References

Abraham, A. D., Neve, K. A., & Lattal, K. M. (2016). Effects of D1 receptor knockout on fear and reward learning. *Neurobiology of Learning and Memory*,

Dopamine signaling is involved in a variety of neurobiological processes that contribute to learning and memory. D1-like dopamine receptors (including D1 and D5 receptors) are thought to be involved in memory and reward processes, but pharmacological approaches have been limited in their ability to distinguish between D1 and D5 receptors. Here, we examine the effects of a specific knockout of D1 receptors in associative learning tasks involving aversive (shock) or appetitive (cocaine) unconditioned stimuli. We find that D1 knockout mice show similar levels of cued and contextual fear conditioning to WT controls following conditioning protocols involving one, two, or four shocks. D1 knockout mice show increased generalization of fear conditioning and extinction across contexts, revealed as increased freezing to a novel context following conditioning and decreased freezing to an extinguished cue during a contextual renewal test. Further, D1 knockout mice show mild enhancements in extinction following an injection of SKF81297, a D1/D5 receptor agonist, suggesting a role for D5 receptors in extinction enhancements induced by nonspecific pharmacological agonists. Finally, although D1 knockout mice show decreased locomotion induced by cocaine, they are able to form a cocaine-induced conditioned place preference. We discuss these findings in terms of the role of dopamine D1 receptors in general learning and memory processes.

Abuzeid, W. M., Mace, J. C., Costa, M. L., Rudmik, L., Soler, Z. M., Kim, G. S., et al. (2016). Outcomes of chronic frontal sinusitis treated with ethmoidectomy: A prospective study. *International Forum of Allergy and Rhinology*, *6*(6), 597-604.

Background: In medically refractory chronic frontal sinusitis, ethmoidectomy without instrumentation of the frontal ostium may resolve frontal disease. Our aim was to determine the efficacy of ethmoidectomy alone for the treatment of chronic frontal sinusitis. Methods: Adults with chronic rhinosinusitis prospectively enrolled in a multicenter study who demonstrated frontal sinusitis on computed tomography were divided into 2 groups: (1) endoscopic sinus surgery (ESS) incorporating ethmoidectomy, but excluding frontal sinusotomy; and (2) ESS incorporating frontal sinusotomy. The primary outcome was improvement in 22-item Sino-Nasal Outcome Test

(SNOT-22) scores. Secondary outcomes included endoscopic scores and use of corticosteroids and antibiotics. Results: A total of 196 cases undergoing frontal sinusotomy and 30 cases treated with ethmoidectomy without frontal sinusotomy were analyzed and were comparable demographically. The prevalence of nasal polyps, previous ESS, asthma, and aspirin intolerance was more common in the frontal sinusotomy group ($p < 0.050$). Preoperative endoscopy and computed tomography scores were higher in the frontal sinusotomy group ($p \leq 0.001$). Postoperatively, both groups showed comparable SNOT-22 scores with worse endoscopy scores in the frontal sinusotomy group ($p = 0.038$). Postoperative improvement in SNOT-22 total and subdomain scores was comparable between groups. Nasal endoscopy scores improved to a greater degree in the frontal sinusotomy group ($p = 0.023$). Duration of postoperative topical steroid use was higher in the frontal sinusotomy group ($p = 0.007$). Revision surgery was needed in 2.6% of frontal sinusotomy patients and 0% of patients without frontal sinusotomy. Conclusion: The treatment of chronic frontal sinusitis through ethmoidectomy is a potential alternative to frontal sinusotomy achieving similar quality of life (QOL) improvements in patients manifesting less severe sinus disease.

Al Sabei, S. D., & Lasater, K. (2016). Simulation debriefing for clinical judgment development: A concept analysis. *Nurse Education Today*, *45*, 42-47.

OBJECTIVE: The aim of this review was to provide an in-depth analysis of debriefing in nursing simulation-based learning. Specifically, the authors sought to describe the debriefing concept within the context of enhancing nursing students' clinical judgment skill. DESIGN: Concept analysis. DATA SOURCES: A literature review was conducted using five electronic databases with the addition of references for relevant papers reviewed. Medline Ovid, Cumulative Index to Nursing and Allied Health (CINAHL) Plus, Educational Resources Information Center (ERIC), ScienceDirect and Google Scholar were searched for articles published in English between 2005 and 2015. Search terms included clinical judgment, debriefing, and simulation. REVIEW METHODS: The Walker and Avant systematic approach was utilized as a concept analysis framework. The analysis informed how the concept is defined in the existing literature. RESULTS: The search resulted in a total of 47 articles. The concept of debriefing was analyzed using seven themes from Walker and Avant: concept definition, defining attributes, antecedents,

consequences, empirical referents, uses of the concept, and a model case. Based on the analysis, an integrative simulation debriefing guide for promoting students' clinical judgment was presented as a vehicle for a consistent approach. CONCLUSIONS: This review identified simulation debriefing as a structured and guided reflection process in which students actively appraise their cognitive, affective, and psychomotor performance within the context of their clinical judgment skill. Reflective debriefing provides students with an opportunity to assume an active role during the learning process. Following a structured debriefing guide can help educators and even students facilitate a learning environment that enhances students' clinical judgment development.

