent, or nonurgent operations. There was also no difference in transport time, time from consultation to arrival, or death of patients according to hospital size. Overall patient mortality was 12%. CONCLUSIONS: Expectedly, most vascular surgery IHTs are for life- or limb-threatening diagnoses, and most of these patients receive an operation. Transfer efficiency and surgical case urgency are similar across hospital sizes. Nonoperative IHTs are sent more often by small hospitals and may represent a resource disparity that would benefit from regionalizing nonurgent vascular care.

Hart, R. A., Rastegar, F., Contag, A., Kane, M., Daniels, A., Klineberg, E., . . . Kebaish, K. (2017). **Inter- and Intra-rater Reliability of the Hart-ISSG Proximal Junctional Failure Severity Scale**. *Spine (Phila Pa 1976)*. doi:10.1097/brs.0000000000002498

STUDY DESIGN: Reliability/external validation study. OBJECTIVE: Investigate inter- and intra-rater reliability of the Hart-ISSG PJFSS and its correlation with operative revision in patients with proximal junctional failure (PJF). SUMMARY OF BACKGROUND DATA: The Hart-ISSG PJFSS is a validated classification system for PJF. Reliability of the PJFSS has not been assessed. METHODS: Sixteen detailed clinical scenarios were assessed using the ISSG PJFSS classification in six categories: neurologic status, axial pain, instrumentation issue, proximal kyphotic angle, level of upper instrumented vertebrae (UIV), and severity of UIV/UIV+1 fracture. Eleven spine surgeons evaluated each case in all six categories during two different assessments, and provided recommendations regarding operative revision or observation for each case. Inter- and intra-rater reliability were calculated based on intraclass correlation coefficients (ICC). RESULTS: All ICCs demonstrated "almost perfect"' (0.817 to 0.988) inter-rater agreement for both assessments, except UIV/UIV+1 fracture severity during the second assessment, which demonstrated "substantial" agreement' (0.692). Five of 6 categories had "almost perfect" mean intra-rater reliability (0.805-0.981), while "instrumentation issue" demonstrated "substantial" mean agreement (0.757). Inter-rater reliability for recommendation of surgical intervention was "almost perfect" during both assessments (0.911 and 0.922, respectively). Mean PJFSS scores between the two assessments were significantly higher for cases recommended for operative revision (8.43 +/- 0.90) versus cases recommended for observation (p < 0.0001). CONCLUSION: The ISSG PJFSS is a reliable and repeatable classification system for assessing patients with proximal junctional failure. Higher PJFSS scales correlate with recommendation for operative revision, extending prior external validation of the PJFSS. LEVEL OF EVIDENCE: 3.

Harvey, N. C., Oden, A., Orwoll, E., Lapidus, J., Kwok, T., Karlsson, M. K., . . . Johansson, H. (2017). **Falls Predict Fractures Independently of FRAX Probability: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study**. *J Bone Miner Res*. doi:10.1002/jbmr.3331

Although prior falls are a well-established predictor of future fracture, there is currently limited evidence regarding the specific value of falls history in fracture risk assessment relative to that of other clinical risk factors and bone mineral density (BMD) measurement. We therefore investigated, across the three Osteoporotic Fractures in Men (MrOS) Study cohorts, whether past falls predicted future fracture independently of FRAX and whether these associations varied with age and follow-up time. Elderly men were recruited from MrOS Sweden, Hong Kong, and USA. Baseline data included falls history (over the preceding 12 months), clinical risk factors, BMD at femoral neck, and calculated FRAX probabilities. An extension of Poisson regression was used to investigate the associations between falls, FRAX probability, and incident fracture, adjusting for age, time since baseline, and cohort in base models; further models were used to investigate interactions with age and follow-up time. Random-effects meta-analysis was used to synthesize the individual country associations. Information on falls and FRAX probability was available for 4365 men in USA (mean age 73.5 years; mean follow-up 10.8 years), 1823 men in Sweden (mean age 75.4 years; mean follow-up 8.7 years), and 1669 men in Hong Kong (mean age 72.4 years; mean follow-up 9.8 years). Rates of past falls were similar

at 20%, 16%, and 15%, respectively. Across all cohorts, past falls predicted incident fracture at any site (hazard ratio [HR] = 1.69; 95% confidence interval [CI] 1.49, 1.90), major osteoporotic fracture (MOF) (HR = 1.56; 95% CI 1.33, 1.83), and hip fracture (HR = 1.61; 95% CI 1.27, 2.05). Relationships between past falls and incident fracture remained robust after adjustment for FRAX probability: adjusted HR (95% CI) any fracture: 1.63 (1.45, 1.83); MOF: 1.51 (1.32, 1.73); and hip: 1.54 (1.21, 1.95). In conclusion, past falls predicted incident fracture independently of FRAX probability, confirming the potential value of falls history in fracture risk assessment. (c) 2017 The Authors. Journal of Bone and Mineral Research Published by Wiley Periodicals Inc.

Haslam, A., Robb, S. W., Hebert, J. R., Huang, H., & Ebell, M. H. (2017). **Greater adherence to a Mediterranean diet is associated with lower prevalence of colorectal adenomas in men of all races**. *Nutrition Research, 48*, 76-84. doi:10.1016/j.nutres.2017.10.003

To examine potential racial differences in Mediterranean diet scores and whether these differences are associated with the prevalence of colorectal adenoma (CRA), a cross-sectional analysis of data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial was performed. The authors hypothesize that people consuming a more Mediterranean-like diet have lower odds of CRA. Flexible sigmoidoscopy was used to determine the presence of colorectal adenoma. Mediterranean diet scores were calculated from food frequency questionnaire responses. Logistic regression was used to determine the association between Mediterranean diet scores and the odds of prevalent CRA, as well as the joint effects of race and diet. Asians, followed by blacks, had higher Mediterranean diet scores than whites. Generally, men with better Mediterranean diet scores (altMED) had lower odds of CRA, but black and Asian men had even lower odds of prevalent CRA with better altMED diet scores than did white men with higher altMED diet scores. In this study population, all men had lower odds of prevalent CRA, but black and Asian men, who had higher (more favorable) altMED diet scores than whites, had even lower odds of prevalent CRA compared with white men. An altMED diet prescription may be especially beneficial for certain subpopulations who may be at higher risk of CRA.

Hassan, M., Prakasam, S., Bain, C., Ghoneima, A., & Liu, S. S. (2017). **A randomized split-mouth clinical trial on effectiveness of amnion-chorion membranes in alveolar ridge preservation: A clinical, radiologic, and morphometric study**. *International Journal of Oral and Maxillofacial Implants, 32*(6), 1389-1398. doi:10.11607/jomi.5875

Purpose: Recent case reports suggest that amnion-chorion membranes (ACM) and dense polytetrafluoroethylene membranes (dPTFE) can be left exposed during ridge preservation. The aim of this study was to compare the effectiveness of these membranes in ridge preservation, particularly when they are intentionally left exposed. Materials and Methods: A split-mouth, single-blind, randomized trial design was used to compare treatments with the two membranes in 22 nonmolar sites on the same arch. Ridge dimensions were recorded clinically and with cone beam computed tomography prior to and 3 months after ridge preservation. Postoperative discomfort was recorded with Visual Analog Scale (VAS) forms. Mixed-model analysis of variance was used to test significance. Results: Clinical and radiographic ridge dimensions were not significantly different between the two treatments. ACM sites had significantly more osteoid and higher bone volume density but significantly less graft particles and bone surface density compared with dPTFE. Mineralized bone area and soft tissue area were not significantly different between the two treatments. ACM sites had significantly lower postoperative VAS scores compared with dPTFE. Conclusion: Intentionally exposed ACM is equally effective in ridge preservation compared with dPTFE. Additionally, ACM use may aid in reducing postoperative VAS scores, and potentially result in better quality of bone available for implant placement, as evidenced by improved histomorphometric measures. © 2017 by Quintessence Publishing Co Inc.

Havel, P. J., Kievit, P., Comuzzie, A. G., & Bremer, A. A. (2017). **Use and Importance of Nonhuman Primates in Metabolic Disease Research: Current State of the Field**. *Ilar j*, 1-18. doi:10.1093/ilar/ilx031

Obesity and its multiple metabolic sequelae, including type 2 diabetes, cardiovascular disease, and fatty liver disease, are becoming increasingly widespread in both the developed and developing world. There is an urgent need to identify new approaches for the prevention and treatment of these costly and prevalent metabolic conditions. Accomplishing this will require the use of appropriate animal models for preclinical and translational investigations in metabolic disease research. Although studies in rodent models are often useful for target/pathway identification and testing hypotheses, there are important differences in metabolic physiology between rodents and primates, and experimental findings in rodent models have often failed to be successfully translated into new, clinically useful therapeutic modalities in humans. Nonhuman primates represent a valuable and physiologically relevant model that serve as a critical translational bridge between basic studies performed in rodent models and clinical studies in humans. The purpose of this review is to evaluate the evidence, including a number of specific examples, in support of the use of nonhuman primate models in metabolic disease research, as well as some of the disadvantages and limitations involved in the use of nonhuman primates. The evidence taken as a whole indicates that nonhuman primates are and will remain an indispensable resource for evaluating the efficacy and safety of novel therapeutic strategies targeting clinically important metabolic diseases, including dyslipidemia and atherosclerosis, type 2 diabetes, hepatic steatosis, steatohepatitis, and hepatic fibrosis, and potentially the cognitive decline and dementia associated with metabolic dysfunction, prior to taking these therapies into clinical trials in humans.

Herbst, R. S., Redman, M. W., Kim, E. S., Semrad, T. J., Bazhenova, L., Masters, G., . . . Gandara, D. R. (2017). **Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): A randomised, phase 3 study**. *The Lancet Oncology*. doi:10.1016/S1470-2045(17)30694-0

Background: EGFR antibodies have shown promise in patients with advanced non-small-cell lung cancer (NSCLC), particularly with squamous cell histology. We hypothesised that EGFR copy number by fluorescence in-situ hybridisation (FISH) can identify patients most likely to benefit from these drugs combined with chemotherapy and we aimed to explore the activity of cetuximab with chemotherapy in patients with advanced NSCLC who are EGFR FISH-positive. Methods: We did this open-label, phase 3 study (SWOG S0819) at 277 sites in the USA and Mexico. We randomly assigned (1:1) eligible patients with treatment-naive stage IV NSCLC to receive paclitaxel (200 mg/m2; every 21 days) plus carboplatin (area under the curve of 6 by modified Calvert formula; every 21 days) or carboplatin plus paclitaxel and bevacizumab (15 mg/kg; every 21 days), either with cetuximab (250 mg/m2 weekly after loading dose; cetuximab group) or without (control group), stratified by bevacizumab treatment, smoking status, and M-substage using a dynamic-balancing algorithm. Co-primary endpoints were progression-free survival in patients with EGFR FISH-positive cancer and overall survival in the entire study population. We analysed clinical outcomes with the intention-to-treat principle and analysis of safety outcomes included patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov (number NCT00946712). Findings: Between Aug 13, 2009, and May 30, 2014, we randomly assigned 1313 patients to the control group (n=657; 277 with bevacizumab and 380 without bevacizumab in the intention-to-treat population) or the cetuximab group (n=656; 283 with bevacizumab and 373 without bevacizumab in the intention-to-treat population). EGFR FISH was assessable in 976 patients and 400 patients (41%) were EGFR FISH-positive. The median follow-up for patients last known to be alive was 35·2 months (IQR 22·9-39·9). After 194 progression-free survival events in the cetuximab group and 198 in the control group in the EGFR FISH-positive subpopulation, progression-free survival did not differ between treatment groups (hazard ratio [HR] 0·92, 95% CI 0·75-1·12; p=0·40; median 5·4 months [95% CI 4·5-5·7] vs 4·8 months [3·9-5·5]). After 570 deaths in the cetuximab group and 593 in the control group, overall survival did not differ between the treatment groups in the entire study population (HR 0·93, 95% CI 0·83-1·04; p=0·22; median 10·9 months [95% CI 9·5-12·0] vs 9·2 months [8·7-10·3]). In the prespecified analysis of EGFR FISH-positive subpopulation with squamous cell histology, overall survival was significantly longer in the cetuximab group than in the control group (HR 0·58, 95% CI 0·36-0·86; p=0·0071), although progression-free survival did not differ between treatment groups in this subgroup (0·68, 0·46-1·01; p=0·055). Overall survival and progression-free survival did not differ among patients who were EGFR FISH non-positive with squamous cell histology (HR 1·04, 95% CI 0·78-1·40; p=0·77;

and 1·02, 0·77-1·36; p=0·88 respectively) or patients with non-squamous histology regardless of EGFR FISH status (for EGFR FISH-positive 0·88, 0·68-1·14; p=0·34; and 0·99, 0·78-1·27; p=0·96; respectively; and for EGFR FISH non-positive 1·00, 0·85-1·17; p=0·97; and 1·03, 0·88-1·20; p=0·69; respectively). The most common grade 3-4 adverse events were decreased neutrophil count (210 [37%] in the cetuximab group vs 158 [25%] in the control group), decreased leucocyte count (103 [16%] vs 74 [20%]), fatigue (81 [13%] vs 74 [20%]), and acne or rash (52 [8%] vs one [<1%]). 59 (9%) patients in the cetuximab group and 31 (5%) patients in the control group had severe adverse events. Deaths related to treatment occurred in 32 (6%) patients in the cetuximab group and 13 (2%) patients in the control group. Interpretation: Although this study did not meet its primary endpoints, prespecified subgroup analyses of patients with EGFR FISH-positive squamous-cell carcinoma cancers are encouraging and support co tinued evaluation of anti-EGFR antibodies in this subpopulation. Funding: National Cancer Institute and Eli Lilly and Company. © 2017 Elsevier Ltd.

Hickey, R. D., & Naugler, W. E. (2017). **Ectopic expansion of engineered human liver tissue seeds using mature cell populations**. *Hepatology*. doi:10.1002/hep.29718

Hill, B., Smith, J., Srinivasa, G., Sonmez, K., Sirasao, A., Gupta, A., & Mukherjee, M. (2017). *Precision medicine and FPGA technology: Challenges and opportunities*.

As genomic medicine becomes part of standard clinical care, Precision Medicine faces a daunting computational challenge in scaling up to support the genomic, image processing and analytics workloads required for millions of patients, especially in oncology clinics. Computational solutions based on heterogeneous hardware platforms like FPGAs have the potential to enable rollout of personalized care for large numbers of patients. We review several clinical use cases to shed light on how FPGA-based solutions can lead to large performance gains and tackle the computational bottlenecks in precision medicine. The biggest barrier to FPGA adoption is their accessibility and the steep learning curve for many bioinformatics and precision medicine codebase development groups. We describe new standard libraries and development environments that will facilitate FPGA-based development and show how they enable performance improvements with modest effort investment. © 2017 IEEE.

Hilton, T. J., Funkhouser, E., Ferracane, J. L., Gordan, V. V., Huff, K. D., Barna, J., . . . Gilbert, G. H. (2017). **Associations of Types of Pain with Crack-Level, Tooth-Level and Patient-Level Characteristics in Posterior Teeth with Visible Cracks: Findings from the National Dental Practice-Based Research Network**. *J Dent*. doi:10.1016/j.jdent.2017.12.014

OBJECTIVES: The objective of this study was to determine which patient traits, behaviors, external tooth and/or crack characteristics correlate with the types of symptoms that teeth with visible cracks exhibit, namely pain on biting, pain due to cold stimuli, or spontaneous pain. METHODS: Dentists in the National Dental Practice-Based Research Network enrolled a convenience sample of subjects each of whom had a single, vital posterior tooth with at least one observable external crack (cracked teeth); 2,858 cracked teeth from 209 practitioners were enrolled. Data were collected at the patient-, tooth-, and crack-level. Generalized estimating equations were used to obtain significant ($p < 0.05$) independent odds ratios (OR) associated with teeth that were painful for 10 outcomes based on types of pain and combinations thereof. RESULTS: Overall, 45% of cracked teeth had one or more symptoms. Pain to cold was the most common symptom, which occurred in 37% of cracked teeth. Pain on biting (16%) and spontaneous pain (11%) were less common. Sixty-five percent of symptomatic cracked teeth had only one type of symptom, of these 78% were painful only to cold. No patient-, tooth- or crack-level characteristic was significantly associated with pain to cold alone. Positive associations for various combinations of pain symptoms were present with cracks that: (1) were on molars; (2) were in occlusion; (3) had a wear facet through enamel; (4) had caries; (5) were evident on a radiograph; (6) ran in more than one direction; (7) blocked transilluminated light; (8) connected with another crack; (9) extended onto the root; (10) extended in more than one direction; or (11) were on the

distal surface. Persons who were < 65 yo or who clench, grind, or press their teeth together also were more likely to have pain symptoms. Pain was less likely in teeth with stained cracks or exposed roots, or in non-Hispanic whites. CONCLUSIONS: Although pain to cold was the most commonly noted pain associated with symptomatic cracked teeth, no patient-, tooth- or crack-level characteristic was significantly associated with pain to cold alone. Characteristics were only associated with pain on biting and/or spontaneous pain with or without pain to cold. CLINICAL SIGNIFICANCE: Although often considered the most reliable diagnosis for a cracked tooth, pain on biting is not the most common symptom of a tooth with a visible crack, but rather pain to cold.

Hodgman, E. I., Cripps, M. W., Mina, M. J., Bulger, E. M., Schreiber, M. A., Brasel, K. J., . . . Phelan, H. A. (2017). **External Validation of a Smartphone App Model to Predict the Need for Massive Transfusion Using Five Different Definitions**. *J Trauma Acute Care Surg*. doi:10.1097/ta.0000000000001756

INTRODUCTION: Previously, a model to predict massive transfusion protocol (activation) was derived using a single-institution dataset. The PROMMTT database was used to externally validate this model's ability to predict both massive transfusion protocol (MTP) activation and massive transfusion (MT) administration using multiple MT definitions. METHODS: The app model was used to calculate the predicted probability of massive transfusion protocol activation or massive transfusion delivery. The five definitions of MT used were: 1) 10 units packed red blood cells (PRBCs) in 24 hours; 2) Resuscitation Intensity score >/= 4; 3) Critical Administration Threshold; 4) 4 units PRBCs in 4 hours; and 5) 6 units PRBCs in 6 hours. Receiver operating curves were plotted to compare the predicted probability of MT with observed outcomes. RESULTS: Of 1245 patients in the dataset, 297 (24%) met definition 1, 570 (47%) met definition 2, 364 (33%) met definition 3, 599 met definition 4 (49.1%), and 395 met definition 5 (32.4%). Regardless of the outcome (MTP activation or MT administration), the predictive ability of the app model was consistent: when predicting activation of the MTP, the area under the curve (AUC) for the model was 0.694 and when predicting MT administration the AUC ranged from 0.695 - 0.711. CONCLUSION: Regardless of the definition of massive transfusion used, the app model demonstrates moderate ability to predict the need for massive transfusion in an external, homogenous population. Importantly, the app allows the model to be iteratively re-calibrated ("machine learning") and thus could improve its predictive capability as additional data are accrued. LEVEL OF EVIDENCE: III STUDY TYPE: Diagnostic test study.

Horowitz, K. M., & Horowitz, B. Z. (2017). Toxicity, Mushroom, Gyromitra *StatPearls*. Treasure Island (FL): StatPearls Publishing

StatPearls Publishing LLC.

Gyromitra esculenta, the false morel, is a toxic mushroom. The mushroom derives its name (esculenta) from the Latin for edible. Certain cultures, as well as many mushroom guides and websites, consider this mushroom safe to eat provided that proper preparation techniques are used to reduce its toxicity. Unfortunately, several incidences of poisoning have been reported in foragers seeking and ingesting the Gyromitra esculenta. In general, most poisonings occur when foragers search for true morels, such as Morchella species, but instead find and consume Gyromitra. The Gyromitra syndrome consists of a gastrointestinal prodrome occurring more than 5 hours after eating Gyromitra esculenta. Acute liver injury can occur over the next 2 days in a significant percentage of cases, and acute kidney injury may occur to a lesser degree. Confusion characterizes acute central nervous system (CNS) toxicity. In the most severe instances, refractory seizures are a feared, but rare, a consequence of the pharmacology of gyromitrin's toxic metabolite, monomethylhydrazine (MMH). Monomethylhydrazine binds to and inhibits pyridoxal phosphokinase, thereby inhibiting activation of vitamin B6 (as pyridoxal 5-phosphate) from functioning as the key co-factor in the synthesis of GABA. The subsequent depletion of GABA leads to CNS excitation and seizures.

Horvath, A., Varallyay, C. G., Schwartz, D., Toth, G. B., Netto, J. P., Barajas, R., . . . Neuwelt, E. A. (2017). **Quantitative comparison of delayed ferumoxytol T1 enhancement with immediate gadoteridol enhancement in high grade gliomas**. *Magn Reson Med*. doi:10.1002/mrm.27028

PURPOSE: Delayed ferumoxytol enhancement on T1 -weighted images appears visually similar to gadoteridol enhancement. The purpose of this study was to quantitatively compare ferumoxytol T1 enhancement to gadoteridol enhancement with an objective, semi-automated method. METHODS: 206 sets of post-gadoteridol and 24 h post-ferumoxytol T1 -weighted scans from 58 high grade glioma patients were analyzed (9 pre-chemoradiation, 111 < 90 days post-chemoradiation, 21 > 90 days post-chemoradiation, 65 post-bevacizumab scans). Enhancement volumes and signal intensities normalized to normal appearing tissue proximal to enhancement were calculated with a semi-automated method. Enhancement cube root volumes (D) and signal intensities (SI) were compared between the 2 contrast agents, and relative difference of D and SI were compared in different treatment groups with multivariate analysis. Within patient differences in D and SI before and after treatment with bevacizumab or steroid were assessed in 26 patients in each treatment group. RESULTS: When compared to gadoteridol, ferumoxytol D was 13.83% smaller and SI was 7.24% lower ($P < 0.0001$). The relative differences in D and SI between the 2 contrast agents were not significantly different between treatment groups ($P > 0.05$). Relative difference in D and SI did not change significantly in response to bevacizumab ($P = 0.5234$ and $P = 0.2442$, respectively) or to steroid ($P = 0.3774$, $P = 0.0741$) in the within patient comparison. CONCLUSION: The correlation between the 2 contrast agents' enhancement size and signal intensity and their similar behavior in response to therapy suggest that ferumoxytol can be used for revealing enhancement in high grade glioma patients. Magn Reson Med, 2017. (c) 2017 International Society for Magnetic Resonance in Medicine.

Hugos, C. L., Chen, Z., Chen, Y., Turner, A. P., Haselkorn, J., Chiara, T., . . . Bourdette, D. (2017). **A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Short- and medium-term benefits**. *Mult Scler*, 1352458517745723. doi:10.1177/1352458517745723

Background Fatigue occurs in 75%-95% of people with multiple sclerosis (MS) and is frequently reported as the most disabling symptom. A multicomponent group program of six weekly 2-hour sessions, Fatigue: Take Control (FTC), was developed from an international MS fatigue management guideline. Objective To determine whether FTC is associated with greater improvements in fatigue than MS: Take Control (MSTC), a similarly structured general MS education program. Methods This four-site, parallel, single-blind, randomized controlled trial compared FTC and MSTC in 204 ambulatory participants with MS. The primary outcome, the Modified Fatigue Impact Scale (MFIS), and secondary outcomes of self-efficacy, physical activity, sleep, and medications were assessed at baseline, program completion, and 3 and 6 months later. Results Mean MFIS scores improved in both groups between baseline and program completion (FTC -4.4, $p < 0.001$; MSTC -3.8, $p < 0.001$), between baseline and 3 months after program completion (FTC -3.2, $p = 0.01$; MSTC -3.3, $p = 0.01$), and between baseline and 6 months after program completion (FTC -5.2, $p < 0.001$; MSTC -4.8, $p < 0.001$). These improvements were not statistically different between groups ($p = 0.64$, 0.92, and 0.82, respectively). Conclusion Participation in FTC modestly improved self-reported fatigue for up to 6 months. This improvement did not differ significantly from that occurring with the control program.

Huisinga, J., Mancini, M., Veys, C., Spain, R., & Horak, F. (2017). **Coherence analysis of trunk and leg acceleration reveals altered postural sway strategy during standing in persons with multiple sclerosis**. *Hum Mov Sci*. doi:10.1016/j.humov.2017.12.009

Balance task performance is affected in persons with multiple sclerosis (PwMS), but the control strategies used to perform specific tasks are not well understood. The purpose of this study was to evaluate segmental control during quiet standing in PwMS and controls to understand whether MS alters use of the ankle and hip strategies to manage postural sway. Coherence of acceleration between the trunk and legs was evaluated with accelerometers placed on the sacrum and lower leg. Thirty-six PwMS and 20 healthy control subjects performed quiet standing with eyes open and closed while center of pressure (CoP) and acceleration of

postural sway was measured. Acceleration frequencies were divided into lower frequencies (</=1.0Hz) and higher frequencies (>1.0Hz) to categorize sway characteristics. With eyes open, coherence was significantly lower in PwMS compared to controls at lower frequencies only. With eyes closed, coherence was significantly lower in PwMS compared to controls, who use an ankle strategy at lower frequencies only, at both lower and higher frequencies. Both groups showed decreased coherence with increasing frequency when eyes were open and closed. Coherence was significantly correlated with CoP sway area in PwMS during the eyes closed condition only. The reduced coherence in PwMS during both lower and higher frequency sway indicates PwMS utilize a mixed ankle-hip sway strategy regardless of sway frequency. This is in contrast to sway in healthy subjects which utilizes an ankle strategy at lower frequencies and a mixed strategy at higher frequencies. Lack of adaptability in segmental control strategy likely contributes to abnormal postural control, as reflected by CoP sway patterns, in PwMS.

Hulen, E., Ervin, A., Schue, A., Evans-Young, G., Saha, S., Yelin, E. H., & Barton, J. L. (2017). **Patient goals in rheumatoid arthritis care: A systematic review and qualitative synthesis**. *Musculoskeletal Care, 15*(4), 295-303. doi:10.1002/msc.1173

OBJECTIVE: During the clinical encounter, rheumatoid arthritis (RA) patient goals for care often go unexplored. The aim of the present systematic review was to identify needs, goals and expectations of RA patients in order better to guide systematic elicitation of patient goals in clinical encounters. METHODS: An academic librarian searched MEDLINE, PsychINFO and the Cochrane Library using a specialized algorithm developed to identify articles about patient goals for RA care. Investigators screened search results according to prespecified inclusion criteria and then reviewed included articles and synthesized the evidence qualitatively, utilizing an inductive approach. RESULTS: A total of 909 titles were retrieved in the literature search, of which 871 were excluded after a title/abstract screen. Of the remaining 38, 22 papers were included in the final review. Investigators identified four major themes in the literature: (a) the bodily experience of RA; (b) achieving normalcy and maintaining wellness; (c) social connectedness and support; and (d) interpersonal and healthcare system interactions. CONCLUSION: Patients' goals when receiving care for RA are multidimensional and span several facets of everyday life. Goals for RA care should be collaboratively developed between patients and providers, with particular attention to the patient's life context and priorities.

Hurtado, D. A., Dumet, L. M., Greenspan, S. A., & Rodriguez, Y. I. (2018). **Social Network Analysis of peer-specific safety support and ergonomic behaviors: An application to safe patient handling**. *Applied Ergonomics, 68*, 132-137. doi:10.1016/j.apergo.2017.11.009

This study applied Social Network Analysis (SNA) to test whether advice-seeking interactions among peers about safe patient handling correlate with a higher frequency of equipment use. Patient-care workers (n=38) at a community hospital in Oregon nominated peers they would consult for advice regarding safe patient handling. Results show a positive correlation between identifying more peers for safe patient handling advice and using equipment more frequently. Moreover, nurses with more reciprocal advice seeking nominations used safe patient handling equipment more frequently. However, employees who would be more consulted about safe patient handling by their peers did not use equipment more frequently than nurses with fewer nominations. Despite the small sample size, the magnitude of the adjusted regressions coefficients ranged between 3 to 4 standard deviations. These results suggest that having more or reciprocal sources of peer-based support may trigger ergonomic related behaviors such as frequent utilization of equipment.

Hwang, S., Rudd, M. K., Finch, L., Peterson, S. E., & Kapur, R. P. (2017). **VACTERL phenotype with mosaic trisomy 5 and uniparental disomy 5**. *Am J Med Genet A*. doi:10.1002/ajmg.a.38579

Ireland, K. E., Maloyan, A., & Myatt, L. (2018). **Melatonin Improves Mitochondrial Respiration in Syncytiotrophoblasts From Placentas of Obese Women**. *Reproductive Sciences, 25*(1), 120-130. doi:10.1177/1933719117704908

Maternal obesity is associated with increased oxidative stress but decreased placental mitochondrial respiration and expression of mitochondrial electron transport chain (ETC) complexes I to V. Melatonin acts as an antioxidant and prevents oxidative stress-induced changes in cytotrophoblasts. Placentas were collected at term by cesarean delivery from obese (first trimester body mass index [BMI] ≥30, n = 10) or lean (BMI < 25, n = 6) women. Cytotrophoblasts were isolated and allowed to syncytialize for 72 hours with or without melatonin (0.1-100 μM) for the last 24 hours. Mitochondrial respiratory parameters were measured in a Seahorse XF24. Expression of ETC complexes I to V and antioxidant enzymes was measured by Western blot. Maternal clinical characteristics of patients were similar except for BMI. No significant improvement in mitochondrial respiration occurred with addition of melatonin to trophoblasts of lean women. However, in trophoblasts from obese women, melatonin (10 and 100 μmol/L) significantly increased maximal respiration (P =.01 and P =.009, respectively) and spare capacity (P =.02 and P =.003, respectively) compared to the untreated control. No differences were detected in the expression of ETC complexes and superoxide dismutase 1 or 2 in trophoblasts treated with melatonin. The expression of glutathione peroxidase, which was significantly greater in trophoblast of obese compared to lean women (P <.05), was decreased back to the level seen in trophoblast of lean women with addition of melatonin (P =.02). Improved spare respiratory capacity, the cellular reserve, could impart a protective effect to the placenta and fetus in an adverse intrauterine environment or in response to additional stressors.

Irizarry, F. J., Kopplin, L. J., Salek, S. S., Adamus, G., Saleh, M., Biggee, K., . . . Rosenbaum, J. T. (2017). **Recovery of outer retinal laminations on optical coherence tomography after treatment of cancer associated retinopathy**. *Am J Ophthalmol Case Rep, 8*, 11-13. doi:10.1016/j.ajoc.2017.08.001

Purpose: To report novel optical coherence tomography findings in a case of anti-alpha-enolase cancer associated retinopathy. Observations: An elderly female presented with bilateral decreased vision and a recent diagnosis of ovarian carcinoma. Optical coherence tomography demonstrated bilateral loss of outer retinal structures and macular edema. Serum testing found antibodies against alpha-enolase and 82-84 kDa proteins. Outer retinal structures showed recovery, macular edema resolved and repeat anti-retinal antibody testing became negative following cancer therapy and topical difluprednate treatment. Conclusions and importance: Cancer associated retinopathy is a paraneoplastic disease that results in damage to retinal structures through an autoimmune response. The damage is generally considered to be irreversible; however, in rare cases, such as observed here, retinal structures may demonstrate recovery after treatment.

Izumi, B. T., Higgins, C. E., Baron, A., Ness, S. J., Allan, B., Barth, E. T., . . . Frank, B. (2017). **Feasibility of Using a Community-Supported Agriculture Program to Increase Access to and Intake of Vegetables among Federally Qualified Health Center Patients**. *Journal of Nutrition Education and Behavior*. doi:10.1016/j.jneb.2017.09.016

Objective: This study explored the feasibility of using a 23-week subsidized community-supported agriculture program to increase access to and intake of vegetables among Federally Qualified Health Center patients. Methods: Outcomes were measured using pre-post intervention surveys (n = 9). Process data were collected in post-intervention surveys and focus groups (n = 15). Results: Most participants (77%) indicated that the program improved their health and all (100%) reported that they were eating a greater variety of vegetables because of their participation in the program. Three themes emerged from the focus groups: increased access to fresh and/or organic vegetables, improved diet quality, and the importance of social support during the program. Conclusions and Implications: Linking subsided community-supported agriculture programs with Federally Qualified Health Centers has the potential to increase access to and intake of

vegetables among low-income patients. However, further research is needed with a larger sample size and a more robust study design. © 2017 Society for Nutrition Education and Behavior.

Jacobs, J., Marino, M., Edelman, A., Jensen, J., & Darney, B. (2017). **Mass media exposure and modern contraceptive use among married West African adolescents**. *European Journal of Contraception and Reproductive Health Care*, 1-11. doi:10.1080/13625187.2017.1409889

PURPOSE: The purpose of this study was to examine whether family planning (FP) messaging is reaching married adolescent women in West Africa, and whether such messaging is associated with increased contraceptive use. MATERIALS AND METHODS: We utilised data from the 2010 Demographic and Health Surveys (DHS) for Burkina Faso and Senegal (women 15-49; N = 17,067 and N = 15,688, respectively). We used chi-square tests to evaluate whether FP messaging exposure (via TV, radio, and/or print) differed according to socio-demographic characteristics. Subsequent analysis focussed on married adolescents (15-19; N = 961 in Burkina Faso, N = 996 in Senegal) which utilised propensity score matching and multivariable logistic regression models to test the association between self-reported FP messaging exposure and modern contraceptive use, knowledge of a modern contraceptive method, and future intention to use contraception. RESULTS: A higher proportion of women 15-49 who reported FP messaging exposure were urban, from higher wealth quintiles, and had higher education levels, compared with unexposed women. A smaller proportion of adolescents reported exposure compared to older age groups. Among married adolescents, there was a positive but non-significant association between FP messaging exposure and use of a modern contraceptive method in Senegal (adjusted odds ratio (aOR) = 2.3; 95% CI: 0.92, 5.73). No such association was found in Burkina Faso (aOR = 0.98; 95% CI: 0.43, 2.26). CONCLUSIONS: Mass media campaigns are not reaching the most vulnerable populations in West Africa, such as adolescents and poorer rural women. Adapting mass media campaigns to address these gaps is important for increasing exposure to FP messaging.

Jahangiri, Y., Kerrigan, T., Li, L., Prosser, D., Brar, A., Righetti, J., . . . Farsad, K. (2017). **Risk factors for stent graft thrombosis after transjugular intrahepatic portosystemic shunt creation**. *Cardiovascular Diagnosis and Therapy, 7*, S150-S158. doi:10.21037/cdt.2017.10.03

Background: To identify risk factors of stent graft thrombosis after transjugular intrahepatic portosystemic shunt (TIPS) creation. Methods: Patients who underwent TIPS creation between June 2003 and January 2016 and with follow-up assessing stent graft patency were included (n=174). Baseline comorbidities, liver function, procedural details and follow-up liver function tests were analyzed in association with hazards of thrombosis on follow-up. Competing risk cox regression models were used considering liver transplant after TIPS creation as the competing risk variable. Results: One-, 2- and 5-year primary patency rates were 94.1%, 91.7% and 78.2%, respectively. Patient age [sub-hazard ratio (sHR): 1.13; P=0.001], body mass index (BMI) <30 (sHR: 33.08; P=0.008) and a higher post-TIPS portosystemic pressure gradient (sHR: 1.14; P=0.023) were significantly associated with TIPS thrombosis in multivariate analysis. A higher rate of TIPS thrombosis was observed in those for whom the procedure was clinically unsuccessful (P=0.014). A significant increase in incidence of thrombosis was noted with increasing tertiles of post-TIPS portosystemic gradients (P value for trend=0.017). Conclusions: Older age, lower BMI and higher post-TIPS portosystemic gradients were associated with higher hazards of shunt thrombosis after TIPS creation using stent grafts. Higher rates of shunt thrombosis were seen in patients for whom TIPS creation was clinically unsuccessful. The association between TIPS thrombosis and higher post-TIPS portosystemic gradients may indicate impaired flow through the shunt, a finding which may be technical or anatomic in nature and should be assessed before procedure completion. © 2017 Cardiovascular Diagnosis and Therapy.

Jain, J. A., Temming, L. A., D'Alton, M. E., Gyamfi-Bannerman, C., Tuuli, M., Louis, J. M., . . . Riley, L. E. (2017). **SMFM Special Report: Reducing Racial and Ethnic Disparities in Maternal Morbidity and Mortality: A Call to Action**. *American Journal of Obstetrics and Gynecology*. doi:10.1016/j.ajog.2017.11.591

Racial and ethnic disparities in maternal morbidity and mortality are an important public health problem in the United States. As racial and ethnic minorities are expected to comprise over one half of the U.S. population by 2050, this issue that must be urgently addressed. Research suggests that the drivers of health disparities occur at three levels: patient, provider, and system. Although we have recognized this issue and identified elements that contribute to it, knowledge must be converted into action to address it. In addition, despite available funding and databases, research directed towards understanding and reducing these disparities is lacking. This document summarizes findings of a workshop convened at the 2016 Society for Maternal-Fetal Medicine's (SMFM) 36(th) Annual Pregnancy meeting in Atlanta, Georgia, to review and make recommendations about immediate actions in clinical care and research that will serve to reduce racial and ethnic disparities in maternal morbidity and mortality in the United States.

Janghorban, M., Langer, E. M., Wang, X., Zachman, D., Daniel, C. J., Hooper, J., . . . Sears, R. C. (2017). **The tumor suppressor phosphatase PP2A-B56alpha regulates stemness and promotes the initiation of malignancies in a novel murine model**. *PLoS ONE, 12*(11), e0188910. doi:10.1371/journal.pone.0188910

Protein phosphatase 2A (PP2A) is a ubiquitously expressed Serine-Threonine phosphatase mediating 30-50% of protein phosphatase activity. PP2A functions as a heterotrimeric complex, with the B subunits directing target specificity to regulate the activity of many key pathways that control cellular phenotypes. PP2A-B56alpha has been shown to play a tumor suppressor role and to negatively control c-MYC stability and activity. Loss of B56alpha promotes cellular transformation, likely at least in part through its regulation of c-MYC. Here we report generation of a B56alpha hypomorph mouse with very low B56alpha expression that we used to study the physiologic activity of the PP2A-B56alpha phosphatase. The predominant phenotype we observed in mice with B56alpha deficiency in the whole body was spontaneous skin lesion formation with hyperproliferation of the epidermis, hair follicles and sebaceous glands. Increased levels of c-MYC phosphorylation on Serine62 and c-MYC activity were observed in the skin lesions of the B56alphahm/hm mice. B56alpha deficiency was found to increase the number of skin stem cells, and consistent with this, papilloma initiation was accelerated in a carcinogenesis model. Further analysis of additional tissues revealed increased inflammation in spleen, liver, lung, and intestinal lymph nodes as well as in the skin lesions, resembling elevated extramedullary hematopoiesis phenotypes in the B56alphahm/hm mice. We also observed an increase in the clonogenicity of bone marrow stem cells in B56alphahm/hm mice. Overall, this model suggests that B56alpha is important for stem cells to maintain homeostasis and that B56alpha loss leading to increased activity of important oncogenes, including c-MYC, can result in aberrant cell growth and increased stem cells that can contribute to the initiation of malignancy.

Jayaram, H., Lozano, D. C., Johnson, E. C., & Morrison, J. C. (2018). **Investigation of MicroRNA Expression in Experimental Glaucoma**. *Methods Mol Biol, 1695*, 287-297. doi:10.1007/978-1-4939-7407-8_19

MicroRNAs are small, endogenous noncoding RNAs that modulate post-transcriptional gene expression. Recent evidence suggests that they may have a potential role in the regulation of the complex biological responses that develop in response to elevated intraocular pressure. However, contemporary microRNA assay techniques (e.g., microarrays and next-generation sequencing) typically require large amounts of RNA template that are often times difficult to obtain from glaucomatous tissue. We describe in detail an experimental protocol utilizing targeted pre-amplification and low-density polymerase chain reaction arrays to circumvent this hurdle. This approach optimizes the simultaneous high-throughput screening of small tissue samples, such as the rodent optic nerve head, for up to 754 microRNA probes while also providing an opportunity for subsequent confirmatory reactions of technical or biological replicates.