Allchin, A., Melchior, M., Fombonne, E., & Surkan, P. J. (2016). Parental social networks during childhood and offspring depression in early adulthood: A lifecourse approach. *Depression and Anxiety*,

BACKGROUND: Little is known on how parental social relationships may affect their children's mental health. We sought to examine the relation between parental social relationship characteristics and subsequent offspring depression in young adulthood. METHODS: We used 2009 Trajectoires Epidemiologiques en Population (TEMPO) study data from 1087 French young adults ages 22 to 35 and parental data from the corresponding Gaz et Electricite (GAZEL) study in 1991. Multivariable logistic regression was used to examine parental social networks, quality of parental relationships, and reciprocity of parental social support measured in 1991 in relation to offspring depression in young adulthood measured using the Adult Self Report in 2009. Analyses were stratified by participant sex. RESULTS: In adjusted models, daughters of parents who reported giving more support to others than they received had 1.72 higher odds (95% CI, 1.09-2.70) of depression in young adulthood. Daughters of parents who were unsatisfied with their social relationships had 2.14 (95% CI, 1.22-3.76) higher odds of depression. Among male participants, there was no statistically significant association between parental relationship satisfaction, reciprocity of parental exchanges, and depression. CONCLUSIONS: Parental relationships during mid-childhood have long-term associations with offspring depression. Results suggest that enhancing social support for parents may have positive implications for their children's mental health.

Alosco, M. L., Jarnagin, J., Tripodis, Y., Platt, M., Martin, B., Chaisson, C., et al. (2016). Olfactory function and associated clinical correlates in former NFL players. *Journal of Neurotrauma*, Professional American football players incur thousands of repetitive head impacts (RHI) throughout their lifetime. The long-term consequences of RHI are not well-characterized, but may include olfactory dysfunction. RHI has been associated with changes to brain regions involved in olfaction, and olfactory impairment is common following traumatic brain injury. Olfactory dysfunction is a frequent early sequelae of neurodegenerative diseases (e.g., Alzheimer's), and RHI is associated with the neurodegenerative disease, chronic traumatic encephalopathy (CTE). We examined olfaction, and its association with clinical measures, in former National Football League (NFL) players. Ninety-five former NFL players (ages 40-69) and 28 same-age controls completed a neuropsychological, and neuropsychiatric evaluation as part of an NIH-funded study. The Brief Smell Identification Test (B-SIT) assessed olfaction. Principal Component Analysis generated a four factor structure of the clinical measures: behavioral/mood, psychomotor speed/executive function, and verbal and visual memory. Former NFL players had worse B-SIT scores relative to controls, p=0.0096. A B-SIT cutoff of 11 had the greatest accuracy (c-statistic=0.61) and specificity (79%) for discriminating former NFL players from controls. In the former NFL players, lower B-SIT scores correlated with greater behavioral/mood impairment, p=0.0254, and worse psychomotor speed/executive functioning, p=0.0464, after controlling for age and education. Former NFL players exhibited lower olfactory test scores relative to controls, and poorer olfactory test performance was associated with worse neuropsychological and neuropsychiatric functioning. Future work that uses more comprehensive tests of olfaction and structural and functioning neuroimaging may improve understanding on the association between RHI and olfaction.

Alt, J. A., Mace, J. C., Smith, T. L., & Soler, Z. M. (2016). Endoscopic sinus surgery improves cognitive dysfunction in patients with chronic rhinosinusitis. *International Forum of Allergy & Rhinology*, BACKGROUND: Patients with chronic rhinosinusitis (CRS) have been found to have cognitive deficit, as identified using the Cognitive Failures Questionnaire (CFQ), but the exact etiology of cognitive decline is unknown. In this study we aimed to determine whether improvement in concomitant inflammation and disease burden in CRS, using endoscopic sinus surgery (ESS),

improves cognitive deficit. We also sought to identify comorbid conditions that effect improvement likelihood. METHODS: Study participants (n = 247) with and without nasal polyposis (CRSwNP, CRSsNP) were prospectively enrolled in this multi-institutional, observational outcomes study. Pre- and postoperative cognitive dysfunction was evaluated using the CFQ instrument. Quality of life (QOL) and disease burden was also evaluated using the Rhinosinusitis Disability Index (RSDI), the 22-item SinoNasal Outcome Test (SNOT-22), nasal endoscopy, computed tomography, and the 2-item Patient Health Questionnaire (PHQ-2). RESULTS: Average CFQ total scores improved significantly (p = 0.012) after ESS for patients with follow-up (n = 141). Participants with CRSwNP (n = 51) reported significant postoperative improvements in mean CFQ total scores (p = 0.002) and CFQ distractibility and blunders domain scores (p 0.086). The magnitude of postoperative improvement in CFQ total and domain mean scores was statistically similar between CRSsNP and CRSwNP (p > 0.115). Depressive disorder, identified using PHQ-2 screening, was the only comorbid condition significantly associated with measurable cognitive deficit (p < 0.001). CONCLUSIONS: Patients with CRS have measurable cognitive decline, and ESS may modestly improve cognitive deficit/CFQ scores. Future investigations are needed to further elucidate the underlying mechanisms responsible for cognitive deficit in patients with CRS and significant associations with depression.

Alumkal, J. J., & Beer, T. M. (2016). Raising the bar for therapeutic trials in advanced prostate cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

Arora, R., & Press, R. D. (2016). Measurement of BCR-ABL1 transcripts on the international scale in the united states: Current status and best practices. *Leukemia & Lymphoma*, , 1-9.
Chronic myeloid leukemia (CML) results from the Philadelphia chromosome (Ph) translocation and expression of its fusion oncoprotein BCR-ABL1. BCR-ABL1 tyrosine kinase inhibitors (TKIs) are the standard therapy for Ph-positive CML. Achievement of deep molecular responses (typically defined as >/=4-log reduction in BCR-ABL1 RNA levels) is an emerging treatment goal becoming attainable for more patients due to the availability of second-generation TKIs. Deep molecular responses are associated with improved long-term outcomes and are required prior to attempting cessation of treatment in treatment-free remission clinical trials. The National Comprehensive

Cancer Network and European LeukemiaNet recommend regular monitoring of BCR-ABL1 RNA levels using real-time quantitative polymerase chain reaction (RQ-PCR). However, BCR-ABL1 RQ-PCR is a complex laboratory-developed test; routine quantitative results from clinical diagnostic laboratories may differ from those used to establish the recommendations. Although an International Scale (IS) was developed for standardized reporting of BCR-ABL1 RNA levels, IS adoption has been slow in the United States, but is now used by the vast majority of laboratories. Here, we discuss the importance of molecular monitoring in CML, gaps between current and best molecular monitoring practices in the United States, and challenges and potential solutions for universal IS adoption in the United States.

Aschner, M., Ceccatelli, S., Daneshian, M., Fritsche, E., Hasiwa, N., Hartung, T., et al. (2016). Reference compounds for alternative test methods to indicate developmental neurotoxicity (DNT) potential of chemicals: Example lists and criteria for their selection and use. *Altex*,
There is a paucity of information concerning the developmental neurotoxicity (DNT) hazard posed by industrial and environmental chemicals. New testing approaches will most likely be based on batteries of alternative and complementary (non-animal) tests. As DNT is assumed to result from the modulation of fundamental neurodevelopmental processes (such as neuronal differentiation, precursor cell migration or neuronal network formation) by chemicals, the first generation of alternative DNT tests target these processes. The advantage of such types of assays is that they capture toxicants with multiple targets and modes-of-action. Moreover, the processes modelled by the assays can be linked to toxicity endophenotypes, i.e. alterations in neural connectivity that form the basis for neurofunctional deficits in man. The authors of this review convened in a workshop to define criteria for the selection of positive/negative controls, to prepare recommendations on their use, and to initiate the setup of a directory of reference chemicals. For initial technical optimization of tests, a set of >50 endpoint-specific control compounds was identified. For further test development, an additional "test" set of 33 chemicals considered to act directly as bona fide DNT toxicantsis proposed, and each chemical is annotated to the extent it fulfills these criteria. A tabular compilation of the original literature used to select the test set chemicals provides information on statistical procedures, and toxic/non-toxic doses (both for pups and dams). Suggestions are provided on how to use the >100 compounds (including

negative controls) compiled here to address specificity, adversity and use of alternative test systems.

Atkins, K. L., Duvall, S. W., Dolata, J. K., Blasco, P. M., & Saxton, S. N. (2016). Part C early intervention enrollment in low birth weight infants at-risk for developmental delays. *Maternal and Child Health Journal*,

Objectives To investigate enrollment patterns in Part C Early Intervention (EI) for low birth weight (LBW) infants (</=2500 g). A secondary aim is to characterize LBW infants that are not enrolled in EI, but would qualify by meeting criteria for a condition associated with a "high-probability" for developmental delays (i.e., Intraventricular Hemorrhage grade III or higher, Apgar score of </=5 at 5 min, and/or birth weight of </=1200 g). Methods Data were gathered from 165 LBW infants participating in a high-risk infant follow-up program. Developmental assessment was completed. Basic demographic information and data regarding enrollment in EI were collected via parent questionnaire. Medical variables were extracted from each infant's electronic medical record. Results 71.5 % of LBW infants were not enrolled in EI. Factors influencing probability of EI enrollment included birth weight, gestational age, developmental test scores, and insurance status. Of the 107 infants living in Oregon who were not enrolled in EI, 42.1 % would qualify for services due to an early medical condition identified in Oregon as a condition associated with a "high-probability" for developmental delays. Conclusions Less than one third of LBW infants were enrolled in EI by their first visit to a high-risk infant follow-up program. Those infants demonstrating developmental delays and public insurance were more likely to be enrolled. The majority of infants who have readily identifiable medical risk factors that qualify them for EI were not enrolled. This study was limited by the constraints implicated by using a clinical sample.

Atkinson, C., Ray, R. M., Li, W., Lin, M. G., Gao, D. L., Shannon, J., et al. (2016). Plasma equol concentration is not associated with breast cancer and fibrocystic breast conditions among women in shanghai, china. *Nutrition Research (New York, N.Y.), 36*(8), 863-871.

Equol (a bacterial metabolite of the soy isoflavone daidzein) is produced by 30% to 50% of humans and may be associated with health outcomes. We hypothesized that plasma equol would

be inversely associated with risks of fibrocystic breast conditions (FBC) and breast cancer (BC). Plasma from women in a breast self-examination trial in Shanghai with BC (n=269) or FBC (n=443), and age-matched controls (n=1027) was analyzed for isoflavones. Equol was grouped into categories (/=45nmol/L) and, among women with daidzein >/=20nmol/L, the log10 equol:daidzein ratio was grouped into tertiles. Where available, non-cancerous tissue (NCT) adjacent to the carcinomas from women with BC were classified as non-proliferative or proliferative (n=130 and 172, respectively). The lesions from women with FBC were similarly classified (n=99 and 92, respectively). Odds ratios (OR) and 95% confidence intervals (CI) were calculated across equol categories and tertiles of log10 equol:daidzein ratio. Equol categories were not associated with FBC or BC (P>.05). For log10 equol:daidzein, compared to controls there were positive associations in the mid tertile for proliferative FBC (OR 2.06, 95% CI 1.08-3.93), BC with proliferative NCT (OR 2.95, 95% CI 1.37-6.35), and all BC regardless of histology (OR 2.37, 95% CI 1.43-3.95). However, trends in ORs with increasing plasma equol values or equol:daidzein ratios were not observed (P>.05). The results of this study do not provide evidence that equol plays a role in the etiology of these breast conditions. However, further work is needed to confirm or refute this conclusion.