Jayaraman, R., Reinier, K., Nair, S., Aro, A. L., Uy-Evanado, A., Rusinaru, C., . . . Chugh, S. S. (2017). **Risk Factors of Sudden Cardiac Death in the Young: A Multiple-Year Community-Wide Assessment**. *Circulation*. doi:10.1161/circulationaha.117.031262

Background -Prevention of sudden cardiac arrest (SCA) in the young remains a largely unsolved public health problem and sports activity is an established trigger. While the presence of standard cardiovascular risk factors in the young can link to future morbidity and mortality in adulthood, the potential contribution of these risk factors to SCA in the young has not been evaluated. Methods -We prospectively ascertained subjects who suffered SCA between the ages of 5-34 years in the Portland, Oregon, USA metropolitan area (2002-2015, catchment population approximately 1 million). We assessed the circumstances, resuscitation outcomes and clinical profile of subjects that suffered SCA by a detailed evaluation of emergency response records, lifetime clinical records and autopsy examination. We specifically evaluated the association of standard cardiovascular risk factors and SCA, and sports as a trigger for SCA in the young. Results -Out of 3775 SCAs in all age groups, 186 (5%) occurred in the young (Mean age 25.9 +/- 6.8, 67% male). In young SCA, overall prevalence of warning signs before SCA was low (29%); and 26 (14%) were associated with sports as a trigger. The remainder (n=160) occurred in other settings categorized as non-sports. Sports-related SCAs accounted for 39% of SCAs aged </=18, 13% of SCAs aged 19-25, and 7% of SCAs aged 25-34. Sports-related SCA cases were more likely to present with shockable rhythms, and survival from cardiac arrest was 2.5-fold higher in sports-related vs. non-sports SCA (28% vs. 11%; p=0.05). Overall, the most common SCA-related conditions were sudden arrhythmic death syndrome (31%), coronary artery disease (22%) and hypertrophic cardiomyopathy (14%). There was an unexpectedly high overall prevalence of established cardiovascular risk factors (obesity, diabetes, hypertension, hyperlipidemia, smoking) with >/=1 risk factor in 58% of SCA cases. Conclusions -Sports was a trigger of SCA in a minority of cases, and in most patients SCA occurred without warning symptoms. Standard cardiovascular risk factors were found in over half of patients, suggesting the potential role of public health approaches that screen for cardiovascular risk factors at earlier ages.

Jeanne, T. L., Hooker, E. R., Nguyen, T., Messer, L. C., Sacks, R. M., Andrea, S. B., & Boone-Heinonen, J. (2017). **High birth weight modifies association between adolescent physical activity and cardiometabolic health in women and not men**. *Preventive Medicine*. doi:10.1016/j.ypmed.2017.12.015

Recent evidence suggests that adverse prenatal development alters physiological response to physical activity, but longitudinal epidemiologic evidence is scant. This study tested the hypothesis that lower physical activity during adolescence and young adulthood is more strongly associated with later cardiovascular disease (CVD) risk and diabetes or prediabetes (DM/PDM) in women and men who were born with high or low birth weight (HBW, LBW), compared to normal birth weight (NBW). We analyzed data from the National Longitudinal Study of Adolescent to Adult Health, a cohort study of US adolescents followed into adulthood (1994-2009). Using sex-stratified multivariable regression, 30-year CVD risk score (calculated using objective measures; n=12,775) and prevalent DM/PDM (n=15,138) at 24-32years of age were each modeled as a function of birth weight category, self-reported moderate-to-vigorous physical activity frequency in adolescence (MVPA1) and young adulthood (MVPA3), and MVPA-birth weight interactions. Greater MVPA1 was associated with lower 30-year CVD risk score and DM/PDM risk in HBW women but not NBW or LBW women. Associations between MVPA1 and 30-year CVD risk or DM/PDM were not modified by HBW in men; or by LBW in women or men. Additionally, birth weight did not modify estimated effects of MVPA3. Findings suggest that frequent MVPA in adolescence may be a particularly important cardiometabolic risk reduction strategy in girls born HBW; however, we found no evidence that birth weight and MVPA interact in cardiometabolic disease risk in men, for MVPA in adulthood, or for LBW.

Jenkins, B. V., Saunders, H. A. J., Record, H. L., Johnson-Schlitz, D. M., & Wildonger, J. (2017). **Effects of mutating α-tubulin lysine 40 on sensory dendrite development**. *Journal of Cell Science, 130*(24), 4120-4131. doi:10.1242/jcs.210203

Microtubules are essential for neuronal structure and function. Axonal and dendritic microtubules are enriched in post-translational modifications that impact microtubule dynamics, transport and microtubule-associated proteins. Acetylation of α-tubulin lysine 40 (K40) is a prominent and conserved modification of neuronal

microtubules. However, the cellular role of microtubule acetylation remains controversial. To resolve how microtubule acetylation might affect neuronal morphogenesis, we mutated endogenous α-tubulin in vivo using a new Drosophila strain that facilitates the rapid knock-in of designer aTub84B alleles (the predominant α-tubulin-encoding gene in flies). Leveraging our new strain, we found that microtubule acetylation, as well as polyglutamylation and (de)tyrosination, is not essential for survival. However, we found that dendrite branch refinement in sensory neurons relies on α-tubulin K40. Mutagenesis of K40 reveals moderate yet significant changes in dendritic lysosome transport, microtubule polymerization and Futsch protein distribution in dendrites but not in axons. Our studies point to an unappreciated role for α-tubulin K40 and acetylation in dendrite morphogenesis. While our results are consistent with the idea that acetylation tunes microtubule function within neurons, they also suggest there may be an acetylation-independent requirement for α-tubulin K40. © 2017. Published by The Company of Biologists Ltd.

Jewell, M. L. (2017). **Commentary on: Cannula vs Sharp Needle for Placement of Soft Tissue Fillers: An Observational Cadaver Study**. *Aesthet Surg J, 38*(1), 89-91. doi:10.1093/asj/sjx223

Jiang, M., Taghizadeh, F., & Steyger, P. S. (2017). **Potential Mechanisms Underlying Inflammation-Enhanced Aminoglycoside-Induced Cochleotoxicity**. *Frontiers in Cellular Neuroscience, 11*, 362. doi:10.3389/fncel.2017.00362

Aminoglycoside antibiotics remain widely used for urgent clinical treatment of life-threatening infections, despite the well-recognized risk of permanent hearing loss, i.e., cochleotoxicity. Recent studies show that aminoglycoside-induced cochleotoxicity is exacerbated by bacteriogenic-induced inflammation. This implies that those with severe bacterial infections (that induce systemic inflammation), and are treated with bactericidal aminoglycosides are at greater risk of drug-induced hearing loss than previously recognized. Incorporating this novel comorbid factor into cochleotoxicity risk prediction models will better predict which individuals are more predisposed to drug-induced hearing loss. Here, we review the cellular and/or signaling mechanisms by which host-mediated inflammatory responses to infection could enhance the trafficking of systemically administered aminoglycosides into the cochlea to enhance the degree of cochleotoxicity over that in healthy preclinical models. Once verified, these mechanisms will be potential targets for novel pharmacotherapeutics that reduce the risk of drug-induced hearing loss (and acute kidney damage) without compromising the life-saving bactericidal efficacy of aminoglycosides.

Johnson, L. A., Torres, E. R., Weber Boutros, S., Patel, E., Akinyeke, T., Alkayed, N. J., & Raber, J. (2017). **Apolipoprotein E4 mediates insulin resistance-associated cerebrovascular dysfunction and the post-prandial response**. *Journal of Cerebral Blood Flow and Metabolism*, 271678x17746186. doi:10.1177/0271678x17746186

Metabolic dysfunction, commonly a result of diets high in saturated fats and sugar, is associated with impaired cognitive function and an increased risk of age-related cognitive decline (ACD) and Alzheimer's disease (AD). Compared to the E3 isoform of apolipoprotein (apoE), the E4 isoform is a major genetic risk factor for ACD, AD, and for developing cognitive impairments following various environmental challenges, including dietary challenges such as a high-fat diet (HFD). Both insulin resistance (IR) and E4 are associated with metabolic and vascular impairments. Deficits in cerebral metabolism and cerebrovascular function have been proposed as initiating events leading to these impairments. In the current study, we employed a model of human apoE targeted replacement mice and HFD-induced obesity to study the potential link between E4 and IR, at rest and following a postprandial challenge. HFD-induced IR was associated with impaired cognition, reduced cerebral blood volume and decreased glucose uptake. These effects were more profound in E4 than E3 mice. Furthermore, the cognitive, metabolic and cerebrovascular responses to an exogenous glucose load showed an apoE isoform-dependent response, with E4, but not E3 mice, acutely benefiting from a spike in blood glucose.

Jones, K. D., Baggs, J. G., & Jones, M. R. (2017). **Selecting US research-intensive doctoral programs in nursing: Pragmatic questions for potential applicants**. *Journal of Professional Nursing*. doi:10.1016/j.profnurs.2017.11.005

Nurses hoping to enter a research intensive doctoral program have a choice of program delivery modes, faculty expertise, and multiple points of entry in addition to the traditional post masters. The American Association of Colleges of Nursing (AACN) lists doctoral programs in nursing in over 300 universities in the United States (U.S.) and Puerto Rico, with most institutions offering more than one type of doctorate. For prospective students who want to maximize their likelihood of significant, sustained scientific impact, identifying research-intensive Doctor of Philosophy (PhD) programs with faculty who have a topic match is key. Embarking on a scientific career requires assessing the curricula and faculty at several institutions. The purpose of this paper is to give prospective students pragmatic guidance in selecting a U.S. research-intensive doctoral program in nursing. We provide a list of published quality indicators in PhD programs as well as potential questions to be addressed to key persons in schools. © 2017.

Jones, S. A., Morales, A. M., Lavine, J. B., & Nagel, B. J. (2017). **Convergent neurobiological predictors of emergent psychopathology during adolescence**. *Birth Defects Res, 109*(20), 1613-1622. doi:10.1002/bdr2.1176

The adolescent brain undergoes significant structural and functional development. Through the use of magnetic resonance imaging in adolescents, it has been demonstrated that the prefrontal cortex, pertinent for executive control, demonstrates protracted development compared to limbic structures, active during emotion and reward processing. This asynchronous development creates a sensitive window during adolescence, in which many psychopathological disorders (i.e., mental health and substance use) emerge. This review outlines longitudinal studies that use magnetic resonance imaging to identify neurobiological predictors of emergent psychopathology (depression, anxiety, and substance use), during adolescence. Studies identifying neurobiological markers that predict onset and escalation of these disorders, as well as those that predict successful treatment outcomes are explored. An emphasis is placed on frontolimbic brain structures, a convergent neurobiological target for both emergent mental health issues and emergent substance use. The literature reviewed herein suggests that reduced volume and cortical thickness in frontolimbic regions, as well as reduced functional activation (particularly during task involving reward or emotional stimuli) in these regions, may serve as a neurobiological predictors of emergent psychopathology in adolescence. This knowledge is crucial, as it may be used to develop neurobiologically targeted prevention and intervention strategies for youth who are at-risk for developing these psychopathologies.

Kambadakone, A. R., Zaheer, A., Le, O., Bhosale, P., Meier, J., Guimaraes, A. R., . . . Tamm, E. (2017). **Multi-institutional survey on imaging practice patterns in pancreatic ductal adenocarcinoma**. *Abdom Radiol (NY)*. doi:10.1007/s00261-017-1433-8

PURPOSE: To study the practice patterns for performance and interpretation of CT/MRI imaging studies in patients with pancreatic ductal adenocarcinoma (PDAC) at multiple institutions using a survey-based assessment. METHODS: In this study, abdominal radiologists/body imagers on the Society of Abdominal Radiology disease-focused panel for PDAC and from multiple institutions participated in an online survey. The survey was designed to investigate the imaging and reporting practice patterns for PDAC. The survey questionnaire addressed the experience of referring providers, choice of imaging modality for diagnosis and follow-up of PDAC, structured imaging templates utilization for PDAC, and experiences with the use of structured reports. RESULTS: The response rate was 89.6% (43/48), with majority of the respondents working in a teaching hospital or academic research center (95.4%). While 86% of radiologists reported use of structured reporting templates in their practice, only 60.5% used standardized templates specific to PDAC. This lower percentage was despite most of them (77%) being aware of existence of PDAC-specific templates and recognizing their benefits, such as preference by referring providers (83%), improved uniformity (100%), and higher accuracy of reports (76.2%). The common impediments to the use of PDAC-specific templates were interference with

efficient workflow (67.5%), lack of interest (52.5%), and complexity of existing templates (47.5%). With regards to imaging practice, 92.7% (n = 40/43) of respondents reported performing dynamic multiphasic pancreatic protocol CT for evaluation of patients with initial suspicion or staging of PDAC. CONCLUSION: Structured reporting templates for PDAC are not universally utilized in subspecialty abdominal/body imaging practices due to concerns of interference with efficient workflow and complexity of templates. Multiphasic pancreatic protocol CT is most frequently performed for evaluation of PDAC.

Kang, S. W., Kim, K. A., Lee, C. H., Yang, S. J., Kang, T. K., Jung, J. H., . . . Jung, S. H. (2017). **A standardized extract of Rhynchosia volubilis Lour. exerts a protective effect on benzalkonium chloride-induced mouse dry eye model**. *Journal of Ethnopharmacology*. doi:10.1016/j.jep.2017.12.041

ETHNOPHARMACOLOGICAL RELEVANCE: In contrast to other leguminous plants generally used as food, Rhynchosia volubilis Loureiro, a small soybean with a black seed coat, has been used as a traditional oriental remedy for various human diseases in Eastern Asia. In this study, we demonstrated the protective effect of R. volubilis against dry eye disease. AIM OF THE STUDY: We aimed to investigate whether a standardized ethanol extract of R. volubilis (EERV) can protect the cornea in a benzalkonium chloride (BAC)-induced mouse dry eye model. MATERIALS AND METHODS: Experimental dry eye was induced by the instillation of 0.2% BAC on mouse cornea. A standardized ethanol extract of R. volubilis (EERV) was orally administered following BAC treatment. The positive control group was treated with commercial eye drops. Fluorescein staining, tear break-up time (BUT), and hematoxylin and eosin staining were evaluated on the ocular surface. Squamous metaplasia and apoptosis in the corneal epithelial layer were detected by immunostaining. Furthermore, the protein expression of cytochrome c, Bcl-2, and Bax was determined. RESULTS: EERV treatment significantly improved fluorescein scoring, BUT, and smoothness in the cornea compared to the vehicle group. In addition, EERV inhibited squamous metaplasia and apoptosis in the cornea. The expression of cytochrome c and Bax was upregulated, while that of Bcl-2 was downregulated in the vehicle group compared with that in the control group. However, EERV treatment inhibited the expression of cytochrome c and Bax, while that of Bcl-2 was improved. CONCLUSION: Standardized EERV could be a beneficial candidate for the treatment of dry eye disease.

Kapepula, P. M., Kabamba Ngombe, N., Tshisekedi Tshibangu, P., Tsumbu, C., Franck, T., Mouithys-Mickalad, A., . . . Frederich, M. (2017). **Comparison of metabolic profiles and bioactivities of the leaves of three edible Congolese Hibiscus species**. *Nat Prod Res, 31*(24), 2885-2892. doi:10.1080/14786419.2017.1305382

Methanolic and dichloromethane extracts from the leaves of Congolese Hibiscus species were characterised by chromatographic and spectroscopic techniques and their in vitro biochemical activities against ROS production were evaluated in cellular models and on an enzyme, myeloperoxidase (MPO), involved in inflammation. Hibiscus acetosella has a chemical fingerprint different from Hibiscus cannabinus and Hibiscus sabdariffa both having similar fingerprints. Major compounds were polyphenols, represented mainly by caffeoyl-hydroxycitric acid for H. acetosella and neochlorogenic acid for the two other species. All extracts displayed high cellular antioxidant activity with IC50 values ranging from 0.5 to 3 mug mL(-1) using lucigenin on neutrophils. Dichloromethane extracts showed more efficient effects on extracellular ROS production and MPO activity. Antioxidant and anti-inflammatory activities of caffeoyl-hydroxycitric acid were significantly higher than those of neochlorogenic acid. The bioactivities of Hibiscus species were positively correlated with their phytochemical content and could justify their use as local nutraceutical resources and medicines.

Karim, A. M., Rumalla, K., King, L. A., & Hullar, T. E. (2017). **The effect of spatial auditory landmarks on ambulation**. *Gait Posture, 60*, 171-174. doi:10.1016/j.gaitpost.2017.12.003

The maintenance of balance and posture is a result of the collaborative efforts of vestibular, proprioceptive, and visual sensory inputs, but a fourth neural input, audition, may also improve balance. Here, we tested the hypothesis that auditory inputs function as environmental spatial landmarks whose effectiveness depends on sound

localization ability during ambulation. Eight blindfolded normal young subjects performed the Fukuda-Unterberger test in three auditory conditions: silence, white noise played through headphones (head-referenced condition), and white noise played through a loudspeaker placed directly in front at 135 centimeters away from the ear at ear height (earth-referenced condition). For the earth-referenced condition, an additional experiment was performed where the effect of moving the speaker azimuthal position to 45, 90, 135, and 180 degrees was tested. Subjects performed significantly better in the earth-referenced condition than in the head-referenced or silent conditions. Performance progressively decreased over the range from 0 degrees to 135 degrees but all subjects then improved slightly at the 180 degrees compared to the 135 degrees condition. These results suggest that presence of sound dramatically improves the ability to ambulate when vision is limited, but that sound sources must be located in the external environment in order to improve balance. This supports the hypothesis that they act by providing spatial landmarks against which head and body movement and orientation may be compared and corrected. Balance improvement in the azimuthal plane mirrors sensitivity to sound movement at similar positions, indicating that similar auditory mechanisms may underlie both processes. These results may help optimize the use of auditory cues to improve balance in particular patient populations.

Keenan, A. B., Jenkins, S. L., Jagodnik, K. M., Koplev, S., He, E., Torre, D., . . . Pillai, A. (2017). **The Library of Integrated Network-Based Cellular Signatures NIH Program: System-Level Cataloging of Human Cells Response to Perturbations**. *Cell Syst*. doi:10.1016/j.cels.2017.11.001

The Library of Integrated Network-Based Cellular Signatures (LINCS) is an NIH Common Fund program that catalogs how human cells globally respond to chemical, genetic, and disease perturbations. Resources generated by LINCS include experimental and computational methods, visualization tools, molecular and imaging data, and signatures. By assembling an integrated picture of the range of responses of human cells exposed to many perturbations, the LINCS program aims to better understand human disease and to advance the development of new therapies. Perturbations under study include drugs, genetic perturbations, tissue micro-environments, antibodies, and disease-causing mutations. Responses to perturbations are measured by transcript profiling, mass spectrometry, cell imaging, and biochemical methods, among other assays. The LINCS program focuses on cellular physiology shared among tissues and cell types relevant to an array of diseases, including cancer, heart disease, and neurodegenerative disorders. This Perspective describes LINCS technologies, datasets, tools, and approaches to data accessibility and reusability.

Kemper, A. R., Krist, A. H., Tseng, C. W., Gillman, M. W., Mabry-Hernandez, I. R., Silverstein, M., . . . Grossman, D. C. (2018). **Challenges in Developing U.S. Preventive Services Task Force Child Health Recommendations**. *Am J Prev Med, 54*(1s1), S63-s69. doi:10.1016/j.amepre.2017.08.023

The U.S. Preventive Services Task Force (USPSTF) uses an objective evidence-based approach to develop recommendations. As part of this process, the USPSTF also identifies important research gaps in scientific evidence. In March 2016, the USPSTF convened an expert panel to discuss its portfolio of child and adolescent recommendations and identify unique methodologic issues when evaluating evidence regarding children and adolescents. The panel identified key domains of challenges, including measuring patient-centered health outcomes; identifying intermediate outcomes predictive of important health outcomes; evaluating the long time horizon needed to assess the balance of benefits and harms; understanding trajectories of growth and development that result in unique windows of time when expected benefits or harms of a preventive service can vary; and considering the perspectives of other individuals who might be affected by the delivery of a preventive service to a child or adolescent. Although the expert panel expressed an interest in being able to make more recommendations for or against preventive services for children and adolescents, it also reinforced the importance of ensuring recommendations were based on sound and sufficient evidence to ensure greatest benefit and minimize unnecessary harms. Accordingly, the need to highlight areas with insufficient evidence is as important as making recommendations. Having identified these key challenges, the USPSTF and other organizations issuing guidelines have an opportunity to advance

their methods of evidence synthesis and identified evidence gaps represent important opportunities for researchers and policy makers.

Kempton, C. L., Recht, M., Neff, A., Wang, M., Buckner, T. W., Soni, A., . . . Cooper, D. L. (2017). **Impact of pain and functional impairment in US adults with haemophilia: Patient-reported outcomes and musculoskeletal evaluation in the pain, functional impairment and quality of life (P-FiQ) study**. *Haemophilia*. doi:10.1111/hae.13377

INTRODUCTION: Standardized and disease-specific patient-reported outcome (PRO) instruments assessing pain, functional impairment and health-related quality of life (HRQoL) in people with haemophilia (PWH) have been used in studies, but infrequently in comprehensive care settings for individual assessment or treatment planning. AIM: To assess the impact of pain and functional impairment on HRQoL in PWH. METHODS: P-FiQ enrolled 381 adult PWH with a history of joint pain/bleeding and included 5 PROs and a clinical joint evaluation (Hemophilia Joint Health Score v2.1 [HJHS]). RESULTS: Median age was 34 years; 49.9% reported a history of joint procedure or surgery. On EQ-5D-5L, most reported problems with mobility (61.4%), usual activities (53.2%) and pain/discomfort (76.1%). On Brief Pain Inventory v2 Short Form, median worst pain (range 0-10) was 6, least pain 1, average pain 3 and current pain 2. Ankles were most frequently reported as the most painful joints (37.4%), followed by knees (23.7%) and elbows (18.9%). On International Physical Activity Questionnaire, 51% reported no activity in the prior week. On SF-36v2 health survey, median subscores were worse for 4 physical health domains vs 4 mental health domains. Among Hemophilia Activities List domains (range 0 [worst]-100 [best]), functions of the legs (median, 66.7) and lying/sitting/kneeling/standing (median, 67.5) were most impacted and self-care least impacted (median, 100.0). On HJHS, ankle scores (median, 6.0; range, 0-40) were worse than elbow/knee scores (median, 4.0/4.0). Results were consistent across PROs/HJHS. CONCLUSION: Data demonstrate challenges of predominantly ankle/knee pain and lower extremity functional impairment in US adult PWH, affecting HRQoL across PROs/HJHS.

Keyashian, K., Duregon, E., Brinkerhof, B. T., Bradley, L., Larson, B., Lim, J., . . . Hooper, J. E. (2017). **Uses and limitations of IgG4 positive plasma cells in evaluating ulcerative colitis**. *Journal of Gastrointestinal and Liver Diseases, 26*(4), 428-429. doi:15403/jgld.2014.1121.261.igg

Khan, A. R., Hansen, B., Wiborg, O., Kroenke, C. D., & Jespersen, S. N. (2017). **Diffusion MRI and MR spectroscopy reveal microstructural and metabolic brain alterations in chronic mild stress exposed rats: A CMS recovery study**. *Neuroimage, 167*, 342-353. doi:10.1016/j.neuroimage.2017.11.053

Chronic mild stress (CMS) induced depression elicits several debilitating symptoms and causes a significant economic burden on society. High variability in the symptomatology of depression poses substantial impediment to accurate diagnosis and therapy outcome. CMS exposure induces significant metabolic and microstructural alterations in the hippocampus (HP), prefrontal cortex (PFC), caudate-putamen (CP) and amygdala (AM), however, recovery from these maladaptive changes are limited and this may provide negative effects on the therapeutic treatment and management of depression. The present study utilized anhedonic rats from the unpredictable CMS model of depression to study metabolic recovery in the ventral hippocampus (vHP) and microstructural recovery in the HP, AM, CP, and PFC. The study employed (1)H MR spectroscopy ((1)H MRS) and in-vivo diffusion MRI (d-MRI) at the age of week 18 (week 1 post CMS exposure) week 20 (week 3 post CMS) and week 25 (week 8 post CMS exposure) in the anhedonic group, and at the age of week 18 and week 22 in the control group. The d-MRI data have provided an array of diffusion tensor metrics (FA, MD, AD, and RD), and fast kurtosis metrics (MKT, WL and WT). CMS exposure induced a significant metabolic alteration in vHP, and significant microstructural alterations were observed in the HP, AM, and PFC in comparison to the age match control and within the anhedonic group. A significantly high level of N-acetylaspartate (NAA) was observed in vHP at the age of week 18 in comparison to age match control and week 20 and week 25 of the

anhedonic group. HP and AM showed significant microstructural alterations up to the age of week 22 in the anhedonic group. PFC showed significant microstructural alterations only at the age of week 18, however, most of the metrics showed significantly higher value at the age of week 20 in the anhedonic group. The significantly increased NAA concentration may indicate impaired catabolism due to astrogliosis or oxidative stress. The significantly increased WL in the AM and HP may indicate hypertrophy of AM and reduced volume of HP. Such metabolic and microstructural alterations could be useful in disease diagnosis and follow-up treatment intervention in depression and similar disorders.

Khatib, B., Cuddy, K., Cheng, A., Patel, A., Sim, F., Amundson, M., . . . Bell, R. B. (2017). **Functional Anatomic Computer Engineered Surgery Protocol for the Management of Self-Inflicted Gunshot Wounds to the Maxillofacial Skeleton**. *Journal of Oral and Maxillofacial Surgery*. doi:10.1016/j.joms.2017.10.017

Purpose: Virtual surgical planning (VSP) is an indispensable aid in craniomaxillofacial reconstruction, yet no protocol is established in facial gunshot wounds. We review our experience with computer-aided reconstruction of self-inflicted facial gunshot wounds (SIGSW'S) and propose a protocol for the staged repair. Methods: A retrospective case series enrolling patients with SIGSW's managed with the Functional Anatomic Computer Engineered Surgical protocol (FACES) was implemented. Subjects were evaluated at least one month postoperatively. Outcome variables were jaw position, facial projection, oro-nasal communication, lip competence, feeding tube and tracheostomy dependence, descriptive statistics were computed. The FACES protocol implemented during the initial hospitalization is as follows 1) damage control; 2) selective debridement; 3) VSP reconstruction back converted into navigation software 4) navigation assisted midfacial skeletal reconstruction; 5) computer aided oro-mandibular reconstruction with or without microvascular free flaps using custom cutting guides/hardware; 6) navigation assisted, computer aided palatomaxillary reconstruction with or without microvascular free flaps using cutting guides/hardware; 7) navigation assisted reconstruction of the internal orbit; 8) and confirmation of accurate reconstruction using intraoperative CT. Results: The sample was composed of 10 patients, mean age of 43 years (range, 28 - 62 years, 70% M), 100% with SIGSW's to the submental/submandibular region. All had satisfactory facial projection (n=10), nine had satisfactory jaw position, were decannulated by one month's follow up and were feeding tube independent (90%). All traumatic oro-antral communications were closed (n=8, 7 surgical, 1 obturator), seven had adequate lip competence (70%). Complications included fibula malunion (n=1), plate exposure (n=2) infection (n=2), intracranial abscess (n=1) and microstomia (n=2). Conclusion: Computer-aided surgery is an indispensable tool in the reconstruction of SIGSW's. Successfully implemented, it proved to be a useful adjunct for: the restoration of orbital volume, facial projection and symmetry; the inset of composite tissue, and the facilitation of dental implant supported prosthetic rehabilitation. © 2017 American Association of Oral and Maxillofacial Surgeons.

Kilberg, M. J., Rasooly, I. R., LaFranchi, S. H., Bauer, A. J., & Hawkes, C. P. (2018). **Newborn Screening in the US May Miss Mild Persistent Hypothyroidism**. *J Pediatr, 192*, 204-208. doi:10.1016/j.jpeds.2017.09.003

OBJECTIVE: To determine if newborn screening (NBS) programs for congenital hypothyroidism in the US use thyroid-stimulating hormone (TSH) cutoffs that are age adjusted to account for the physiologic 4-fold reduction in TSH concentrations over the first few days of life. STUDY DESIGN: All NBS programs in the US were contacted and asked to provide information on their NBS protocols, TSH cutoffs, and whether these cutoffs were age adjusted. RESULTS: Of 51 NBS programs, 28 request a repeat specimen if the initial eluted serum TSH concentration is mildly increased (between the cutoff and a median upper limit of 50 mU/L), whereas 14 programs perform a routine second screen in all infants. Although these specimens are typically collected between 1 week and 1 month of life, 16 of the 28 programs with a discretionary second test and 8 of 14 programs with a routine second test do not have age-adjusted TSH cutoffs after the first 48 hours of life. CONCLUSIONS: There is variation in NBS practices for screening for congenital hypothyroidism across the US, and many programs do not adjust the TSH cutoff beyond the first 2 days of life. Samples are processed when received from older infants, often to retest borderline initial results. This approach will miss congenital hypothyroidism in infants with persistent mild TSH elevations. We recommend that all NBS programs

provide age-adjusted TSH cutoffs, and suggest developing a standard approach to screening for congenital hypothyroidism in the US.

Kim, S., McClave, S. A., Martindale, R. G., Miller, K. R., & Hurt, R. T. (2017). **Hypoalbuminemia and clinical outcomes: What is the mechanism behind the relationship?** *American Surgeon, 83*(11), 1220-1227.

Albumin has a number of important physiologic functions, which include maintaining oncotic pressure, transporting various agents (fatty acids, bile acids, cholesterol, metal ions, and drugs), scavenging free oxygen radicals, acting as an antioxidant, and exerting an antiplatelet effect. Hypoalbuminemia in adults, defined by an intravascular albumin level of <3.5 g/dL, is associated with poor postoperative outcomes in patients undergoing surgical intervention. Although the relationship of hypoalbuminemia and poor surgical outcome has been known for many years, the pathophysiology behind the relationship is unclear. Three theoretical constructs might explain this relationship. First, albumin might serve as a nutritional marker, such that hypoalbuminemia represents poor nutritional status in patients who go on to experience poor postoperative outcomes. Second, albumin has its own pharmacologic characteristics as an antioxidant or transporter, and therefore, the lack of albumin might result in a deficiency of those functions, resulting in poor postoperative outcomes. Or third, albumin is known to be a negative acute phase protein, and as such hypoalbuminemia might represent an increased inflammatory status of the patient, potentially leading to poor outcomes. A thorough review of the literature reveals the fallacy of these arguments and fails to show a direct cause and effect between low albumin levels per se and adverse outcomes. Interventions designed solely to correct preoperative hypoalbuminemia, in particular intravenous albumin infusion, do little to change the patient's course of hospitalization. While surgeons may use albumin levels on admission for their prognostic value, they should avoid therapeutic strategies whose main endpoint is correction of this abnormality.

Kim, S. J., Campbell, J. P., Ostmo, S., Jonas, K. E., Chan, R. V. P., & Chiang, M. F. (2017). **Changes in Relative Position of Choroidal Versus Retinal Vessels in Preterm Infants**. *Invest Ophthalmol Vis Sci, 58*(14), 6334-6341. doi:10.1167/iovs.17-22687

Purpose: The purpose of this study was to characterize a novel finding that relative positions of choroidal and retinal vessels change over time in preterm infants and to identify factors associated with this finding using quantitative analysis. Methods: Fundus images were obtained prospectively through a retinopathy of prematurity (ROP) cohort study. Images were excluded if choroidal vessels could not be identified. Changes in relative position of characteristic choroidal landmarks with respect to retinal vessels between two time points 5 to 7 weeks apart were measured. Univariate and multivariate regression analyses were performed to identify associated factors with the amount of change. Results: The discovery and replication cohorts included 45 and 58 patients, respectively. Ninety-two of them (89%) were non-Hispanic Caucasians. Changes in relative position of choroidal versus retinal vessels were detected in all eyes of the discovery and replication cohorts (mean amount = 0.42 +/- 0.12 and 0.35 +/- 0.12 mm, respectively). On combined multiple regression analysis of the two cohorts, type 1 ROP, higher postmenstral age at the first time point, and shorter distance from optic disc to choroidal landmark were significantly associated with less change in relative position. Conclusions: Choroidal vessels grow anteriorly with respect to retinal vessels at posterior pole in preterm infants, suggesting relatively faster peripheral growth of choroidal versus retinal vessels. Eyes with severe ROP showed less difference in growth, which might represent alterations in choroidal development due to advanced ROP. These findings may contribute to better understanding about the physiology of choroidal development and involvement in ROP.

King, C. J., Woodward, J., Schwartzman, J., Coleman, D. J., Lisac, R., Wang, N. J., . . . Alumkal, J. J. (2017). **Integrative molecular network analysis identifies emergent enzalutamide resistance mechanisms in prostate cancer**. *Oncotarget, 8*(67), 111084-111095. doi:10.18632/oncotarget.22560

Recent work demonstrates that castration-resistant prostate cancer (CRPC) tumors harbor countless genomic aberrations that control many hallmarks of cancer. While some specific mutations in CRPC may be actionable, many others are not. We hypothesized that genomic aberrations in cancer may operate in concert to promote drug resistance and tumor progression, and that organization of these genomic aberrations into therapeutically targetable pathways may improve our ability to treat CRPC. To identify the molecular underpinnings of enzalutamideresistant CRPC, we performed transcriptional and copy number profiling studies using paired enzalutamide-sensitive and resistant LNCaP prostate cancer cell lines. Gene networks associated with enzalutamide resistance were revealed by performing an integrative genomic analysis with the PAthway Representation and Analysis by Direct Reference on Graphical Models (PARADIGM) tool. Amongst the pathways enriched in the enzalutamide-resistant cells were those associated with MEK, EGFR, RAS, and NFKB. Functional validation studies of 64 genes identified 10 candidate genes whose suppression led to greater effects on cell viability in enzalutamide-resistant cells as compared to sensitive parental cells. Examination of a patient cohort demonstrated that several of our functionally-validated gene hits are deregulated in metastatic CRPC tumor samples, suggesting that they may be clinically relevant therapeutic targets for patients with enzalutamide-resistant CRPC. Altogether, our approach demonstrates the potential of integrative genomic analyses to clarify determinants of drug resistance and rational co-targeting strategies to overcome resistance. © King et al.

Ko, S. H., Nauta, A. C., Morrison, S. D., Hu, M. S., Zimmermann, A. S., Chung, M. T., . . . Longaker, M. T. (2018). **PHD-2 Suppression in Mesenchymal Stromal Cells Enhances Wound Healing**. *Plast Reconstr Surg, 141*(1), 55e-67e. doi:10.1097/prs.0000000000003959

BACKGROUND: Cell therapy with mesenchymal stromal cells is a promising strategy for tissue repair. Restoration of blood flow to ischemic tissues is a key step in wound repair, and mesenchymal stromal cells have been shown to be proangiogenic. Angiogenesis is critically regulated by the hypoxia-inducible factor (HIF) superfamily, consisting of transcription factors targeted for degradation by prolyl hydroxylase domain (PHD)-2. The aim of this study was to enhance the proangiogenic capability of mesenchymal stromal cells and to use these modified cells to promote wound healing. METHODS: Mesenchymal stromal cells harvested from mouse bone marrow were transduced with short hairpin RNA (shRNA) against PHD-2; control cells were transduced with scrambled shRNA (shScramble) construct. Gene expression quantification, human umbilical vein endothelial cell tube formation assays, and wound healing assays were used to assess the effect of PHD knockdown mesenchymal stromal cells on wound healing dynamics. RESULTS: PHD-2 knockdown mesenchymal stromal cells overexpressed HIF-1alpha and multiple angiogenic factors compared to control ($p < 0.05$). Human umbilical vein endothelial cells treated with conditioned medium from PHD-2 knockdown mesenchymal stromal cells exhibited increased formation of capillary-like structures and enhanced migration compared with human umbilical vein endothelial cells treated with conditioned medium from shScramble-transduced mesenchymal stromal cells ($p < 0.05$). Wounds treated with PHD-2 knockdown mesenchymal stromal cells healed at a significantly accelerated rate compared with wounds treated with shScramble mesenchymal stromal cells ($p < 0.05$). Histologic studies revealed increased blood vessel density and increased cellularity in the wounds treated with PHD-2 knockdown mesenchymal stromal cells ($p < 0.05$). CONCLUSIONS: Silencing PHD-2 in mesenchymal stromal cells augments their proangiogenic potential in wound healing therapy. This effect appears to be mediated by overexpression of HIF family transcription factors and up-regulation of multiple downstream angiogenic factors.

Koczkowska, M., Chen, Y., Callens, T., Gomes, A., Sharp, A., Johnson, S., . . . Messiaen, L. M. (2017). **Genotype-Phenotype Correlation in NF1: Evidence for a More Severe Phenotype Associated with Missense Mutations Affecting NF1 Codons 844-848**. *American Journal of Human Genetics*. doi:10.1016/j.ajhg.2017.12.001

Neurofibromatosis type 1 (NF1), a common genetic disorder with a birth incidence of 1:2,000-3,000, is characterized by a highly variable clinical presentation. To date, only two clinically relevant intragenic genotype-phenotype correlations have been reported for NF1 missense mutations affecting p.Arg1809 and a single amino acid

deletion p.Met922del. Both variants predispose to a distinct mild NF1 phenotype with neither externally visible cutaneous/plexiform neurofibromas nor other tumors. Here, we report 162 individuals (129 unrelated probands and 33 affected relatives) heterozygous for a constitutional missense mutation affecting one of five neighboring NF1 codons-Leu844, Cys845, Ala846, Leu847, and Gly848-located in the cysteine-serine-rich domain (CSRD). Collectively, these recurrent missense mutations affect approximately 0.8% of unrelated NF1 mutation-positive probands in the University of Alabama at Birmingham (UAB) cohort. Major superficial plexiform neurofibromas and symptomatic spinal neurofibromas were more prevalent in these individuals compared with classic NF1-affected cohorts (both $p < 0.0001$). Nearly half of the individuals had symptomatic or asymptomatic optic pathway gliomas and/or skeletal abnormalities. Additionally, variants in this region seem to confer a high predisposition to develop malignancies compared with the general NF1-affected population ($p = 0.0061$). Our results demonstrate that these NF1 missense mutations, although located outside the GAP-related domain, may be an important risk factor for a severe presentation. A genotype-phenotype correlation at the NF1 region 844-848 exists and will be valuable in the management and genetic counseling of a significant number of individuals.

Koday, M. T., Leonard, J. A., Munson, P., Forero, A., Koday, M., Bratt, D. L., . . . Fuller, D. H. (2017). **Multigenic DNA vaccine induces protective cross-reactive T cell responses against heterologous influenza virus in nonhuman primates**. *PLoS ONE, 12*(12), e0189780. doi:10.1371/journal.pone.0189780

Recent avian and swine-origin influenza virus outbreaks illustrate the ongoing threat of influenza pandemics. We investigated immunogenicity and protective efficacy of a multi-antigen (MA) universal influenza DNA vaccine consisting of HA, M2, and NP antigens in cynomolgus macaques. Following challenge with a heterologous pandemic H1N1 strain, vaccinated animals exhibited significantly lower viral loads and more rapid viral clearance when compared to unvaccinated controls. The MA DNA vaccine induced robust serum and mucosal antibody responses but these high antibody titers were not broadly neutralizing. In contrast, the vaccine induced broadly-reactive NP specific T cell responses that cross-reacted with the challenge virus and inversely correlated with lower viral loads and inflammation. These results demonstrate that a MA DNA vaccine that induces strong cross-reactive T cell responses can, independent of neutralizing antibody, mediate significant cross-protection in a nonhuman primate model and further supports development as an effective approach to induce broad protection against circulating and emerging influenza strains.

Koopmann, M. C., & McLafferty, R. B. (2017). **Advances in Operative Thrombectomy for Lower Extremity Venous Thrombosis**. *Surgical Clinics of North America*. doi:10.1016/j.suc.2017.11.005

Lower extremity deep venous thrombosis is a leading cause of morbidity and mortality. The mainstay of therapy is medical. However, anticoagulation does not remove the thrombus and restore venous patency. In select patients, early thrombus removal and anticoagulation can restore venous patency, preserve venous valve function, and may reduce the incidence of postthrombotic syndrome. Catheter-directed therapies are minimally invasive with low complication rates. However, in patients with a contraindication to thrombolytic agents who can receive anticoagulation, open thrombectomy should be considered if indications for thrombus removal are met and patients are good operative risks. © 2017.

Kozhimannil, K. B., Muoto, I., Darney, B. G., Caughey, A. B., & Snowden, J. M. (2017). **Early Elective Delivery Disparities between Non-Hispanic Black and White Women after Statewide Policy Implementation**. *Womens Health Issues*. doi:10.1016/j.whi.2017.11.008

BACKGROUND: In 2011, Oregon implemented a policy that reduced the state's rate of early (before 39 weeks' gestation) elective (without medical need) births. OBJECTIVE: This analysis measured differential policy effects by race, examining whether Oregon's policy was associated with changes in non-Hispanic Black-White disparities in early elective cesarean and labor induction. METHODS: We used Oregon birth certificate data, defining prepolicy (2008-2010) and postpolicy (2012-2014) periods, including non-Hispanic Black and

White women who gave birth during these periods (n = 121,272). We used longitudinal spline models to assess policy impacts by race and probability models to measure policy-associated changes in Black-White disparities. RESULTS: We found that the prepolicy Black-White differences in early elective cesarean (6.1% vs. 4.3%) were eliminated after policy implementation (2.8% vs. 2.5%); adjusted models show decreases in the odds of elective early cesarean among Black women after the policy change (adjusted odds ratio, 0.47; 95% confidence interval, 0.22-1.00; p = .050) and among White women (adjusted odds ratio, 0.79; 95% confidence interval, 0.67-0.93; p = .006). Adjusted probability models indicated that policy implementation resulted in a 1.75-percentage point narrowing (p = .011) in the Black-White disparity in early elective cesarean. Early elective induction also decreased, from 4.9% and 4.7% for non-Hispanic Black and non-Hispanic White women to 3.8% and 2.5%, respectively; the policy was not associated with a statistically significant change in disparities. CONCLUSIONS: A statewide policy reduced racial disparities in early elective cesarean, but not early elective induction. Attention to differential policy effects by race may reveal changes in disparities, even when that is not the intended focus of the policy.