Austin, J., Dodge, H. H., Riley, T., Jacobs, P. G., Thielke, S., & Kaye, J. (2016). A smart-home system to unobtrusively and continuously assess loneliness in older adults. *IEEE Journal of Translational Engineering in Health and Medicine, 4*

Loneliness is a common condition in older adults and is associated with increased morbidity and mortality, decreased sleep quality, and increased risk of cognitive decline. Assessing loneliness in older adults is challenging due to the negative desirability biases associated with being lonely. Thus, it is necessary to develop more objective techniques to assess loneliness in older adults. In this paper, we describe a system to measure loneliness by assessing in-home behavior using wireless motion and contact sensors, phone monitors, and computer software as well as algorithms developed to assess key behaviors of interest. We then present results showing the accuracy of the system in detecting loneliness in a longitudinal study of 16 older adults who agreed to have the sensor platform installed in their own homes for up to 8 months. We show that loneliness is significantly associated with both time out-of-home (β = -0.88 and $p<0.01$) and

number of computer sessions (β = 0.78 and p<0.05). R2 for the model was 0.35. We also show the model's ability to predict out-of-sample loneliness, demonstrating that the correlation between true loneliness and predicted out-of-sample loneliness is 0.48. When compared with the University of California at Los Angeles loneliness score, the normalized mean absolute error of the predicted loneliness scores was 0.81 and the normalized root mean squared error was 0.91. These results represent first steps toward an unobtrusive, objective method for the prediction of loneliness among older adults, and mark the first time multiple objective behavioral measures that have been related to this key health outcome. © 2016 IEEE.

Aylor, M., Campbell, E. M., Winter, C., & Phillipi, C. A. (2016). Resident notes in an electronic health record: A mixed-methods study using a standardized intervention with qualitative analysis. *Clinical Pediatrics,*

Adoption of electronic health records (EHRs) has forced a transition in medical documentation, yet little is known about clinician documentation in the EHR. This study compares electronic inpatient progress notes written by residents pre- and post introduction of standardized note templates and investigates resident perceptions of EHR documentation. A total of 454 resident progress notes pre- and 610 notes post-template introduction were identified. Note length was 263 characters shorter (P = .004) and mean end time was 73 minutes later (P < .0001) with new template implementation. In subanalysis of 100 notes, the assessment and plan section was 46 words shorter with the new template (P < .01). Among survey respondents, 89% liked the new note templates, 78% stated the new templates facilitated note completion. The resident focus group revealed ambivalence toward the EHR's contribution to note writing. Note templates resulted in shorter notes. Residents appreciate electronic note templates but are unsure if the EHR supports note writing overall.

Azarisamani, A., Petrisor, D., Wright, J., & Ghali, G. E. (2016). Metastatic melanotic neuroectodermal tumor of infancy: Report of a case and review of the literature. *Journal of Oral and Maxillofacial Surgery : Official Journal of the American Association of Oral and Maxillofacial Surgeons,*

Melanotic neuroectodermal tumors of infancy (MNTI) are rapidly growing pigmented tumors that occur predominantly within bony head and neck structures. There are fewer than 400 cases

reported in the literature with the majority affecting the maxilla. Locations in other intraosseous and extraosseous structures have been characterized, including the mandible (6% of MNTIs). Infants in the first year of life are primarily affected. Surgical resection is the primary treatment modality with and without adjuvant chemotherapy for malignant tumors, which comprise less than 25 cases in the literature, and of metatstatic mandibular tumors, which has only been documented in one other case. The purpose of this investigation is to review associated literature and present a case highlighting treatment considerations of a metastatic mandibular MNTI. We present the case of a six month old boy with a rapidly growing bluish mass of the right mandible. Preoperatively incisional biopsy led to a diagnosis of MNTI and subsequent surgical planning involved hemimandibulectomy from the right mandibular condyle to the left posterior body region with one centimeter margins. At the time of initial surgery, enlarged lymph nodes removed from the neck demonstrated abnormality consistent with metastatic spread of the tumor. Islands of tumor cells were noted: small, round, bluestaining cells resembling neuroblasts with mitotic activity as well as pigmented cells containing melanin. Because of regional node metastasis, chemotherapy was completed following surgery. The patient recovered and was followed without evidence of recurrence. At 3.5 years postresection, a secondary reconstruction was completed using a fibula osteocutaneous free flap combined with a costochondral rib graft. In reviewing similar cases of malignant MNTI reported in the literature, a search of the MEDLINE database until 2014 was performed. These were evaluated based on management type and outcome, including surgical and chemotherapeutic treatments and the incidence of recurrence or metastasis.

Bacchi, A., & Pfeifer, C. S. (2016). Rheological and mechanical properties and interfacial stress development of composite cements modified with thio-urethane oligomers. *Dental Materials, 32*(8), 978-986.

Objectives Thio-urethane oligomers have been shown to reduce stress and increase toughness in highly filled composite materials. This study evaluated the influence of thio-urethane backbone structure on rheological and mechanical properties of resin cements modified with a fixed concentration of the oligomers. Methods Thio-urethane oligomers (TU) 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-UDMA-TEGDMA (5:3:2). 60 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), and notched specimens (ASTM Standard E399-90) for fracture toughness (KIC). PS was measured on the Bioman. Viscosity (V) and gel-points (defined as the crossover between storage and loss shear moduli (G'/G")) were obtained with rheometry. Glass transition temperature (Tg), cross-link density and homogeneity of the network were obtained with dynamic mechanical analysis. Film-thickness was evaluated according to ISO 4049. Results DC and mechanical properties increased and Rpmax and PS decreased with the addition of TUs. Gelation (G'/G") was delayed and DC at G'/G" increased in TU groups. Tg and cross-link density dropped in TU groups, while oligomers let to more homogenous networks. An increase in V was observed, with no effect on film-thickness. Significant reductions in PS were achieved at the same time conversion and mechanical properties increased. Significance The addition of thio-urethane oligomers proved successful in improving several key properties of resin cements, without disrupting the procedures dentists use to polymerize the material. This approach has potential to be translated to commercial materials very readily.