Krey, J. F., Dumont, R. A., Wilmarth, P. A., David, L. L., Johnson, K. R., & Barr-Gillespie, P. G. (2017). **ELMOD1 stimulates ARF6-GTP hydrolysis to stabilize apical structures in developing vestibular hair cells**. *J Neurosci*. doi:10.1523/jneurosci.2658-17.2017

Sensory hair cells require control of physical properties of their apical plasma membranes for normal development and function. Members of the ARF small GTPase family regulate membrane trafficking and cytoskeletal assembly in many cells. We identified ELMOD1, a guanine nucleoside triphosphatase activating protein (GAP) for ARF6, as the most highly enriched ARF regulator in hair cells. To characterize ELMOD1 control of trafficking, we analyzed mice of both sexes from a strain lacking functional ELMOD1 (roundabout; rda). In rda/rda mice, cuticular plates of utricle hair cells initially formed normally, then degenerated after postnatal day 5 (P5); large numbers of vesicles invaded the compromised cuticular plate. Hair bundles initially developed normally, but the cell's apical membrane lifted away from the cuticular plate, and stereocilia elongated and fused. Membrane trafficking in type I hair cells, measured by FM1-43 dye labeling, was altered in rda/rda mice. Consistent with the proposed GAP role for ELMOD1, the ARF6 GTP/GDP ratio was significantly elevated in rda/rda utricles as compared to controls, and the level of ARF6-GTP was correlated with the severity of the rda/rda phenotype. These results suggest that conversion of ARF6 to its GDP-bound form is necessary for final stabilization of the hair bundle.SIGNIFICANCE STATEMENTAssembly of the mechanically sensitive hair bundle of sensory hair cells requires growth and reorganization of apical actin and membrane structures. Hair bundles and apical membranes in mice with mutations in the Elmod1 gene degenerate after formation, suggesting that the ELMOD1 protein stabilizes these structures. We show that ELMOD1 is a GTPase-activating protein in hair cells for the small GTP-binding protein ARF6, known to participate in actin assembly and membrane trafficking. We propose that conversion of ARF6 into the GDP-bound form in the apical domain of hair cells is essential for stabilizing apical actin structures like the hair bundle and ensuring that the apical membrane forms appropriately around the stereocilia.

Krishnaswami, S., Stephens, C. Q., Yang, G. P., Nwomeh, B. C., Swaroop, M., Nadler, E. P., . . . Orloff, S. L. (2017). **An academic career in global surgery: a position paper from the Society of University Surgeons Committee on Academic Global Surgery**. *Surgery*. doi:10.1016/j.surg.2017.10.019

In recent years, as the high burden of surgical disease and poor access to surgical care in low- and middle-income countries have gained recognition as major public health problems, interest in global health has surged among surgical trainees and faculty. Traditionally, clinical volunteerism was at the forefront of the high-income country response to the significant burden of surgical disease in low- and middle-income countries. However, sustainable strategies for providing surgical care in low- and middle-income countries increasingly depend on bilateral clinical, research, and education collaborations to ensure effective resource allocation and contextual relevance. Academic global surgery creates avenues for interested surgeons to combine scholarship and education with their clinical global surgery passions through incorporation of basic/translational, education, clinical outcomes, or health services research with global surgery. Training in

global health, either within residency or through advanced degrees, can provide the necessary skills to develop and sustain such initiatives. We further propose that creating cross-continental, bidirectional collaborations can maximize funding opportunities. Academic institutions are uniquely positioned to lead longitudinal and, importantly, sustainable global surgery efforts. However, for the individual global surgeon, the career path forward may be unclear. This paper reviews the development of academic global surgery, delineates the framework and factors critical to training global surgeons, and proposes models for establishing an academic career in this field. Overall, with determination, the academic global surgeon will not only carve out a niche of expertise but will define this critical field for future generations.

Kriz, D., Piantino, J., Fields, D., & Williams, C. (2017). **Pediatric Hypothermic Submersion Injury and Protective Factors Associated with Optimal Outcome: A Case Report and Literature Review**. *Children (Basel), 5*(1). doi:10.3390/children5010004

Drowning is the 3rd leading cause of unintentional injury death worldwide, with the highest rates of fatality among young children. Submersion injuries with cardiac arrest can lead to long-term neurologic morbidity. Severe hypothermic submersion injuries have complex treatment courses and survivors have variable neurocognitive outcomes. We describe the course of a hypothermic submersion injury in a 6-year-old previously healthy boy. The description includes premorbid and post-injury neurocognitive functioning. A review of the literature of pediatric cold-water submersion injury was performed. Despite prolonged cardiopulmonary resuscitation (>100 min) and water temperature well above freezing, our patient had an optimal neurocognitive outcome following hypothermic submersion injury. Available literature is limited but suggests that increased submersion time, increased duration of resuscitation, and higher water temperatures are associated with worse outcomes. Care guidelines have been created, but outcomes related to these guidelines have not been studied. Our case highlights potential important determinants of outcome after drowning. Incident specific characteristics and therapeutic interventions should be considered when evaluating this population. Treatment guidelines based on currently available literature may fail to incorporate all potential variables, and consideration should be given to prolonged resuscitative efforts based on individual case characteristics until further data is available.

Kudenchuk, P. J., Leroux, B. G., Daya, M., Rea, T., Vaillancourt, C., Morrison, L. J., . . . Dorian, P. (2017). **Antiarrhythmic Drugs for Nonshockable-Turned-Shockable Out-of-Hospital Cardiac Arrest:The ALPS Study (Amiodarone, Lidocaine, or Placebo)**. *Circulation, 136*(22), 2119-2131. doi:10.1161/CIRCULATIONAHA.117.028624

Background: Out-of-hospital cardiac arrest (OHCA) commonly presents with nonshockable rhythms (asystole and pulseless electric activity). It is unknown whether antiarrhythmic drugs are safe and effective when nonshockable rhythms evolve to shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia [VF/VT]) during resuscitation. Methods: Adults with nontraumatic OHCA, vascular access, and VF/VT anytime after ≥1 shock(s) were prospectively randomized, double-blind, to receive amiodarone, lidocaine, or placebo by paramedics. Patients presenting with initial shock-refractory VF/VT were previously reported. The current study was a prespecified analysis in a separate cohort that initially presented with nonshockable OHCA and was randomized on subsequently developing shock-refractory VF/VT. The primary outcome was survival to hospital discharge. Secondary outcomes included discharge functional status and adverse drug-related effects. Results: Of 37 889 patients with OHCA, 3026 with initial VF/VT and 1063 with initial nonshockable-turned-shockable rhythms were treatment-eligible, were randomized, and received their assigned drug. Baseline characteristics among patients with nonshockable-turned-shockable rhythms were balanced across treatment arms, except that recipients of a placebo included fewer men and were less likely to receive bystander cardiopulmonary resuscitation. Active-drug recipients in this cohort required fewer shocks, supplemental doses of their assigned drug, and ancillary antiarrhythmic drugs than recipients of a placebo ($P<0.05$). In all, 16 (4.1%) amiodarone, 11 (3.1%) lidocaine, and 6 (1.9%) placebo-treated patients survived to hospital discharge ($P=0.24$). No significant interaction between treatment assignment and discharge survival occurred with the initiating OHCA rhythm (asystole, pulseless electric activity, or VF/VT). Survival in each of

these categories was consistently higher with active drugs, although the trends were not statistically significant. Adjusted absolute differences (95% confidence interval) in survival from nonshockable-turned-shockable arrhythmias with amiodarone versus placebo were 2.3% (-0.3, 4.8), P=0.08, and for lidocaine versus placebo 1.2% (-1.1, 3.6), P=0.30. More than 50% of these survivors were functionally independent or required minimal assistance. Drug-related adverse effects were infrequent. Conclusions: Outcome from nonshockable-turned-shockable OHCA is poor but not invariably fatal. Although not statistically significant, point estimates for survival were greater after amiodarone or lidocaine than placebo, without increased risk of adverse effects or disability and consistent with previously observed favorable trends from treatment of initial shock-refractory VF/VT with these drugs. Together the findings may signal a clinical benefit that invites further investigation. Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01401647. © 2017 American Heart Association, Inc.

Kurre, P. (2017). **Hematopoietic development - a gap in our understanding of inherited bone marrow failure**. *Experimental Hematology*. doi:10.1016/j.exphem.2017.12.003

Inherited bone marrow failure syndromes (IBMFS) represent a heterogeneous group of multisystem disorders that typically present with cytopenia in early childhood. Efforts to understand the underlying hematopoietic stem cell (HSC) losses have generally focused on postnatal hematopoiesis. However, reflecting the role of many of the involved genes in core cellular functions and the diverse non-hematologic abnormalities seen in patients at birth, studies have begun to explore IBMFS manifestations during fetal development. Here, I consider the current evidence for fetal deficits in the HSC pool and highlight emerging concepts regarding the origins and unique pathophysiology of hematopoietic failure in IBMFS.

Kwon, S., Chin, K., Nederlof, M., & Gray, J. W. (2017). **Quantitative, in situ analysis of mRNAs and proteins with subcellular resolution**. *Sci Rep, 7*(1), 16459. doi:10.1038/s41598-017-16492-1

We describe here a method, termed immunoFISH, for simultaneous in situ analysis of the composition and distribution of proteins and individual RNA transcripts in single cells. Individual RNA molecules are labeled by hybridization and target proteins are concurrently stained using immunofluorescence. Multicolor fluorescence images are acquired and analyzed to determine the abundance, composition, and distribution of hybridized probes and immunofluorescence. We assessed the ability of immunoFISH to simultaneous quantify protein and transcript levels and distribution in cultured HER2 positive breast cancer cells and human breast tumor samples. We demonstrated the utility of this assay in several applications including demonstration of the existence of a layer of normal myoepithelial KRT14 expressing cells that separate HER2+ cancer cells from the stromal and immune microenvironment in HER2+ invasive breast cancer. Our studies show that immunoFISH provides quantitative information about the spatial heterogeneity in transcriptional and proteomic features that exist between and within cells.

Lama, A., Drennan, S. L., Johnson, R. C., Rubenstein, G. L., & Cambronne, E. D. (2017). **Identification of Conserved ABC Importers Necessary for Intracellular Survival of Legionella pneumophila in Multiple Hosts**. *Front Cell Infect Microbiol, 7*, 485. doi:10.3389/fcimb.2017.00485

It is established that the human pathogen Legionella pneumophila becomes significantly augmented for infection of macrophages after intracellular growth in amoebae when compared to like-strains cultivated in laboratory media. Based on this observation, we reasoned that the most critical virulence determinants of L.p. are expressed by responding to stimuli generated by the protozoan host specifically; a process we term "protozoan-priming." We sought to identify L.p. virulence factors that were required for replication in amoebae in order to highlight the genes necessary for production of the most infectious form of the bacterium. Using a transposon mutagenesis screen, we successfully identified 12 insertions that produced bacteria severely attenuated for growth in amoebae, while retaining a functional Dot/Icm type IVb secretion system. Seven of these insertion mutants were found dispensable for growth in macrophages, revealing

attractive therapeutic targets that reside upstream of the pathogen-human interface. Two candidates identified, lpg0730 and lpg0122 were required for survival and replication in amoebae and macrophage host cells. Both genes are conserved among numerous important human pathogenic bacteria that can persist or replicate in amoebae. Each gene encodes a component of an ATP binding cassette (ABC) transport complex of unknown function. We demonstrate the lpg0730 ortholog in Francisella tularensis subsp. novicida to be essential for colonization of both protozoan and mammalian host cells, highlighting conserved survival mechanisms employed by bacteria that utilize protozoa as an environmental reservoir for replication.

Lamble, A. J., Dietz, M., Laderas, T., McWeeney, S., & Lind, E. F. (2017). **Integrated functional and mass spectrometry-based flow cytometric phenotyping to describe the immune microenvironment in acute myeloid leukemia**. *Journal of Immunological Methods*. doi:10.1016/j.jim.2017.11.010

A hallmark of the development of cancer is its ability to avoid detection and elimination by the immune system. There are many identified mechanisms of this immune evasion that can be measured both phenotypically and functionally. Functional studies directly show the ability of the tumor microenvironment to suppress immune responses, typically measured as lymphocyte proliferation, cytokine production or killing ability. While a direct measurement of function is ideal, these assays require ex vivo activation which may not accurately mimic in vivo conditions. Phenotypic assays can directly measure the distribution and activation of immune cell types rapidly after isolation, preserving the conditions present in the patient. While conventional flow cytometry is a rapid and well established assay, it currently allows for measurement of only 12-14 parameters. Mass spectrometry-based flow cytometry, or CyTOF, offers the ability to measure 3-fold more parameters than conventional optical-based modalities providing an advantage in depth of analysis that can be crucial for precious human samples. The goal of this report is to describe the system our group has developed to measure both the phenotype and function of immune cells in the bone marrow of patients with acute myeloid leukemia. We hope to explain our system in the context of previous studies aimed at measuring immune status in tumors and to inform the reader as to some experimental approaches our group has found useful in developing the basic data required to rationally pursue immune-based therapies for patients with cancer. © 2017 Elsevier B.V.

Lamme, J., Edelman, A., Padua, E., & Jensen, J. T. (2017). **Evaluation of the challenges faced in increasing contraceptive access within a community college population**. *Contracept Reprod Med, 2*, 25. doi:10.1186/s40834-017-0051-8

Background: Research demonstrates removing barriers to access, decreasing costs and offering same-day placement of long-acting reversible contraception (LARC) increases contraceptive uptake in young women. For those in community college (CC), LARC utilization might reduce the risk of dropout and improve degree completion. We identified a local school who had documented an unmet need for on-campus services through a recent student assessment. We then established an on-campus, same day contraceptive clinic at the CC as part of a clinical trial. We found that students did not use the service even after multiple attempts to increase awareness and we ended the study. Here, we report lessons learned from attempting research in this environment in addition to results from a follow-up survey to determine why students did not access the clinical resource. Students reported that they already had good access to contraception and preferred to get their healthcare off-campus. This study demonstrates the complexities of studying highly focused interventions to influence access to care in the current health care environment with ever changing regulations. Trial registration: NCT02735551 . Registered April 6, 2016.

Lammers, A., Wang, R., Cetnar, J., & Prasad, V. (2017). **Time from US Food and Drug Administration approval to publication of data for cancer drugs: a comparison of first and subsequent approvals**. *Blood Cancer J, 7*(12), 637. doi:10.1038/s41408-017-0008-9

Lee, G. Q., Bangsberg, D. R., Mo, T., Lachowski, C., Brumme, C. J., Zhang, W., . . . Harrigan, P. R. (2017). **Prevalence and clinical impacts of HIV-1 intersubtype recombinants in Uganda revealed by near-full-genome population and deep sequencing approaches**. *AIDS, 31*(17), 2345-2354. doi:10.1097/QAD.0000000000001619

Objectives: HIV-1 subtypes A1 and D cocirculate in a rural community in Mbarara, Uganda. This study examines HIV-1 intersubtype recombination in this community under a full-genome sequencing context. We aim to estimate prevalence, examine time trends, and test for clinical correlates and outcomes associated with intersubtype recombinants. Methods: Near-full-genome HIV-1 Sanger sequence data were collected from plasma samples of 504 treatment-naïve individuals, who then received protease inhibitor or nonnucleoside reverse transcriptase inhibitor-containing regimens and were monitored for up to 7.5 years. Subtypes were inferred by Los Alamos Recombinant Identification Program (RIP) 3.0 and compared with Sanger/REGA and MiSeq/RIP. 'Nonrecombinants' and 'recombinants' infections were compared in terms of pretherapy viral load, CD4 + cell count, posttherapy time to virologic suppression, virologic rebound, first CD4 + rise above baseline and sustained CD4 + recovery. Results: Prevalence of intersubtype recombinants varied depending on the genomic region examined: gag (15%), prrt (11%), int (8%), vif (10%), vpr (2%), vpu (9%), GP120 (8%), GP41 (18%), and nef (4%). Of the 200 patients with near-full-genome data, prevalence of intersubtype recombination was 46%; the most frequently observed recombinant was A1-D (25%). Sanger/REGA and MiSeq/RIP yielded generally consistent results. Phylogenetic tree revealed most recombinants did not share common ancestors. No temporal trend was observed (all P>0.1). Subsequent subtype switches were detected in 27 of 143 (19%) study participants with follow-up sequences. Nonrecombinant versus recombinants infections were not significantly different in any pre nor posttherapy clinical correlates examined (all P>0.2). Conclusion: Intersubtype recombination was highly prevalent (46%) in Uganda if the entire HIV genome was considered, but was neither associated with clinical correlates nor therapy outcomes.

Lee, S. H., Terndrup, C., Phan, P. H., Zaeh, S. E., Atsina, K., Minkove, N., . . . Desai, S. V. (2017). **A Randomized Cohort Controlled Trial to Compare Intern Sign-Out Training Interventions**. *Journal of Hospital Medicine, 12*(12), 979-983. doi:10.12788/jhm.2843

BACKGROUND: Although previous studies have investigated the efficacy of specific sign-out protocols (such as the illness severity, patient summary, action list, situation awareness and contingency planning, and synthesis by reviewer [I-PASS] bundle), the implementation of a bundle can be time consuming and costly. We compared 4 sign-out training pedagogies on sign-out quality. OBJECTIVE: To evaluate training interventions that best enhance multidimensional sign-out quality measured by information exchange, task accountability, and personal responsibility. INTERVENTION: Four general internal medicine firms were randomly assigned into 1 of the following 4 training interventions: didactics (control), I-PASS, policy mandate on task accountability, and Plan-Do-Study-Act (PDSA). SETTING: First-year interns at a large, Mid-Atlantic internal medicine residency program. MEASUREMENTS: Eight trained observers examined 10 days each in the pre- and postintervention periods for each firm using a standardized sign-out checklist. RESULTS: Pre- and postintervention differences showed significant improvements in the transfer of patient information, task accountability, and personal responsibility for the I-PASS, policy mandate, and PDSA groups, respectively, in line with their respective training foci. Compared to the control, I-PASS reported the best improvements in sign-out quality, although there was room to improve in task accountability and responsibility. CONCLUSIONS: Different training emphases improved different dimensions of sign-out quality. A combination of training pedagogies is likely to yield optimal results.

Leichman, C. G., McDonough, S. L., Smalley, S. R., Billingsley, K. G., Lenz, H. J., Beldner, M. A., . . . Hochster, H. S. (2017). **Cetuximab Combined With Induction Oxaliplatin and Capecitabine, Followed by Neoadjuvant Chemoradiation for Locally Advanced Rectal Cancer: SWOG 0713**. *Clin Colorectal Cancer*. doi:10.1016/j.clcc.2017.10.008

BACKGROUND: Neoadjuvant chemoradiation (NCRT) is standard treatment for locally advanced rectal cancer. Pathologic complete response (pCR) has associated with improved survival. In modern phase III trials of NCRT, pCR ranges from 10% to 20%. Cetuximab improves response in KRAS (KRAS proto-oncogene) wild type (wt) metastatic colorectal cancer. S0713 was designed to assess improvement in pCR with additional use of cetuximab with induction chemotherapy and NCRT for locally advanced, KRAS-wt rectal cancer. PATIENTS AND METHODS: Patient eligibility: stage II to III biopsy-proven, KRAS-wt rectal adenocarcinoma; no bowel obstruction; adequate hematologic, hepatic and renal function; performance status of 0 to 2. Target enrollment: 80 patients. TREATMENT: induction chemotherapy with wCAPOX (weekly capecitabine and oxaliplatin) and cetuximab followed by the same regimen concurrent with radiation (omitting day 15 oxaliplatin). If fewer than 7 pCRs were observed at planned interim analysis after 40 patients received all therapy, the study would close. Eighty eligible patients would provide 90% power given a true pCR rate > 35% at a significance of 0.04. The regimen would lack future interest if pCR probability was </= 20%. RESULTS: Between February 2009 and April 2013, 83 patients registered. Four were ineligible and 4 not treated, leaving 75 evaluable for clinical outcomes and toxicity, of whom 65 had surgery. Of 75 patients, 20 had pCR (27%; 95% confidence interval [CI], 17%-38%); 19 (25%) had microscopic cancer; 36 (48%) had minor/no response (including 10 without surgery). Three-year disease-free survival was 73% (95% CI, 63%-83%). CONCLUSION: Our trial did not meet the pCR target of 35%. Toxicity was generally acceptable. This regimen cannot be recommended outside the clinical trial setting.

Leo, R. J., McLeod, M., & Veeder, T. A. (2017). **Self-mutilation after recent-onset psychosis**. *Current Psychiatry, 16*(12), 48-55.

Leonard, J., & Stock, W. (2017). **Progress in adult ALL: incorporation of new agents to frontline treatment**. *Hematology: The Education Program of the American Society of Hematology, 2017*(1), 28-36. doi:10.1182/asheducation-2017.1.28

Treatment of acute lymphoblastic leukemia (ALL) in adults remains a challenge, as the delivery of intensive chemotherapeutic regimens in this population is less feasible than it is in the pediatric population. This has led to higher rates of treatment-related toxicity as well as lower overall survival in the adult population. Over the past several years, a host of novel therapies (eg, immunotherapy and targeted therapies) with better tolerability than traditional chemotherapy are now being introduced into the relapsed/refractory population with very encouraging results. Additionally, insights into how to choose effective therapies for patients while minimizing drug toxicity through pharmacogenomics and the use of minimal residual disease (MRD) monitoring to escalate/de-escalate therapy have enhanced our ability to reduce treatment-related toxicity. This has led to the design of a number of clinical trials which incorporate both novel therapeutics as well as MRD-directed treatment pathways into the frontline setting. The use of increasingly personalized treatment strategies for specific disease subsets combined with standardized and rapid molecular diagnostic testing in the initial diagnosis and frontline treatment of ALL will hopefully lead to further improvements in survival for our adult patients.

Leturiondo, M., de Gauna, S. R., Ruiz, J. M., Gutierrez, J. J., Leturiondo, L. A., Gonzalez-Otero, D. M., . . . Daya, M. (2017). **Influence of chest compression artefact on capnogram-based ventilation detection during out-of-hospital cardiopulmonary resuscitation**. *Resuscitation*. doi:10.1016/j.resuscitation.2017.12.013

BACKGROUND: Capnography has been proposed as a method for monitoring the ventilation rate during cardiopulmonary resuscitation (CPR). A high incidence (above 70%) of capnograms distorted by chest compression induced oscillations has been previously reported in out-of-hospital (OOH) CPR. The aim of the study was to better characterize the chest compression artefact and to evaluate its influence on the performance of a capnogram-based ventilation detector during OOH CPR. METHODS: Data from the MRx

monitor-defibrillator were extracted from OOH cardiac arrest episodes. For each episode, presence of chest compression artefact was annotated in the capnogram. Concurrent compression depth and transthoracic impedance signals were used to identify chest compressions and to annotate ventilations, respectively. We designed a capnogram-based ventilation detection algorithm and tested its performance with clean and distorted episodes. RESULTS: Data were collected from 232 episodes comprising 52654 ventilations, with a mean (+/-SD) of 227 (+/-118) per episode. Overall, 42% of the capnograms were distorted. Presence of chest compression artefact degraded algorithm performance in terms of ventilation detection, estimation of ventilation rate, and the ability to detect hyperventilation. CONCLUSION: Capnogram-based ventilation detection during CPR using our algorithm was compromised by the presence of chest compression artefact. In particular, artefact spanning from the plateau to the baseline strongly degraded ventilation detection, and caused a high number of false hyperventilation alarms. Further research is needed to reduce the impact of chest compression artefact on capnographic ventilation monitoring.

Li, S., Hsieh, T. C., Rehder, K. J., Nett, S., Kamat, P., Napolitano, N., . . . Nishisaki, A. (2017). **Frequency of Desaturation and Association With Hemodynamic Adverse Events During Tracheal Intubations in PICUs**. *Pediatr Crit Care Med*. doi:10.1097/pcc.0000000000001384

OBJECTIVES: Oxygen desaturation during tracheal intubation is known to be associated with adverse ICU outcomes in critically ill children. We aimed to determine the occurrence and severity of desaturation during tracheal intubations and the association with adverse hemodynamic tracheal intubation-associated events. DESIGN: Retrospective cohort study as a part of the National Emergency Airway Registry for Children Network's quality improvement project from January 2012 to December 2014. SETTING: International PICUs. PATIENTS: Critically ill children younger than 18 years undergoing primary tracheal intubations in the ICUs. INTERVENTIONS: tracheal intubation processes of care and outcomes were prospectively collected using standardized operational definitions. We defined moderate desaturation as oxygen saturation less than 80% and severe desaturation as oxygen saturation less than 70% during tracheal intubation procedures in children with initial oxygen saturation greater than 90% after preoxygenation. Adverse hemodynamic tracheal intubation-associated event was defined as cardiac arrests, hypo or hypertension requiring intervention, and dysrhythmia. MEASUREMENTS AND MAIN RESULTS: A total of 5,498 primary tracheal intubations from 31 ICUs were reported. Moderate desaturation was observed in 19.3% associated with adverse hemodynamic tracheal intubation-associated events (9.8% among children with moderate desaturation vs 4.4% without desaturation; $p < 0.001$). Severe desaturation was observed in 12.9% of tracheal intubations, also significantly associated with hemodynamic tracheal intubation-associated events. After adjusting for patient, provider, and practice factors, the occurrence of moderate desaturation was independently associated with hemodynamic tracheal intubation-associated events: adjusted odds ratio 1.83 (95% CI, 1.34-2.51; $p < 0.001$). The occurrence of severe desaturation was also independently associated with hemodynamic tracheal intubation-associated events: adjusted odds ratio 2.16 (95% CI, 1.54-3.04; $p < 0.001$). Number of tracheal intubation attempts was also significantly associated with the frequency of moderate and severe desaturations ($p < 0.001$). CONCLUSIONS: In this large tracheal intubation quality improvement database, we found moderate and severe desaturation are reported among 19% and 13% of all tracheal intubation encounters. Moderate and severe desaturations were independently associated with the occurrence of adverse hemodynamic events. Future quality improvement interventions may focus to reduce desaturation events.

Lieberman, D. (2018). **Is it safe to wait 10 years after a negative baseline screening colonoscopy result?** *Gastrointest Endosc, 87*(1), 260-261. doi:10.1016/j.gie.2017.05.041

Lim, M. C., Boland, M. V., McCannel, C. A., Saini, A., Chiang, M. F., Epley, K. D., & Lum, F. (2017). **Adoption of Electronic Health Records and Perceptions of Financial and Clinical Outcomes Among Ophthalmologists in the United States**. *JAMA Ophthalmol*. doi:10.1001/jamaophthalmol.2017.5978

Importance: Assessing the rate of electronic health record (EHR) adoption and ophthalmologists' perceptions on financial and clinical productivity is important in understanding how to direct future design and health care policy. Objective: To assess adoption rate and perceptions of financial and clinical outcomes of EHRs among ophthalmologists in the United States. Design, Setting, and Participants: Population-based, cross-sectional study. A random sample of 2000 ophthalmologists was generated on the basis of mailing address zip codes from the 2015 American Academy of Ophthalmology US active membership database, which included more than 18000 ophthalmologists. A survey was sent by email to assess adoption rate of EHRs, perceptions of financial and clinical productivity, and engagement with Medicare and Medicaid programs that incentivize the use of EHRs. The survey was conducted between 2015 and 2016. Main Outcomes and Measures: Adoption rate of EHRs and perceptions of financial and clinical productivity. Results: The adoption rate of EHRs among surveyed ophthalmologists (348 respondents) was 72.1%. The responding ophthalmologists perceived that their net revenues and productivity have declined and that practice costs are higher with EHR use. Of those who attested for stage 1 of the EHR incentive program, 83% had already or were planning to attest to stage 2, but 9% had no plans. Conclusions and Relevance: The adoption of EHRs by ophthalmologists has more than doubled since a 2011 survey and is similar to that of primary care physicians (79%). In comparison with 2 previous surveys of ophthalmologists, respondents had more negative perceptions of EHR productivity outcomes and effect on practice costs, although financial data were not collected in this survey to support these opinions. These negative perceptions suggest that more attention should be placed on improving the efficiency and usability of EHR systems.

Lin, M., Gong, P., Yang, T., Ye, J., Albin, R. L., & Dodge, H. H. (2017). **Big Data Analytical Approaches to the NACC Dataset: Aiding Preclinical Trial Enrichment**. *Alzheimer Disease and Associated Disorders*. doi:10.1097/wad.0000000000000228

BACKGROUND: Clinical trials increasingly aim to retard disease progression during presymptomatic phases of Mild Cognitive Impairment (MCI) and thus recruiting study participants at high risk for developing MCI is critical for cost-effective prevention trials. However, accurately identifying those who are destined to develop MCI is difficult. Collecting biomarkers is often expensive. METHODS: We used only noninvasive clinical variables collected in the National Alzheimer's Coordinating Center (NACC) Uniform Data Sets version 2.0 and applied machine learning techniques to build a low-cost and accurate Mild Cognitive Impairment (MCI) conversion prediction calculator. Cross-validation and bootstrap were used to select as few variables as possible accurately predicting MCI conversion within 4 years. RESULTS: A total of 31,872 unique subjects, 748 clinical variables, and additional 128 derived variables in NACC data sets were used. About 15 noninvasive clinical variables are identified for predicting MCI/aMCI/naMCI converters, respectively. Over 75% Receiver Operating Characteristic Area Under the Curves (ROC AUC) was achieved. By bootstrap we created a simple spreadsheet calculator which estimates the probability of developing MCI within 4 years with a 95% confidence interval. CONCLUSIONS: We achieved reasonably high prediction accuracy using only clinical variables. The approach used here could be useful for study enrichment in preclinical trials where enrolling participants at risk of cognitive decline is critical for proving study efficacy, and also for developing a shorter assessment battery.

Lindly, O. J., Thorburn, S., Heisler, K., Reyes, N. M., & Zuckerman, K. E. (2017). **Parents' Use of Complementary Health Approaches for Young Children with Autism Spectrum Disorder**. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-017-3432-6

Knowledge of why parents use complementary health approaches (CHA) for children with autism spectrum disorder (ASD) is limited. We conducted a mixed methods study to better understand factors influencing parents' decision to use CHA for ASD. Parent-reported data about CHA use were collected on a probability sample of 352 young children with ASD in Denver, Colorado; Los Angeles, California; or Portland, Oregon. Follow-back interviews were conducted with 31 parents. CHA use was negatively associated with older child age and positively associated with parents' belief ASD has major consequences, living in Portland or Denver, and

medication use. Nine themes help explain these results. Study findings may have utility for healthcare providers working with children with ASD and their families regarding CHA.

Linos, E., Admassu, N., Sabry-Elnaggar, H., Li, P. M., & Choo, E. (2017). **Doctor fails: early warning signs of physician fatigue?** *Bmj, 359*, j5503. doi:10.1136/bmj.j5503

Liu, N., Chaudhry, M. T., Xie, Z., Kreth, J., & Merritt, J. (2017). **Identification of new degrons in Streptococcus mutans reveals a novel strategy for engineering targeted, controllable proteolysis**. *Frontiers in Microbiology, 8*(DEC). doi:10.3389/fmicb.2017.02572

Recently, controllable, targeted proteolysis has emerged as one of the most promising new strategies to study essential genes and otherwise toxic mutations. One of the principal limitations preventing the wider adoption of this approach is due to the lack of easily identifiable species-specific degrons that can be used to trigger the degradation of target proteins. Here, we report new advancements in the targeted proteolysis concept by creating the first prokaryotic N-terminal targeted proteolysis system. We demonstrate how proteins from the LexA-like protein superfamily can be exploited as species-specific reservoirs of N- and/or C-degrons, which are easily identifiable due to their proximity to strictly conserved residues found among LexA-like proteins. Using the LexA-like regulator HdiR of Streptococcus mutans, we identified two separate N-degrons derived from HdiR that confer highly efficient constitutive proteolysis upon target proteins when added as N-terminal peptide tags. Both degrons mediate degradation via AAA+ family housekeeping proteases with one degron primarily targeting FtsH and the other targeting the ClpP-dependent proteases. To modulate degron activity, our approach incorporates a hybrid N-terminal protein tag consisting of the ubiquitin-like protein NEDD8 fused to an HdiR degron. The NEDD8 fusion inhibits degron function until the NEDD8-specific endopeptidase NEDP1 is heterologously expressed to expose the N-degron. By fusing the NEDD8-degron tag onto GFP, luciferase, and the pleiotropic regulator RNase J2, we demonstrate that the N-terminal proteolysis approach exhibits far superior performance compared to the classic transcriptional depletion approach and is similarly applicable for the study of highly toxic mutations.

Lozano, D. C., Choi, D., Jayaram, H., Morrison, J. C., & Johnson, E. C. (2018). **Utilizing RNA-Seq to Identify Differentially Expressed Genes in Glaucoma Model Tissues, Such as the Rodent Optic Nerve Head**. *Methods Mol Biol, 1695*, 299-310. doi:10.1007/978-1-4939-7407-8_20

Understanding the cellular pathways activated by elevated intraocular pressure (IOP) is crucial for the development of more effective glaucoma treatments. Microarray studies have previously been used to identify several key gene expression changes in early and extensively injured ONH, as well as in the retina. Limitations of microarrays include that they can only be used to detect transcripts that correspond to existing genomic sequencing information and their narrower dynamic range. However, RNA sequencing (RNA-seq) is a powerful tool for investigating known transcripts, as well as for exploring new ones (including noncoding RNAs and small RNAs), is more quantitative, and has the added benefit that the data can be re-analyzed as new sequencing information becomes available. Here, we describe an RNA-seq method specifically developed for identifying differentially expressed genes in optic nerve heads of eyes exposed to elevated intraocular pressure. The methods described here could also be applied to small tissue samples (less than 100 ng in total RNA yield) from retina, optic nerve, or other regions of the central nervous system.

Lu, E., Shatzel, J. J., Salati, J., & DeLoughery, T. G. (2017). **The Safety of Low-Molecular-Weight Heparin During and After Pregnancy**. *Obstetrical and Gynecological Survey, 72*(12), 721-729. doi:10.1097/ogx.0000000000000505

Importance: In industrialized countries, venous thromboembolism remains a leading cause of mortality in pregnant women. Low-molecular-weight heparin (LMWH) is the most commonly recommended anticoagulant in pregnancy, having been proven effective and safe in multiple prospective clinical trials. Objective: The aim of this article is to outline existing recommendations for proper use of LMWH in pregnancy and data on risks of LMWH. Evidence Acquisition: Wereviewed guidelines froma number of professional societies.We also examined the current literature behind the various risks associated with LMWH use. Results: Our review outlines the current data that guide the use of LMWH in pregnancy. With prophylactic dosing, LMWH comes with a 0.5% risk of antepartum bleeding and a 1% risk of postpartum hemorrhage that is not different from clinical trial controls. With treatment dosing, there is a 1.5% risk of antepartum bleeding and a 2% risk of postpartum hemorrhage. Overall, current evidence behind these risks is limited, and this review suggests areas of further study moving forward.

Lucke-Wold, B. P., Logsdon, A. F., Nguyen, L., Eltanahay, A., Turner, R. C., Bonasso, P., . . . Rosen, C. L. (2018). **Supplements, nutrition, and alternative therapies for the treatment of traumatic brain injury**. *Nutritional Neuroscience, 21*(2), 79-91. doi:10.1080/1028415X.2016.1236174

Studies using traditional treatment strategies for mild traumatic brain injury (TBI) have produced limited clinical success. Interest in treatment for mild TBI is at an all time high due to its association with the development of chronic traumatic encephalopathy and other neurodegenerative diseases, yet therapeutic options remain limited. Traditional pharmaceutical interventions have failed to transition to the clinic for the treatment of mild TBI. As such, many pre-clinical studies are now implementing non-pharmaceutical therapies for TBI. These studies have demonstrated promise, particularly those that modulate secondary injury cascades activated after injury. Because no TBI therapy has been discovered for mild injury, researchers now look to pharmaceutical supplementation in an attempt to foster success in human clinical trials. Non-traditional therapies, such as acupuncture and even music therapy are being considered to combat the neuropsychiatric symptoms of TBI. In this review, we highlight alternative approaches that have been studied in clinical and pre-clinical studies of TBI, and other related forms of neural injury. The purpose of this review is to stimulate further investigation into novel and innovative approaches that can be used to treat the mechanisms and symptoms of mild TBI.

Maghen, A., Vargas, G. B., Connor, S. E., Nassiri, S., Hicks, E. M., Kwan, L., . . . Veale, J. (2017). **Spirituality and Religiosity of Non-Directed (Altruistic) Living Kidney Donors**. *J Clin Nurs*. doi:10.1111/jocn.14223

AIMS AND OBJECTIVES: To describe the spirituality and religiosity (S&R) of 30 non-directed (altruistic) living kidney donors (NDDs) in the United States (U.S.) and explore how they may have affected their motivations to donate and donation process experiences. BACKGROUND: The rise in NDDs and their ability to initiate kidney chains offers a novel approach to help alleviate the overextended kidney transplant waitlist in the U.S. However, little is known about the NDDs' motivations, characteristics, and experiences. DESIGN: We conducted a qualitative-dominant study and used a grounded theory approach to analyze data. METHODS: Thirty participants completed in-depth interviews between April 2013 and April 2015. Three analysts independently read and coded interview transcripts. Grounded theory techniques were used to develop descriptive categories and identify topics related to the NDD donation experience. RESULTS: Sixteen of the 30 NDDs discussed the topic of S&R when describing their donation experiences, regardless of whether they were actively practicing a religion at the time of donation. Specifically, three themes were identified within S&R: motivation to donate, support in the process, and justification of their donation decisions post-donation. CONCLUSIONS: Findings from this study are the first to describe how S&R influenced the experiences of U.S. NDDs and may help improve NDD educational resources for future spiritual or religious NDDs, and the overall NDD donation experience in efforts to increase the living donor pool. RELEVANCE TO CLINICAL PRACTICE: Spirituality and religiosity are often overlooked yet potentially influential factors in Western medicine, as demonstrated through the experiences of Jehovah's Witnesses and their religious restrictions while undergoing surgery and the beliefs of Christian Scientists against taking medications and receiving medical procedures. Understanding needs of NDDs specifically with S&R can better position kidney

transplant centers and teams to improve pre-donation screening of NDD candidates and provide support services during the donation process. This article is protected by copyright. All rights reserved.

Mainor, A. G., Decosimo, K., Escoffrey, C., Farris, P., Shannon, J., Winters-Stone, K., . . . Leeman, J. (2017). **Scaling Up and Tailoring the "Putting Public Health in Action" Training Curriculum**. *Health Promot Pract*, 1524839917741486. doi:10.1177/1524839917741486

Despite access to a growing menu of evidence-based interventions, public health practitioners continue to underuse them, in part because practitioners may require new knowledge, skills, and resources to do so. Numerous foundations, universities, governmental agencies, and consultants are providing trainings to address the gaps in practitioners' capacity. To most significantly affect population health, these trainings need to reach practitioners who may have limited access to on-site trainings. Despite the number of organizations offering trainings, little is known about how to scale up trainings to efficiently extend their reach or how to tailor trainings to the needs of different intervention. The Cancer Prevention and Control Research Network and its collaborating centers have developed a training curriculum and delivered it in both in-person and distance formats to a range of audiences. The purpose of this article is to describe the training curriculum and findings from the Network's evaluation of approaches used to scale up delivery of the "Putting Public Health Evidence in Action" curriculum and tailor content for specific evidence-based interventions.

Marmaduke, P., Marmaduke, S., Breitenstein, M., Selden, N., & Burchiel, K. (2017). **In Memoriam: Mary Ellen Dandy Marmaduke, 1927 to 2017**. *Neurosurgery*. doi:10.1093/neuros/nyx573

Marmor, M. F., & Albert, D. M. (2017). **Preface**. *Foundations of Ophthalmology: Great Insights that Established the Discipline*, v. doi:10.1007/978-3-319-59641-9

Martin, M. J., Bush, L. D., Inaba, K., Byerly, S., Schreiber, M., Peck, K. A., . . . Long, W. (2017). **Cervical spine evaluation and clearance in the intoxicated patient: A prospective Western Trauma Association Multi-Institutional Trial and Survey**. *J Trauma Acute Care Surg, 83*(6), 1032-1040. doi:10.1097/ta.0000000000001650

BACKGROUND: Intoxication often prevents clinical clearance of the cervical spine (Csp) after trauma leading to prolonged immobilization even with a normal computed tomography (CT) scan. We evaluated the accuracy of CT at detecting clinically significant Csp injury, and surveyed participants on related opinions and practice. METHODS: A prospective multicenter study (2013-2015) at 17 centers. All adult blunt trauma patients underwent structured clinical examination and imaging including a Csp CT, with follow-up thru discharge. alcohol- and drug-intoxicated patients (TOX+) were identified by serum and/or urine testing. Primary outcomes included the incidence and type of Csp injuries, the accuracy of CT scan, and the impact of TOX+ on the time to Csp clearance. A 36-item survey querying local protocols, practices, and opinions in the TOX+ population was administered. RESULTS: Ten thousand one hundred ninety-one patients were prospectively enrolled and underwent CT Csp during the initial trauma evaluation. The majority were men (67%), had vehicular trauma or falls (83%), with mean age of 48 years, and mean Injury Severity Score (ISS) of 11. The overall incidence of Csp injury was 10.6%. TOX+ comprised 30% of the cohort (19% EtOH only, 6% drug only, and 5% both). TOX+ were significantly younger (41 years vs. 51 years; $p < 0.01$) but with similar mean Injury Severity Score (11) and Glasgow Coma Scale score (13). The TOX+ cohort had a lower incidence of Csp injury versus nonintoxicated (8.4% vs. 11.5%; $p < 0.01$). In the TOX+ group, CT had a sensitivity of 94%, specificity of 99.5%, and negative predictive value (NPV) of 99.5% for all Csp injuries. For clinically significant injuries, the NPV was 99.9%, and there were no unstable Csp injuries missed by CT (NPV, 100%). When CT Csp was negative, TOX+ led to longer immobilization versus sober patients (mean, 8 hours vs. 2 hours; $p < 0.01$), and

prolonged immobilization (>12 hrs) in 25%. The survey showed marked variations in protocols, definitions, and Csp clearance practices among participating centers, although 100% indicated willingness to change practice based on these data. CONCLUSION: For intoxicated patients undergoing Csp imaging, CT scan was highly accurate and reliable for identifying clinically significant spine injuries, and had a 100% NPV for identifying unstable injuries. CT-based clearance in TOX+ patients appears safe and may avoid unnecessary prolonged immobilization. There was wide disparity in practices, definitions, and opinions among the participating centers. LEVEL OF EVIDENCE: Diagnostic tests or criteria, level II.

Matsui, Y., Horikawa, M., Jahangiri Noudeh, Y., Kaufman, J. A., Kolbeck, K. J., & Farsad, K. (2017). **Baseline tumor Lipiodol uptake after transarterial chemoembolization for hepatocellular carcinoma: Identification of a threshold value predicting tumor recurrence**. *Radiology and Oncology, 51*(4), 393-400. doi:10.1515/raon-2017-0030

The aim of the study was to evaluate the association between baseline Lipiodol uptake in hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) with early tumor recurrence, and to identify a threshold baseline uptake value predicting tumor response. A single-institution retrospective database of HCC treated with Lipiodol-TACE was reviewed. Forty-six tumors in 30 patients treated with a Lipiodol-chemotherapy emulsion and no additional particle embolization were included. Baseline Lipiodol uptake was measured as the mean Hounsfield units (HU) on a CT within one week after TACE. Washout rate was calculated dividing the difference in HU between the baseline CT and follow-up CT by time (HU/month). Cox proportional hazard models were used to correlate baseline Lipiodol uptake and other variables with tumor response. A receiver operating characteristic (ROC) curve was used to identify the optimal threshold for baseline Lipiodol uptake predicting tumor response. During the follow-up period (mean 5.6 months), 19 (41.3%) tumors recurred (mean time to recurrence = 3.6 months). In a multivariate model, low baseline Lipiodol uptake and higher washout rate were significant predictors of early tumor recurrence (P = 0.001 and < 0.0001, respectively). On ROC analysis, a threshold Lipiodol uptake of 270.2 HU was significantly associated with tumor response (95% sensitivity, 93% specificity). Baseline Lipiodol uptake and washout rate on follow-up were independent predictors of early tumor recurrence. A threshold value of baseline Lipiodol uptake > 270.2 HU was highly sensitive and specific for tumor response. These findings may prove useful for determining subsequent treatment strategies after Lipiodol TACE.

Matsuo, K., Ross, M. S., Im, D. D., Klobocista, M. M., Bush, S. H., Johnson, M. S., . . . Roman, L. D. (2017). **Significance of venous thromboembolism in women with uterine carcinosarcoma**. *Gynecologic Oncology*. doi:10.1016/j.ygyno.2017.11.036

OBJECTIVE: To identify risk factors for venous thromboembolism (VTE) and to examine the association of VTE and survival in women with uterine carcinosarcoma. METHODS: This multicenter retrospective study examined 906 women who underwent primary surgical treatment for stage I-IV uterine carcinosarcoma. Time-dependent analyses were performed for cumulative incidence of VTE after surgery on multivariate models. RESULTS: There were 72 (7.9%) women who developed VTE after surgery with 1-, 2-, and 5-year cumulative incidences being 5.1%, 7.3%, and 10.2%, respectively. On multivariate analysis, older age (hazard ratio [HR] per year 1.03, P=0.012), non-Asian race (HR 6.28, P<0.001), large body habitus (HR per kg/m(2) 1.04, P=0.014), residual disease at surgery (HR 3.04, P=0.003), tumor size >/=5cm (HR 2.73, P=0.003), and stage IV disease (HR 2.12, P=0.025) were independently associated with increased risk of developing VTE. A risk pattern analysis identified that obese Non-Asian women with large tumors (13.7% of population) had the highest incidence of VTE (2-year cumulative rate, 26.1%) whereas Asian women with no residual disease (47.1% of population) had the lowest (2-year cumulative rate, 1.6%) (P<0.001). Presence of carcinoma/sarcoma in metastatic sites was significantly associated with increased risk of VTE compared to carcinoma alone (2-year rates, 31.2% versus 8.4%, P=0.049). VTE was independently associated with decreased progression-free survival on multivariate models (5-year rates, 24.9% versus 47.2%, HR 1.46, 95%CI 1.05-2.04, P=0.026). CONCLUSION: Our study suggests that VTE represents a surrogate marker of

aggressive tumor behavior and diminished patient condition in uterine carcinosarcoma; obese Non-Asian women with large tumors carry a disproportionally high risk of VTE, suggesting that long-term prophylaxis may benefit this population.

McCarty, D., Priest, K. C., & Korthuis, P. T. (2017). **Treatment and Prevention of Opioid Use Disorder: Challenges and Opportunities**. *Annual Review of Public Health*. doi:10.1146/annurev-publhealth-040617-013526

Treatment for opioid use disorder in the United States evolved in response to changing federal policy and advances in science. Inpatient care began in 1935 with the US Public Health Service Hospitals in Lexington, Kentucky, and Fort Worth, Texas. Outpatient clinics emerged in the 1960s to provide aftercare. Research advances led to opioid agonist and opioid antagonist therapies. When patients complete opioid withdrawal, return to use is often rapid and frequently deadly. US and international authorities recommend opioid agonist therapy (i.e., methadone or buprenorphine). Opioid antagonist therapy (i.e., extended-release naltrexone) may also inhibit return to use. Prevention efforts emphasize public and prescriber education, use of prescription drug monitoring programs, and safe medication disposal options. Overdose education and naloxone distribution promote access to rescue medication and reduce opioid overdose fatalities. Opioid use disorder prevention and treatment must embrace evidence-based care and integrate with physical and mental health care. Expected final online publication date for the Annual Review of Public Health Volume 39 is April 1, 2018. Please see http://www.annualreviews.org/page/journal/pubdates for revised estimates.

McCay, R., Lyles, A. A., & Larkey, L. (2017). **Nurse Leadership Style, Nurse Satisfaction, and Patient Satisfaction: A Systematic Review**. *Journal of Nursing Care Quality*. doi:10.1097/ncq.0000000000000317

The purpose of this systematic review was to synthesize current evidence on nursing leadership styles, nurse satisfaction, and patient satisfaction. Results suggest that relational leadership traits contribute to greater nurse satisfaction whereas task-oriented styles may decrease nurse satisfaction. Minimal information for the connection between nursing leadership and patient satisfaction was found.

McClelland, S., Sandler, K. A., Degnin, C., Chen, Y., & Mitin, T. (2017). **Active Surveillance for Low and Intermediate Risk Prostate Cancer: Opinions of North American Genitourinary Oncology Expert Radiation Oncologists**. *Clinical Genitourinary Cancer*. doi:10.1016/j.clgc.2017.10.021

Introduction: The ProtecT trial has provided level 1 evidence supporting active surveillance for prostate cancer patients with low-risk and intermediate-risk disease. The effect of these findings on the opinions of North American genitourinary (GU) experts regarding the role of active surveillance for these patients has not been previously examined. Materials and Methods: A survey was distributed to 88 practicing North American GU physicians serving on decision-making committees of cooperative group research organizations. Questions pertained to appropriateness of active surveillance in patients with low-risk and intermediate-risk (Gleason 3+4) disease. Opinions regarding active surveillance were correlated with practice patterns using Fisher exact test. Results: Forty-two radiation oncologists completed the survey. Forty percent had been in practice for more than 20 years; 90% practice at an academic center. Forty-five percent see ≥ 20 patients per month in consultation. More than 95% (40 of 42) recommended active surveillance for Gleason 6 disease, whereas only 17% recommended active surveillance for Gleason 3+4 disease. There were no demographic differences between supporters or opponents regarding active surveillance with regard to monthly patient volume, practice type, likelihood of self-identifying as an expert brachytherapist, belief in advanced imaging techniques, or preferred default external beam radiation therapy dose/fractionation for either low-risk or intermediate-risk disease. However, there was a trend toward greater support of active surveillance for Gleason 3+4 disease among experts having practiced < 10 years versus ≥ 10 years (P = .085). Conclusion: Active surveillance is almost universally supported by North American GU expert radiation oncologists for low-risk prostate cancer. However, there is very weak support for this strategy in Gleason 3+4 disease despite the ProtecT trial providing level 1 evidentiary support in both risk groups. There were no significant

differences between experts supporting versus opposing active surveillance for either low-risk or intermediate-risk disease. These preferences might affect the design of future clinical studies, influencing the adoption of active surveillance in North American clinical practice. © 2017 Elsevier Inc.

McCully, B. H., Underwood, S. J., Kiraly, L., Holcomb, J. B., Robinson, B. R. H., Minei, J. P., . . . Schreiber, M. A. (2018). **The effects of cryopreserved red blood cell transfusion on tissue oxygenation in obese trauma patients**. *J Trauma Acute Care Surg, 84*(1), 104-111. doi:10.1097/ta.0000000000001717

BACKGROUND: Low tissue oxygenation (StO2) is associated with poor outcomes in obese trauma patients. A novel treatment could be the transfusion of cryopreserved packed red blood cells (CPRBCs), which the in vitro biochemical profile favors red blood cell (RBC) function. We hypothesized that CPRBC transfusion improves StO2 in obese trauma patients. METHODS: Two hundred forty-three trauma patients at five Level I trauma centers who required RBC transfusion were randomized to receive one to two units of liquid packed RBCs (LPRBCs) or CPRBCs. Demographics, injury severity, StO2, outcomes, and biomarkers of RBC function were compared in nonobese (body mass index [BMI] < 30) and obese (BMI >/= 30) patients. StO2 was also compared between obese patients with BMI of 30 to 34.9 and BMI >/= 35. StO2 was normalized and expressed as % change after RBC transfusion. A p value less than 0.05 indicated significance. RESULTS: Patients with BMI less than 30 (n = 141) and BMI of 30 or greater (n = 102) had similar Injury Severity Score, Glasgow Coma Scale, and baseline StO2. Plasma levels of free hemoglobin, an index of RBC lysis, were lower in obese patients after CPRBC (125 [72-259] mug/mL) versus LPRBC transfusion (230 [178-388] mug/mL; p < 0.05). StO2 was similar in nonobese patients regardless of transfusion type, but improved in obese patients who received CPRBCs (104 +/- 1%) versus LPRPCs (99 +/- 1%, p < 0.05; 8 hours after transfusion). Subanalysis showed improved StO2 after CPRBC transfusion was specific to BMI of 35 or greater, starting 5 hours after transfusion (p < 0.05 vs. LPRBCs). CPRBCs did not improve clinical outcomes in either group. CONCLUSION: CPRBC transfusion is associated with increased StO2 and lower free hemoglobin levels in obese trauma patients, but did not improve clinical outcomes. Future studies are needed to determine if CPRBC transfusion in obese patients attenuates hemolysis to improve StO2. LEVEL OF EVIDENCE: Therapeutic, level IV.

McMurtrey, C., Harriff, M. J., Swarbrick, G. M., Duncan, A., Cansler, M., Null, M., . . . Lewinsohn, D. M. (2017). **T cell recognition of Mycobacterium tuberculosis peptides presented by HLA-E derived from infected human cells**. *PLoS ONE, 12*(11). doi:10.1371/journal.pone.0188288

HLA-E is a non-conventional MHC Class I molecule that has been recently demonstrated to present pathogen-derived ligands, resulting in the TCR-dependent activation of αβ CD8+ T cells. The goal of this study was to characterize the ligandome displayed by HLA-E following infection with Mycobacterium tuberculosis (Mtb) using an in-depth mass spectrometry approach. Here we identified 28 Mtb ligands derived from 13 different source proteins, including the Esx family of proteins. When tested for activity with CD8+ T cells isolated from sixteen donors, nine of the ligands elicited an IFN-γ response from at least one donor, with fourteen of 16 donors responding to the Rv0634A19-29 peptide. Further evaluation of this immunodominant peptide response confirmed HLA-E restriction and the presence of Rv0634A19-29-reactive CD8+ T cells in the peripheral blood of human donors. The identification of an Mtb HLA-E ligand that is commonly recognized may provide a target for a non-traditional vaccine strategy.

Meehan, T. F., Conte, N., Goldstein, T., Inghirami, G., Murakami, M. A., Brabetz, S., . . . Bult, C. J. (2017). **PDX-MI: Minimal information for patient-derived tumor xenograft models**. *Cancer Research, 77*(21), e62-e66. doi:10.1158/0008-5472.CAN-17-0582

Patient-derived tumor xenograft (PDX) mouse models have emerged as an important oncology research platform to study tumor evolution, mechanisms of drug response and resistance, and tailoring chemotherapeutic approaches for individual patients. The lack of robust standards for reporting on PDX models has hampered the ability of researchers to find relevant PDX models and associated data. Here we present the PDX models minimal information standard (PDX-MI) for reporting on the generation, quality assurance, and use of PDX models. PDX-MI defines the minimal information for describing the clinical attributes of a patient's tumor, the processes of implantation and passaging of tumors in a host mouse strain, quality assurance methods, and the use of PDX models in cancer research. Adherence to PDX-MI standards will facilitate accurate search results for oncology models and their associated data across distributed repository databases and promote reproducibility in research studies using these models. Cancer Res; 77(21); e62-66. © 2017 American Association for Cancer Research.

Michelotti, M., de Korne, D. F., Weizer, J. S., Lee, P. P., Flanagan, D., Kelly, S. P., . . . Hingorani, M. (2017). **Mapping standard ophthalmic outcome sets to metrics currently reported in eight eye hospitals**. *BMC Ophthalmology, 17*(1), 269. doi:10.1186/s12886-017-0667-0

BACKGROUND: To determine alignment of proposed international standard outcomes sets for ophthalmic conditions to metrics currently reported by eye hospitals. METHODS: Mixed methods comparative benchmark study, including eight eye hospitals in Australia, India, Singapore, Sweden, U.K., and U.S. All are major international tertiary care and training centers in ophthalmology. Main outcome measure is consistency of ophthalmic outcomes measures reported. RESULTS: International agreed standard outcomes (ICHOM) sets are available for cataract surgery (10 metrics) and macular degeneration (7 metrics). The eight hospitals reported 22 different metrics for cataract surgery and 2 for macular degeneration, which showed only limited overlap with the proposed ICHOM metrics. None of the hospitals reported patient reported visual functioning or vision-related quality of life outcomes measures (PROMs). Three hospitals (38%) reported rates for uncomplicated cataract surgeries only. There was marked variation in how and at what point postoperatively visual outcomes following cataract, cornea, glaucoma, strabismus and oculoplastics procedures were reported. Seven (87.5%) measured post-operative infections and four (50%) measured 30 day unplanned reoperation rates. CONCLUSIONS: Outcomes reporting for ophthalmic conditions currently widely varies across hospitals internationally and does not include patient-reported outcomes. Reaching consensus on measures and consistency in data collection will allow meaningful comparisons and provide an evidence base enabling improved sharing of "best practices" to improve eye care globally. Implementation of international standards is still a major challenge and practice-based knowledge on measures should be one of the inputs of the international standardization process.

Minko, I. G., Rizzo, C. J., & Stephen Lloyd, R. (2017). **Mutagenic potential of nitrogen mustard-induced formamidopyrimidine DNA adduct: Contribution of the non-canonical α-anomer**. *Journal of Biological Chemistry, 292*(46), 18790-18799. doi:10.1074/jbc.M117.802520

Nitrogen mustards (NMs) are DNA-alkylating compounds that represent the earliest anticancer drugs. However, clinical use of NMs is limited because of their own mutagenic properties. The mechanisms of NM-induced mutagenesis remain unclear. The major product of DNA alkylation by NMs is a cationic NM-N7-dG adduct that can yield the imidazole ringfragmented lesion, N5-NM-substituted formamidopyrimidine (NM-Fapy-dG). Characterization of this adduct is complicated because it adopts different conformations, including both a canonical β- and an unnatural α-anomeric configuration. Although formation of NM-Fapy-dG in cellular DNA has been demonstrated, its potential role in NM-induced mutagenesis is unknown. Here, we created site-specifically modified singlestranded vectors for replication in primate (COS7) or Escherichia coli cells. In COS7 cells, NM-Fapy-dG caused targeted mutations, predominantly G → T transversions, with overall frequencies of 11-12%. These frequencies were ~2-fold higher than that induced by 8-oxo-dG adduct. Replication in E. coli was essentially error-free. To elucidate themechanismsof bypass of NM-Fapy-dG, we performed replication assays in vitro with a high-fidelity DNA polymerase, Saccharomyces cerevisiae polymerase (pol) δ. It was found that pol δ could catalyze high-fidelity synthesis past NMFapy-dG, but only

on a template subpopulation, presumably containing the β-anomeric adduct. Consistent with the low mutagenic potential of the β-anomer in vitro, the mutation frequency was significantly reduced when conditions for vector preparation were modified to favor this configuration. Collectively, these data implicate the α-anomeras amajorcontributor toNM-Fapy-dG-induced mutagenesis in primate cells. © 2017 by The American Society for Biochemistry and Molecular Biology, Inc.

Mitrugno, A., Sylman, J. L., Rigg, R. A., Tassi Yunga, S., Shatzel, J. J., Williams, C. D., & McCarty, O. J. T. (2017). **Carpe low-dose aspirin: the new anti-cancer face of an old anti-platelet drug**. *Platelets*, 1-6. doi:10.1080/09537104.2017.1416076

Cancer metastasis is a dynamic process during which cancer cells separate from a primary tumor, migrate through the vessel wall into the bloodstream, and extravasate at distant sites to form secondary colonies. During this process, circulating tumor cells are subjected to shear stress forces from blood flow, and in contact with plasma proteins and blood cells of the immune and hemostatic system, including platelets. Many studies have shown an association between high platelet count and cancer metastasis, suggesting that platelets may play an occult role in tumorigenesis. This mini-review summarizes recent and emerging discoveries of mechanisms by which cancer cells activate platelets and the role of activated platelets in promoting tumor growth and metastasis. Moreover, the review discusses how aspirin has the potential for being clinically used as an adjuvant in cancer therapy.

Mohr, C. D., McCabe, C. T., Haverly, S. N., Hammer, L. B., & Carlson, K. F. (2018). **Drinking Motives and Alcohol Use: The SERVe Study of U.S. Current and Former Service Members**. *J Stud Alcohol Drugs, 79*(1), 79-87.

OBJECTIVE: Hazardous drinking in the armed forces is a significant problem. Alcohol use motivations, known risk factors for problem drinking, have been underexplored in this population. Our study extends knowledge about drinking motives among current and former U.S. service members and provides recommendations on their utility in identifying alcohol-related problems by examining the factor structure of multidimensional drinking motives and their association to alcohol use. METHOD: Post-9/11 separated service members and current reservists were recruited from 35 Oregon employers to participate in a workplace study of supervisor support. The resulting sample (N = 509; 84% male; mean age = 39) completed a baseline assessment, which included a comprehensive drinking motives assessment. RESULTS: Drinkers comprised 88% of the sample, with a mean Alcohol Use Disorders Identification Test (AUDIT) score of 5.4 (SD = 4.6); 23.9% scored 8 or more. The four-factor structure of the Drinking Motives Questionnaire-Revised, short form (DMQ-R-SF) was affirmed through confirmatory factor analysis. Internal drinking motives related to enhancement (positive) and coping (negative) were most predictive of alcohol use; coping motives were uniquely predictive of alcohol-related problems, when drinking quantity/frequency, as well as psychological distress, were controlled for. Coping motives also mediate the relationship between psychological distress and AUDIT scores. Results thus demonstrated the generalizability of the DMQ-R-SF motives measure for use with separated service members and reservists. CONCLUSIONS: Drinking motives, assessed by the DMQ-R-SF, represent reliable and important predictors of drinking and associated problems among service members. Inclusion of motivated drinking questions may enhance screening for alcohol-related problems among current and former service members.

Moldavan, M., Cravetchi, O., & Allen, C. N. (2017). **GABA transporters regulate tonic and synaptic GABAA receptor-mediated currents in the suprachiasmatic nucleus neurons**. *Journal of Neurophysiology, 118*(6), 3092-3106. doi:10.1152/jn.00194.2017

GABA is a principal neurotransmitter in the hypothalamic suprachiasmatic nucleus (SCN) that contributes to intercellular communication between individual circadian oscillators within the SCN network and the stability and precision of the circadian rhythms. GABA transporters (GAT) regulate the extracellular GABA concentration and modulate GABAA receptor (GABAAR)-mediated currents. GABA transport inhibitors were

applied to study how GABAAR-mediated currents depend on the expression and function of GAT. Nipecotic acid inhibits GABA transport and induced an inward tonic current in concentration-dependent manner during whole cell patch-clamp recordings from SCN neurons. Application of either the selective GABA transporter 1 (GAT1) inhibitors NNC-711 or SKF-89976A, or the GABA transporter 3 (GAT3) inhibitor SNAP-5114, produced only small changes of the baseline current. Coapplication of GAT1 and GAT3 inhibitors induced a significant GABAAR-mediated tonic current that was blocked by gabazine. GAT inhibitors decreased the amplitude and decay time constant and increased the rise time of spontaneous GABAAR-mediated postsynaptic currents. However, inhibition of GAT did not alter the expression of either GAT1 or GAT3 in the hypothalamus. Thus GAT1 and GAT3 functionally complement each other to regulate the extracellular GABA concentration and GABAAR-mediated synaptic and tonic currents in the SCN. Coapplication of SKF-89976A and SNAP-5114 (50 microM each) significantly reduced the circadian period of Per1 expression in the SCN by 1.4 h. Our studies demonstrate that GAT are important regulators of GABAAR-mediated currents and the circadian clock in the SCN.NEW & NOTEWORTHY In the suprachiasmatic nucleus (SCN), the GABA transporters GAT1 and GAT3 are expressed in astrocytes. Inhibition of these GABA transporters increased a tonic GABA current and reduced the circadian period of Per1 expression in SCN neurons. GAT1 and GAT3 showed functional cooperativity: inhibition of one GAT increased the activity but not the expression of the other. Our data demonstrate that GABA transporters are important regulators of GABAA receptor-mediated currents and the circadian clock.

Monteiro, N., Thrivikraman, G., Athirasala, A., Tahayeri, A., Franca, C. M., Ferracane, J. L., & Bertassoni, L. E. (2017). **Photopolymerization of cell-laden gelatin methacryloyl hydrogels using a dental curing light for regenerative dentistry**. *Dent Mater*. doi:10.1016/j.dental.2017.11.020

Photopolymerized hydrogels, such as gelatin methacryloyl (GelMA), have desirable biological and mechanical characteristics for a range of tissue engineering applications. OBJECTIVE: This study aimed to optimize a new method to photopolymerize GelMA using a dental curing light (DL). METHODS: Lithium acylphosphinate photo-initiator (LAP, 0.05, 0.067, 0.1% w/v) was evaluated for its ability to polymerize GelMA hydrogel precursors (10% w/v) encapsulated with odontoblast-like cells (OD21). Different irradiances (1650, 2300 and 3700mW/cm(2)) and photo-curing times (5-20s) were tested, and compared against the parameters typically used in UV light photopolymerization (45mW/cm(2), 0.1% w/v Irgacure 2959 as photoinitiator). Physical and mechanical properties of the photopolymerized GelMA hydrogels were determined. Cell viability was assessed using a live and dead assay kit. RESULTS: Comparing DL and UV polymerization methods, the DL method photopolymerized GelMA precursor faster and presented larger pore size than the UV polymerization method. The live and dead assay showed more than 80% of cells were viable when hydrogels were photopolymerized with the different DL irradiances. However, the cell viability decreased when the exposure time was increased to 20s using the 1650mW/cm(2) intensity, and when the LAP concentration was increased from 0.05 to 0.1%. Both DL and UV photocrosslinked hydrogels supported a high percentage of cell viability and enabled fabrication of micropatterns using a photolithography microfabrication technique. SIGNIFICANCE: The proposed method to photopolymerize GelMA cell-laden hydrogels using a dental curing light is effective and represents an important step towards the establishment of chair-side procedures in regenerative dentistry.

Morrison, J. C., Johnson, E. C., & Cepurna, W. O. (2018). **Hypertonic Saline Injection Model of Experimental Glaucoma in Rats**. *Methods Mol Biol, 1695*, 11-21. doi:10.1007/978-1-4939-7407-8_2

A reliable method of creating chronic elevation of intraocular pressure (IOP) in rodents is an important tool in reproducing and studying the mechanisms of optic nerve injury that occur in glaucoma. In addition, such a model could provide a valuable method for testing potential neuroprotective treatments. This paper outlines the basic methods for producing obstruction of aqueous humor outflow and IOP elevation by injecting hypertonic saline (a sclerosant) into the aqueous outflow pathway. This is one of several rodent glaucoma models in use today. In this method, a plastic ring is placed around the equator of the eye to restrict injected saline to the limbus. By inserting a small glass microneedle in an aqueous outflow vein in the episclera and

injecting hypertonic saline toward the limbus, the saline is forced into Schlemm's canal and across the trabecular meshwork. The resultant inflammation and scarring of the anterior chamber angle occurs gradually, resulting in a rise in IOP after approximately 1 week. This article will describe the equipment necessary for producing this model and the steps of the technique itself.

Mott, S., Fogg, N., Foote, N., Hillier, M., Lewis, D. A., McDowell, B. M., . . . Vann-Patterson, A. (2017). **Society of Pediatric Nurses' Core Competencies for the Pediatric Nurse**. *J Pediatr Nurs*. doi:10.1016/j.pedn.2017.11.006

Mowery, A., Light, T., & Clayburgh, D. (2018). **Venous thromboembolism incidence in head and neck surgery patients: Analysis of the Veterans Affairs Surgical Quality Improvement Program (VASQIP) database**. *Oral Oncology, 77*, 22-28. doi:10.1016/j.oraloncology.2017.12.002

Objective Venous thromboembolism (VTE) may cause significant postoperative morbidity and mortality; research in other surgical fields suggests an elevated VTE risk persists up to 30 days after surgery, beyond hospital discharge. We performed a review of the Veteran's Affairs Surgical Quality Improvement Project (VASQIP) database to determine the 30-day incidence of VTE following head and neck surgery and assess the proportion of VTE that occur post-discharge. Materials and methods A retrospective review was performed of all head and neck ablative procedures captured in the VASQIP database between 1991 and 2015. Post-operative VTE incidence was determined and the relationship of pre-operative data and post-operative mortality to VTE incidence was assessed. Results 48,986 patients were included in the study; there were 152 VTE events (0.31%) and 39 (25.7%) occurred post-discharge. Lower VTE rates were found in parotidectomies (0.22%) and thyroid/parathyroid cases (0.23%), and higher rates in free flap (1.52%) and laryngectomy cases (0.69%). Age >70, recent weight loss, low serum albumin, and increased surgical time were all associated with increased VTE incidence on multivariate analysis. 90-day mortality in patients without VTE was 2.1% compared to 19.7% in patients who experienced a VTE. Conclusion While the documented rate of VTE in a national dataset is relatively low following head and neck surgeries, it is elevated with certain procedure categories and following long operations, and a significant proportion of VTE occur post-discharge. This study provides baseline data to better inform efforts to risk-stratify and customize thromboprophylaxis for patients undergoing head and neck procedures. © 2017

Mudambi, L., Miller, R., & Eapen, G. A. (2017). **Malignant central airway obstruction**. *J Thorac Dis, 9*(Suppl 10), S1087-s1110. doi:10.21037/jtd.2017.07.27

This review comprehensively describes recent advances in the management of malignant central airway obstruction (CAO). Malignant CAO can be a dramatic and devastating manifestation of primary lung cancer or metastatic disease. A variety of diagnostic modalities are available to provide valuable information to plan a therapeutic intervention. Clinical heterogeneity in the presentation of malignant CAO provides opportunities to adapt and utilize endoscopic technology and tools in many ways. Mechanical debulking, thermal tools, cryotherapy and airway stents are methods and instruments used to rapidly restore airway patency. Delayed bronchoscopic methods, such as photodynamic therapy (PDT) and brachytherapy can also be utilized in specific non-emergent situations to establish airway patency. Although data regarding the success and complications of therapeutic interventions are retrospective and characterized by clinical and outcome measure variability, the symptoms of malignant CAO can often be successfully palliated. Assessment of risks and benefits of interventions in each individual patient during the decision-making process forms the critical foundation of the management of malignant CAO.

Muench, J. (2017). **Balint work and the creation of medical knowledge**. *International Journal of Psychiatry in Medicine*, 91217417745288. doi:10.1177/0091217417745288

Michael Balint's pioneering work in primary care was not simply the application of psychodynamic theory to the complex problems and relationships encountered by clinicians. Rather, Balint's work was part of a wider conversation in Western epistemology that had already begun to break down the enlightenment rationalist agenda. Since the time of Descartes, we sought to find certain truth through decontextualizing and abstracting problems, and through separation of the observer from the thing observed, with a focus on finding universal timeless laws that could be generalized. By the mid-1950s, it was clear that this agenda was insufficient to answer important questions about what it means to be human and to live a healthy and happy life. Balint's experiment was a return to a method of knowledge creation that is case based, narrative, local, timely, particular, and especially considers specific contexts for finding solutions to problems. For current healthcare reform efforts to be effective, we must include Balint's focus on the context of the doctor, patient, and their relationship, as well as development of practical wisdom (i.e. Aristotelian phronesis) that we know in medicine as professional judgment. The case study method of the Balint group is one of the few and best formal methods to teach and practice this way of knowing.

Murphy-Baum, B. L., & Taylor, W. R. (2017). **Diverse inhibitory and excitatory mechanisms shape temporal tuning in transient OFF alpha ganglion cells in the rabbit retina**. *J Physiol*. doi:10.1113/jp275195

The twenty to thirty types of ganglion cell in the mammalian retina represent parallel signalling pathways that convey different information to the brain. Alpha ganglion cells are selective for high temporal frequencies in visual inputs, which makes them particularly sensitive to rapid motion. Although alpha ganglion cells have been studied in several species, the synaptic basis for their selective temporal tuning remains unclear. Here, we analyse excitatory synaptic inputs to transient OFF alpha ganglion cells (t-OFF alpha GCs) in the rabbit retina. We show that convergence of excitatory and inhibitory synaptic inputs within the bipolar cell terminals presynaptic to the t-OFF alpha GCs shifts the temporal tuning to higher temporal frequencies. GABAergic inhibition suppresses the excitatory input at low frequencies, but potentiates it at high frequencies. TTX-sensitive channels in presynaptic bipolar cells also contribute to boosting responses at high frequencies. Crossover glycinergic inhibition and sodium channel activity in the presynaptic bipolar cells also potentiate high frequency excitatory inputs. We found differences in the spatial and temporal properties, and contrast sensitivities of these mechanisms. These differences in stimulus selectivity allow these mechanisms to generate bandpass temporal tuning of t-OFF alpha GCs over a range of visual conditions. This article is protected by copyright. All rights reserved.

Mwimanzi, F., Toyoda, M., Mahiti, M., Mann, J. K., Martin, J. N., Bangsberg, D., . . . Ueno, T. (2018). **Resistance of Major Histocompatibility Complex Class B (MHC-B) to Nef-Mediated Downregulation Relative to that of MHC-A Is Conserved among Primate Lentiviruses and Influences Antiviral T Cell Responses in HIV-1-Infected Individuals**. *J Virol, 92*(1). doi:10.1128/jvi.01409-17

Patient-derived HIV-1 subtype B Nef clones downregulate HLA-A more efficiently than HLA-B. However, it remains unknown whether this property is common to Nef proteins across primate lentiviruses and how antiviral immune responses may be affected. We examined 263 Nef clones from diverse primate lentiviruses including different pandemic HIV-1 group M subtypes for their ability to downregulate major histocompatibility complex class A (MHC-A) and MHC-B from the cell surface. Though lentiviral Nef proteins differed markedly in their absolute MHC-A and MHC-B downregulation abilities, all lentiviral Nef lineages downregulated MHC-A, on average, 11 to 32% more efficiently than MHC-B. Nef genotype/phenotype analyses in a cohort of HIV-1 subtype C-infected patients (n = 168), together with site-directed mutagenesis, revealed Nef position 9 as a subtype-specific determinant of differential HLA-A versus HLA-B downregulation activity. Nef clones harboring nonconsensus variants at codon 9 downregulated HLA-B (though not HLA-A) significantly better than those harboring the consensus sequence at this site, resulting in reduced recognition of infected target cells by HIV-1-specific CD8(+) effector cells in vitro Among persons expressing protective HLA class I alleles, carriage of Nef codon 9 variants was also associated with reduced ex vivo HIV-specific T cell responses. Our results demonstrate that Nef's inferior ability to downregulate MHC-B compared to that of

MHC-A is conserved across primate lentiviruses and suggest that this property influences antiviral cellular immune responses.IMPORTANCE Primate lentiviruses encode the Nef protein that plays an essential role in establishing persistent infection in their respective host species. Nef interacts with the cytoplasmic region of MHC-A and MHC-B molecules and downregulates them from the infected cell surface to escape recognition by host cellular immunity. Using a panel of Nef alleles isolated from diverse primate lentiviruses including pandemic HIV-1 group M subtypes, we demonstrate that Nef proteins across all lentiviral lineages downregulate MHC-A approximately 20% more effectively than MHC-B. We further identify a naturally polymorphic site at Nef position 9 that contributes to the MHC-B downregulation function in HIV-1 subtype C and show that carriage of Nef variants with enhanced MHC-B downregulation ability is associated with reduced breadth and magnitude of MHC-B-restricted cellular immune responses in HIV-infected individuals. Our study underscores an evolutionarily conserved interaction between lentiviruses and primate immune systems that may contribute to pathogenesis.

Nakai, Y., Nagashima, A., Hayakawa, A., Osuki, T., Jeong, J. W., Sugiura, A., . . . Asano, E. (2018). **Four-dimensional map of the human early visual system**. *Clinical Neurophysiology, 129*(1), 188-197. doi:10.1016/j.clinph.2017.10.019

OBJECTIVE: We generated a large-scale, four-dimensional map of neuronal modulations elicited by full-field flash stimulation. METHODS: We analyzed electrocorticography (ECoG) recordings from 63 patients with focal epilepsy, and delineated the spatial-temporal dynamics of visually-elicited high-gamma70-110 Hz amplitudes on a standard brain template. We then clarified the neuronal events underlying visual evoked potential (VEP) components, by correlating with high-gamma amplitude measures. RESULTS: The medial-occipital cortex initially revealed rapid neural activation followed by prolonged suppression, reflected by augmentation of high-gamma activity lasting up to 100ms followed by attenuation lasting up to 1000ms, respectively. With a number of covariate factors incorporated into a prediction model, the eccentricity representation independently predicted the magnitude of post-activation suppression, which was more intense in regions representing more parafoveal visual fields compared to those of more peripheral fields. The initial negative component on VEP was sharply contoured and co-occurred with early high-gamma augmentation, whose offset then co-occurred with a large positive VEP peak. A delayed negative VEP peak was blunt and co-occurred with prolonged high-gamma attenuation. CONCLUSIONS: Eccentricity-dependent gradient in neural suppression in the medial-occipital region may explain the functional difference between peripheral and parafoveal/central vision. Early negative and positive VEP components may reflect neural activation, whereas a delayed negative VEP peak reflecting neural suppression. SIGNIFICANCE: Our observation provides the mechanistic rationale for transient scotoma or mild flash-blindness, characterized by physiological afterimage preferentially formed in central vision following intense but non-injurious light exposure.

Ndayambaje, A., Anderson, R., Yoder, C. M., Ewing, H., & Thomson, D. R. (2017). **Human resources for health (HRH) midwives mentoring program and episiotomy rates at muhima hospital, Rwanda: A retrospective cross-sectional study**. *Rwanda Medical Journal, 74*(2), 7-11.

BACKGROUND: Despite strong evidence against routine episiotomies, numerous unnecessary episiotomies occur each year in Rwanda and other countries leading to long-term maternal complications. The Ministry of Health-led Human Resources for Health (HRH) program in Rwanda aims to improve the quality of health care delivery by increasing the capacity of doctors, nurses, and midwives. HRH pairs international and domestic doctors, nurses, and midwives to provide in-service training and daily bed-side mentorship, and to exchange best practices. This study evaluates the effect of the HRH midwifery in-service mentoring program on change of episiotomy rates at Muhima Hospital in Kigali, Rwanda. METHODS: This retrospective pre-post intervention study of episiotomy rates used data from vaginal births sequentially sampled from the hospital birth register during six-month periods before (2012, n=264) and after (2014, n=394) the intervention was implemented. Percentages and chi-squared tests were used to compare episiotomy rates before and after the intervention, including in subgroups of women. Logistic regression was used to test for any differences between groups.

RESULTS: Pre-intervention and post-intervention populations were similar in terms of age (p=0.488), parity (p=0.080), shift of birth (p=0.280), and baby weight (p=0.190). The change in episiotomy rate from 35.6% in 2012 to 11.7% in 2014 was statistically significant (p<0.001), after adjusting for other characteristics. BACKGROUND: Despite strong evidence against routine episiotomies, numerous unnecessary episiotomies occur each year in Rwanda and other countries leading to long-term maternal complications. The Ministry of Health-led Human Resources for Health (HRH) program in Rwanda aims to improve the quality of health care delivery by increasing the capacity of doctors, nurses, and midwives. HRH pairs international and domestic doctors, nurses, and midwives to provide in-service training and daily bed-side mentorship, and to exchange best practices. This study evaluates the effect of the HRH midwifery in-service mentoring program on change of episiotomy rates at Muhima Hospital in Kigali, Rwanda. DISCUSSION: This study found a substantial decrease in episiotomy rates at Muhima Hospital following implementation of a two-year in-service mentoring program. More research is needed to separate the effects of general health system strengthening versus the intervention on episiotomy rate, but initial findings are positive.

Nelson, J., Karempelis, P., Dunitz, J., Hunter, R., & Boyer, H. (2017). **Pulmonary aspiration of sinus secretions in patients with cystic fibrosis**. *Int Forum Allergy Rhinol*. doi:10.1002/alr.22043

BACKGROUND: Indirect evidence suggests that sinonasal secretions are aspirated into the lungs of patients with cystic fibrosis (CF), contributing to infection, subsequent tissue damage, and decreased lung function. Our objective is to determine whether sinonasal secretions are transferred to the lungs in patients with CF-related sinus disease and healthy subjects, particularly in the recumbent position and during sleep. METHODS: We performed a prospective, controlled trial to detect pulmonary aspiration of radiolabeled albumin applied to the nasal mucosa of study subjects with chronic sinusitis related to CF and control subjects without sinus disease. Radioactive counts were measured in the lungs and compared to background counts in both groups after 8 hours of rest/sleep. RESULTS: Complete data was collected on 12 CF patients and 6 controls. Eleven patients with CF demonstrated higher lung counts than background counts. The average counts of radiolabeled albumin in the lungs of CF patients were significantly greater than background counts ($p = 0.03$). Controls did not demonstrate this finding ($p > 0.90$), with only one-half demonstrating lung counts greater than background counts. CONCLUSION: This study provides direct evidence of aspiration of sinonasal secretions into the lungs of patients with CF and healthy adults in the recumbent position. The fact that both patients and controls aspirated secretions suggests that aspiration alone does not account for the pathogenesis of lung disease in CF patients.

Nelson, J. W., Ferdaus, M. Z., McCormick, J. A., Minnier, J., Kaul, S., Ellison, D. H., & Barnes, A. P. (2017). **Endothelial Transcriptomics Reveals Activation of Fibrosis-Related Pathways in Hypertension**. *Physiological Genomics*, physiolgenomics.00111.02017. doi:10.1152/physiolgenomics.00111.2017

Hypertension poses a significant challenge to vasculature homeostasis and stands as the most common cardiovascular disease in the world. Its effects are especially profound on endothelial cells that form the inner lining of the vasculature and are directly exposed to the effects of excess pressure. Here, we characterize the in vivo transcriptomic response of cardiac endothelial cells to hypertension by rapidly isolating these cells from the spontaneous hypertension mouse model BPH/2J and its normotensive BPN/3J control strain and performing and RNA sequencing on both. Comparison of transcriptional differences between these groups reveals statistically significant changes in cellular pathways consistent with cardiac fibrosis found in hypertensive animals. Importantly, many of the fibrosis-linked genes identified also differ significantly between juvenile pre-hypertensive and adult hypertensive BPH/2J mice, suggesting that these transcriptional differences are hypertension-related. We examined the dynamic nature of these transcriptional changes by testing whether blood pressure normalization using either a calcium channel blocker (amlodipine) or a angiotensin II receptor blocker (losartan) is able to reverse these expression patterns associated with hypertension. We find that blood pressure reduction is capable of reversing some gene-expression patterns while other transcripts are recalcitrant to therapeutic intervention. This illuminates

the possibility that unmanaged hypertension may irreversibly alter some endothelial transcriptional patterns despite later intervention. This study quantifies how endothelial cells are remodeled at the molecular level in cardiovascular pathology and advances our understanding of the transcriptional events associated with endothelial response to hypertensive challenge.