Bagby, G. C. (2016). Multifunctional fanconi proteins, inflammation and the fanconi phenotype. *Ebiomedicine, 8*, 10-11.

Baird, L. C. (2016). First treatment in infants with hydrocephalus: The case for endoscopic third Ventriculostomy/Choroid plexus cauterization. *Neurosurgery, 63 Suppl 1*, 78-82.

Bakewell-Sachs, S. (2016). Academic-practice partnerships: Driving and supporting educational changes. *The Journal of Perinatal & Neonatal Nursing, 30*(3), 184-186.

The 3 recognized missions of academic nursing-education, practice, and research-are not new. Yet, the continued separation of nursing education and service, with a lack of integration between

schools of nursing and clinical practice, continues to be discussed as contributing to academic programs that produce graduates unready for clinical practice, research that does not adequately support clinical care needs, and isolation of both the nurse faculty from the clinical enterprise and clinicians from the education and research missions. Recently, academic-practice partnerships have been reemphasized as a concept and mechanism for supporting changes in nursing education and improving clinical care. This article highlights some of the driving forces behind the focus on academic-practice partnerships and summarizes 3 changes in education.

Barbara, T. M. (2016). White matter shifts in MRI: Rehabilitating the lorentz sphere in magnetic resonance. *Journal of Magnetic Resonance (San Diego, Calif.: 1997), 270*, 40-46.

A thorough exposition and analysis of the role of the Lorentz sphere in magnetic resonance is presented from the fundamental standpoint of macroscopic magnetostatics. The analysis will be useful to those interested in understanding susceptibility and chemical shift contributions to frequency shifts in magnetic resonance. Though the topic is mature, recent research on white matter shifts in the brain promotes the notion of replacing the Lorentz sphere with a generalized Lorentzian cylinder, and has put into question the long standing spherical approach when elongated structures are present. The cavity shape issue can be resolved by applying Helmholtz's theorem, which can be expressed in a differential and an integral formulation. The general validity of the Lorentz sphere for any situation is confirmed. Furthermore, a clear exposition of the "generalized approach" is offered, using the language of Lorentz's theory. With the rehabilitation of the Lorentz sphere settled, one must consider alternative contributions to white matter shifts and a likely candidate is the effect of molecular environment on chemical shifts.

Barragan, F., Irwin, J. C., Balayan, S., Erikson, D. W., Chen, J. C., Houshdaran, S., et al. (2016). Human endometrial fibroblasts derived from mesenchymal progenitors inherit progesterone resistance and acquire an inflammatory phenotype in the endometrial niche in endometriosis. *Biology of Reproduction, 94*(5)

Human endometrium undergoes cyclic regeneration involving stem/progenitor cells, but the role of resident endometrial mesenchymal stem cells (eMSC) as progenitors of endometrial stromal fibroblasts (eSF) has not been definitively demonstrated. In endometriosis, eSF display

progesterone (P4) resistance with impaired decidualization in vivo and in vitro. To investigate eMSC as precursors of eSF and whether endometriosis P4 resistance is inherited from eMSC, we analyzed transcriptomes of eutopic endometrium eMSC and eSF isolated by fluorescenceactivated cell sorting (FACS) from endometriosis (eMSCendo, eSFendo) and controls (eMSCcontrol, eSFcontrol) and their derived primary cultures. Differentially expressed lineage-associated genes (LG) of FACS-isolated eMSC and eSF were largely conserved in endometriosis. In culture, eSFcontrol maintained in vitro expression of a subset of eSF LG and decidualized in vitro with P4. The eMSCcontrol cultures differentiated in vitro to eSF lineage, down-regulating eMSC LG and up-regulating eSF LG, showing minimal transcriptome differences versus eSFcontrol cultures and decidualizing in vitro. Cultured eSFendo displayed less in vitro LG stability and did not decidualize in vitro. In vitro, eMSCendo differentiated to eSF lineage but showed more differentially expressed genes versus eSFendo cultures, and did not decidualize in vitro, demonstrating P4 resistance inherited from eMSCendo. Compared to controls, cultures from tissuederived eSFendo uniquely had a pro-inflammatory phenotype not present in eMSCendo differentiated to eSF in vitro, suggesting divergent niche effects for in vivo versus in vitro lineage differentiation. These findings substantiate eMSC as progenitors of eSF and reveal eSF in endometriosis as having P4 resistance inherited from eMSC and a pro-inflammatory phenotype acquired within the endometrial niche.

Barrett, D. M., Gerecci, D., & Wang, T. D. (2016). Facelift controversies. *Facial Plastic Surgery Clinics of North America*, *24*(3), 357-366.

The primary purpose of the facelift is to restore the shape, volume, and contours of the youthful face. Facelift surgery has evolved over the years into multiple techniques to accomplish the same results. This article discusses the common controversies in facelift surgery and evaluates the best available evidence to guide surgical decision-making. In regard to the salient question of whether there is a "best" technique, the literature suggests that the options are generally equal in efficacy. This highlights the need for high-quality research with standardized preoperative assessment and evaluation of postoperative results to better assess outcomes.