Neumann, J. L., Mau, L. W., Virani, S., Denzen, E. M., Boyle, D. A., Boyle, N. J., . . . Burns, L. J. (2017). **Burnout, Moral Distress, Work-Life Balance, and Career Satisfaction among Hematopoietic Cell Transplantation Professionals**. *Biol Blood Marrow Transplant*. doi:10.1016/j.bbmt.2017.11.015

A projected shortage of hematopoietic cell transplantation (HCT) health professionals was identified as a major issue during the National Marrow Donor Program/Be The Match System Capacity Initiative. Work-related distress and work-life balance were noted to be potential barriers to recruitment/retention. This study examined these barriers and their association with career satisfaction across HCT disciplines. A cross-sectional, 90-item, web-based survey was administered to advanced practice providers, nurses, physicians, pharmacists, and social workers in 2015. Participants were recruited from membership lists of 6 professional groups. Burnout (measured with the Maslach Burnout Inventory subscales of emotional exhaustion and depersonalization) and moral distress (measured by Moral Distress Scale-Revised) were examined to identify work-related distress. Additional questions addressed demographics, work-life balance, and career satisfaction. Of 5759 HCT providers who received an individualized invitation to participate, 914 (16%) responded; 627 additional participants responded to an open link survey. Significant differences in demographic and practice characteristics existed across disciplines ($P < .05$). The prevalence of burnout differed across disciplines ($P < .05$) with an overall prevalence of 40%. Over one-half of pharmacists had burnout, whereas social workers had the lowest prevalence at less than one-third. Moral distress scores ranged from 0 to 336 and varied by discipline ($P < .05$); pharmacists had the highest mean score (62.9 +/- 34.8) and social workers the lowest (42.7 +/- 24.4). In multivariate and univariate analyses, variables contributing to burnout varied by discipline; however, moral distress was a significant contributing factor for all providers. Those with burnout were more likely to report inadequate work-life balance and a low level of career satisfaction; however, overall there was a high level of career satisfaction across disciplines. Burnout, moral distress, and inadequate work-life balance existed at a variable rate in all HCT disciplines, yet career satisfaction was high. These results suggest specific areas to address in the work environment for HCT health professionals, especially the need for relief of moral distress and a greater degree of personal time. As the creation of healthy work environments is increasingly emphasized to improve quality care and decrease costs, these findings should be used by HCT leadership to develop interventions that mitigate work-related distress and in turn foster recruitment and retention of HCT providers.

Newton, Y., Novak, A. M., Swatloski, T., McColl, D. C., Chopra, S., Graim, K., . . . Stuart, J. M. (2017). **TumorMap: Exploring the molecular similarities of cancer samples in an interactive portal**. *Cancer Research, 77*(21), e111-e114. doi:10.1158/0008-5472.CAN-17-0580

Vast amounts of molecular data are being collected on tumor samples, which provide unique opportunities for discovering trends within and between cancer subtypes. Such cross-cancer analyses require computational methods that enable intuitive and interactive browsing of thousands of samples based on their molecular similarity. We created a portal called TumorMap to assist in exploration and statistical interrogation of high-dimensional complex "omics" data in an interactive and easily interpretable way. In the TumorMap, samples are arranged on a hexagonal grid based on their similarity to one another in the original genomic space and are rendered with Google's Map technology. While the important feature of this public portal is the ability for the users to build maps from their own data, we pre-built genomic maps from several previously published projects. We demonstrate the utility of this portal by presenting results obtained from The Cancer Genome Atlas project data.

Nigg, J. T., & Song, M. (2018). **ADHD and Early Experience: Revisiting the Case of Low Birth Weight**. *Pediatrics, 141*(1). doi:10.1542/peds.2017-3488

Noriea, A. H., Redmond, N., Weil, R. A., Curry, W. A., Peek, M. E., & Willett, L. L. (2017). **Development of a multifaceted health disparities curriculum for medical residents**. *Family Medicine, 49*(10), 796-802.

BACKGROUND AND OBJECTIVES: Health disparities education is required during residency training. However, residency program directors cite numerous barriers to implementing disparities curricula, and few publications describing successful disparities curricula exist in the literature. In this report, we describe the development, implementation, and early evaluation of a longitudinal health disparities curriculum for resident physicians. We provide resource references, process, and didactic toolkits to facilitate use by other residency programs. METHODS: We used a standard, six-step model for curricular design, implementation, and evaluation. We assessed feasibility of curricular development including practicality (program cost and time requirements) and demand (resident engagement). We also assessed program and learner outcomes, including number of didactic and clinic sessions delivered and resident preparedness, attitudes, and skill in caring for vulnerable patients. RESULTS: We designed, implemented, and evaluated our curriculum in less than 1 year, with no external funding. Time costs included 100 chief resident and 20 faculty hours for curricular development, followed by 20 chief resident and 16 faculty hours for implementation. In the first year of our curriculum, 21% of residents (16 of 75) participated. We created eight didactic sessions and delivered four as intended. Residents provided 84 free clinic sessions for uninsured patients and reported increased preparedness and skill caring for vulnerable patients in 15 of 20 measured domains. Residents also reported 20 commitments to change on themes that comprehensively reflected the content of our first curricular year. CONCLUSIONS: It is possible to design a disparities curriculum, overcome cited barriers, and improve educational outcomes related to the care of vulnerable patients.

Novogrodsky, E., Yaghoubian, A., Connor, S. E., Hicks, E., Vargas, G. B., Nassiri, S., . . . Veale, J. L. (2017). **The Role of Media in Non-Directed (Altruistic) Living Kidney Donation**. *Health Communication*, 1-9. doi:10.1080/10410236.2017.1405480

This study seeks to characterize how non-directed living kidney donors use media and informational resources over the course of their kidney donation journey. We conducted semi-structured interviews with non-directed donors (NDDs) who initiated kidney transplant chains. Interview transcripts were reviewed and references to media or informational resources were classified by type and pattern of use. More than half (57%) of NDDs reported that an identifiable media or informational resource resulted in their initial interest in donation. Two-thirds (67%) of NDDs cited the influence of stories and personal narratives on their decision to donate. After transplant, media and informational resources were used to promote organ donation, connect with other donors or recipients, and reflect on donation. From the study's findings, we conclude that media and informational resources play an important role in the process of donation for NDDs, including inspiring interest in donation through personal narratives. Media sources provide emotionally and intellectually compelling discussions that motivate potential donors. The results of this study may facilitate the development of more targeted outreach to potential donors through use of personal narratives in articles and television programming about donation.

Noyes, M. P., & Denard, P. J. (2017). **Arthroscopic Superior Capsular Reconstruction: Indications and Outcomes**. *Operative Techniques in Sports Medicine*. doi:10.1053/j.otsm.2017.10.005

Irreparable massive rotator cuff tears remain a problematic condition, especially for the young patient. Options such as partial repair or reverse total shoulder arthroplasty have led to satisfactory short-term outcomes but function can decline over time. Arthroscopic superior capsular reconstruction (SCR) provides a new

alternative for joint preservation in these patients, and our early clinical results with this technique has been promising. © 2017 Elsevier Inc.

Nugent, S. M., Golden, S. E., Thomas, C. R., Jr., Deffebach, M. E., Sukumar, M. S., Schipper, P. H., . . . Slatore, C. (2017). **Patient-clinician communication among patients with stage I lung cancer**. *Supportive Care in Cancer*. doi:10.1007/s00520-017-3992-1

PURPOSE: Limited data exist about patient-centered communication (PCC) and patient-centered outcomes among patients who undergo surgery or stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC). We aimed to examine the relationship between PCC and decision-making processes among NSCLC patients, using baseline data from a prospective, multicenter study. METHODS: Patients with stage 1 NSCLC completed a survey prior to treatment initiation. The survey assessed sociodemographic characteristics, treatment decision variables, and patient psychosocial outcomes: health-related quality of life (HRQOL), treatment self-efficacy, decisional conflict, and PCC. RESULTS: Fifty-two percent (n = 85) of 165 individuals planned to receive SBRT. There were no baseline differences detected on patient psychosocial outcomes between those who planned to receive SBRT or surgery. All participants reported high HRQOL (M = 72.5, SD = 21.3) out of 100, where higher scores indicate better functioning; high self-efficacy (M = 1.5, SD = 0.5) out of 6, where lower numbers indicate higher self-efficacy; minimal decisional conflict (M = 15.2, SD = 12.7) out of 100, where higher scores indicate higher decisional conflict; and high levels of patient-centered communication (M = 2.4, SD = 0.8) out of 7 where higher scores indicate worse communication. Linear regression analyses adjusting for sociodemographic and clinical variables showed that higher quality PCC was associated with higher self-efficacy (beta = 0.17, p = 0.03) and lower decisional conflict (beta = 0.42, p < 0.001). CONCLUSIONS: Higher quality PCC was associated with higher self-efficacy and lower decisional conflict. Self-efficacy and decisional conflict may influence subsequent health outcomes. Therefore, our findings may inform future research and clinical programs that focus on communication strategies to improve these outcomes.

O'Neil, M. E., Laman-Maharg, B., Schnurr, P. P., Carlson, K. F., Twamley, E. W., Peterson, C., . . . Sayer, N. A. (2017). **Objective cognitive impairment and subjective cognitive problems in veterans initiating psychotherapy for posttraumatic stress disorder: An exploratory study**. *Applied Neuropsychology:Adult*, 1-8. doi:10.1080/23279095.2017.1395334

The prevalence of cognitive impairment in Veterans initiating an evidence-based psychotherapy (EBP) for posttraumatic stress disorder (PTSD) is not yet established and has implications for service delivery. Our objectives were to (1) describe the type, severity, and prevalence of objective cognitive impairment and subjective cognitive problems experienced by Veterans at the time they began an EBP for PTSD and (2) determine whether assessments of objective cognitive impairment and subjective cognitive problems agree. We conducted objective and subjective (self-report) cognitive assessments in a sample of 38 Veterans initiating EBP for PTSD at one Veterans Affairs Medical Center. Thirty Veterans produced valid assessments. Almost half (14/30) of the participants demonstrated objective impairment in one or more cognitive domains, primarily in the areas of learning, memory, and processing speed. Almost all (29/30) participants endorsed moderate or greater cognitive problems on at least one self-report measure. After adjustment for multiple comparisons, there were no significant correlations between objective and subjective assessments. Objective cognitive impairment and subjective cognitive problems are common in Veterans beginning an EBP for PTSD. Longitudinal research on a larger sample is warranted to better understand relationships among subjective cognitive problems, objective cognitive impairment, and PTSD treatment participation and outcomes. © 2017 Taylor & Francis Group, LLC

Oh, T., Scheer, J. K., Smith, J. S., Hostin, R., Robinson, C., Gum, J. L., . . . Ames, C. P. (2017). **Potential of predictive computer models for preoperative patient selection to enhance overall quality-adjusted life years**

gained at 2-year follow-up: a simulation in 234 patients with adult spinal deformity. *Neurosurgical Focus, 43*(6), E2. doi:10.3171/2017.9.focus17494

OBJECTIVE Patients with adult spinal deformity (ASD) experience significant quality of life improvements after surgery. Treatment, however, is expensive and complication rates are high. Predictive analytics has the potential to use many variables to make accurate predictions in large data sets. A validated minimum clinically important difference (MCID) model has the potential to assist in patient selection, thereby improving outcomes and, potentially, cost-effectiveness. METHODS The present study was a retrospective analysis of a multiinstitutional database of patients with ASD. Inclusion criteria were as follows: age >/= 18 years, radiographic evidence of ASD, 2-year follow-up, and preoperative Oswestry Disability Index (ODI) > 15. Forty-six variables were used for model training: demographic data, radiographic parameters, surgical variables, and results on the health-related quality of life questionnaire. Patients were grouped as reaching a 2-year ODI MCID (+MCID) or not (-MCID). An ensemble of 5 different bootstrapped decision trees was constructed using the C5.0 algorithm. Internal validation was performed via 70:30 data split for training/testing. Model accuracy and area under the curve (AUC) were calculated. The mean quality-adjusted life years (QALYs) and QALYs gained at 2 years were calculated and discounted at 3.5% per year. The QALYs were compared between patients in the +MCID and -MCID groups. RESULTS A total of 234 patients met inclusion criteria (+MCID 129, -MCID 105). Sixty-nine patients (29.5%) were included for model testing. Predicted versus actual results were 50 versus 40 for +MCID and 19 versus 29 for -MCID (i.e., 10 patients were misclassified). Model accuracy was 85.5%, with 0.96 AUC. Predicted results showed that patients in the +MCID group had significantly greater 2-year mean QALYs (p = 0.0057) and QALYs gained (p = 0.0002). CONCLUSIONS A successful model with 85.5% accuracy and 0.96 AUC was constructed to predict which patients would reach ODI MCID. The patients in the +MCID group had significantly higher mean 2-year QALYs and QALYs gained. This study provides proof of concept for using predictive modeling techniques to optimize patient selection in complex spine surgery.

O'Hara, M. J., Murray, N. J., Carter, J. C., Kellogg, C. M., & Link, J. M. (2018). **Hydroxamate column-based purification of zirconium-89 (89Zr) using an automated fluidic platform**. *Applied Radiation and Isotopes, 132*, 85-94. doi:10.1016/j.apradiso.2017.10.048

Zirconium-89 (89Zr) is a long-lived (t1/2 = 78.4 h) positron-emitting isotope that is useful for positron emission tomography (PET) based diagnostic imaging using radiolabeled antibodies. Hydroxamate resin columns are predominantly used for the purification of 89Zr from cyclotron bombarded natY targets dissolved in strong HCl. 89Zr is conventionally eluted from the resin in 1 M oxalic acid (H2C2O4), a complexant that is conducive to follow-on binding of 89Zr through a transchelation process to the deferoxamine siderophore. In the present study, we determined that a lower concentration of H2C2O4 eluent (0.8 M) is adequate to efficiently remove 89Zr from a column containing 100 mg hydroxamate resin. As a result, less buffering agents are needed to be added to the 89Zr product fraction prior to labeling. A simple automated fluidic system prototype has been developed to perform the steps required for 89Zr purification using a hydroxamate resin column (column conditioning in HCl, Y target dissolution, dissolved target solution load onto column, column washes using HCl and water, and 89Zr elution). The system performance was evaluated using several cyclotron bombarded Y targets; 89Zr product fractions demonstrated excellent chemical recoveries from these targets, with 1.0 mL product volumes yielding 89±2% of the column elution peak activity and 84±2% of 89Zr recovered from the target (at EOB). These results compare favorably with previously published 89Zr product volumes and yields, despite the lower concentration of H2C2O4 eluent employed. Transchelation of resulting 89Zr product fractions was performed to assess product quality. The effective specific activity (ESA) ranged between 44(7) and 109(22) TBq·mmole-1, while the bindable metals concentration, a metric introduced for assessing and comparing product purity, ranged between 43(7) and 115(27) nmole·g-1. © 2017 Elsevier Ltd

Onaitis, M. W., Furnary, A. P., Kosinski, A. S., Kim, S., Boffa, D., Tong, B. C., . . . Fernandez, F. G. (2018). **Prediction of Long-Term Survival After Lung Cancer Surgery for Elderly Patients in The Society of Thoracic**

Surgeons General Thoracic Surgery Database. *Annals of Thoracic Surgery, 105*(1), 309-316. doi:10.1016/j.athoracsur.2017.06.071

Background Prior risk models using the STS General Thoracic Surgery database (STS-GTSD) have been limited to 30-day outcomes. We have now linked STS data to Medicare data and sought to create a risk prediction model for long-term mortality after lung cancer resection in patients older than 65 years. Methods The STS-GTSD was linked to Medicare data for lung cancer resections from 2002 to 2013 as previously reported. Successful linkage was performed in 29,899 lung cancer resection patients. Cox proportional hazards modeling was used to create a long-term survival model. Variable selection was performed using statistically significant univariate factors and known clinical predictors of outcome. Calibration was assessed by dividing the cohort into deciles of predicted survival and discrimination assessed with a C-statistic corrected for optimism via 1,000 bootstrap replications. Results Median age was 73 years (interquartile range, 68 to 78 years), and 48% of the patients were male. Of the 29,094 patients with nonmissing pathologic stage, 69% were stage I, 18% stage II, 11% stage III, and 2% stage IV. Procedure performed was lobectomy in 69%, bilobectomy in 3%, pneumonectomy in 3%, segmentectomy in 7%, sleeve lobectomy in 1%, and wedge resection in 17%. Thoracoscopic approach was performed in 47% of resections. The final Cox model reveals that stage and age are the strongest predictors of long-term survival. Even after controlling for stage, wedge resection, segmentectomy, bilobectomy, and pneumonectomy are all associated with increased hazard of death in comparison with lobectomy. Thoracoscopic approach is associated with improved long-term survival in comparison with thoracotomy. Other modifiable predictive factors include smoking and low body mass index. Calibration of the model demonstrates excellent performance across all survival deciles and a C-statistic of 0.694. Conclusions The STS-GTSD-Medicare long-term risk model includes several novel factors associated with mortality. Although medical factors predict long-term survival, age and stage are the strong predictors. Despite this, procedure choice and thoracoscopic/open approach are potentially modifiable predictors of long-term survival after lung cancer resection. © 2018 The Society of Thoracic Surgeons

Onoday, H. (2017). **Yesterday, Today, Tomorrow**. *Journal of the Dermatology Nurses' Association, 9*(6), 293-294. doi:10.1097/JDN.0000000000000359

Ortiz, D., Guiguemde, W. A., Hammill, J. T., Carrillo, A. K., Chen, Y., Connelly, M., . . . Landfear, S. M. (2017). **Discovery of novel, orally bioavailable, antileishmanial compounds using phenotypic screening**. *PLoS Negl Trop Dis, 11*(12), e0006157. doi:10.1371/journal.pntd.0006157

Leishmaniasis is a parasitic infection that afflicts approximately 12 million people worldwide. There are several limitations to the approved drug therapies for leishmaniasis, including moderate to severe toxicity, growing drug resistance, and the need for extended dosing. Moreover, miltefosine is currently the only orally available drug therapy for this infection. We addressed the pressing need for new therapies by pursuing a two-step phenotypic screen to discover novel, potent, and orally bioavailable antileishmanials. First, we conducted a high-throughput screen (HTS) of roughly 600,000 small molecules for growth inhibition against the promastigote form of the parasite life cycle using the nucleic acid binding dye SYBR Green I. This screen identified approximately 2,700 compounds that inhibited growth by over 65% at a single point concentration of 10 muM. We next used this 2700 compound focused library to identify compounds that were highly potent against the disease-causing intra-macrophage amastigote form and exhibited limited toxicity toward the host macrophages. This two-step screening strategy uncovered nine unique chemical scaffolds within our collection, including two previously described antileishmanials. We further profiled two of the novel compounds for in vitro absorption, distribution, metabolism, excretion, and in vivo pharmacokinetics. Both compounds proved orally bioavailable, affording plasma exposures above the half-maximal effective concentration (EC50) concentration for at least 12 hours. Both compounds were efficacious when administered orally in a murine model of cutaneous leishmaniasis. One of the two compounds exerted potent activity against trypanosomes, which are kinetoplastid parasites related to Leishmania species. Therefore, this compound could help control multiple parasitic diseases. The promising pharmacokinetic

profile and significant in vivo efficacy observed from our HTS hits highlight the utility of our two-step phenotypic screening strategy and strongly suggest that medicinal chemistry optimization of these newly identified scaffolds will lead to promising candidates for an orally available anti-parasitic drug.

Papp, K. A., Bachelez, H., Blauvelt, A., Winthrop, K. L., Romiti, R., Ohtsuki, M., . . . Strober, B. (2017). **Infections from seven clinical trials of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriasis**. *British Journal of Dermatology*. doi:10.1111/bjd.15723

Background: Infections are associated with biological therapies in psoriasis. Objectives: To summarize the incidence of infections in patients with moderate-to-severe psoriasis treated with ixekizumab, an anti-interleukin-17A monoclonal antibody. Methods: Infections are summarized from an integrated database of seven controlled and uncontrolled ixekizumab psoriasis trials. Data are presented from placebo-controlled induction (weeks 0-12; UNCOVER-1, UNCOVER-2 and UNCOVER-3) and maintenance periods (weeks 12-60; UNCOVER-1 and UNCOVER-2), and all patients exposed to ixekizumab pooled from all seven trials. Comparisons with etanercept were made during the induction period of two trials (UNCOVER-2 and UNCOVER-3). Incidence and exposure-adjusted incidence rates (IRs) per 100 patient-years (PYs) are reported. Results: Overall, 4209 patients were treated with ixekizumab (6480 PY). During induction (weeks 0-12), overall infection rates were higher in patients treated with ixekizumab (27%) vs. placebo (23%, P < 0·05); however, specific infection rates were comparable overall across treatment groups. IRs of infections did not increase with longer-term exposure. For all patients treated with ixekizumab (all seven trials), the incidence of serious infections was low (2%, IR 1·3). Candida infections, including eight cases of oesophageal candidiasis, were adequately managed with antifungal therapy, were noninvasive and did not lead to discontinuation. Conclusions: Overall, infections occurred in a higher percentage of patients treated with ixekizumab vs. placebo during the first 12 weeks of treatment; however, specific infection rates were comparable overall across treatment groups. Incidences of serious infections were low and similar across treatment groups.

Parasa, S., Vennalaganti, S., Gaddam, S., Vennalaganti, P., Young, P., Gupta, N., . . . Sharma, P. (2017). **Development and Validation of a Model to Determine Risk of Progression of Barrett's Esophagus to Neoplasia**. *Gastroenterology*. doi:10.1053/j.gastro.2017.12.009

BACKGROUND & AIMS: A system is needed to determine the risk of patients with Barrett's esophagus for progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC). We developed and validated a model to determine of progression to HGD or EAC in patients with BE, based on demographic data and endoscopic and histologic findings at the time of index endoscopy. METHODS: We performed a longitudinal study of patients with BE at 5 centers in United States and 1 center in Netherlands enrolled in the Barrett's Esophagus Study database from 1985 through 2014. Patients were excluded from the analysis if they had less than 1 year of follow up, were diagnosed with HGD or EAC within the past year, were missing baseline histologic data, or had no intestinal metaplasia. Seventy percent of the patients were used to derive the model and 30% were used for the validation study. The primary outcome was development of HGD or EAC during the follow-up period (median 5.9 years). Survival analysis was performed using the Kaplan-Meier method. We assigned a specific number of points to each BE risk factor, and point totals (scores) were used to create categories of low, intermediate, and high risk. We used Cox regression to compute hazard ratios (HR) and 95% CIs to determine associations between risk of progression and scores. RESULTS: Of 4584 patients in the database, 2697 were included in our analysis (84.1% men; 87.6% Caucasian; mean age, 55.4+/-20.1 years; mean body mass index, 27.9+/-5.5; mean length of BE, 3.7 cm+/-3.2). During the follow-up period, 154 patients (5.7%) developed HGD or EAC, with an annual rate of progression of 0.95%. Male sex, smoking, length of BE, and baseline-confirmed low-grade dysplasia were significantly associated with progression. Scores assigned identified patients with BE that progressed to HGD or EAC with a c-statistic of 0.76 (95% CI, 0.72-0.80) (P<.001). The calibration slope was 0.9966 (P=.99), determined from the validation cohort. CONCLUSIONS: We developed a scoring system (called progression of BE (PIB) score) based on male sex, smoking, length of BE, and baseline low-grade dysplasia) that identified patients with BE at low,

intermediate, and high risk groups for HGD or EAC. This scoring system might be used in management of patients.

Patel, M. R., Ellerton, J., Infante, J. R., Agrawal, M., Gordon, M., Aljumaily, R., . . . Apolo, A. B. (2017). **Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial**. *Lancet Oncology*. doi:10.1016/s1470-2045(17)30900-2

BACKGROUND: The approval of anti-programmed death ligand 1 (PD-L1) and anti-programmed death 1 agents has expanded treatment options for patients with locally advanced or metastatic urothelial carcinoma. Avelumab, a human monoclonal anti-PD-L1 antibody, has shown promising antitumour activity and safety in this disease. We aimed to assess the safety profile in patients (both post-platinum therapy and cisplatin-naive) treated with avelumab and to assess antitumour activity of this drug in post-platinum patients. METHODS: In this pooled analysis of two cohorts from the phase 1 dose-expansion JAVELIN Solid Tumor study, patients aged 18 years and older with histologically or cytologically confirmed locally advanced or metastatic urothelial carcinoma that had progressed after at least one previous platinum-based chemotherapy were enrolled from 80 cancer treatment centres or hospitals in the USA, Europe, and Asia. Eligible patients had adequate end-organ function, an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 3 months, and at least one measurable lesion. Cisplatin-ineligible patients who might have been previously treated in the perioperative setting, including platinum-naive patients, were also eligible. Patients unselected for PD-L1 expression received avelumab (10 mg/kg, 1 h intravenous infusion) every 2 weeks until confirmed disease progression, unacceptable toxicity, or other criterion for withdrawal. The primary endpoint for this efficacy expansion cohort was confirmed best overall response (according to RECIST version 1.1), adjudicated by independent review. Safety analysis was done in all patients who received at least one dose of avelumab. Antitumour activity was assessed in post-platinum patients who received at least one dose of avelumab. This trial is registered with ClinicalTrials.gov, number NCT01772004; enrolment in this cohort of patients with metastatic urothelial carcinoma is closed and the trial is ongoing. FINDINGS: Between Sept 3, 2014, and March 15, 2016, 329 patients with advanced metastatic urothelial carcinoma were screened for enrolment into this study; 249 patients were eligible and received treatment with avelumab for a median of 12 weeks (IQR 6.0-19.7) and followed up for a median of 9.9 months (4.3-12.1). Safety and antitumour activity were evaluated at data cutoff on June 9, 2016. In 161 post-platinum patients with at least 6 months of follow-up, a best overall response of complete or partial response was recorded in 27 patients (17%; 95% CI 11-24), including nine (6%) complete responses and 18 (11%) partial responses. The most frequent treatment-related adverse events (any grade in >/=10% patients) were infusion-related reaction (73 [29%]; all grade 1-2) and fatigue (40 [16%]). Grade 3 or worse treatment-related adverse events occurred in 21 (8%) of 249 patients, the most common of which were fatigue (four [2%]), and asthenia, elevated lipase, hypophosphataemia, and pneumonitis in two (1%) patients each. 19 (8%) of 249 patients had a serious adverse event related to treatment with avelumab, and one treatment-related death occurred (pneumonitis). INTERPRETATION: Avelumab showed antitumour activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma; a manageable safety profile was reported in all avelumab-treated patients. These data provide the rationale for therapeutic use of avelumab in metastatic urothelial carcinoma and it has received accelerated US FDA approval in this setting on this basis. FUNDING: Merck KGaA, and Pfizer Inc.

Patel, M. R., Ellerton, J., Infante, J. R., Agrawal, M., Gordon, M., Aljumaily, R., . . . Apolo, A. B. (2017). **Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): Pooled results from two expansion cohorts of an open-label, phase 1 trial**. *The Lancet Oncology*. doi:10.1016/S1470-2045(17)30900-2

Background: The approval of anti-programmed death ligand 1 (PD-L1) and anti-programmed death 1 agents has expanded treatment options for patients with locally advanced or metastatic urothelial carcinoma. Avelumab, a human monoclonal anti-PD-L1 antibody, has shown promising antitumour activity and safety in this

disease. We aimed to assess the safety profile in patients (both post-platinum therapy and cisplatin-naive) treated with avelumab and to assess antitumour activity of this drug in post-platinum patients. Methods: In this pooled analysis of two cohorts from the phase 1 dose-expansion JAVELIN Solid Tumor study, patients aged 18 years and older with histologically or cytologically confirmed locally advanced or metastatic urothelial carcinoma that had progressed after at least one previous platinum-based chemotherapy were enrolled from 80 cancer treatment centres or hospitals in the USA, Europe, and Asia. Eligible patients had adequate end-organ function, an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 3 months, and at least one measurable lesion. Cisplatin-ineligible patients who might have been previously treated in the perioperative setting, including platinum-naive patients, were also eligible. Patients unselected for PD-L1 expression received avelumab (10 mg/kg, 1 h intravenous infusion) every 2 weeks until confirmed disease progression, unacceptable toxicity, or other criterion for withdrawal. The primary endpoint for this efficacy expansion cohort was confirmed best overall response (according to RECIST version 1.1), adjudicated by independent review. Safety analysis was done in all patients who received at least one dose of avelumab. Antitumour activity was assessed in post-platinum patients who received at least one dose of avelumab. This trial is registered with ClinicalTrials.gov, number NCT01772004; enrolment in this cohort of patients with metastatic urothelial carcinoma is closed and the trial is ongoing. Findings: Between Sept 3, 2014, and March 15, 2016, 329 patients with advanced metastatic urothelial carcinoma were screened for enrolment into this study; 249 patients were eligible and received treatment with avelumab for a median of 12 weeks (IQR 6·0-19·7) and followed up for a median of 9·9 months (4·3-12·1). Safety and antitumour activity were evaluated at data cutoff on June 9, 2016. In 161 post-platinum patients with at least 6 months of follow-up, a best overall response of complete or partial response was recorded in 27 patients (17%; 95% CI 11-24), including nine (6%) complete responses and 18 (11%) partial responses. The most frequent treatment-related adverse events (any grade in ≥10% patients) were infusion-related reaction (73 [29%]; all grade 1-2) and fatigue (40 [16%]). Grade 3 or worse treatment-related adverse events occurred in 21 (8%) of 249 patients, the most common of which were fatigue (four [2%]), and asthenia, elevated lipase, hypophosphataemia, and pneumonitis in two (1%) patients each. 19 (8%) of 249 patients had a serious adverse event related to treatment with avelumab, and one treatment-related death occurred (pneumonitis). Interpretation: Avelumab showed antitumour activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma; a manageable safety profile was reported in all avelumab-treated patients. These data provide the rationale for therapeutic use of avelumab in metastatic urothelial carcinoma and it has received accelerated US FDA approval in this setting on this basis. Funding: Merck KGaA, and Pfizer Inc.

Pattanasin, S., Dunne, E. F., Wasinrapee, P., Tongtoyai, J., Chonwattana, W., Sriporn, A., . . . Curlin, M. E. (2017). **Screening for Chlamydia trachomatis and Neisseria gonorrhoeae infection among asymptomatic men who have sex with men in Bangkok, Thailand**. *International Journal of STD and AIDS*, 956462417744904. doi:10.1177/0956462417744904

We report positivity rates of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) infection at each anatomic site among asymptomatic men who have sex with men (MSM). We calculated the number needed to screen (NNS) to detect CT and NG infection at each anatomic site. From 2006 to 2010, we enrolled Thai MSM, age >/= 18 years into the Bangkok MSM Cohort Study. Participants underwent physical examination and had rectal, urethral, and pharyngeal screening for CT and NG infection using nucleic acid amplification tests (NAATs). Of 1744 enrollees, 1696 (97.2%) had no symptoms of CT and NG infection. The positivity rates of CT and NG infection at any site were 14.3% (rectum, urethra, pharynx) and 6.4% (rectum, urethra), respectively. The NNS to detect rectal CT and rectal NG infections was 10 and 16, respectively ($p < 0.05$). For urethral infection, the NNS of CT was lower than the NNS of NG (22, 121: $p < 0.05$). The lowest NNS found for rectal CT infection was in HIV-infected MSM (6, 5-8). Asymptomatic CT and NG infection were common among MSM in Bangkok, Thailand and frequently detected in the rectum. In setting where screening in all specimens using NAAT is not feasible, rectal screening should be a priority.

Perry, C. K., McCalmont, J. C., Ward, J. P., Menelas, H. K., Jackson, C., De Witz, J. R., . . . Seguin, R. A. (2017). **Mujeres Fuertes y Corazones Saludables: adaptation of the StrongWomen -healthy hearts program for rural Latinas using an intervention mapping approach**. *BMC Public Health, 17*(1), 982. doi:10.1186/s12889-017-4842-2

OBJECTIVE: To describe our use of intervention mapping as a systematic method to adapt an evidence-based physical activity and nutrition program to reflect the needs of rural Latinas. METHODS: An intervention mapping process involving six steps guided the adaptation of an evidence based physical activity and nutrition program, using a community-based participatory research approach. We partnered with a community advisory board of rural Latinas throughout the adaptation process. RESULTS: A needs assessment and logic models were used to ascertain which program was the best fit for adaptation. Once identified, we collaborated with one of the developers of the original program (StrongWomen - Healthy Hearts) during the adaptation process. First, essential theoretical methods and program elements were identified, and additional elements were added or adapted. Next, we reviewed and made changes to reflect the community and cultural context of the practical applications, intervention strategies, program curriculum, materials, and participant information. Finally, we planned for the implementation and evaluation of the adapted program, Mujeres Fuertes y Corazones Saludables, within the context of the rural community. A pilot study will be conducted with overweight, sedentary, middle-aged, Spanish-speaking Latinas. Outcome measures will assess change in weight, physical fitness, physical activity, and nutrition behavior. CONCLUSIONS: The intervention mapping process was feasible and provided a systematic approach to balance fit and fidelity in the adaptation of an evidence-based program. Collaboration with community members ensured that the components of the curriculum that were adapted were culturally appropriate and relevant within the local community context.

Pilkonis, P. A., Yu, L., Dodds, N. E., Johnston, K. L., Lawrence, S. M., Hilton, T. F., . . . McCarty, D. (2017). **An item bank for abuse of prescription pain medication from the Patient-Reported Outcomes Measurement Information System (PROMIS®)**. *Pain Medicine (United States), 18*(8), 1516-1527. doi:10.1093/pm/pnw233

Objective. There is a need to monitor patients receiving prescription opioids to detect possible signs of abuse. To address this need, we developed and calibrated an item bank for severity of abuse of prescription pain medication as part of the Patient- Reported Outcomes Measurement Information System (PROMIS®). Methods. Comprehensive literature searches yielded an initial bank of 5,310 items relevant to substance use and abuse, including abuse of prescription pain medication, from over 80 unique instruments. After qualitative item analysis (i.e., focus groups, cognitive interviewing, expert review, and item revision), 25 items for abuse of prescribed pain medication were included in field testing. Items were written in a first-person, past-tense format, with a three-month time frame and five response options reflecting frequency or severity. The calibration sample included 448 respondents, 367 from the general population (ascertained through an internet panel) and 81 from community treatment programs participating in the National Drug Abuse Treatment Clinical Trials Network. Results. A final bank of 22 items was calibrated using the two-parameter graded response model from item response theory. A seven-item static short form was also developed. The test information curve showed that the PROMIS® item bank for abuse of prescription pain medication provided substantial information in a broad range of severity. Conclusion. The initial psychometric characteristics of the item bank support its use as a computerized adaptive test or short form, with either version providing a brief, precise, and efficient measure relevant to both clinical and community samples.

Platt, E. J., Smith, L., & Thayer, M. J. (2017). **L1 retrotransposon antisense RNA within ASAR lncRNAs controls chromosome-wide replication timing**. *J Cell Biol*. doi:10.1083/jcb.201707082

Mammalian cells replicate their chromosomes via a temporal replication program. The ASAR6 and ASAR15 genes were identified as loci that when disrupted result in delayed replication and condensation of entire human chromosomes. ASAR6 and ASAR15 are monoallelically expressed long noncoding RNAs that remain

associated with the chromosome from which they are transcribed. The chromosome-wide effects of ASAR6 map to the antisense strand of an L1 retrotransposon within ASAR6 RNA, deletion or inversion of which delayed replication of human chromosome 6. Furthermore, ectopic integration of ASAR6 or ASAR15 transgenes into mouse chromosomes resulted in delayed replication and condensation, an increase in H3K27me3, coating of the mouse chromosome with ASAR RNA, and a loss of mouse Cot-1 RNA expression in cis. Targeting the antisense strand of the L1 within ectopically expressed ASAR6 RNA restored normal replication timing. Our results provide direct evidence that L1 antisense RNA plays a functional role in chromosome-wide replication timing of mammalian chromosomes.

Posner, M., Murray, K. L., McDonald, M. S., Eighinger, H., Andrew, B., Drossman, A., . . . Lampi, K. J. (2017). **The zebrafish as a model system for analyzing mammalian and native alpha-crystallin promoter function**. *PeerJ, 5*, e4093. doi:10.7717/peerj.4093

Previous studies have used the zebrafish to investigate the biology of lens crystallin proteins and their roles in development and disease. However, little is known about zebrafish alpha-crystallin promoter function, how it compares to that of mammals, or whether mammalian alpha-crystallin promoter activity can be assessed using zebrafish embryos. We injected a variety of alpha-crystallin promoter fragments from each species combined with the coding sequence for green fluorescent protein (GFP) into zebrafish zygotes to determine the resulting spatiotemporal expression patterns in the developing embryo. We also measured mRNA levels and protein abundance for all three zebrafish alpha-crystallins. Our data showed that mouse and zebrafish alphaA-crystallin promoters generated similar GFP expression in the lens, but with earlier onset when using mouse promoters. Expression was also found in notochord and skeletal muscle in a smaller percentage of embryos. Mouse alphaB-crystallin promoter fragments drove GFP expression primarily in zebrafish skeletal muscle, with less common expression in notochord, lens, heart and in extraocular regions of the eye. A short fragment containing only a lens-specific enhancer region increased lens and notochord GFP expression while decreasing muscle expression, suggesting that the influence of mouse promoter control regions carries over into zebrafish embryos. The two paralogous zebrafish alphaB-crystallin promoters produced subtly different expression profiles, with the aBa promoter driving expression equally in notochord and skeletal muscle while the alphaBb promoter resulted primarily in skeletal muscle expression. Messenger RNA for zebrafish alphaA increased between 1 and 2 days post fertilization (dpf), alphaBa increased between 4 and 5 dpf, but alphaBb remained at baseline levels through 5 dpf. Parallel reaction monitoring (PRM) mass spectrometry was used to detect alphaA, aBa, and alphaBb peptides in digests of zebrafish embryos. In whole embryos, alphaA-crystallin was first detected by 2 dpf, peaked in abundance by 4-5 dpf, and was localized to the eye. alphaBa was detected in whole embryo at nearly constant levels from 1-6 dpf, was also localized primarily to the eye, and its abundance in extraocular tissues decreased from 4-7 dpf. In contrast, due to its low abundance, no alphaBb protein could be detected in whole embryo, or dissected eye and extraocular tissues. Our results show that mammalian alpha-crystallin promoters can be efficiently screened in zebrafish embryos and that their controlling regions are well conserved. An ontogenetic shift in zebrafish aBa-crystallin promoter activity provides an interesting system for examining the evolution and control of tissue specificity. Future studies that combine these promoter based approaches with the expanding ability to engineer the zebrafish genome via techniques such as CRISPR/Cas9 will allow the manipulation of protein expression to test hypotheses about lens crystallin function and its relation to lens biology and disease.

Potter, D. R., Miyazawa, B. Y., Gibb, S. L., Deng, X., Togaratti, P. P., Croze, R. H., . . . Pati, S. (2017). **Mesenchymal Stem Cell Derived Extracellular Vesicles Attenuate Pulmonary Vascular Permeability and Lung Injury Induced by Hemorrhagic Shock and Trauma**. *J Trauma Acute Care Surg*. doi:10.1097/ta.0000000000001744

BACKGROUND: Mesenchymal Stem Cells (MSCs) have been shown to mitigate vascular permeability in hemorrhagic shock (HS) and trauma induced brain and lung injury. Mechanistically, paracrine factors secreted from MSCs have been identified that can recapitulate many of the potent biologic effects of MSCs in animal models of disease. Interestingly, MSC derived extracellular vesicles (EVs), contain many of these key soluble factors, and

have therapeutic potential independent of the parent cells. In this study we sought to determine whether MSC derived EVs (MSC EVs) could recapitulate the beneficial therapeutic effects of MSCs on lung vascular permeability induced by HS in mice. METHODS: MSC Extracellular vesicles (EVs) were isolated from human bone marrow derived MSCs by ultracentrifugation. A mouse model of fixed pressure hemorrhagic shock (HS) was utilized to study the effects of shock, shock + MSCs and Shock + MSC EVs on lung vascular endothelial permeability. Mice were administered MSCs, MSC EVs, or saline IV. Lung tissue was harvested and assayed for permeability, RhoA/Rac1 activation, and for differential phospho-protein expression. In vitro, human lung microvascular cells (HLMVEC) junctional integrity was evaluated by immunocytochemistry and endothelial cell impedance assays (ECIS). RESULTS: HS induced lung vascular permeability was significantly decreased by both MSC and MSC EV infusion. Phospho-protein profiling of lung tissue revealed differential activation of proteins and pathways related to cytoskeletal rearrangement and regulation of vascular permeability by MSCs and MSC EVs. Lung tissue from treatment groups demonstrated decreased activation of the cytoskeletal GTPase RhoA. In vitro, HLMVECS, MSC CM but not MSC-EVs prevented thrombin induced EC permeability as measured by ECIS and immunocytochemistry of VE-Cadherin and actin. CONCLUSION: MSCs and MSC EVs modulate cytoskeletal signaling and attenuate lung vascular permeability after HS. MSC EVs may potentially be used as a novel "stem cell free" therapeutic to treat HS induced lung injury. LEVELS OF EVIDENCE: N/A Preclinical study.