Barstow, C. K., Nagel, C. L., Clasen, T. F., & Thomas, E. A. (2016). Process evaluation and assessment of use of a large scale water filter and cookstove program in rwanda. *BMC Public Health, 16*, 584-016-3237-0.

BACKGROUND: In an effort to reduce the disease burden in rural Rwanda, decrease poverty associated with expenditures for fuel, and minimize the environmental impact on forests and greenhouse gases from inefficient combustion of biomass, the Rwanda Ministry of Health (MOH) partnered with DelAgua Health (DelAgua), a private social enterprise, to distribute and promote the use of improved cookstoves and advanced water filters to the poorest quarter of households (Ubudehe 1 and 2) nationally, beginning in Western Province under a program branded Tubeho Neza ("Live Well"). The project is privately financed and earns revenue from carbon credits under the United Nations Clean Development Mechanism. METHODS: During a 3-month period in late 2014, over 470,000 people living in over 101,000 households were provided free water filters and cookstoves. Following the distribution, community health workers visited nearly 98 % of households to perform household level education and training activities. Over 87 % of households were visited again within 6 months with a basic survey conducted. Detailed adoption surveys were conducted among a sample of households, 1000 in the first round, 187 in the second. RESULTS: Approximately a year after distribution, reported water filter use was above 90 % (+/- 4 % CI) and water present in filter was observed in over 76 % (+/-6 % CI) of households, while the reported primary stove was nearly 90 % (+/-4.4 % CI) and of households cooking at the time of the visit, over 83 % (+/-5.3 % CI) were on the improved stove. There was no observed association between household size and stove stacking behavior. CONCLUSIONS: This program suggests that free distribution is not a determinant of low adoption. It is plausible that continued engagement in households, enabled by Ministry of Health support and carbon financed revenue, contributed to high adoption rates. Overall, the program was able to demonstrate a privately financed, public health intervention can achieve high levels of initial adoption and usage of household level water filtration and improved cookstoves at a large scale.

Barton, J. L., Trupin, L., Schillinger, D., Evans-Young, G., Imboden, J., Montori, V. M., et al. (2016). Use of low-literacy decision aid to enhance knowledge and reduce decisional conflict among a diverse population of adults with rheumatoid arthritis: Results of a pilot study. *Arthritis Care and*

Research, *68*(7), 889-898.

Objective: Despite innovations in treatment of rheumatoid arthritis (RA), adherence is poor and disparities persist. Shared decision making (SDM) promotes patient engagement and enhances adherence; however, few tools support SDM in RA. Our objective was to pilot a low-literacy medication guide and decision aid to facilitate patient-clinician conversations about RA medications. Methods: RA patients were consecutively enrolled into 1 of 3 arms: 1) control; patients received existing medication guide prior to clinic visit, 2) adapted guide prior to visit, and 3) adapted guide prior to plus decision aid during visit. Outcomes were collected immediately postvisit, at 1-week, and at 3- and 6-month interviews. Eligible adults had to have failed at least 1 disease-modifying antirheumatic drug and fulfill 1 of the following: age >65 years, immigrant, non–English speaker, less than high school education, limited health literacy, and racial/ethnic minority. Primary outcomes were knowledge of RA medications, decisional conflict, and acceptability of interventions. Results: The majority of 166 patients were immigrants (66%), non–English speakers (54%), and had limited health literacy (71%). Adequate RA knowledge postvisit in arm 3 was higher (78%) than arm 1 (53%; adjusted odds ratio 2.7, 95% confidence interval 1.2, 6.1). Among patients with a medication change, there was lower (better) mean decisional conflict in arms 2 and 3 (P = 0.03). There were no significant differences in acceptability. Conclusion: A low-literacy medication guide and decision aid was acceptable, improved knowledge, and reduced decisional conflict among vulnerable RA patients. Enhancing knowledge and patient engagement with decision support tools may lead to medication choices better aligned with RA patients' values and preferences. © 2016, American College of Rheumatology

Beachler, D. C., Yanik, E. L., Martin, B. I., Pfeiffer, R. M., Mirza, S. K., Deyo, R. A., et al. (2016). Bone morphogenetic protein use and cancer risk among patients undergoing lumbar arthrodesis: A case-cohort study using the SEER-medicare database. *The Journal of Bone and Joint Surgery.American Volume*, *98*(13), 1064-1072.

BACKGROUND: Recombinant bone morphogenetic proteins (BMPs) are growth factors utilized in lumbar arthrodeses. Limited data from randomized trials suggest that BMP may increase cancer risk. We sought to evaluate cancer risk and mortality following the use of BMP in lumbar

arthrodesis. METHODS: Within the linked Surveillance, Epidemiology, and End Results (SEER) Program-Medicare cohort, we conducted a case-cohort study of 7,278 individuals who were >/=65 years of age and had undergone a lumbar arthrodesis from 2004 to 2011. Of these patients, 3,627 were individuals in a 5% random subcohort of Medicare enrollees in SEER areas including 191 who developed cancer, and there were 3,651 individuals outside the subcohort who developed cancer. Weighted Cox proportional-hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for cancer on the basis of exposure to BMP. RESULTS: In the SEER-Medicare subcohort, 30.7% of individuals who underwent a lumbar arthrodesis received BMP. BMP was not associated with overall cancer risk in univariate analyses (HR, 0.92 [95% CI, 0.82 to 1.02]) or after adjustment for demographic characteristics, comorbidities, hospital size, history of cancer, and calendar year (adjusted HR, 0.94 [95% CI, 0.84 to 1.05]). Individual cancer types were also not significantly elevated ($p > 0.05$ for all) in BMP users compared with nonusers. In addition, BMP use was not associated with a new cancer in people who had cancer prior to undergoing lumbar arthrodesis (adjusted HR, 1.04 [95% CI, 0.71 to 1.52]) or with mortality after a cancer diagnosis (adjusted HR, 1.05 [95% CI, 0.93 to 1.19]). CONCLUSIONS: In a large population of elderly U.S. adults undergoing lumbar arthrodesis, BMP use was not associated with cancer risk or mortality. LEVEL OF EVIDENCE: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Beauchamp, G. A., & Perrone, J. (2016). Making surveys count: Enhancing the rigor of survey-based research in medical toxicology. *Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology*,

Bellur, S., Jain, M., Cuthbertson, D., Krakow, D., Shapiro, J. R., Steiner, R. D., et al. (2016). Cesarean delivery is not associated with decreased at-birth fracture rates in osteogenesis imperfecta. *Genetics in Medicine, 18*(6), 570-576.

Purpose: Osteogenesis imperfecta (OI) predisposes to recurrent fractures. Patients with the moderate to severe forms of OI present with antenatal fractures, and the mode of delivery that would be safest for the fetus is not known. Methods: We conducted systematic analyses of the

largest cohort of individuals with OI (n = 540) enrolled to date in the OI Linked Clinical Research Centers. Self-reported at-birth fracture rates were compared among individuals with OI types I, III, and IV. Multivariate analyses utilizing backward-elimination logistic regression model building were performed to assess the effect of multiple covariates, including method of delivery, on fracture-related outcomes. Results: When accounting for other covariates, at-birth fracture rates did not differ based on whether delivery was by vaginal route or by cesarean delivery (CD). Increased birth weight conferred higher risk for fractures irrespective of the delivery method. In utero fracture, maternal history of OI, and breech presentation were strong predictors for choosing CD. Conclusion: Our study, the largest to analyze the effect of various factors on at-birth fracture rates in OI, shows that CD is not associated with decreased fracture rate. With the limitation that the fracture data were self-reported in this cohort, these results suggest that CD should be performed only for other maternal or fetal indications, not for the sole purpose of fracture prevention in OI. © 2016 American College of Medical Genetics and Genomics.

Ben-Ami, E., Barysauskas, C. M., von Mehren, M., Heinrich, M. C., Corless, C. L., Butrynski, J. E., et al. (2016). Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*,

BACKGROUND: This investigator-initiated trial provided the justification for the phase III GRID study resulting in worldwide regulatory approval of regorafenib as a third-line therapy for patients with metastatic gastrointestinal stromal tumors (GIST). We report the genotype analyses, long-term safety, and activity results from this initial trial of regorafenib in GIST. PATIENTS AND METHODS: The trial was conducted between February 2010 and January 2014, among adult patients with metastatic GIST, after failure of at least imatinib and sunitinib. Patients received regorafenib orally, 160 mg once daily, days 1-21 of a 28-day cycle. Clinical benefit rate (CBR), defined as complete or partial response (PR), or stable disease lasting >/=16 weeks per RECIST 1.1, progression-free survival (PFS), overall survival (OS), long-term safety data, and metabolic response by functional imaging were assessed. RESULTS: Thirty-three patients received at least one dose of regorafenib. The median follow-up was 41 months. CBR

was documented in 25 of 33 patients [76%; 95% confidence interval (CI) 58% to 89%], including six PRs. The median PFS was 13.2 months (95% CI 9.2-18.3 months) including four patients who remained progression-free at study closure, each achieving clinical benefit for more than 3 years (range 36.8-43.5 months). The median OS was 25 months (95% CI 13.2-39.1 months). Patients whose tumors harbored a KIT exon 11 mutation demonstrated the longest median PFS (13.4 months), whereas patients with KIT/PDGFRA wild-type, non-SDH-deficient tumors experienced a median 1.6 months PFS ($P < 0.0001$). Long-term safety profile is consistent with previous reports; hand-foot skin reaction and hypertension were the most common reasons for dose reduction. Notably, regorafenib induced objective responses and durable benefit in SDH-deficient GIST. CONCLUSIONS: Long-term follow-up of patients with metastatic GIST treated with regorafenib suggests particular benefit among patients with primary KIT exon 11 mutations and those with SDH-deficient GIST. Dose modifications are frequently required to manage treatment-related toxicities. CLINICAL TRIAL NUMBER: NCT01068769.

Bennett, R. M. (2016). Pain management in fibromyalgia. *Pain Management*, *6*(4), 313-316.

Benthin, C., Pannu, S., Khan, A., Gong, M., & NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. (2016). The nature and variability of automated practice alerts derived from electronic health records in a U.S. nationwide critical care research network. *Annals of the American Thoracic Society*,

RATIONALE: The nature, variability and extent of early warning clinical practice alerts derived from automated query of electronic health records (e-alerts) currently employed in acute care settings for clinical care or research is unknown. OBJECTIVES: To describe e-alerts in current use in acute care settings at medical centers participating in a nationwide critical care research network. METHODS: We surveyed investigators at 38 institutions involved in the NIH-funded Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL) for quantitative and qualitative analysis. MEASUREMENTS AND MAIN RESULTS: Thirty sites completed the survey (79% response rate). All sites utilized electronic health record systems. Epic Systems was used at 56% of sites: the others used alternate commercially available vendors or homegrown systems. Respondents at 57% sites represented in this survey used e-alerts. All

but one of these 17 sites used an e-alert for early detection of sepsis-related syndromes, and 35% used an e-alert for pneumonia. E-alerts were triggered by abnormal laboratory values (37%), vital signs (37%) or radiology reports (15%), and were used about equally for clinical decision support and research. Only 59% of sites with e-alerts have evaluated them either for accuracy or for validity. CONCLUSIONS: A majority of the research network sites participating in this survey use e-alerts for early notification of potential threats to hospitalized patients; however, there was significant variability in the nature of e-alerts between institutions. Utilization of one common electronic health record vendor at over half of the participating sites suggests that it may be possible to standardize e-alerts across multiple sites in research networks, particularly among sites using the same medical record platform.