Prasad, V. (2017). **Nusinersen for Spinal Muscular Atrophy: Are We Paying Too Much for Too Little?** *JAMA Pediatr*. doi:10.1001/jamapediatrics.2017.4360

Prasad, V. (2017). **Why the US Centers for Medicare and Medicaid Services (CMS) should have required a randomized trial of Foundation Medicine (F1CDx) prior to paying for it**. *Annals of Oncology*. doi:10.1093/annonc/mdx786

Prasad, V. (2018). **Tisagenlecleucel - The first approved CAR-T-cell therapy: Implications for payers and policy makers**. *Nature Reviews Clinical Oncology, 15*(1), 11-12. doi:10.1038/nrclinonc.2017.156

Prasad, V., Kaestner, V., & Mailankody, S. (2017). **Cancer Drugs Approved Based on Biomarkers and Not Tumor Type-FDA Approval of Pembrolizumab for Mismatch Repair-Deficient Solid Cancers**. *JAMA Oncol*. doi:10.1001/jamaoncol.2017.4182

Prasad, V., & Obley, A. (2017). **Is "precision medicine" ready to use in primary care practice?** *American Family Physician, 96*(12), 769-770.

Raber, J. (2018). **Corrigendum to "Novel images and novel locations of familiar images as sensitive translational cognitive tests in humans" [Behav. Brain Res. 285 (2015) 53–59](S0166432815000637)(10.1016/j.bbr.2015.01.046)**. *Behavioural Brain Research, 339*, 305. doi:10.1016/j.bbr.2017.11.016

The author regret that reference #1 was incorrectly referenced due to an error in generating and processing of the proofs. The correct reference for #1 is "Ennaceur, A., & Delacour, J. (1988). A new one trial test for

neurobiological studies of memory in rats. Beh Brain Res, 31, 47–59. The authors would like to apologise for any inconvenience caused. © 2017

Raifman, J. R., Gebo, K. A., Mathews, W. C., Korthuis, P. T., Ghanem, K. G., Aberg, J. A., . . . Berry, S. A. (2017). **Gonorrhea and Chlamydia Case Detection Increased When Testing Increased in a Multisite US HIV Cohort, 2004-2014**. *Journal of Acquired Immune Deficiency Syndromes, 76*(4), 409-416. doi:10.1097/qai.0000000000001514

OBJECTIVES: Annual screening for gonorrhea [Neisseria gonorrhoeae (NG)] and chlamydia [Chlamydia trachomatis (CT)] is recommended for all sexually active persons living with HIV but is poorly implemented. Studies demonstrating no increases in NG and/or CT (NG/CT) case detection in clinics that successfully expanded NG/CT screening raise questions about this broad screening approach. We evaluated NG/CT case detection in the HIV Research Network during 2004-2014, a period of expanding testing. METHODS: We analyzed linear time trends in annual testing (patients tested divided by all patients in care), test positivity (patients positive divided by all tested), and case detection (the number of patients with a positive result divided by all patients in care) using multivariate repeated measures logistic regression. We determined trends overall and stratified by men who have sex with men (MSM), men who have sex exclusively with women, and women. RESULTS: Among 15,614 patients (50% MSM, 26% men who have sex exclusively with women, and 24% women), annual NG/CT testing increased from 22% in 2004 to 60% in 2014 [adjusted odds ratio (AOR) per year 1.22 (1.21-1.22)]. Despite the increase in testing, test positivity also increased [AOR per year 1.10 (1.07-1.12)], and overall case detection increased from 0.8% in 2004 to 3.9% in 2014 [AOR per year 1.20 (1.17-1.22)]. Case detection was highest among MSM but increased over time among all 3 groups. CONCLUSIONS: NG/CT case detection increased as testing expanded in the population. This supports a broad approach to NG/CT screening among persons living with HIV to decrease transmission and complications of NG/CT and of HIV.

Ramchandran, S., Protopsaltis, T. S., Sciubba, D., Scheer, J. K., Jalai, C. M., Daniels, A., . . . Ames, C. P. (2017). **Prospective multi-centric evaluation of upper cervical and infra-cervical sagittal compensatory alignment in patients with adult cervical deformity**. *European Spine Journal*. doi:10.1007/s00586-017-5395-x

PURPOSE: Reciprocal mechanisms for standing alignment have been described in thoraco-lumbar deformity but have not been studied in patients with primary cervical deformity (CD). The purpose of this study is to report upper- and infra-cervical sagittal compensatory mechanisms in patients with CD and evaluate their changes post-operatively. METHODS: Global spinal alignment was studied in a prospective database of operative CD patients. Inclusion criteria were any of the following: cervical kyphosis (CK) > 10 degrees , cervical scoliosis > 10 degrees , cSVA (C2-C7 Sagittal vertical axis) > 4 cm or CBVA (Chin Brow Vertical Angle) > 25 degrees . For this study, patients who had previous fusion outside C2 to T4 segments were excluded. Patients were sub-classified by increasing severity of cervical kyphosis [CL (cervical lordosis): < 0 degrees , CK-low 0 degrees - 10 degrees , CK-high > 10 degrees] and cSVA (cSVA-low 0-4 cm, cSVA-mid 4-6 cm, cSVA-high > 6 cm) and were compared for pre- and 3-month post-operative regional and global sagittal alignment to determine compensatory recruitment. RESULTS: 75 CD patients (mean age 61.3 years, 56% women) were included. Patients with progressively larger CK had a progressive increase in C0-C2 (CL = 34 degrees , CK-low = 37 degrees , CK-high = 44 degrees , p = 0.004), C2Slope and T1Slope-CL (p < 0.05). As the cSVA increased, there was progressive increase in C2Slope, T1Slope and TS-CL (p < 0.05) and patients compensated through increasing C0-C2 (cSVA-low = 33 degrees , cSVA-mid = 40 degrees , cSVA-high = 43 degrees , p = 0.007) and pelvic tilt (cSVA-low = 14.9 degrees , cSVA-mid = 24.1 degrees , cSVA-high = 24.9 degrees , p = 0.02). At 3 months post-op, with significant improvement in cervical alignment, there was relaxation of C0-C2 (39 degrees -35 degrees , p = 0.01) which positively correlated with magnitude of deformity correction. CONCLUSIONS: Patients with cervical malalignment compensate with upper cervical hyper-lordosis, presumably for the maintenance of horizontal gaze. As cSVA increases, patients also tend to exhibit increased pelvic retroversion. Following surgical treatment, there was relaxation of upper cervical compensation.

Ramraj, R., Garcia, A., Mosen, D., Waiwaiole, L., & Smith, N. (2017). **Utility of Fecal Calprotectin in Evaluation of Chronic Gastrointestinal Symptoms in Primary Care**. *Clinical Pediatrics*, 9922817744607. doi:10.1177/0009922817744607

Fecal calprotectin (FC) is a marker of intestinal inflammation. Data are limited on utility of routine FC testing in pediatric primary care. Participants 0 to 18 years old who had an FC test in the years 2010-2014 were retrospectively identified. Those with less than a year of follow-up or a prior diagnosis of inflammatory bowel disease (IBD) were excluded. In all, 84% (689/822) had normal FC; no participant with normal FC was diagnosed with IBD in the subsequent 12 months. Also, 16% (133/822) had elevated FC, and 31% of those (42/133) were diagnosed with IBD. FC values for IBD and non-IBD groups were 1084 microg/g (interquartile range [IQR] = 514.4-2000) and 27.05 microg/g (IQR = 15.6-62.6; P < .001), respectively. Abdominal pain was the primary indication. In this cohort, sensitivity of FC for IBD is 100%, and specificity is 88%. The FC test can be an excellent tool in the primary care setting to exclude IBD and avoid unnecessary referrals and colonoscopies.

Rao, S. V., Moran, A. E., & Graff, J. N. (2017). **Predictors of response and resistance to checkpoint inhibitors in solid tumors**. *Ann Transl Med, 5*(23), 468. doi:10.21037/atm.2017.09.35

Reidling, J. C., Relano-Gines, A., Holley, S. M., Ochaba, J., Moore, C., Fury, B., . . . Thompson, L. M. (2017). **Human Neural Stem Cell Transplantation Rescues Functional Deficits in R6/2 and Q140 Huntington's Disease Mice**. *Stem Cell Reports*. doi:10.1016/j.stemcr.2017.11.005

Huntington's disease (HD) is an inherited neurodegenerative disorder with no disease-modifying treatment. Expansion of the glutamine-encoding repeat in the Huntingtin (HTT) gene causes broad effects that are a challenge for single treatment strategies. Strategies based on human stem cells offer a promising option. We evaluated efficacy of transplanting a good manufacturing practice (GMP)-grade human embryonic stem cell-derived neural stem cell (hNSC) line into striatum of HD modeled mice. In HD fragment model R6/2 mice, transplants improve motor deficits, rescue synaptic alterations, and are contacted by nerve terminals from mouse cells. Furthermore, implanted hNSCs are electrophysiologically active. hNSCs also improved motor and late-stage cognitive impairment in a second HD model, Q140 knockin mice. Disease-modifying activity is suggested by the reduction of aberrant accumulation of mutant HTT protein and expression of brain-derived neurotrophic factor (BDNF) in both models. These findings hold promise for future development of stem cell-based therapies.

Richardson, D. M., Keller, T. E., Wolf, D. S. S., Zell, A., Morris, C., & Crespo, C. J. (2017). **BUILD EXITO: A multi-level intervention to support diversity in health-focused research**. *BMC Proceedings, 11*. doi:10.1186/s12919-017-0080-y

Background and purpose: As part of the NIH BUILD initiative to diversify the scientific workforce, the EXITO project is a large multi-institutional effort to provide comprehensive support and training for undergraduates from traditionally underrepresented student populations who aspire to health-related research careers. Portland State University, a major public urban university that prioritizes student access and opportunity, and Oregon Health & Science University, a research-intensive academic health center, lead the EXITO network comprised of eleven 2-year and 4-year institutions of higher education spanning Oregon, Washington, Alaska, Hawaii, Guam, American Samoa, and the Northern Mariana Islands. The EXITO project aims for impact in biomedical research by training diverse scholars from indigenous and underserved communities affected by adverse health disparities. Project approach: Guided by socio-ecological theory, the EXITO project is a multi-level intervention offering a three-year research training pathway for scholars in the biomedical, behavioral,

health, and social sciences. Fundamental components of the model include student outreach and engagement, integrated curricular enhancements, intensive research experiences, multi-faceted developmental mentoring, supportive community and services, and rigorous evaluation and quality improvement. EXITO also advances faculty and institutional development in these domains by holding curriculum development conferences, creating research learning communities, awarding pilot project research funding, providing mentor training and ongoing support, collaborating with other research equity programs, and developing campus infrastructure and services to support scholars with diverse backgrounds and needs. Highlights: The large and geographically broad network of EXITO institutions engages a range of diverse students, including indigenous populations and students beginning post-secondary education at community colleges. The EXITO model specifically accommodates many students transferring from 2-year partner institutions and facilitates seamless transfer to the 4-year institution. EXITO features several approaches to research training, including supported summer entry into research placements, the incorporation of responsible conduct of research content into general education curriculum, and the intentional matching of scholars with three types of mentors (e.g., peer, career, research). Implications: EXITO provides an example of a comprehensive research training initiative for traditionally underrepresented students that can be implemented across a diverse range of 2-year and 4-year institutions. © 2017 The Author(s).

Riddle, M. C. (2018). **In an Anniversary Year, Diabetes Care Takes a Selfie**. *Diabetes Care, 41*(1), 3-5. doi:10.2337/dci17-0054

Riddle, M. C., Bolli, G. B., Avogaro, A., Alvarez, M. G., Merino-Trigo, A., Boelle-Le Corfec, E., & Home, P. D. (2017). **Assessment of hypoglycaemia during basal insulin therapy: Temporal distribution and risk of events using a predefined or an expanded definition of nocturnal events**. *Diabetes and Metabolism*. doi:10.1016/j.diabet.2017.12.001

AIM: To describe in type 2 diabetes the 24-hour distribution of hypoglycaemia and compare the frequency of nocturnal events based on a predefined nocturnal window or an expanded interval, using illustrative data for two insulin glargine formulations. METHODS: Temporal distribution of hypoglycaemic events was assessed descriptively and by profile using participant-level data from three randomized trials comparing insulin glargine 300 U/mL (Gla-300) and 100 U/mL (Gla-100). Risk of hypoglycaemia and annualized event rates were compared for the predefined nocturnal interval (00:00 to 05:59h) and an expanded window (22:00h to the pre-breakfast glucose measurement). RESULTS: Confirmed (</=3.9mmol/L [</=70 mg/dL]) or severe hypoglycaemic events were reported most frequently between 06:00 and 10:00 h with both insulins. Nearly threefold more events were identified using the expanded nocturnal interval. Risk of >/=1 nocturnal event was 25% lower with Gla-300 than Gla-100 with the predefined, and 16% lower with the expanded interval; annualized event rates were 31% and 24% lower with the predefined and expanded window, respectively. The between-insulin difference in number of nocturnal events depended markedly on the chosen nocturnal interval (556 vs. 1145 fewer events with Gla-300 using the predefined vs. expanded interval). CONCLUSIONS: The predefined 00:00-05:59h nocturnal interval excluded many hypoglycaemic events occurring during the actual overnight interval. While Gla-300 reduced hypoglycaemic events versus Gla-100 (regardless of the interval considered), the results obtained using the expanded window better reflect the clinical experience of people treated with basal insulin.

Rivera, H. M., & Stincic, T. L. (2017). **Estradiol and the control of feeding behavior**. *Steroids*. doi:10.1016/j.steroids.2017.11.011

This review lays out the evidence for the role of E2 in homeostatic and hedonic feeding across several species. While significant effort has been expended on homeostatic feeding research, more studies for hedonic feeding need to be conducted (i.e. are there increases in meal size and enhanced motivation to natural food

rewards). By identifying the underlying neural circuitry involved, one can better delineate the mechanisms by which E2 influences feeding behavior. By utilizing more selective neural targeting techniques, such as optogenetics, significant progress can be made toward this goal. Together, behavioral and physiological techniques will help us to better understand neural deficits that can increase the risk for obesity in the absence of E2 (menopause) and aid in developing therapeutic strategies. © 2017 Elsevier Inc.

Robbeloth, H., Ragucci, M., & DeShazo, K. (2017). **Evidence-Based Acquisition: A Real Life Account of Managing the Program Within The Orbis Cascade Alliance**. *Serials Librarian, 73*(3-4), 240-247. doi:10.1080/0361526X.2017.1388331

In 2015 the Orbis Cascade Alliance investigated a consortium wide evidence-based acquisition (EBA) model to incorporate into its established eBook program, and began a pilot of Wiley's Usage Based Collection Management Model. EBA is an acquisition model that grants library patrons access to a title list over an agreed-upon time period for a pre-negotiated amount of money, and titles from that list are then selected for purchase based on the evidence of usage from the initial access period. This article shares the consortium's experiences evaluating usage, managing titles and records, controlling duplication, predicting costs, and the inclusion of MARC records to enhance discoverability. ©, Published with license by Taylor & Francis Group, LLC © 2017 Hilary Robbeloth, Matthew Ragucci and Kristina DeShazo.

Roberts, S., & Ullman, B. (2017). **Parasite polyamines as pharmaceutical targets**. *Current Pharmaceutical Design, 23*(23), 3325-3341. doi:10.2174/1381612823666170601101644

There is an urgent need for the identification and validation of new therapeutic targets in protozoan parasites because currently available drugs are limited in number and usefulness, and no vaccines are available. The discovery that alpha-difluoromethylornithine, an inhibitor of polyamine biosynthesis, is an efficacious treatment for African Sleeping Sickness caused by the protozoan parasite Trypanosoma brucei, has validated the polyamine pathway as a target in protozoan parasites. Polyamines are ubiquitous organic cations that play critical roles in key cellular processes such as growth, differentiation, and macromolecular biosynthesis. In recent years, remarkable progress has been made in the characterization of the polyamine pathway in a variety of protozoan parasites and this review will highlight surprising and unique features that could lead to new therapeutic strategies. © 2017 Bentham Science Publishers.

Roberts, V. H. J., Lo, J. O., Lewandowski, K. S., Blundell, P., Grove, K. L., Kroenke, C. D., . . . Frias, A. E. (2018). **Adverse Placental Perfusion and Pregnancy Outcomes in a New Nonhuman Primate Model of Gestational Protein Restriction**. *Reproductive Sciences, 25*(1), 110-119. doi:10.1177/1933719117704907

Maternal malnutrition during pregnancy impacts fetal growth, with developmental consequences that extend to later life outcomes. In underdeveloped countries, this malnutrition typically takes the form of poor dietary protein content and quality, even if adequate calories are consumed. Here, we report the establishment of a nonhuman primate model of gestational protein restriction (PR) in order to understand how placental function and pregnancy outcomes are affected by protein deficiency. Rhesus macaques were assigned to either a control diet containing 26% protein or switched to a 13% PR diet prior to conception and maintained on this PR diet throughout pregnancy. Standard fetal biometry, Doppler ultrasound of uteroplacental blood flow, ultrasound-guided amniocentesis, and contrast-enhanced ultrasound (CE-US) to assess placental perfusion were performed mid-gestation (gestational day 85 [G85] where term is G168) and in the early third trimester (G135). Our data demonstrate that a 50% reduction in dietary protein throughout gestation results in reduced placental perfusion, fetal growth restriction, and a 50% rate of pregnancy loss. In addition, we demonstrate reduced total protein content and evidence of fetal hypoxia in the amniotic fluid. This report highlights the use of CE-US for in vivo assessment of placental vascular function. The ability to detect placental dysfunction, and thus a compromised pregnancy, early in gestation, may facilitate the

development of interventional strategies to optimize clinical care and improve long-term offspring outcomes, which are future areas of study in this new model. © 2017, © The Author(s) 2017.

Robinson, B. R. H., Cohen, M. J., Holcomb, J. B., Pritts, T. A., Gomaa, D., Fox, E. E., . . . Bulger, E. M. (2017). **Risk Factors for the Development of Acute Respiratory Distress Syndrome Following Hemorrhage**. *Shock*. doi:10.1097/shk.0000000000001073

BACKGROUND: The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study evaluated the effects of plasma and platelets on hemostasis and mortality after hemorrhage. The pulmonary consequences of resuscitation strategies that mimic whole blood, remain unknown. METHODS: A secondary analysis of the PROPPR study was performed. Injured patients predicted to receive a massive transfusion were randomized to 1:1:1 vs. 1:1:2 plasma-platelet-RBC ratios at 12 Level I North American trauma centers. Patients with survival >24 hours, an ICU stay, and a recorded PaO2/FiO2 (P/F) ratio were included. ARDS was defined as a P/F ratio < 200, with bilateral pulmonary infiltrates, and adjudicated by investigators. RESULTS: 454 patients were reviewed (230 received 1:1:1, 224 1:1:2). Age, sex, injury mechanism, and regional abbreviated injury scale (AIS) scores did not differ between cohorts. Tidal volume, PEEP, and lowest P/F ratio did not differ. No significant differences in ARDS rates (14.8 vs. 18.4%), ventilator-free (24 vs. 24) or ICU-free days (17.5 vs. 18), hospital length of stay (22 vs. 18 days), or 30-day mortality were found (28 vs. 28%). ARDS was associated with blunt injury (OR 3.61 [1.53-8.81] p < 0.01) and increasing chest AIS (OR 1.40 [1.15-1.71] p < 0.01). Each 500 mL of crystalloid infused during hours 0-6 was associated with a 9% increase in the rate of ARDS (OR 1.09 [1.04-1.14] p < 0.01). Blood given at 0-6 or 7-24 hours were not risk factors for lung injury. CONCLUSION: Acute crystalloid exposure, but not blood products, is a potentially modifiable risk factor for the prevention of ARDS following hemorrhage.

Rodriguez, M. I., Gaffield, M. E., Han, L., & Caughey, A. B. (2017). **Re-Evaluating the Possible Increased Risk of HIV Acquisition With Progestin-Only Injectables Versus Maternal Mortality and Life Expectancy in Africa: A Decision Analysis**. *Glob Health Sci Pract, 5*(4), 581-591. doi:10.9745/ghsp-d-17-00243

OBJECTIVE: The association between increased risk of HIV acquisition and use of progestin-only injectables (POIs) is controversial. We sought to compare the competing risks of maternal mortality and HIV acquisition with use of POIs using updated data on this association and considering an expanded number of African countries. METHODS: We designed a decision-analytic model to compare the benefits and risks of POIs on the competing risks of maternal mortality and HIV acquisition on life expectancy for women in 9 African countries. For the purposes of this analysis, we assumed that POIs were associated with an increased risk of HIV acquisition (hazards ratio of 1.4). Our primary outcome was life-years and the population was women of reproductive age (15-49 years) in these countries, who did not have HIV infection and were not currently planning a pregnancy. Probabilities for each variable included in the model, such as HIV incidence, access to antiretroviral therapy, and contraceptive prevalence, were obtained from the literature. Univariate and multivariate sensitivity analyses were performed to check model assumptions and explore how uncertainty in estimates would affect the model results. RESULTS: In all countries, discontinuation of POIs without replacement with an equally effective contraceptive method would result in decreased life expectancy due to a significant increase in maternal deaths. While the removal of POIs from the market would result in the prevention of some new cases of HIV, the life-years gained from this are mitigated due to the marked increase in neonatal HIV cases and maternal mortality with associated life-years lost. In all countries, except South Africa, typical-use contraceptive failure rates with POIs would need to exceed 39%, and more than half of women currently using POIs would have to switch to another effective method, for the removal of POIs to demonstrate an increase in total life-years. CONCLUSION: Women living in sub-Saharan Africa cope with both high rates of HIV infection and high rates of pregnancy-related maternal death relative to the rest of the world. Based on the most current estimates, our model suggests that removal of POI contraception from the market without effective and acceptable contraception replacement would have a net negative effect on maternal health, life expectancy, and mortality under a variety of scenarios.

Rogers, T. S., Harrison, S., Swanson, C., Cauley, J. A., Barrett-Connor, E., Orwoll, E., . . . Lane, N. E. (2017). **Rest-activity circadian rhythms and bone mineral density in elderly men**. *Bone Rep, 7*, 156-163. doi:10.1016/j.bonr.2017.11.001

Background: Disrupted rest-activity circadian rhythm (RAR) patterns have been associated with poor health outcomes (i.e. diminished cognitive function, increased risk of dementia and falls). Circadian time cues in bone influence the differentiation of osteoblasts and osteoclasts, and bone turnover markers exhibit circadian variation; relationships between bone outcomes and RAR are emerging areas of research. We evaluated associations between RAR and areal bone mineral density (aBMD) at the total hip and femoral neck in older men from the Osteoporotic Fractures in Men (MrOS) cohort. We hypothesized that weaker RAR patterns would be associated with lower aBMD. Methods: MrOS is an ongoing prospective cohort study following ambulatory men >/= 65 years (n = 5994) at 6 U.S. clinics (baseline enrollment 3/2000-4/2002); participants for this analysis are from an ancillary study, Outcomes of Sleep Disorders in Older Men (MrOS Sleep). We included data from men who had technically adequate measures of RAR and aBMD at Sleep Visit 1 (12/2003-3/2005), with repeat aBMD at core Visit 3 (3/2007-3/2009) (n = 2412; mean age at Sleep Visit 1: 75.7 +/- 5.2 years). aBMD was measured by dual energy x-ray absorptiometry (DXA). Actigraphs worn on the non-dominant wrist were used to collect circadian activity data over 4.8 +/- 0.8 consecutive 24-hour periods. An extension of the traditional cosine curve was used to fit RAR to the activity data [Ancoli-Israel et al., 2003; Marler et al., 2006]. Six RAR parameters were evaluated: acrophase (time of peak activity), amplitude (rhythm strength), mesor (mean of activity fitted curve), pseudo F-statistic (overall circadian rhythmicity of rest and activity), alpha statistic (daytime to nighttime activity ratio), and beta statistic (daytime activity). Associations between RAR and aBMD (Sleep Visit 1), and RAR and DeltaaBMD (Sleep Visit 1-Visit 3) were assessed with generalized linear models. Covariates included age, clinic site, physical activity, race, comorbidity, body mass index (BMI), smoking, alcohol, caffeine, beta blocker use, serum 25(OH) vitamin D and urinary melatonin and calcium. Results: Pseudo F-statistic was significantly associated with total hip aBMD (p-trend = 0.009), femoral neck aBMD (p-trend = 0.007) and total hip DeltaaBMD (p-trend = 0.017) in minimally adjusted models but not after multivariate (MV) adjustment. Alpha statistic was significantly associated with femoral neck aBMD (p-trend = 0.029) and femoral neck DeltaaBMD (p-trend = 0.019) in minimally adjusted models; significance was retained in the femoral neck DeltaaBMD model (p-trend = 0.034) after MV adjustment. There were no consistent, significant associations between the other RAR variables and aBMD or DeltaaBMD. Conclusions: The data demonstrate modest associations between overall circadian rhythmicity of rest and activity (measured by pseudo F-statistic), as well as daytime to nighttime activity ratio (measured by alpha statistic), aBMD and DeltaaBMD, but adjustment for covariates related to lifestyle, BMI and comorbidities attenuated most of these associations. These results suggest that RAR patterns are not independently associated with aBMD or four-year DeltaaBMD at the total hip or femoral neck in older men, but additional research is needed.

Roh-Johnson, M., Shah, A. N., Stonick, J. A., Poudel, K. R., Kargl, J., Yang, G. H., . . . Moens, C. B. (2017). **Macrophage-Dependent Cytoplasmic Transfer during Melanoma Invasion In Vivo**. *Developmental Cell, 43*(5), 549-562.e546. doi:10.1016/j.devcel.2017.11.003

Interactions between tumor cells and tumor-associated macrophages play critical roles in the initiation of tumor cell motility. To capture the cellular interactions of the tumor microenvironment with high-resolution imaging, we directly visualized tumor cells and their interactions with macrophages in zebrafish. Live imaging in zebrafish revealed that macrophages are dynamic, yet maintain sustained contact with tumor cells. In addition, the recruitment of macrophages to tumor cells promotes tumor cell dissemination. Using a Cre/LoxP strategy, we found that macrophages transfer cytoplasm to tumor cells in zebrafish and mouse models. Remarkably, macrophage cytoplasmic transfer correlated with melanoma cell dissemination. We further found that macrophages transfer cytoplasm to tumor cells upon cell contact in vitro. Thus, we present a model in which macrophage/tumor cell contact allows for the transfer of cytoplasmic molecules from macrophages to tumor cells corresponding to increased tumor cell motility and dissemination.

Romer Thomsen, K., Blom Osterland, T., Hesse, M., & Feldstein Ewing, S. W. (2017). **The intersection between response inhibition and substance use among adolescents**. *Addict Behav, 78*, 228-230. doi:10.1016/j.addbeh.2017.11.043

Problems related to the capacity to successfully engage response inhibition are considered a risk factor for the development of substance use disorders (SUDs), but the evidence has been predominantly cross-sectional. In this commentary, we argue that recent longitudinal studies with multi-modal measures of response inhibition can improve understanding of how response inhibition may intersect with substance use among adolescents. Most Stop-Signal studies suggest that slower response inhibition predicts substance use progressions, with one multi-site study showing greater fronto-parietal activity indicative of risk. Most Go-NoGo studies suggest that blunted activation of prefrontal cortical areas during response inhibition predicts substance use progressions, while commission errors are less effective in identifying adolescents at risk. Studies differ in subject populations, outcome measures, statistical methods, and BOLD response contrasts, which challenge the capacity to compare and generalize findings. We encourage research teams throughout the globe to undertake multi-modal, longitudinal studies to assess brain functioning with large sample sizes, and when possible, before significant substance use potentially obscures interpretation of findings. Systematic review and meta-analysis of this growing literature are also important goals for future research.

Roselli, C. E. (2017). **Neurobiology of Gender Identity and Sexual Orientation**. *Journal of Neuroendocrinology*. doi:10.1111/jne.12562

Sexual identity and sexual orientation are independent components of a person's sexual identity. These dimensions are most often in harmony with each other and with an individual's genital sex, but not always. This review discusses the relationship of sexual identity and sexual orientation to prenatal factors that act to shape the development of the brain and the expression of sexual behaviors in animals and humans. One major influence discussed relates to organizational effects that the early hormone environment exerts on both gender identity and sexual orientation. Evidence that gender identity and sexual orientation are masculinized by prenatal exposure to testosterone and feminized in it absence is drawn from basic research in animals, correlations of biometric indices of androgen exposure and studies of clinical conditions associated with disorders in sexual development. There are, however, important exceptions to this theory that have yet to be resolved. Family and twin studies indicate that genes play a role, but no specific candidate genes have been identified. Evidence that relates to the number of older brothers implicates maternal immune responses as a contributing factor for male sexual orientation. It remains speculative how these influences might relate to each other and interact with postnatal socialization. Nonetheless, despite the many challenges to research in this area, existing empirical evidence makes it clear that there is a significant biological contribution to the development of an individual's sexual identity and sexual orientation. This article is protected by copyright. All rights reserved.

Ross, A. M., Ilic, K., Kiyoshi-Teo, H., & Lee, C. S. (2017). **Psychometric analysis of the leadership environment scale (LENS): Outcome from the Oregon research initiative on the organisation of nursing (ORION)**. *Journal of Nursing Management*. doi:10.1111/jonm.12572

AIM: The purpose of this study was to establish the psychometric properties of the new 16-item leadership environment scale. BACKGROUND: The leadership environment scale was based on complexity science concepts relevant to complex adaptive health care systems. METHODS: A workforce survey of direct-care nurses was conducted (n = 1,443) in Oregon. Confirmatory factor analysis, exploratory factor analysis, concordant validity test and reliability tests were conducted to establish the structure and internal consistency of the leadership environment scale. RESULTS: Confirmatory factor analysis indices approached acceptable thresholds of fit with a single factor solution. Exploratory factor analysis showed improved fit with a two-factor model solution; the factors were labelled 'influencing relationships' and 'interdependent system supports'. Moderate to strong convergent validity was observed between the leadership environment

scale/subscales and both the nursing workforce index and the safety organising scale. Reliability of the leadership environment scale and subscales was strong, with all alphas >/=.85. CONCLUSIONS: The leadership environment scale is structurally sound and reliable. IMPLICATIONS FOR NURSING MANAGEMENT: Nursing management can employ adaptive complexity leadership attributes, measure their influence on the leadership environment, subsequently modify system supports and relationships and improve the quality of health care systems. The leadership environment scale is an innovative fit to complex adaptive systems and how nurses act as leaders within these systems.

Ross, D. A., & Bridges, K. J. (2017). **Technique of Minimally Invasive Cervical Foraminotomy**. *Oper Neurosurg (Hagerstown), 13*(6), 693-701. doi:10.1093/ons/opx053

BACKGROUND: Posterior cervical foraminotomy is a long utilized and commonly performed procedure, but has been supplanted in many cases by anterior procedures. With the advent of minimally invasive techniques, posterior foraminotomy may again deserve a prominent place in the treatment of cervical foraminal stenosis. OBJECTIVE: To report in detail a successfully utilized minimally invasive technique and the results in a large series of patients, by a single author. METHODS: The technique is described and illustrated in detail. A retrospective review of the use of this technique in a large series is reported. RESULTS: Precise details of the technique are described with specific attention to complication avoidance. In over 360 cases, there have been no nerve root injuries other than idiopathic C5 palsies, no wound infections, and a single durotomy that required no specific treatment. CONCLUSION: Minimally invasive posterior cervical foraminotomy is a well-tolerated and effective procedure which can be performed with minimal complications when attention to detail is maintained.

Ross, S. M., Catena, M., Twardzik, E., Hospodar, C., Cook, E., Ayyagari, A., . . . Logan, S. W. (2017). **Feasibility of a Modified Ride-on Car Intervention on Play Behaviors during an Inclusive Playgroup**. *Physical & Occupational Therapy in Pediatrics*, 1-17. doi:10.1080/01942638.2017.1400491

AIMS: Children with mobility related disabilities often experience limited participation and access to social interactions. An emerging pediatric powered mobility device are modified ride-on cars that provide self-directed mobility experiences to children with disabilities. This study aimed to determine: (1) the feasibility of a modified ride-on car intervention during an inclusive playgroup, (2) the effect of a modified ride-on car intervention on the play behaviors of children with and without mobility related disabilities. METHOD: A single-subject research design was implemented. Thirteen children participated in a weekly inclusive playgroup. The five children with mobility related disabilities were provided modified ride-on cars during the intervention. Children's play behaviors were classified with Howes' Peer Play Scale. Intervention effects were examined using nonoverlap of all pairs (NAP). RESULTS: The intervention was feasible based on participants' good attendance, retention rates, and successful use of modified ride-on cars. Overall children did not experience significant changes in play behaviors, with a few exceptions for decreased solitary, and increased parallel play, and/or direct peer interaction, among children with mobility related disabilities. Future research could examine modified ride-on car use by children with mobility related disabilities focusing on changes in unique play interactions between children with and without disabilities.

Sadhu, J. M., Lee, P. C., Stewart, C., Carson, N. J., Usher, C., Maneta, E., . . . Jacobson, S. L. (2017). **Lessons from the Launch: Program Directors Reflect on Implementing the Child and Adolescent Psychiatry Milestones**. *Academic Psychiatry*. doi:10.1007/s40596-017-0852-8

Sadovsky, Y., Caughey, A. B., DiVito, M., D'Alton, M. E., & Murtha, A. P. (2017). **Research to knowledge: Promoting the training of physician-scientists in the biology of pregnancy**. *American Journal of Obstetrics and Gynecology*. doi:10.1016/j.ajog.2017.09.024

Common disorders of pregnancy, such as preeclampsia, preterm birth, and fetal growth abnormalities, continue to challenge perinatal biologists seeking insights into disease pathogenesis that will result in better diagnosis, therapy, and disease prevention. These challenges have recently been intensified with discoveries that associate gestational diseases with long-term maternal and neonatal outcomes. Whereas modern high-throughput investigative tools enable scientists and clinicians to noninvasively probe the maternal-fetal genome, epigenome, and other analytes, their implications for clinical medicine remain uncertain. Bridging these knowledge gaps depends on strengthening the existing pool of scientists with expertise in basic, translational, and clinical tools to address pertinent questions in the biology of pregnancy. Although PhD researchers are critical in this quest, physician-scientists would facilitate the inquiry by bringing together clinical challenges and investigative tools, promoting a culture of intellectual curiosity among clinical providers, and helping transform discoveries into relevant knowledge and clinical solutions. Uncertainties related to future administration of health care, federal support for research, attrition of physician-scientists, and an inadequate supply of new scholars may jeopardize our ability to address these challenges. New initiatives are necessary to attract current scholars and future generations of researchers seeking expertise in the scientific method and to support them, through mentorship and guidance, in pursuing a career that combines scientific investigation with clinical medicine. These efforts will promote breadth and depth of inquiry into the biology of pregnancy and enhance the pace of translation of scientific discoveries into better medicine and disease prevention.

Saluja, S., Nwomeh, B., Finlayson, S. R. G., Holterman, A. L., Jawa, R. S., Jayaraman, S., . . . Shrime, M. G. (2017). **Guide to research in academic global surgery: A statement of the Society of University Surgeons Global Academic Surgery Committee**. *Surgery*. doi:10.1016/j.surg.2017.10.013

Global surgery is an emerging academic discipline that is developing in tandem with numerous policy and advocacy initiatives. In this regard, academic global surgery will be crucial for measuring the progress toward improving surgical care worldwide. However, as a nascent academic discipline, there must be rigorous standards for the quality of work that emerges from this field. In this white paper, which reflects the opinion of the Global Academic Surgery Committee of the Society for University Surgeons, we discuss the importance of research in global surgery, the methodologies that can be used in such research, and the challenges and benefits associated with carrying out this research. In each of these topics, we draw on existing examples from the literature to demonstrate our points. We conclude with a call for continued, high-quality research that will strengthen the discipline's academic standing and help us move toward improved access to and quality of surgical care worldwide.

Sanborn, R. E., Ross, H. J., Aung, S., Acheson, A., Moudgil, T., Puri, S., . . . Fox, B. A. (2017). **A pilot study of an autologous tumor-derived autophagosome vaccine with docetaxel in patients with stage IV non-small cell lung cancer**. *J Immunother Cancer, 5*(1), 103. doi:10.1186/s40425-017-0306-6

BACKGROUND: Tumor-derived autophagosome vaccines (DRibbles) have the potential to broaden immune response to poorly immunogenic tumors. METHODS: Autologous vaccine generated from tumor cells harvested from pleural effusions was administered to patients with advanced NSCLC with the objectives of assessing safety and immune response. Four patients were vaccinated and evaluable for immune response; each received two to four doses of vaccine. Study therapy included two cycles of docetaxel 75 mg/m(2) on days 1 and 29 to treat the tumor, release hidden antigens and produce lymphopenia. DRibbles were to be administered intradermally on days 14, 43, 57, 71, and 85, together with GM-CSF (50 mug/d x 6d, administered via SQ mini pump). Peripheral blood was tested for immune parameters at baseline and at each vaccination. RESULTS: Three of four patients had tumor cells available for testing. Autologous tumor-specific immune response was seen in two of the three, manifested by IL-5 (1 patient after 3 doses), and IFN-gamma, TNF-alpha, IL-5, IL-10 (after 4 doses in one patient). All 4 patients had evidence of specific antibody responses against potential tumor antigens. All patients came off study after 4 or fewer vaccine treatments due to progression of disease. No significant immune toxicities were seen during the course of the study. CONCLUSIONS: DRibble

vaccine given with GM-CSF appeared safe and capable of inducing an immune response against tumor cells in this small, pilot study. There was no evidence of efficacy in this small poor-prognosis patient population, with treatment not feasible. Trial registration NCT00850785, initial registration date February 23, 2009.

Sanders, D. B., Juel, V. C., Harati, Y., Smith, A. G., Peltier, A. C., Marburger, T., . . . Jacobus, D. P. (2017). **3,4-Diaminopyridine Base Effectively Treats the Weakness of Lambert-Eaton Myasthenia**. *Muscle Nerve*. doi:10.1002/mus.26052

INTRODUCTION: 3,4-diaminopyridine has been used to treat Lambert Eaton myasthenia (LEM) for thirty years despite the lack of conclusive evidence of efficacy. METHODS: We conducted a randomized double-blind placebo-controlled withdrawal study in LEM patients who had been on stable regimens of 3,4-diaminopyridine base (3,4-DAP) for >/= 3 months. The primary efficacy endpoint was >30% deterioration in Triple Timed Up-and-Go (3TUG) times during tapered drug withdrawal. The secondary endpoint was self-assessment of LEM-related weakness (W-SAS). RESULTS: 32 participants were randomized to continuous 3,4-DAP or placebo. None of the 14 receiving continuous 3,4-DAP had >30% deterioration in 3TUG time vs 72% of the 18 who tapered to placebo ($p<0.0001$). W-SAS similarly demonstrated an advantage for continuous treatment over placebo ($p<0.0001$). Need for rescue and adverse events were more common in the placebo group. DISCUSSION: This trial provides significant evidence of efficacy of 3,4-DAP in the maintenance of strength in LEM.

Saraceni, M. M., Scott, E., Maziarz, R. T., Siegel, M. B., Bassale, S., Jiing, S., & Medvedova, E. (2017). **Modified HyperCVAD Versus Bortezomib-HyperCAD in Patients With Relapsed/Refractory Multiple Myeloma**. *Clinical Lymphoma, Myeloma and Leukemia*. doi:10.1016/j.clml.2017.10.008

Introduction: Multiple myeloma (MM) is an incurable plasma cell malignancy, in which aggressive relapses might require salvage cytotoxic infusional chemotherapy. Several clinical trials that reported the efficacy of bortezomib led to institutional practice changes in which vincristine was replaced with bortezomib in the modified hyperCVAD regimen, creating a new treatment regimen, named "bortezomib-hyperCAD.". Patients and Methods: We retrospectively describe the effectiveness and tolerability of 2 chemotherapy regimens among 33 patients with relapsed and/or refractory MM. Patients who received ≥ 1 cycle of modified hyperCVAD or bortezomib-hyperCAD between 2011 and 2015 were assessed. Results: The median number of cycles administered in each arm was 2. The overall response rate was 40% (6 partial responses) in the modified hyperCVAD group and 44.4% (1 complete response, 1 very good partial response, and 6 partial responses) in the bortezomib-hyperCAD group (Fisher exact P = .80). Median progression-free survival (PFS) and median overall survival (OS) for patients in the modified hyperCVAD group was 6.3 months and 11.1 months, respectively. This was comparable with patients in the bortezomib-hyperCAD group, who had a median PFS of 6.6 months and a median OS of 13.8 months (log rank P = .54 and .66, respectively). There was no statistically significant association between treatment arm and febrile neutropenia, emergency department visits, hospitalizations, or peripheral neuropathy (all Fisher exact P values > .05). Conclusion: Overall effectiveness and tolerability outcomes were similar between modified hyperCVAD and bortezomib-hyperCAD, with both regimens showing an impressive response rate among refractory and heavily pretreated patients with relapsed MM.

Shah, S. L., Anderson, J. C., Shatzel, J. J., Toor, A., & Dickson, R. C. (2017). **The Epidemiology and Clinical Associations of Portal Vein Thrombosis in Hospitalized Patients With Cirrhosis: A Nationwide Analysis From the National Inpatient Sample**. *Journal of Hospital Medicine*. doi:10.12788/jhm.2888

Background: objective: design, setting, patients: intervention: measurements: conclusions:

Shanks, J. D., Izumi, B., Sun, C., Martin, A., & Byker Shanks, C. (2017). **Teaching Undergraduate Students to Visualize and Communicate Public Health Data with Infographics**. *Front Public Health, 5*, 315. doi:10.3389/fpubh.2017.00315

The purpose of this study was to explore the degree to which an infographic assignment facilitated student learning around health science issues, as well as the ways in which the assignment was an effective teaching tool. The objectives of the assignment were to (1) understand the purposes of and potential uses for infographics, (2) cultivate creative visual communication skills, and (3) disseminate a complex health topic to diverse audiences. The infographic assignment was developed at Montana State University and piloted at Portland State University. Students were assigned to small groups of three or four to create an infographic focused on a health science issue. The assignment was divided into four steps: brainstorming, developing, designing, and finalizing. Focus groups were conducted to assess how learning occurred throughout the assignment and identify any opportunities for modification of the assignment. This study was conducted with freshman students enrolled at Portland State University, a public university located in downtown Portland, OR, USA. Thirty four students completed the assignment and 31 students participated in one of three focus groups. Four themes emerged from focus groups: (1) Communicating Science-Related Topics to Non-experts, (2) Developing Professional Skills, (3) Understanding Health Issues, and (4) Overall Experience. This article outlines the assignment, discusses focus group results, and presents assignment modifications. It is clear that the infographic assignment facilitated learning about accessing and translating data. This assignment is ideally suited for use with diverse college-age audiences in health education and health promotion fields.

Shaw, C. M., Shah, S., Kapoor, B. S., Cain, T. R., Caplin, D. M., Farsad, K., . . . Lorenz, J. M. (2017). **ACR Appropriateness Criteria® Radiologic Management of Central Venous Access**. *Journal of the American College of Radiology, 14*(11), S506-S529. doi:10.1016/j.jacr.2017.08.053

Obtaining central venous access is one of the most commonly performed procedures in hospital settings. Multiple devices such as peripherally inserted central venous catheters, tunneled central venous catheters (eg, Hohn catheter, Hickman catheter, C. R. Bard, Inc, Salt Lake City UT), and implantable ports are available for this purpose. The device selected for central venous access depends on the clinical indication, duration of the treatment, and associated comorbidities. It is important for health care providers to familiarize themselves with the types of central venous catheters available, including information about their indications, contraindications, and potential complications, especially the management of catheters in the setting of catheter-related bloodstream infections. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.

Sheean, A. J., Hartzler, R. U., Denard, P. J., Ladermann, A., Sanders, T. G., Zlatkin, M. B., & Burkhart, S. S. (2017). **Preoperative Radiographic Risk Factors for Incomplete Arthroscopic Supraspinatus Tendon Repair in Massive Rotator Cuff Tears**. *Arthroscopy*. doi:10.1016/j.arthro.2017.09.046

PURPOSE: To determine if preoperative imaging findings of massive rotator cuff (RC) tears were associated with (1) incomplete arthroscopic repair and (2) the use of advanced mobilization techniques (interval slides) and/or the use of a load-sharing rip stop repair construct. METHODS: Eighty-six consecutive patients who underwent arthroscopic repair for massive RC tears performed by a single surgeon between July 2013 and July 2015 were retrospectively evaluated. Previously proposed radiographic risk factors for irreparability (acromiohumeral distances, tangent sign, and the Goutallier stage of fatty infiltration for the supraspinatus) were analyzed. Associations between preoperative imaging characteristics and intraoperative results of RC

surgery were determined using binary logistic regressions and Fisher's exact tests. The interobserver reliability of imaging characteristics was determined using intraclass correlation coefficients (ICCs). RESULTS: Seventy-six massive RC tears were fully reparable (88%). In the case of 10 RC tears (12%), a complete repair was not obtained. Inability to obtain a complete repair of the supraspinatus was associated with a positive tangent sign (30% irreparable) versus a negative tangent sign (6.3% irreparable, odds ratio [OR] = 6.3, P = .0102) and with Goutallier grade 3-4 fatty infiltration of the supraspinatus (42.9% irreparable) versus grade 0-2 fatty infiltration (5.7% irreparable, OR = 11.8, P = .001). Advanced arthroscopic techniques (interval slides or load-sharing rip stop) for dealing with poor-quality or retracted tendon were used in 62% of cases; however, no associations were found between preoperative imaging characteristics and these techniques. Interobserver reliability was moderate (ICC = 0.75-0.90) for the tangent sign (ICC = 0.78) and high-grade (Goutallier 3-4) fatty infiltration of the supraspinatus (ICC = 0.74). CONCLUSIONS: A positive tangent sign and/or high-grade fatty infiltration (Goutallier 3-4) of the supraspinatus were risk factors for incomplete RC repair. However, these were not completely predictive of reparability because the majority of massive RC tears with these imaging characteristics were still fully reparable. LEVEL OF EVIDENCE: Level IV, therapeutic case series.

Shi, M., Flores, B., Li, P., Gillings, N., McMillan, K. L., Ye, J., . . . Hu, M. C. (2017). **Effects of Erythropoietin Receptor Activity on Angiogenesis, Tubular Injury and Fibrosis in Acute Kidney Injury: A "U-Shaped" Relationship**. *Am J Physiol Renal Physiol*, ajprenal.00306.02017. doi:10.1152/ajprenal.00306.2017

Erythropoietin receptor (EpoR) is widely expressed but its renoprotective action is unexplored. To examine the role of EpoR in vivo in the kidney, we induced acute kidney injury (AKI) by ischemia-reperfusion in mice with different EpoR bioactivities in the kidney. EpoR bioactivity was reduced by knock-in of wild type human EpoR, which is hypo-functional relative to murine EpoR, and a renal tubule-specific EpoR knockout. These mice had lower EPO/EpoR activity and lower autophagy flux in renal tubules. Upon AKI induction, they exhibited worse renal function and structural damage, and more apoptosis at the acute stage (< 7 days), and slower recovery with more tubulointerstitial fibrosis at the subacute stage (14 days). In contrast, mice with hyperactive EpoR signaling from knock-in of a constitutively active human EpoR had higher autophagic flux, milder kidney damage and better renal function at the acute stage, but surprisingly, worse tubulointerstitial fibrosis and renal function at the subacute stage. Either excess or deficient EpoR activity in the kidney was associated with abnormal peritubular capillaries and tubular hypoxia, creating a "U-shape" relationship. The direct effects of EpoR on tubular cells were confirmed ex vivo by a hydrogen peroxide model using primary cultured proximal tubule cells with different EpoR activities. In summary, normal EPO/EpoR signaling in renal tubules provides defense against renal tubular injury, maintains the autophagy-apoptosis balance and peritubular capillary integrity. High and low EPO/EpoR bioactivities both lead to vascular defect, and high EpoR activity overides the tubular protective effects in AKI recovery.

Sison, E. A. R., Kurre, P., & Kim, Y. M. (2017). **Understanding the bone marrow microenvironment in hematologic malignancies: A focus on chemokine, integrin, and extracellular vesicle signaling**. *Pediatric Hematology and Oncology*, 1-14. doi:10.1080/08880018.2017.1395938

Signaling between leukemia cells and nonhematopoietic cells in the bone marrow microenvironment contributes to leukemia cell growth and survival. This complicated extrinsic mechanism of chemotherapy resistance relies on a number of pathways and factors, some of which have yet to be determined. Research on cell-cell crosstalk the bone marrow microenvironment in acute leukemia was presented at the 2016 annual Therapeutic Advances in Childhood Leukemia (TACL) investigator meeting. This review summarizes the mini-symposium proceedings and focuses on chemokine signaling via the cell surface receptor CXCR4, adhesion molecule signaling via integrin alpha4, and crosstalk between leukemia cells and the bone marrow microenvironment that is mediated through extracellular vesicles.

Sonnenberg, A. (2017). **Limitations of teaching endoscopy**. *Eur J Gastroenterol Hepatol*. doi:10.1097/meg.0000000000001041

BACKGROUND AND AIM: Endoscopic procedures of the gastrointestinal tract represent a category of diagnostic tests that considerably rely on skills and dexterity of a human tester. The present analysis aimed to delineate factors that affect the success of teaching endoscopy and potentially limit the acquisition of new skills and knowledge. METHODS: The performance of the endoscopist is described in terms of sensitivity and specificity. The outcomes of sequential testing and acquisition of new knowledge are calculated using matrix algebra. Teaching is modeled as an iterative process with an incremental improvement in a fellow's performance matrix. RESULTS: As a diagnostician, an endoscopist cannot measure beyond his/her own level of competence. The cognition and endoscopic skills of both the fellow and the attending physician determine how fast the fellow's endoscopic performance improves over time. The better the fellow's and the attending's abilities are to recognize and amend residual deficiencies, the faster the fellow's endoscopic performance improves. Severe or even complete diagnostic incompetence by either party can draw out the training process or even result in a complete standstill, respectively. CONCLUSION: The description of endoscopic performance in terms of test characteristics provides valuable insights into the influence of endoscopic performance characteristics on the outcome of endoscopy and on the constraints of teaching endoscopic skills.

Stanfield, J. R., Wampler, R. K., Wu, J., Stewart, J., Snyder, T. A., & Long, J. W. (2017). *Design of a miniature pump for chronic mechanical circulatory support using computational fluid dynamics and flow visualization*.

Stickney Ferguson, S., Randall, J., Dabney, J., Kalbacker, M. E., Boyle, N., Thao, V., . . . Denzen, E. M. (2017). **Perceived Workforce Challenges among Clinical Social Workers in Hematopoietic Cell Transplantation Programs**. *Biol Blood Marrow Transplant*. doi:10.1016/j.bbmt.2017.12.793

Sumowski, J. F., McDonnell, G. V., & Bourdette, D. (2018). **Diet in multiple sclerosis: Science takes a seat at the table**. *Neurology, 90*(1), 14-15. doi:10.1212/wnl.0000000000004775

Sun, B. C., Charlesworth, C. J., Lupulescu-Mann, N., Young, J. I., Kim, H., Hartung, D. M., . . . McConnell, K. J. (2017). **Effect of Automated Prescription Drug Monitoring Program Queries on Emergency Department Opioid Prescribing**. *Ann Emerg Med*. doi:10.1016/j.annemergmed.2017.10.023

STUDY OBJECTIVE: We assess whether an automated prescription drug monitoring program intervention in emergency department (ED) settings is associated with reductions in opioid prescribing and quantities. METHODS: We performed a retrospective cohort study of ED visits by Medicaid beneficiaries. We assessed the staggered implementation (pre-post) of automated prescription drug monitoring program queries at 86 EDs in Washington State from January 1, 2013, to September 30, 2015. The outcomes included any opioid prescribed within 1 day of the index ED visit and total dispensed morphine milligram equivalents. The exposure was the automated prescription drug monitoring program query intervention. We assessed program effects stratified by previous high-risk opioid use. We performed multiple sensitivity analyses, including restriction to pain-related visits, restriction to visits with a confirmed prescription drug monitoring program query, and assessment of 6 specific opioid high-risk indicators. RESULTS: The study included 1,187,237 qualifying ED visits (898,162 preintervention; 289,075 postintervention). Compared with the preintervention period, automated prescription drug monitoring program queries were not significantly associated with reductions in the proportion of visits with opioid prescribing (5.8 per 1,000 encounters; 95% confidence interval [CI] -0.11 to 11.8) or the amount of prescribed morphine milligram equivalents

(difference 2.66; 95% CI -0.15 to 5.48). There was no evidence of selective reduction in patients with previous high-risk opioid use (1.2 per 1,000 encounters, 95% CI -9.5 to 12.0; morphine milligram equivalents 1.22, 95% CI -3.39 to 5.82). The lack of a selective reduction in high-risk patients was robust to all sensitivity analyses. CONCLUSION: An automated prescription drug monitoring program query intervention was not associated with reductions in ED opioid prescribing or quantities, even in patients with previous high-risk opioid use.

Sun, B. C., Lupulescu-Mann, N., Charlesworth, C. J., Kim, H., Hartung, D. M., Deyo, R. A., & McConnell, K. J. (2017). **Does Prescription Opioid Shopping Increase Overdose Rates in Medicaid Beneficiaries?** *Annals of Emergency Medicine*. doi:10.1016/j.annemergmed.2017.10.007

Study objective: The link between prescription opioid shopping and overdose events is poorly understood. We test the hypothesis that a history of prescription opioid shopping is associated with increased risk of overdose events. Methods: This is a secondary analysis of a linked claims and controlled substance dispense database. We studied adult Medicaid beneficiaries in 2014 with prescription opioid use in the 6 months before an ambulatory care or emergency department visit with a pain-related diagnosis. The primary outcome was a nonfatal overdose event within 6 months of the cohort entry date. The exposure of interest (opioid shopping) was defined as having opioid prescriptions by different prescribers with greater than or equal to 1-day overlap and filled at 3 or more pharmacies in the 6 months before cohort entry. We used a propensity score to match shoppers with nonshoppers in a 1:1 ratio. We calculated the absolute difference in outcome rates between shoppers and nonshoppers. Results: We studied 66,328 patients, including 2,571 opioid shoppers (3.9%). There were 290 patients (0.4%) in the overall cohort who experienced a nonfatal overdose. In unadjusted analyses, shoppers had higher event rates than nonshoppers (rate difference of 4.4 events per 1,000; 95% confidence interval 0.8 to 7.9). After propensity score matching, there were no outcome differences between shoppers and nonshoppers (rate difference of 0.4 events per 1,000; 95% confidence interval -4.7 to 5.5). These findings were robust to various definitions of opioid shoppers and look-back periods. Conclusion: Prescription opioid shopping is not independently associated with increased risk of overdose events.

Sun, L. W., Carroll, J., & Lujan, B. J. (2017). **Photoreceptor disruption and vision loss associated with central serous retinopathy**. *Am J Ophthalmol Case Rep, 8*, 74-77. doi:10.1016/j.ajoc.2017.10.002

Purpose: To present ophthalmic imaging findings in the case of a 40-year-old male with sustained visual loss after a single episode of acute central serous retinopathy (CSR). Observations: A male subject presented with visual acuity decline to 20/50 OS and was diagnosed with acute CSR. The initial pigment epithelial detachment and subretinal fluid resolved within 6 weeks, but visual acuity remained impaired. Using directional optical coherence tomography (D-OCT) and confocal and split-detector adaptive optics scanning light ophthalmoscopy (AOSLO), we imaged pathologic alterations in the photoreceptor mosaic of the affected eye. A foveal region of intermittent missing cones, a temporal parafoveal region of confluent missing cones, and a nasal parafoveal region of misdirected cones were observed. Conclusions and Importance: Pathologic alterations in photoreceptor microanatomy underlie residual visual acuity deficits in this case of acute CSR. Observations of missing cones correlated well across all imaging modalities in the fovea and the temporal parafoveal region of missing cones. However, in the nasal parafovea where cones were present but misdirected, D-OCT and AOSLO may be able to identify and image photoreceptors with greater fidelity as compared to non-directional SDOCT (spectral domain OCT). D-OCT may thus have a clinical role in rapidly assessing photoreceptor mosaic integrity in pathology.

Swanson, C. M., Kohrt, W. M., Buxton, O. M., Everson, C. A., Wright, K. P., Jr., Orwoll, E. S., & Shea, S. A. (2017). **The Importance of the Circadian System & Sleep for Bone Health**. *Metabolism*. doi:10.1016/j.metabol.2017.12.002

Adequate sleep timed appropriately during the circadian night is important for numerous biological processes and systems. New evidence suggests that both sleep timing and duration may be important for optimal bone health as well. This review examines the diurnal variation of bone turnover markers (BTMs) and the importance of circadian clock genes in regulating bone mass. In addition, this review explores the evidence for a link between shift work (and its associated disturbances in sleep duration/quality and circadian alignment) and alterations in bone metabolism and bone health. Finally, we review how commonly used medications and over-the-counter substances (e.g. caffeine, melatonin) complicate the relationship between sleep and circadian disorders and bone health.

Taguchi, K., Harper, J. D., Stoller, M. L., Duty, B. D., Sorensen, M. D., Sur, R. L., . . . Chi, T. (2017). **Identifying factors associated with need for flexible ureteroscope repair: a Western Endourology STone (WEST) research consortium prospective cohort study**. *Urolithiasis*. doi:10.1007/s00240-017-1013-y

Maintenance of flexible ureteroscopes can involve high costs and administrative burden. Instrument fragility necessitates eventual repair, rendering scopes inaccessible during refurbishment. We conducted a multi-institutional prospective cohort study to identify perioperative factors influencing flexible ureteroscope durability. Patients undergoing flexible ureteroscopy (URS) at six United States endourology centers were enrolled between August 2014 and June 2015. Surgeon self-reported concern and satisfaction with scope performance as well as upward and downward angles of deflection for each scope tip were measured before and after each procedure. The need for scope repair was determined by the operating surgeon at the time of the procedure and recorded. 424 URS cases using 74 flexible ureteroscopes were identified. Scope repair was required in 28 cases (6.6%) involving 26 scopes (35.1%). Upon univariate analysis, shorter patient height, absence of guidewire use, presence of a ureteral access sheath (UAS), longer procedure time, larger stone size, lithotrite type, surgeon training level, and self-reported concern were associated with scope repair. Upon multivariate analysis, UAS use (OR = 2.53, p = 0.005) and degree loss of scope upward flexion during a case (OR = 1.02, p = 0.03) increased the odds of a scope needing repair while the use of safety guidewire decreased the odds of a scope repair (OR = 0.50, p = 0.045). Lithotrite use and surgeon concern were associated with degree loss of scope upward flexion. The use of a UAS, absence of a safety guidewire, and the loss of upward ureteroscope flexion should be considered when evaluating means of optimizing reusable ureteroscope durability.

Taylor, N. J., Mitra, N., Goldstein, A. M., Tucker, M. A., Avril, M. F., Azizi, E., . . . Kanetsky, P. A. (2017). **Germline Variation at CDKN2A and Associations with Nevus Phenotypes among Members of Melanoma Families**. *J Invest Dermatol, 137*(12), 2606-2612. doi:10.1016/j.jid.2017.07.829

Germline mutations in CDKN2A are frequently identified among melanoma kindreds and are associated with increased atypical nevus counts. However, a clear relationship between pathogenic CDKN2A mutation carriage and other nevus phenotypes including counts of common acquired nevi has not yet been established. Using data from GenoMEL, we investigated the relationships between CDKN2A mutation carriage and 2-mm, 5-mm, and atypical nevus counts among blood-related members of melanoma families. Compared with individuals without a pathogenic mutation, those who carried one had an overall higher prevalence of atypical (odds ratio = 1.64; 95% confidence interval = 1.18-2.28) nevi but not 2-mm nevi (odds ratio = 1.06; 95% confidence interval = 0.92-1.21) or 5-mm nevi (odds ratio = 1.26; 95% confidence interval = 0.94-1.70). Stratification by case status showed more pronounced positive associations among non-case family members, who were nearly three times (odds ratio = 2.91; 95% confidence interval = 1.75-4.82) as likely to exhibit nevus counts at or above the median in all three nevus categories simultaneously when harboring a pathogenic mutation (vs. not harboring one). Our results support the hypothesis that unidentified nevogenic genes are co-inherited with CDKN2A and may influence carcinogenesis.

Than, K. D., Mummaneni, P. V., Bridges, K. J., Tran, S., Park, P., Chou, D., . . . Mundis, G. M., Jr. (2017). **Complication rates associated with open versus percutaneous pedicle screw instrumentation among patients**

undergoing minimally invasive interbody fusion for adult spinal deformity. *Neurosurgical Focus, 43*(6), E7. doi:10.3171/2017.8.focus17479

OBJECTIVE High-quality studies that compare outcomes of open and minimally invasively placed pedicle screws for adult spinal deformity are needed. Therefore, the authors compared differences in complications from a circumferential minimally invasive spine (MIS) surgery and those from a hybrid surgery. METHODS A retrospective review of a multicenter database of patients with spinal deformity who were treated with an MIS surgery was performed. Database inclusion criteria included an age of >/= 18 years and at least 1 of the following: a coronal Cobb angle of > 20 degrees , a sagittal vertical axis of > 5 cm, a pelvic incidence-lumbar lordosis angle of > 10 degrees , and/or a pelvic tilt of > 20 degrees . Patients were propensity matched according to the levels instrumented. RESULTS In this database, a complete data set was available for 165 patients, and after those who underwent 3-column osteotomy were excluded, 137 patients were available for analysis; 76 patients remained after propensity matching (MIS surgery group 38 patients, hybrid surgery group 38 patients). The authors found no difference in demographics, number of levels instrumented, or preoperative and postoperative radiographic results. At least 1 complication was suffered by 55.3% of patients in the hybrid surgery group and 44.7% of those in the MIS surgery group (p = 0.359). Patients in the MIS surgery group had significantly fewer neurological, operative, and minor complications than those in the hybrid surgery group. The reoperation rates in both groups were similar. The most common complication category for the MIS surgery group was radiographic and for the hybrid surgery group was neurological. Patients in both groups experienced postoperative improvement in their Oswestry Disability Index and visual analog scale (VAS) back and leg pain scores (all p < 0.05); however, MIS surgery provided a greater reduction in leg pain according to VAS scores. CONCLUSIONS Overall complication rates in the MIS and hybrid surgery groups were similar. MIS surgery resulted in significantly fewer neurological, operative, and minor complications. Reoperation rates in the 2 groups were similar, and despite complications, the patients reported significant improvement in their pain and function.

Thapa, N., Pham, R., Cole, C., Meinershagen, M., Bowman, P. W., & Ray, A. (2017). **Therapeutic leukocytapheresis in infants and children with leukemia and hyperleukocytosis: A single institution experience**. *Journal of Clinical Apheresis*. doi:10.1002/jca.21610

BACKGROUND: Hyperleukocytosis, defined as white blood cell (WBC) count above 100 x 10(9) /L, has high early morbidity and mortality from leukostasis-related complications, namely intracranial hemorrhage and pulmonary distress. Initiating chemotherapy without prior leukocytoreduction may lead to tumor lysis syndrome (TLS). Therapeutic leukocytapheresis (TL) is used as one leukocytoreductive intervention; however, its safety and efficacy in pediatric leukemia has not been established. The purpose of this study is to evaluate safety of TL in pediatric patients and assess the efficacy of TL in reducing WBC count in pediatric leukemia. METHODS: Retrospective chart review was conducted on 14 patients with acute lymphoblastic leukemia (ALL) and 5 with acute myeloid leukemia (AML) who underwent TL during the period 2000-2014 at a single institution. RESULTS: Mean WBC count of 19 patients who received TL was 483.2 x 10(9) /L (547.1 in ALL, 304.3 in AML); a portion of patients presented with central nervous system symptoms (15%), respiratory symptoms (10%), or both (10%). TL reduced WBC count (mean 50.7% reduction after a single TL procedure; additional 17.1% reduction after a second TL procedure in 6 patients). Short-term survival immediately following TL was 100% without any major procedural complication. Mean survival time in patients with AML was 1.5 years and with ALL was 6.5 years. CONCLUSIONS: TL significantly reduces WBC number in pediatric leukemia patients as young as 22 days old. In our retrospective study, TL was not associated with any significant complications and suggests that TL is a safe initial procedure in pediatric leukemia.

Thomas, C. R., Jr. (2017). **Single-fraction radiotherapy and early subjective improvement in pain**. *JAMA Oncology, 3*(7), 960. doi:10.1001/jamaoncol.2016.6723

Thomas, C. R., Jr. (2018). **In Regard to Chapman and Jagsi**. *Int J Radiat Oncol Biol Phys, 100*(1), 278. doi:10.1016/j.ijrobp.2017.10.008

Thosar, S. S., Niederhausen, M., Lapidus, J., Fino, N. F., Cigarroa, J., Minnier, J., . . . Burchill, L. J. (2017). **Self-regulated use of a wearable activity sensor is not associated with improvements in physical activity, cardiometabolic risk or subjective health status**. *Br J Sports Med*. doi:10.1136/bjsports-2017-098512

Tita, A. T., Doherty, L., Roberts, J. M., Myatt, L., Leveno, K. J., Varner, M. W., . . . Sorokin, Y. (2017). **Adverse Maternal and Neonatal Outcomes in Indicated Compared with Spontaneous Preterm Birth in Healthy Nulliparas: A Secondary Analysis of a Randomized Trial**. *American Journal of Perinatology*. doi:10.1055/s-0037-1608787

Tkachenko, O. Y., Delimitreva, S., Wedi, E., Scheerer-Bernhard, J. U., Valle, R. R., & Nayudu, P. L. (2017). **Effects of oxygen concentration in IVM/IVF on marmoset monkey oocyte maturation and embryo development**. *Animal Reproduction, 14*(4), 1170-1178. doi:10.21451/1984-3143-AR896

The effect of oxygen (O2) concentration on in vitro development of the oocytes from antral follicles of naturally cycling common marmosets (Callithrix jacchus) has been investigated. Different O2 concentrations during in vitro maturation (20 or 8%) and during in vitro fertilization (20 or 5%) have been applied in three combinations: 8-5, 20-20, 20-5 (maturation and fertilization, respectively). Additionally, 8-20 conditions were tested in a pre-study, but since no fertilization occurred, this test group was excluded from further experiments. Oocyte maturation rate was significantly higher after IVM in 20% than in 8% O2 (MI: 91% in 20-20 vs. 78% in 8-5; MII: 69 vs. 45% in 20-5 and 50% in 8-5, P < 0.05 for all). The lowest rate of embryo development occurred after maturation under 8% O2 (59% in 8-5 vs. 95% in 20-20 and 83% in 20-5, P < 0.05 for all), strongly suggesting this low tension may produce hypoxic conditions during maturation, which damages the oocytes. In conclusion, 20% O2 was shown to be significantly superior to 8% O2 for marmoset oocyte maturation, and 5% O2 was to be preferred over 20% for IVF, based on a trend for better embryo morphology and rates of progression.

Tkachenko, O. Y., Scheerer-Bernhard, J. U., Delimitreva, S., Wedi, E., Valle, R. R., Heistermann, M., & Nayudu, P. L. (2017). **A retrospective analysis of adverse effects of an in vivo fluoroquinolone antibiotic enrofloxacin treatment on oocyte quality in the common marmoset**. *Reproductive Toxicology, 75*, 86-95. doi:10.1016/j.reprotox.2017.12.004

Here we report a retrospective analysis of negative effects of routine enrofloxacin treatment of recurrent diarrhea on the ovary and the developing oocytes of the common marmoset, a small New World primate. The most deleterious effect on oocytes was observed about two months post treatment suggesting that the enrofloxacin effect is on early growing follicles. Manifestations of toxicity included decreased numbers of growing follicles and recovered culturable oocytes, as well as signs of early atresia of granulosa cells. In addition, increased amounts of holed stroma after treatment strongly suggested increased death of the early growing follicles. Of the oocytes judged to be of adequate quality for culture, maturation rates were not affected but fertilization of in vitro matured MII oocytes and subsequent cleavage rates were severely reduced in the enrofloxacin treated animals. Further, the arrested oocytes, which failed to mature or fertilize, showed obvious meiotic spindle abnormalities.

Tokunboh, I., Vales Montero, M., Zopelaro Almeida, M. F., Sharma, L., Starkman, S., Szeder, V., . . . Saver, J. L. (2018). **Visual Aids for Patient, Family, and Physician Decision Making About Endovascular Thrombectomy for Acute Ischemic Stroke**. *Stroke, 49*(1), 90-97. doi:10.1161/strokeaha.117.018715

BACKGROUND AND PURPOSE: Rapid decision making optimizes outcomes from endovascular thrombectomy for acute cerebral ischemia. Visual displays facilitate swift review of potential outcomes and can accelerate decision processes. METHODS: From patient-level, pooled randomized trial data, 100 person-icon arrays (Kuiper-Marshall personographs) were generated showing beneficial and adverse effects of endovascular thrombectomy for patients with acute cerebral ischemia and large vessel occlusion using (1) automated (algorithmic) and (2) expert-guided joint outcome table specification. RESULTS: For the full 7-category modified Rankin Scale, thrombectomy added to IV tPA (intravenous tissue-type plasminogen activator) alone had number needed to treat to benefit 2.9 (95% confidence interval, 2.6-3.3) and number needed to harm 68.9 (95% confidence interval, 40-250); thrombectomy for patients ineligible for IV tPA had number needed to treat to benefit 2.3 (95% confidence interval, 2.1-2.5) and number needed to harm 100 (95% confidence interval, 62.5-250). Visual displays of treatment effects on 100 patients showed: with thrombectomy added to IV tPA alone, 34 patients have better disability outcome, including 14 more normal or near normal (modified Rankin Scale, 0-1); with thrombectomy for patients ineligible for IV tPA, 44 patients have a better disability outcome, including 16 more normal or nearly normal. Displays also showed that harm (increased modified Rankin Scale final disability) occurred in 1 of 100 patients in both populations, mediated by increased new territory infarcts. The person-icon figures integrated these outcomes, and early side-effects, in a single display. CONCLUSIONS: Visual decision aids are now available to rapidly educate healthcare providers, patients, and families about benefits and risks of endovascular thrombectomy, both when added to IV tPA in tPA-eligible patients and as the sole reperfusion treatment in tPA-ineligible patients.

Trenaman, L., Boonen, A., Guillemin, F., Hiligsmann, M., Hoens, A., Marra, C., . . . Bansback, N. (2017). **OMERACT Quality-adjusted Life-years (QALY) Working Group: Do Current QALY Measures Capture What Matters to Patients?** *J Rheumatol, 44*(12), 1899-1903. doi:10.3899/jrheum.161112

OBJECTIVE: To understand the limitations with current patient-reported outcome measures (PROM) used to generate quality-adjusted life-years (QALY) in rheumatology, and set a research agenda. METHODS: Two activities were undertaken. The first was a scoping review of published studies that have used PROM to generate QALY in rheumatology between 2011 and 2016. The second was an interactive "eyeball test" exercise at Outcome Measures in Rheumatology 13 that compared subdomains of widely used generic PROM, as identified through the scoping review, to subdomains of the Assessment of SpondyloArthritis Health Index (ASAS-HI) condition-specific PROM for ankylosing spondylitis. RESULTS: The scoping review included 39 studies. Five different PROM have been used to generate QALY in rheumatology; however, the EQ-5D and Short Form 6 Dimensions (SF-6D) were used most frequently (in 32 and 9 of included studies, respectively). Special interest group participants identified energy/drive and sleep as 2 key subdomains of the ASAS-HI instrument that may be missed by the EQ-5D, and sexual function as potentially missed by the SF-6D. Participants also expressed concerns that aspects of the process of care and non-health outcomes may be missed. Three ways of incorporating additional subdomains were discussed, including using an alternative generic PROM, modifying an existing generic PROM with "bolt-on" subdomain(s), and generating societal weights for a condition-specific PROM. CONCLUSION: Three priorities for future research were identified: understanding whether the EQ-5D and SF-6D identify what matters to patients with different rheumatic conditions, analyzing how much patients value process or non-health outcomes, and identifying which approaches to incorporating a greater number of subdomains into the QALY are being undertaken in other disease areas.

True, C., Abbott, D. H., Roberts, C. T., Jr., & Varlamov, O. (2017). **Sex Differences in Androgen Regulation of Metabolism in Nonhuman Primates**. *Advances in Experimental Medicine and Biology, 1043*, 559-574. doi:10.1007/978-3-319-70178-3_24

The in-depth characterization of sex differences relevant to human physiology requires the judicious use of a variety of animal models and human clinical data. Nonhuman primates (NHPs) represent an important experimental system that bridges rodent studies and clinical investigations. NHP studies have been especially useful in understanding the role of sex hormones in development and metabolism and also allow the elucidation of the effects of pertinent dietary influences on physiology pertinent to disease states such as obesity and diabetes. This chapter summarizes the current state of our understanding of androgen effects on male and female NHP metabolism relevant to hypogonadism in human males and polycystic ovary syndrome in human females. This review will also focus on the interaction between altered androgen levels and dietary restriction and excess, in particular the Western-style diet that underlies significant human pathophysiology.

Tseng, A. (2017). **Huddling up: Expanding clinic huddles**. *Annals of Family Medicine, 15*(6), 584. doi:10.1370/afm.2156

Turner, K. O., Genta, R. M., & Sonnenberg, A. (2017). **Lesions of All Types Exist in Colon Polyps of All Sizes**. *Am J Gastroenterol*. doi:10.1038/ajg.2017.439

OBJECTIVES: Although large polyps are known to harbor more advanced neoplasia than small polyps, the extent of the relationship between size and type is not fully known. The study aim was to establish benchmarks for the prevalence of different histologic polyp types among varying size categories. METHODS: The Miraca Life Sciences Database is an electronic repository of histopathologic patient records from private practices throughout the United States. We extracted the records of 483,998 unique patients who underwent colonoscopy with polypectomy between January 2008 and December 2014. A total of 550,811 polyps were stratified by their endoscopic size measurement. Polyps of each size were further stratified as hyperplastic polyp (HP), tubular adenoma (TA), tubulovillous adenoma (TVA), sessile serrated adenoma/polyp, and adenocarcinoma. RESULTS: Of all 550,811 polyps, 447,343 (81%) were 1-9 mm in size, and 103,517 (19%) were 10 mm or larger. A fraction of 18,591/550,811 polyps (3.4%) harbored histologic features of advanced adenoma, such as TVA, high-grade dysplasia, or cancer. Of these, 4,725/18,591 (25%) occurred in polyps 1-9 mm and 13,868/18,591 (75%) occurred in polyps 10 mm or larger. The fractions of advanced adenoma were 0.6% (0.5-0.6%) in 1-5 mm polyps and 2.1% (2.0-2.2%) in 6-9 mm polyps, as compared to 13.4% (13.2-13.6%) in polyps 10 mm or larger. The frequency of HP significantly decreased with increasing polyp size, whereas the frequency of TA remained largely unaffected by polyp size. CONCLUSIONS: While advanced histopathology was found more frequently in colorectal polyps of larger than smaller size, one quarter of all advanced histopathology existed in polyps of <10 mm.Am J Gastroenterol advance online publication, 12 December 2017; doi:10.1038/ajg.2017.439.

Tyner, J. W. (2017). **DNA distress creates lethal opportunity in MPN**. *Blood, 130*(26), 2814-2816. doi:10.1182/blood-2017-11-813006

Vairamani, K., Merjaneh, L., Casano-Sancho, P., Sanli, M. E., David, A., Metherell, L. A., . . . Hwa, V. (2017). **Novel Dominant-Negative GH Receptor Mutations Expands the Spectrum of GHI and IGF-I Deficiency**. *J Endocr Soc, 1*(4), 345-358. doi:10.1210/js.2016-1119

Context: Autosomal-recessive mutations in the growth hormone receptor (GHR) are the most common causes for primary growth hormone insensitivity (GHI) syndrome with classical GHI phenotypically characterized by severe short stature and marked insulin-like growth factor (IGF)-I deficiency. We report three families with dominant-negative heterozygous mutations in the intracellular domain of the GHR causing a nonclassical GHI phenotype. Objective: To determine if the identified GHR heterozygous variants exert potential dominant-negative effects and are the cause for the GHI phenotype in our patients. Results: All three

mutations (c.964dupG, c.920_921insTCTCAAAGATTACA, and c.945+2T>C) are predicted to result in frameshift and early protein termination. In vitro functional analysis of variants c.964dupG and c.920_921insTCTCAAAGATTACA (c.920_921ins14) suggests that these variants are expressed as truncated proteins and, when coexpressed with wild-type GHR, mimicking the heterozygous state in our patients, exert dominant-negative effects. Additionally, we provide evidence that a combination therapy of recombinant human growth hormone (rhGH) and rhIGF-I improved linear growth to within normal range for one of our previously reported patients with a characterized, dominant-negative GHR (c.899dupC) mutation. Conclusion: Dominant-negative GHR mutations are causal of the mild GHI with substantial growth failure observed in our patients. Heterozygous defects in the intracellular domain of GHR should, therefore, be considered in cases of idiopathic short stature and IGF-I deficiency. Combination therapy of rhGH and rhIGF-I improved growth in one of our patients.

Valdebenito, B., Tullume-Vergara, P. O., Gonzalez, W., Kreth, J., & Giacaman, R. A. (2017). **In silico analysis of the competition between Streptococcus sanguinis and Streptococcus mutans in the dental biofilm**. *Molecular Oral Microbiology*. doi:10.1111/omi.12209

During dental caries, the dental biofilm modifies the composition of the hundreds of involved bacterial species. Changing environmental conditions predisposes competition. A pertinent model to exemplify the complex interplay of the microorganisms in the human dental biofilm is the competition between Streptococcus sanguinis (S. sanguinis) and Streptococcus mutans (S. mutans). It has been reported that children and adults harbor greater numbers of S. sanguinis in the oral cavity, associated with carious-free teeth. Conversely, S. mutans is predominant in individuals with a high number of carious lesions. Competition between both microorganisms stems from the production of H2 O2 by S. sanguinis and mutacins, a type of bacteriocins, by S. mutans. There is limited evidence on how S. sanguinis survives its own H2 O2 levels, or if it has other mechanisms that might aid in the competition against S. mutans, nonetheless. We performed a genomic and metabolic pathway comparison, coupled with a comprehensive literature review to better understand the competition between the two species. Results indicated that S. sanguinis can outcompete S. mutans by the production of an enzyme capable to metabolize H2 O2 . S. mutans, however, lacks the enzyme and is susceptible to the peroxide from S. sanguinis. In addition, S. sanguinis can generate energy through gluconeogenesis and seems to have evolved different communication mechanisms, indicating that novel proteins may be responsible for intra-species communication.

Valentine-Maher, S. K., Butterfield, P. G., & Laustsen, G. (2017). **Environmental Health: Advancing Emancipatory Policies for the Common Good**. *ANS: Advances in Nursing Science*. doi:10.1097/ans.0000000000000194

Human health is substantially impacted by the state of the environment, and environmental degradation has a disproportionate impact on persons with less immediate access to financial and social power. This article calls for upstream nursing action to address the natural environment in order to turn about health injustices and improve health for all. Such action would move nursing towards a greater actualization of the nursing environmental domain. The health impacts of climate change, air and water quality, and toxic chemical exposure are substantiated and specific policy leadership recommendations are proposed. Recommended actions include work to build environmental health literacy and empowerment, advocacy for regulatory protection and enforcement, and environmental engagement within health care systems.

van Epps, P., Maier, M., Lund, B., Howren, M. B., Beck, B., Beste, L., . . . Ohl, M. E. (2017). **"Medication Adherence in a Nationwide Cohort of Veterans Initiating Pre-Exposure Prophylaxis (PrEP) to Prevent HIV Infection"**. *Journal of Acquired Immune Deficiency Syndromes*. doi:10.1097/qai.0000000000001598

BACKGROUND: Current guidelines for pre-exposure prophylaxis (PrEP) to prevent HIV infection call for long-term, daily use of tenofovir disoproxil fumarate / emtricitabine (TDF/FTC). Little is known about long-term

adherence with TDF/FTC prescribed for PrEP in routine clinical practice. SETTING: Veterans Health Administration (VHA) clinics METHODS:: We used VHA data to create a nationwide cohort of Veterans initiating PrEP between July 1, 2012 and June 30, 2016. We examined pharmacy refill data to estimate adherence based on the proportion of days covered (PDC) by TDF/FTC in the first year, and used logistic regression to identify patient characteristics associated with high adherence (i.e. PDC > 0.8). We also quantified how often Veterans discontinued PrEP in the first year, based on a gap of 120 days or more in medication possession. RESULTS: Among 1,086 individuals initiating PrEP, the median PDC for TDF/FTC in the first year was 0.74 (IQR 0.40-0.92). In multivariable analysis, high adherence was associated with older age (odds ratio 1.97; 1.41-2.74 for age 50-64 compared to < 35), white compared to black race (odds ratio 2.12; 1.53 - 2.93), and male sex (odds ratio 3.39; 1.37-8.42). Forty-four percent discontinued PrEP in the first year. CONCLUSIONS: First-year adherence with TDF/FTC was overall high in a nationwide cohort of PrEP users. Differences in adherence by age, race, and gender suggest potential for disparities in PrEP effectiveness in routine clinical practice.

Vasiliadis, H. M., Diallo, F. B., Rochette, L., Smith, M., Langille, D., Lin, E., . . . Lesage, A. (2017). **Temporal Trends in the Prevalence and Incidence of Diagnosed ADHD in Children and Young Adults between 1999 and 2012 in Canada: A Data Linkage Study**. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 62*(12), 818-826. doi:10.1177/0706743717714468

OBJECTIVE: There is a need for the routine monitoring of treated attention-deficit hyperactivity disorder (ADHD) for timely policy making. The objective is to report and assess over a decade the prevalence and incidence of diagnosed ADHD in Canada. METHODS: Administrative linked patient data from the provinces of Manitoba, Ontario, Quebec, and Nova Scotia were obtained from the same sources as the Canadian Chronic Diseases Surveillance Systems to assess the prevalence and incidence of a primary physician diagnosis of ADHD (ICD-9 and ICD-10 codes: 314, F90.x) for consultations in outpatient and inpatient settings (Med-Echo in Quebec, the Canadian Institute of Health Information Discharge Abstract Database in the 3 other provinces, plus the Ontario Mental Health Reporting System). Dates of service, diagnosis, and physician specialty were retained. The estimates were presented in yearly brackets between 1999-2000 and 2011-2012 by age and sex groups. RESULTS: The prevalence of ADHD between 1999 and 2012 increased in all provinces and for all groups. The prevalence was approximately 3 times higher in boys than in girls, and the highest prevalence was observed in the 10- to 14-year age group. The incidence increased between 1999 and 2012 in Manitoba, Quebec, and Nova Scotia but remained stable in Ontario. Incident cases were more frequently diagnosed by general practitioners followed by either psychiatrists or paediatricians depending on the province. CONCLUSION: The prevalence and incidence of diagnosed ADHD did not increase similarly across all provinces in Canada between 1999 and 2012. Over half of cases were diagnosed by a general practitioner.

Vatankhah, N., & Jahangiri, Y. (2017). **Reply**. *Journal of Vascular Surgery, 66*(6), 1915-1916. doi:10.1016/j.jvs.2017.08.040

Veazie, S., Peterson, K., Ansari, Y., Chung, K. A., Gibbons, C. H., Raj, S. R., & Helfand, M. (2017). **Fludrocortisone for orthostatic hypotension**. *Cochrane Database of Systematic Reviews, 2017*(12). doi:10.1002/14651858.CD012868

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: To identify and evaluate the benefits and harms of fludrocortisone for orthostatic hypotension.

Vidaković, S., Božanović, T., Dokic, M., Pilić, I., Pejovic, T., & Ljubić, A. (2017). **Pregnancy after treatment for adult granulose cell tumor: A case report**. *Clinical and Experimental Obstetrics and Gynecology, 44*(6), 964-965. doi:10.12891/ceog3965.2017

Granulosa cell tumors are sex-cord stromal tumors, and since their incidence is very low, it is difficult to design treatment and evaluate its efficacy. In these cases it is very difficult and challenging to give any advice regarding future pregnancies. In the present case, since treatment of granulosa cell tumor was affected by decision to have another pregnancy, one is inevitably concerned whether the pregnancy and hormonal status regarding pregnancy could change prognostic factors regarding the tumor itself. After the pregnancy the patient declined hysterectomy and her reasons were mainly that she felt safe because the second look during cesarean section showed no evidence of the disease. There are no sufficient data in the literature regarding planned pregnancies during the course of follow up for granulosa cell tumors.

Walcott, A. T., & Ryabinin, A. E. (2017). **Alcohol's Effects on Pair-Bond Maintenance in Male Prairie Voles**. *Front Psychiatry, 8*, 226. doi:10.3389/fpsyt.2017.00226

Alcohol abuse can have devastating effects on social relationships. In particular, discrepant patterns of heavy alcohol consumption are associated with increased rates of separation and divorce. Previous studies have attempted to model these effects of alcohol using socially monogamous prairie voles. These studies showed that alcohol consumption can inhibit the formation of pair bonds in this species. While these findings indicated that alcohol's effects on social attachments can involve biological mechanisms, the formation of pair bonds does not properly model long-term human attachments. To overcome this caveat, this study explored whether discordant or concordant alcohol consumption between individuals within established pairs affects maintenance of pair bonds in male prairie voles. Male and female prairie voles were allowed to form a pair bond for 1 week. Following this 1-week cohabitation period, males received access to 10% continuous ethanol; meanwhile, their female partners had access to either alcohol and water or just water. When there was a discrepancy in alcohol consumption, male prairie voles showed a decrease in partner preference (PP). Conversely, when concordant drinking occurred, males showed no inhibition in PP. Further analysis revealed a decrease in oxytocin immunoreactivity in the paraventricular nucleus of alcohol-exposed males that was independent of the drinking status of their female partners. On the other hand, only discordant alcohol consumption resulted in an increase of FosB immunoreactivity in the periaqueductal gray of male voles, a finding suggesting a potential involvement of this brain region in the effects of alcohol on maintenance of pair bonds. Our studies provide the first evidence that alcohol has effects on established pair bonds and that partner drinking status plays a large role in these effects.

Wang, Z., Camino, A., Zhang, M., Wang, J., Hwang, T. S., Wilson, D. J., . . . Jia, Y. (2017). **Automated detection of photoreceptor disruption in mild diabetic retinopathy on volumetric optical coherence tomography**. *Biomed Opt Express, 8*(12), 5384-5398. doi:10.1364/boe.8.005384

Diabetic retinopathy is a pathology where microvascular circulation abnormalities ultimately result in photoreceptor disruption and, consequently, permanent loss of vision. Here, we developed a method that automatically detects photoreceptor disruption in mild diabetic retinopathy by mapping ellipsoid zone reflectance abnormalities from en face optical coherence tomography images. The algorithm uses a fuzzy c-means scheme with a redefined membership function to assign a defect severity level on each pixel and generate a probability map of defect category affiliation. A novel scheme of unsupervised clustering optimization allows accurate detection of the affected area. The achieved accuracy, sensitivity and specificity were about 90% on a population of thirteen diseased subjects. This method shows potential for accurate and fast detection of early biomarkers in diabetic retinopathy evolution.

Wardzala, C., Murchison, C., Loftis, J. M., Schenning, K. J., Mattek, N., Woltjer, R., . . . Wilhelm, C. J. (2017). **Sex differences in the association of alcohol with cognitive decline and brain pathology in a cohort of octogenarians**. *Psychopharmacology (Berl)*. doi:10.1007/s00213-017-4791-6

RATIONALE: The beneficial effects of moderate alcohol may differ in aging men versus women. OBJECTIVES: Cognitive and functional decline and neuropathology were investigated in a cohort of aging men and women with diverse alcohol histories. METHODS: Non-demented (Clinical Dementia Rating (CDR) of </= 0.5 and a Mini-Mental State Examination (MMSE) score of > 24), autonomously living participants were tracked in longitudinal aging studies to examine self-report and objective tests of rates of decline in a cohort (n = 486) of octogenarians. Neurofibrillary tangles (NFTs; Braak stage) and neuritic plaques (NPs) were staged at autopsy in a subset of participants (n = 149) using current standard neuropathologic diagnostic criteria. RESULTS: Moderate drinking men had an attenuated rate of decline compared to rare/never drinkers and women on the MMSE and CDR sum of boxes. In contrast, moderate drinking women had a reduced rate of decline only in the Logical Memory Delayed Recall Test (LMDR) compared to rare/never drinkers and men. Moderate alcohol consumption was associated with a reduction in the incidence of advanced (stages 5-6) Braak NFT stage in men ($p < 0.05$), with no effect in women. CONCLUSIONS: In this cohort, men experienced a broader range of beneficial effects associated with alcohol. Alcohol's effects may differ in men and women in important ways that suggest a narrower beneficial window.

Warne, D., Dulacki, K., Spurlock, M., Meath, T., Davis, M. M., Wright, B., & McConnell, K. J. (2017). **Adverse childhood experiences (ACE) among American Indians in South Dakota and associations with mental health conditions, alcohol use, and smoking**. *Journal of Health Care for the Poor and Underserved, 28*(4), 1559-1577. doi:10.1353/hpu.2017.0133

Objectives. To assess the prevalence of Adverse Childhood Experiences (ACEs) and their association with behavioral health in American Indian (AI) and non-AI populations in South Dakota. Methods. We included the validated ACE questionnaire in a statewide health survey of 16,001 households. We examined the prevalence of ACEs and behavioral health conditions in AI and non-AI populations and associations between ACEs and behavioral health. Results. Compared with non-AIs, AIs displayed higher prevalence of ACEs including abuse, neglect, and household dysfunction and had a higher total number of ACEs. For AIs and non-AIs, having six or more ACEs significantly increased the odds for depression, anxiety, PTSD, severe alcohol misuse, and smoking compared with individuals with no ACEs. Conclusions. American Indians in South Dakota experience more ACEs, which may contribute to poor behavioral health. Preventing and mitigating the effects of ACEs may have a significant impact on health disparities in AI populations. © Meharry Medical College.

Weichenhan, D., Wang, Q., Adey, A., Wolf, S., Shendure, J., Eils, R., & Plass, C. (2018). **Tagmentation-Based Library Preparation for Low DNA Input Whole Genome Bisulfite Sequencing**. *Methods Mol Biol, 1708*, 105-122. doi:10.1007/978-1-4939-7481-8_6

Aberrations of the DNA methylome contribute to onset and progression of diseases. Whole genome bisulfite sequencing (WGBS) is the only analytical method covering the complete methylome. Alternative methods requiring less DNA than WGBS analyze only a minor portion of the methylome and do not cover important regulatory features like enhancers and noncoding RNAs. In tagmentation-based WGBS (TWGBS), several DNA and time-consuming steps of the conventional WGBS library preparation are circumvented by the use of a hyperactive transposase, which simultaneously fragments DNA and appends sequencing adapters. TWGBS requires only nanogram amounts of DNA and, thus, is well suited to study precious biological specimens such as sorted cells or micro-dissected tissue samples.

Weintraub, S., Besser, L., Dodge, H. H., Teylan, M., Ferris, S., Goldstein, F. C., . . . Morris, J. C. (2017). **Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS)**. *Alzheimer Disease and Associated Disorders*. doi:10.1097/wad.0000000000000223

INTRODUCTION: The neuropsychological battery of the Uniform Data Set (UDSNB) was implemented in 2005 by the National Institute on Aging (NIA) Alzheimer Disease Centers program to measure cognitive performance in dementia and mild cognitive impairment due to Alzheimer Disease. This paper describes a revision, the UDSNB 3.0. METHODS: The Neuropsychology Work Group of the NIA Clinical Task Force recommended revisions through a process of due diligence to address shortcomings of the original battery. The UDSNB 3.0 covers episodic memory, processing speed, executive function, language, and constructional ability. Data from 3602 cognitively normal participants in the National Alzheimer Coordinating Center database were analyzed. RESULTS: Descriptive statistics are presented. Multivariable linear regression analyses demonstrated score differences by age, sex, and education and were also used to create a normative calculator available online. DISCUSSION: The UDSNB 3.0 neuropsychological battery provides a valuable non proprietary resource for conducting research on cognitive aging and dementia.

Weir-McCall, J. R., Villines, T. C., Shaw, L. J., Abbara, S., Ferencik, M., Nieman, K., . . . Nicol, E. (2017). **Highlights of the Twelfth Annual Scientific Meeting of the Society of Cardiovascular Computed Tomography**. *Journal of Cardiovascular Computed Tomography*. doi:10.1016/j.jcct.2017.11.001

The 12th Annual Scientific Meeting of the SCCT, held from July 6 to July 9 in Washington, DC, was one of the largest to date with 724 attendants from 34 countries, 130 invited talks, 4 "Read with the Experts" sessions, 42 oral abstracts presented, 20 rapid fire posters and 164 poster presentations with the abstracts of all of these published in the JCCT. This article summarises the many themes and topics of presentation and discussion in this meeting, and the many technical advances that are likely to impact future clinical practice and feature in future meetings.

Weiss, A. R., Guo, W., Richardson, R., & Bachevalier, J. (2017). **Intact perceptual ability, but impaired familiarity judgment, after neonatal perirhinal lesions in rhesus macaques**. *Dev Cogn Neurosci, 28*, 54-64. doi:10.1016/j.dcn.2017.10.006

The perirhinal cortex is known to support high-level perceptual abilities as well as familiarity judgments that may affect recognition memory. We tested whether poor perceptual abilities or a loss of familiarity judgment contributed to the recognition memory impairments reported earlier in monkeys with PRh lesions received in infancy (Neo-PRh) (Weiss and Bachevalier, 2016; Zeamer et al., 2015). Perceptual abilities were assessed using a version of the Visual Paired Comparison task with black&white (B&W) stimuli, and familiarity judgments were assessed using the Constant Negative task requiring repeated familiarization exposures. Adult monkeys with Neo-PRh lesions were able to recognize B&W stimuli after short delays, suggesting that their perceptual abilities were within the range of control animals. However, the same Neo-PRh monkeys were slower to acquire the Constant Negative task, requiring more exposures to objects before judging them as familiar compared to control animals. Taken together, the data help to account for the differential patterns of functional compensation on previously reported recognition tasks following neonatal versus adult-onset PRh lesions, and provide further support to the view that the PRh is involved in familiarity processes.

Werntz, R. P., Shoureshi, P., Gillis, K., Kapadia, A., Jiang, D., Amling, C., & Barry, J. M. (2017). **A Simple Neobladder Using a Porcine Model: The Double Limb U-Pouch**. *Urology*. doi:10.1016/j.urology.2017.11.031

OBJECTIVE: To create a simple neobladder and determine whether the double limb U-Pouch (DLUP) has the same capacity and compliance as a Studer or Camey I neobladder. To develop an orthotopic diversion that can be

applied to robotic surgery with laboratory data supporting the concept. MATERIALS AND METHODS: Kidneys, ureters, bladders, and small intestine were obtained from pigs at the time of scheduled autopsy after completion of institutionally approved investigational trauma protocols. A Camey I neobladder, spherical neobladder, and double-limbed small intestinal pouch (D-LUP), were constructed from 40 cm segments of small intestine. They were compared for capacity, compliance and pouch-to-urethra anastomotic distance. RESULTS: The cystometric capacity at 30 cm H2O for the Camey I, Studer, and D-LUP neobladders were 250mL, 350mL, and 430mL, respectively. The pouch-to-urethra anastomotic distance was 0 cm for the Camey I, 10 cm for the spherical reservoir, and 0 cm for the D-LUP. Compliance was 10mL/cm H20 for the Camey 1, 15 mL/cm H2O for the sphere, and 16mL/cm H20 for the D-LUP. CONCLUSION: The D-LUP neobladder was simple to construct, had a more dependent ileo-urethrostomy site, larger capacity, and similar compliance when compared with a spherical neobladder.

Whelan, J. S., & Davis, L. E. (2017). **Osteosarcoma, Chondrosarcoma, and Chordoma**. *J Clin Oncol*, Jco2017751743. doi:10.1200/jco.2017.75.1743

Osteosarcoma (OS), chondrosarcoma, and chordoma are characterized by multiple challenges to the investigator, clinician, and patient. One consequence of their rarity among sarcomas, as well as their biologic and clinical heterogeneity, is that management guidelines are inadequate to inform the range of individual patient-treatment decisions from diagnosis, approaches to surgery, chemotherapy, radiotherapy, treatment of recurrence, palliative care, and quality of survivorship. Of high-grade sarcomas, OSs are among the most curable, with more than two-thirds of patients with localized disease likely to achieve long-term survival. Neoadjuvant chemotherapy comprising cisplatin, doxorubicin, and methotrexate with intercalated surgery is the standard of care for resectable OS in those younger than 40 years. Outcomes for OS presenting with unresectable metastases or recurrent disease, or in those older than 40 years are generally poor. Overall results have improved little for all patients with OS, and new treatments are needed. Surgical resection remains the cornerstone of management for chondrosarcoma and chordoma. However, the application of new biologic insights to therapeutic development indicates that improved treatments may soon be routine for patients with chondrosarcoma and chordoma for whom surgery alone is inadequate. For all these uncommon diseases, patients should be offered specialist expert care delivered by experienced multidisciplinary teams in high-volume centers.

Wicher, S. A., Lawson, K. L., Jacoby, D. B., Fryer, A. D., & Drake, M. G. (2017). **Ozone-induced eosinophil recruitment to airways is altered by antigen sensitization and tumor necrosis factor-alpha blockade**. *Physiol Rep, 5*(24). doi:10.14814/phy2.13538

Ozone is an atmospheric pollutant that causes lung inflammation and airway hyperresponsiveness. Ozone's effects occur in two distinct phases that are mediated by different populations of eosinophils. In the acute phase 1 day after exposure, mature airway-resident eosinophils alter parasympathetic nerve function that results in airway hyperresponsiveness. At this time point, the severity of hyperresponsiveness correlates with the number of eosinophils in close proximity to airway nerves, but not with eosinophils in bronchoalveolar lavage. Three days later, newly divided eosinophils are recruited to airways by a tumor necrosis factor-alpha-dependent mechanism. These new eosinophils paradoxically attenuate ozone-induced airway hyperresponsiveness. Ozone's effects on airway tissue eosinophils and nerve-associated eosinophils 3 days after exposure are unknown. Thus, we tested ozone's effects on eosinophils in airway subepithelium and around airway nerves 1 and 3 days after ozone in nonsensitized and ovalbumin-sensitized guinea pigs with or without the tumor necrosis factor-alpha antagonist, etanercept, and compared changes in eosinophils with ozone-induced airway hyperresponsiveness. More eosinophils were present in small, noncartilaginous airways and along small airway nerves compared to large cartilaginous airways in all treatment groups. The number of airway and nerve-associated eosinophils were unaffected 1 day after ozone exposure, whereas significantly fewer airway eosinophils were present 3 days later. Airway and nerve-associated eosinophils were also decreased in small airways 3 days after ozone in sensitized animals. These changes were blocked by etanercept. Airway eosinophils, but not nerve-associated or bronchoalveolar lavage eosinophils correlated

with airway hyperresponsiveness 3 days after ozone. Our findings indicate ozone causes persistent alterations in airway eosinophils and reinforce the importance of characterizing eosinophils' effects within distinct airway compartments.

Widman, D. G., Young, E., Nivarthi, U., Swanstrom, J. A., Royal, S. R., Yount, B. L., . . . Baric, R. S. (2017). **Transplantation of a quaternary structure neutralizing antibody epitope from dengue virus serotype 3 into serotype 4**. *Sci Rep, 7*(1), 17169. doi:10.1038/s41598-017-17355-5

Dengue vaccine trials have revealed deficits in our understanding of the mechanisms of protective immunity, demonstrating a need to measure epitope-specific antibody responses against each DENV serotype. HmAb 5J7 binds to a complex, 3-monomer spanning quaternary epitope in the DENV3 envelope (E) protein, but it is unclear whether all interactions are needed for neutralization. Structure guided design and reverse genetics were used to sequentially transplant larger portions of the DENV3-specific 5J7 mAb epitope into dengue virus serotype 4 (DENV4). We observed complete binding and neutralization only when the entire 3 monomer spanning epitope was transplanted into DENV4, providing empirical proof that cooperative monomer-hmAb 5J7 interactions maximize activity. The rDENV4/3 virus containing the most expanded 5J7 epitope was also significantly more sensitive than WT DENV4 to neutralization by DENV3 primary immune sera. We conclude that the hinge-spanning region of the 5J7 quaternary epitope is a target for serotype-specific neutralizing antibodies after DENV3 infection.

Wilson, L. M., Cross, R. R., & Duell, P. B. (2017). **Reduced psychological distress in familial chylomicronemia syndrome after patient support group intervention**. *Journal of Clinical Lipidology*. doi:10.1016/j.jacl.2017.11.002

Familial chylomicronemia syndrome (FCS) is a rare genetic disorder that is associated with severe hypertriglyceridemia and complications that often include recurrent pancreatitis beginning in childhood. Patients with FCS frequently struggle to maintain normality in their lives as a consequence of the necessity to severely restrict their intake of dietary fat coupled with the constant threat of recurrent pancreatitis. Patients typically face a high level of psychological stress and anxiety in association with reduced measures of quality of life. Routine medical care for affected patients usually does not adequately address the day-to-day struggles that accompany a diagnosis of FCS, resulting in ongoing suffering for many patients. We describe herein the highly beneficial effects of a support group interaction for a patient with FCS.

Windsor, M. A., Sun, S. J. J., Frick, K. D., Swanson, E. A., Rosenfeld, P. J., & Huang, D. (2018). **Estimating Public and Patient Savings From Basic Research-A Study of Optical Coherence Tomography in Managing Antiangiogenic Therapy**. *Am J Ophthalmol, 185*, 115-122. doi:10.1016/j.ajo.2017.09.027

PURPOSE: To compare patient and Medicare savings from the use of optical coherence tomography (OCT) in guiding therapy for neovascular age-related macular degeneration (nvAMD) to the research investments made in developing OCT by the National Institutes of Health (NIH) and the National Science Foundation (NSF). DESIGN: Observational cohort study. METHODS: Main outcome measures were spending by Medicare as tracked by Current Procedural Terminology codes on intravitreal injections (67028), retinal OCT imaging (92134), and anti-vascular endothelial growth factor (anti-VEGF) treatment-specific J-codes (J0178, J2778, J9035, J3490, and J3590). These claims were identified from the Medicare Provider Utilization and Payment Data from the Centers for Medicare and Medicaid Services among fee-for-service (FFS) Medicare beneficiaries from 2012 to 2015; 2008 claims were acquired from the 100% FFS Part B Medicare Claims File. OCT research costs were determined by searching for grants awarded by NIH and NSF from inception to 2015. All costs and savings were discounted by 3% annually and adjusted for inflation to 2015 dollars. RESULTS: From 2008 to 2015, the United States government and nvAMD patients have accrued an estimated savings of $9.0 billion and $2.2 billion, respectively, from the use of OCT to guide personalized anti-VEGF treatment. The $9.0 billion represents a 21-fold return on government investment into developing the

technology through NIH and NSF grants. CONCLUSIONS: Although an overall cost-benefit ratio of government-sponsored research is difficult to estimate because the benefit may be diffuse and delayed, the investment in OCT over 2 decades has been recouped many times over in just a few years through better personalized therapy.

Wolff, T. A., Krist, A. H., LeFevre, M., Jonas, D. E., Harris, R. P., Siu, A., . . . Bibbins-Domingo, K. (2018). **Update on the Methods of the U.S. Preventive Services Task Force: Linking Intermediate Outcomes and Health Outcomes in Prevention**. *Am J Prev Med, 54*(1s1), S4-s10. doi:10.1016/j.amepre.2017.08.032

The U.S. Preventive Services Task Force (USPSTF) is an independent body of experts who make evidence-based recommendations about clinical preventive services using a transparent and objective process. Developing recommendations on a clinical preventive service requires evidence of its effect on health outcomes. Health outcomes are symptoms, functional levels, and conditions that affect a patient's quantity or quality of life and are measured by assessments of physical or psychologic well-being. Intermediate outcomes are pathologic, physiologic, psychologic, social, or behavioral measures related to a preventive service. Given the frequent lack of evidence on health outcomes, the USPSTF uses evidence on intermediate outcomes when appropriate. The ultimate goal is to determine precisely a consistent relationship between the direction and magnitude of change in an intermediate outcome with a predictable resultant direction and magnitude of change in the health outcomes. The USPSTF reviewed its historical use of intermediate outcomes, reviewed methods of other evidence-based guideline-making bodies, consulted with other experts, and reviewed scientific literature. Most important were the established criteria for causation, tenets of evidence-based medicine, and consistency with its current standards. Studies that follow participants over time following early treatment, stratify patients according to treatment response, and adjust for important confounders can provide useful information about the association between intermediate and health outcomes. However, such studies remain susceptible to residual confounding. The USPSTF will exercise great caution when making a recommendation that depends on the evidence linking intermediate and health outcomes because of inherent evidence limitations.

Wright, T. B., Ball, D., & Hersh, W. (2017). **Query expansion using MeSH terms for dataset retrieval: OHSU at the bioCADDIE 2016 dataset retrieval challenge**. *Database: The Journal of Biological Databases and Curation, 2017*. doi:10.1093/database/bax065

Database URL: https://biocaddie.org/benchmark-data.

Wu, Y. P., Kohlmann, W., Curtin, K., Yu, Z., Hanson, H. A., Hashibe, M., . . . Leachman, S. A. (2017). **Melanoma risk assessment based on relatives' age at diagnosis**. *Cancer Causes Control*. doi:10.1007/s10552-017-0994-8

PURPOSE: The aim of this study was to determine risk for melanoma among individuals who have a first- or second-degree relative with a history of melanoma, based on the unaffected individual's age and age at diagnosis of the relative. METHODS: The study employed a case-control design using a statewide database linked with a Surveillance Epidemiology and End Results cancer registry. A population-based sample of individuals who received at least one diagnosis of first primary, malignant melanoma (n = 14,281), as well as their first- and second-degree relatives, was included. Control individuals with no history of melanoma (n = 70,889) were matched to cases on birth year, gender, race/ethnicity, and county at birth. RESULTS: Risk for melanoma among relatives of melanoma patients declined with relative's age and age at diagnosis. Individuals between ages 40 and 49 who are first-degree relatives of melanoma patients diagnosed between ages 40 and 49 had the greatest risk for melanoma compared with individuals without a first-degree relative with a melanoma history (HR 4.89; 95% CI 3.11-7.68). Increased melanoma risk among second-degree relatives of patients was typically lower than that for first-degree relatives. CONCLUSIONS: Risk for melanoma, at earlier ages than expected, is increased among relatives of individuals with a history of melanoma, particularly if the melanoma case was diagnosed at a young age. Further research on the relationship between age at

diagnosis and relative's melanoma risk could inform melanoma screening recommendations for individuals with a family history of the disease.

Wyatt, A. W., Annala, M., Aggarwal, R., Beja, K., Feng, F., Youngren, J., . . . Gleave, M. E. (2017). **Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer**. *J Natl Cancer Inst, 109*(12). doi:10.1093/jnci/djx118

Background: Real-time knowledge of the somatic genome can influence management of patients with metastatic castration-resistant prostate cancer (mCRPC). While routine metastatic tissue biopsy is challenging in mCRPC, plasma circulating tumor DNA (ctDNA) has emerged as a minimally invasive tool to sample the tumor genome. However, no systematic comparisons of matched "liquid" and "solid" biopsies have been performed that would enable ctDNA profiling to replace the need for direct tissue sampling. Methods: We performed targeted sequencing across 72 clinically relevant genes in 45 plasma cell-free DNA (cfDNA) samples collected at time of metastatic tissue biopsy. We compared ctDNA alterations with exome sequencing data generated from matched tissue and quantified the concordance of mutations and copy number alterations using the Fisher exact test and Pearson correlations. Results: Seventy-five point six percent of cfDNA samples had a ctDNA proportion greater than 2% of total cfDNA. In these patients, all somatic mutations identified in matched metastatic tissue biopsies were concurrently present in ctDNA. Furthermore, the hierarchy of variant allele fractions for shared mutations was remarkably similar between ctDNA and tissue. Copy number profiles between matched liquid and solid biopsy were highly correlated, and individual copy number calls in clinically actionable genes were 88.9% concordant. Detected alterations included AR amplifications in 22 (64.7%) samples, SPOP mutations in three (8.8%) samples, and inactivating alterations in tumor suppressors TP53 , PTEN , RB1 , APC , CDKN1B , BRCA2 , and PIK3R1 . In several patients, ctDNA sequencing revealed robust changes not present in paired solid biopsy, including clinically relevant alterations in the AR, WNT, and PI3K pathways. Conclusions: Our study shows that, in the majority of patients, a ctDNA assay is sufficient to identify all driver DNA alterations present in matched metastatic tissue and supports development of DNA biomarkers to guide mCRPC patient management based on ctDNA alone.

Xu, J., Xu, F., Lawson, M. S., Tkachenko, O. Y., Ting, A. Y., Kahl, C. A., . . . Bishop, C. V. (2017). **Anti-Mullerian hormone is a survival factor and promotes the growth of rhesus macaque preantral follicles during matrix-free culture**. *Biology of Reproduction*. doi:10.1093/biolre/iox181

Anti-Mullerian hormone (AMH) plays a key role during ovarian follicular development, with local actions associated with a dynamic secretion profile by growing follicles. While results for AMH effects on antral follicle growth and function are consistent among studies in various species, any effects on preantral follicle development remain controversial. Therefore, experiments were conducted to investigate the direct actions and role of AMH during follicle development at the preantral stage. Macaque-specific short-hairpin RNAs (shRNAs) targeting AMH mRNA were incorporated into adenoviral vectors to decrease AMH gene expression in rhesus macaque follicles. Secondary follicles were isolated from adult macaque ovaries and cultured individually in the ultra-low-attachment dish containing defined medium supplemented with follicle-stimulating hormone and insulin for 5 weeks. Follicles were randomly assigned to treatment groups: (a) control, (b) non-targeting control shRNA-vector, (c) AMH shRNA-vector, (d) AMH shRNA-vector + recombinant human AMH, and (e) recombinant human AMH. Follicle survival and growth were assessed. Culture media were analyzed for steroid hormone and paracrine factor concentrations. For in vivo study, the non-targeting control shRNA-vector and AMH shRNA-vector were injected into macaque ovaries. Ovaries were collected 9 days post-injection for morphology and immunohistochemistry assessment. Decreased AMH expression reduced preantral follicle survival and growth in nonhuman primates. Supplemental AMH treatment in the culture media promoted preantral follicle growth to the small antral stage in vitro with increased steroid hormone and paracrine factor production, as well as oocyte maturation. These data demonstrate that AMH is a critical follicular paracrine/autocrine factor positively impacting preantral follicle survival and growth in primates.

Yang, J., Chandwani, R., Zhao, R., Wang, Z., Jia, Y., Huang, D., & Liu, G. (2017). **Polarization-multiplexed, dual-beam swept source optical coherence tomography angiography**. *J Biophotonics*. doi:10.1002/jbio.201700303

A polarization-multiplexed, dual-beam setup is proposed to expand the field of view for a swept source optical coherence tomography angiography (OCTA) system. This method used a Wollaston prism to split sample path light into two orthogonal-polarized beams. This allowed two beams to shine on the cornea at an angle separation of ~ 14 degrees, which led to a separation of ~ 4.2 mm on the retina. A 3-mm glass plate was inserted into one of the beam paths to set a constant path length difference between the two polarized beams so the interferogram from the two beams are coded at different frequency bands. The resulting OCTA images from the two beams were coded with a depth separation of ~ 2 mm. 5x5 mm(2) angiograms from the two beams were obtained simultaneously in 4 seconds. The two angiograms then were montaged to get a wider field of view (FOV) of ~ 5x9.2 mm(2) .

Yang, L. Q., Sliter, M., Cheung, J. H., Sinclair, R. R., & Mohr, C. (2017). **The Dark Side of Helping: Does Returning the Favor from Coworkers Hurt Employee Work Engagement?** *Journal of Business and Psychology*, 1-20. doi:10.1007/s10869-017-9522-9

This study investigated the potential "dark side" of helping behavior at work -- operationalized as provision of social support to coworkers. Drawing from the emotional contagion literature and Conservation of Resources (COR) theory, we proposed and tested a moderated mediational model to examine the mechanisms by which social support received from one's coworkers contribute to the support recipient's work engagement. Employing data from a 12-week-long weekly diary among 142 acute care nurses, we did not find support for the proposed negative relationship between providing social support to coworkers and support providers' work engagement, nor for the overall mediational effect of the relationship between received coworker support and work engagement through support provision. However, we found that some work contextual factors (i.e., stable social support climates from coworkers and supervisors) moderated the weekly processes through which nurses' repaying social support received from coworkers predicts their subsequent work engagement. Specifically, providing support to coworkers had stronger beneficial effects on providers' engagement when coworker/supervisor support climates were relatively low; support received from coworkers had stronger indirect beneficial effects on nurses' engagement when coworker/supervisor support climates were relatively low. Our study findings highlight the complexity of the relationship between social support dynamics and work engagement, and that emotional contagion and COR theory may be insufficient, on their own, to explain social support dynamics between coworkers. We also discuss implications of the findings for managerial practices related to support dynamics at work.

Yonge, J. D., Bohan, P. K., Watson, J. J., Connelly, C. R., Eastes, L., & Schreiber, M. A. (2017). **The Respiratory Rate: A Neglected Triage Tool for Pre-hospital Identification of Trauma Patients**. *World J Surg*. doi:10.1007/s00268-017-4353-4

BACKGROUND: Under-triaged trauma patients have worse clinical outcomes. We evaluated the capability of four pre-hospital variables to identify this population at the lowest level trauma activation (level 3). METHODS: A retrospective review of adult trauma activations from 2004 to 2014 was completed. Pre-hospital vital signs and Glasgow Coma Scale were converted to categorical variables. Patients were under-triaged based on meeting current level 1 or 2 criteria, or requiring a pre-defined critical intervention. Logistic regression was used to determine the association between the pre-hospital variables and under-triaged patients. Odds ratios and 95% confidence intervals were calculated for a comprehensive model, grouping all causes of under-triage as a single unit, and 16 individual models, one for each under-triage criterion. A new level 2 criterion was generated and internally validated. RESULTS: In total, 12,332 activations occurred during the study period. Four hundred and sixty-six (5.9%) patients were under-triaged. Compared to patients with a normal respiratory rate (RR), tachypneic patients were more likely to be under-triaged for any reason, OR 1.7

[1.3-2.1], p < 0.001. In the individual event analysis, tachypneic patients were more likely to have flail chest, OR 22 [2.9-168.3], p = 0.003; require a chest tube, OR 3 [1.8-4.9], p < 0.001; or require emergent intubation, OR 1.6 [1.1-2.8], p = 0.04, compared to patients with a normal RR. The data-driven triage modification was tachypnea with suspected thoracic injury which reduced the under-triage rate by 1.2%. CONCLUSION: Tachypnea with suspected thoracic injury is the strongest level 2 triage modification to reduce level 3 under-triage.

Yu, G., Tzouvelekis, A., Wang, R., Herazo-Maya, J. D., Ibarra, G. H., Srivastava, A., . . . Kaminski, N. (2017). **Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function**. *Nature Medicine*. doi:10.1038/nm.4447

Thyroid hormone (TH) is critical for the maintenance of cellular homeostasis during stress responses, but its role in lung fibrosis is unknown. Here we found that the activity and expression of iodothyronine deiodinase 2 (DIO2), an enzyme that activates TH, were higher in lungs from patients with idiopathic pulmonary fibrosis than in control individuals and were correlated with disease severity. We also found that Dio2-knockout mice exhibited enhanced bleomycin-induced lung fibrosis. Aerosolized TH delivery increased survival and resolved fibrosis in two models of pulmonary fibrosis in mice (intratracheal bleomycin and inducible TGF-beta1). Sobetirome, a TH mimetic, also blunted bleomycin-induced lung fibrosis. After bleomycin-induced injury, TH promoted mitochondrial biogenesis, improved mitochondrial bioenergetics and attenuated mitochondria-regulated apoptosis in alveolar epithelial cells both in vivo and in vitro. TH did not blunt fibrosis in Ppargc1a- or Pink1-knockout mice, suggesting dependence on these pathways. We conclude that the antifibrotic properties of TH are associated with protection of alveolar epithelial cells and restoration of mitochondrial function and that TH may thus represent a potential therapy for pulmonary fibrosis.

Zabriskie, M. S., Antelope, O., Verma, A. R., Draper, L. R., Eide, C. A., Pomicter, A. D., . . . O'Hare, T. (2017). **A novel AGGF1-PDGFRbeta fusion in pediatric T-cell acute lymphoblastic leukemia**. *Haematologica*. doi:10.3324/haematol.2017.165282

Zhang, H., Reister Schultz, A., Luty, S., Rofelty, A., Su, Y., Means, S., . . . Tyner, J. W. (2017). **Characterization of the leukemogenic potential of distal cytoplasmic CSF3R truncation and missense mutations**. *Leukemia, 31*(12), 2752-2760. doi:10.1038/leu.2017.126

An increasing number of variants of unknown significance are being identified in leukemia patients with the application of deep sequencing and these include CSF3R cytoplasmic mutations. Previous studies have demonstrated oncogenic potential of certain CSF3R truncation mutations prior to internalization motifs. However, the oncogenic potential of truncating the more distal region of CSF3R cytoplasmic domain as well as cytoplasmic missense mutations remains uncharacterized. Here we identified that CSF3R distal cytoplasmic truncation mutations (Q793-Q823) also harbored leukemogenic potential. Mechanistically, these distal cytoplasmic truncation mutations demonstrated markedly decreased receptor degradation, probably owing to loss of the de-phosphorylation domain (residues N818-F836). Furthermore, all truncations prior to Q823 demonstrated increased expression of the higher molecular weight CSF3R band, which is shown to be essential for the receptor surface expression and the oncogenic potential. We further demonstrated that sufficient STAT5 activation is essential for oncogenic potential. In addition, CSF3R K704A demonstrated transforming capacity due to interruption of receptor ubiquitination and degradation. In summary, we have expanded the region of the CSF3R cytoplasmic domain in which truncation or missense mutations exhibit leukemogenic capacity, which will be useful for evaluating the relevance of CSF3R mutations in patients and helpful in defining targeted therapy strategies.

Zhao, M., Xu, D., Wu, D., Whittaker, J. W., Terkeltaub, R., & Lu, Y. (2017). **Nanocapsules of oxalate oxidase for hyperoxaluria treatment**. *Nano Research*, 1-7. doi:10.1007/s12274-017-1898-3

Enzyme therapeutics have great potential for the treatment of systemic disorders such as urolithiasis and nephrocalcinosis, which are caused by the excessive accumulation of oxalate. However, exogenous enzymes have short half-lives in vivo and elicit high immunogenicity, which largely limit the therapeutic outcomes. Herein, we report a delivery strategy whereby therapeutic enzymes are encapsulated within a thin zwitterionic polymer shell to form enzyme nanocapsules. The strategy is exemplified by the encapsulation of oxalate oxidase (OxO) for the treatment of hyperoxaluria, because as-synthesized OxO nanocapsules have a prolonged blood circulation half-life and elicit reduced immunogenicity. Our design of enzyme nanocapsules that enable the systemic delivery of therapeutic enzymes can be extended to various biomedical applications. [Figure not available: see fulltext.]

Zhao, M. T., Chen, H., Liu, Q., Shao, N. Y., Sayed, N., Wo, H. T., . . . Wu, J. C. (2017). **Molecular and functional resemblance of differentiated cells derived from isogenic human iPSCs and SCNT-derived ESCs**. *Proc Natl Acad Sci U S A, 114*(52), E11111-e11120. doi:10.1073/pnas.1708991114

Patient-specific pluripotent stem cells (PSCs) can be generated via nuclear reprogramming by transcription factors (i.e., induced pluripotent stem cells, iPSCs) or by somatic cell nuclear transfer (SCNT). However, abnormalities and preclinical application of differentiated cells generated by different reprogramming mechanisms have yet to be evaluated. Here we investigated the molecular and functional features, and drug response of cardiomyocytes (PSC-CMs) and endothelial cells (PSC-ECs) derived from genetically relevant sets of human iPSCs, SCNT-derived embryonic stem cells (nt-ESCs), as well as in vitro fertilization embryo-derived ESCs (IVF-ESCs). We found that differentiated cells derived from isogenic iPSCs and nt-ESCs showed comparable lineage gene expression, cellular heterogeneity, physiological properties, and metabolic functions. Genome-wide transcriptome and DNA methylome analysis indicated that iPSC derivatives (iPSC-CMs and iPSC-ECs) were more similar to isogenic nt-ESC counterparts than those derived from IVF-ESCs. Although iPSCs and nt-ESCs shared the same nuclear DNA and yet carried different sources of mitochondrial DNA, CMs derived from iPSC and nt-ESCs could both recapitulate doxorubicin-induced cardiotoxicity and exhibited insignificant differences on reactive oxygen species generation in response to stress condition. We conclude that molecular and functional characteristics of differentiated cells from human PSCs are primarily attributed to the genetic compositions rather than the reprogramming mechanisms (SCNT vs. iPSCs). Therefore, human iPSCs can replace nt-ESCs as alternatives for generating patient-specific differentiated cells for disease modeling and preclinical drug testing.

Zhao, N., Zhang, A. S., Wortham, A. M., Jue, S., Knutson, M. D., & Enns, C. A. (2017). **The Tumor Suppressor, P53, Decreases the Metal Transporter, ZIP14**. *Nutrients, 9*(12). doi:10.3390/nu9121335

Loss of p53's proper function accounts for over half of identified human cancers. We identified the metal transporter ZIP14 (Zinc-regulated transporter (ZRT) and Iron-regulated transporter (IRT)-like Protein 14) as a p53-regulated protein. ZIP14 protein levels were upregulated by lack of p53 and downregulated by increased p53 expression. This regulation did not fully depend on the changes in ZIP14's mRNA expression. Co-precipitation studies indicated that p53 interacts with ZIP14 and increases its ubiquitination and degradation. Moreover, knockdown of p53 resulted in higher non-transferrin-bound iron uptake, which was mediated by increased ZIP14 levels. Our study highlights a role for p53 in regulating nutrient metabolism and provides insight into how iron and possibly other metals such as zinc and manganese could be regulated in p53-inactivated tumor cells.