Berger, E. R., Clements, R. H., Morton, J. M., Huffman, K. M., Wolfe, B. M., Nguyen, N. T., et al. (2016). The impact of different surgical techniques on outcomes in laparoscopic sleeve gastrectomies: The first report from the metabolic and bariatric surgery accreditation and quality improvement program (MBSAQIP). *Annals of Surgery*,

OBJECTIVE: Questions remain regarding best surgical techniques to use for a laparoscopic sleeve gastrectomy (LSG) including the use of staple line reinforcement (SLR), bougie size (BS), and distance from the pylorus (DP) where the staple line is initiated. Our objectives were to assess the impact of these techniques on 30-day outcomes and to evaluate the impact of these techniques on weight loss and comorbidities at 1 year. METHODS: Using the MBSAQIP data registry, univariate analyses and hierarchical logistical regression models were developed to analyze outcomes for techniques of LSG at patient and surgeon-level. RESULTS: A total of 189,477 LSG operations were performed by 1634 surgeons at 720 centers from 2012 to 2014. Eighty percent of surgeons used SLR, 20% did not. SLR cases were associated with higher leak rates (0.96% vs 0.65%, odds ratio [OR] 1.20 95% confidence interval [CI] 1.00-1.43) and lower bleed rates (0.75% vs 1.00%, OR 0.74 95% CI 0.63-0.86) compared to no SLR at patient level. At the surgeon level, leak rates remained significant, but bleeding events became nonsignificant. BS >/=38 was associated with significantly lower leak rates compared to BS /=40 was associated with increased weight loss. DP had no impact on leaks or bleeds but showed an increase in weight loss with increasing DP. CONCLUSION: LSG is a safe procedure with a low morbidity rate.

SLR is associated with increased leak rates. A surgeon should consider risks, benefits, and costs of these surgical techniques when performing a LSG and selectively utilize those that, in their hands, minimize morbidity while maximizing clinical effectiveness.

Berland, M. A., Ulloa-Leal, C., Barria, M., Wright, H., Dissen, G. A., Silva, M. E., et al. (2016). Seminal plasma induces ovulation in llamas in the absence of a copulatory stimulus: Role of nerve growth factor as an ovulation-inducing factor. *Endocrinology, 157*(8), 3224-3232.

Llamas are considered to be reflex ovulators. However, semen from these animals is reported to be rich in ovulation-inducing factor(s), one of which has been identified as nerve growth factor (NGF). These findings suggest that ovulation in llamas may be elicited by chemical signals contained in semen instead of being mediated by neural signals. The present study examines this notion. Llamas displaying a preovulatory follicle were assigned to four groups: group 1 received an intrauterine infusion (IUI) of PBS; group 2 received an IUI of seminal plasma; group 3 was mated to a male whose urethra had been surgically diverted (urethrostomized male); and group 4 was mated to an intact male. Ovulation (detected by ultrasonography) occurred only in llamas mated to an intact male or given an IUI of seminal plasma and was preceded by a surge in plasma LH levels initiated within an hour after coitus or IUI. In both ovulatory groups, circulating beta-NGF levels increased within 15 minutes after treatment, reaching values that were greater and more sustained in llamas mated with an intact male. These results demonstrate that llamas can be induced to ovulate by seminal plasma in the absence of copulation and that copulation alone cannot elicit ovulation in the absence of seminal plasma. In addition, our results implicate beta-NGF as an important mediator of seminal plasma-induced ovulation in llamas because ovulation does not occur if beta-NGF levels do not increase in the bloodstream, a change that occurs promptly after copulation with an intact male or IUI of seminal plasma.

Bharadwaj, A. S., Stempel, A. J., Olivas, A., Franzese, S. E., Ashander, L. M., Ma, Y., et al. (2016). Molecular signals involved in human B cell migration into the retina: In vitro investigation of ICAM-1, VCAM-1, and CXCL13. *Ocular Immunology and Inflammation*, , 1-9.

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.

Billups, S. J., Olson, K. L., Saseen, J. J., Irwin, A. N., Touchette, D. R., Chennault, R. R., et al. (2016). Evaluation of the effect of A structured program to guide residents' experience in research (ASPIRE) on pharmacy residents' knowledge, confidence, and attitude toward research. *Pharmacotherapy*, *36*(6), 631-637.

Study Objective: To evaluate the effect of A Structured Program to guide Resident Experience in Research (ASPIRE) on pharmacy residents' knowledge, confidence, and attitude toward research. Design: Nonrandomized controlled study using data from a validated questionnaire administered through an online survey. Participants: Of 60 pharmacy residents (residency year 2013–2014) who completed the baseline assessment, the 41 residents who also completed the follow-up assessment were included in the final analysis; of those, 26 Colorado pharmacy postgraduate year 1 (PGY1) and year 2 (PGY2) residents were enrolled in ASPIRE between July 2013 and June 2014 (intervention group) and 16 PGY1 and PGY2 pharmacy residents outside of Colorado did not participate in ASPIRE (control group). Measurements and Main Results: Both the intervention and control groups completed a pre- and post-assessment at the beginning (July 2013 [baseline]) and end (May/June 2014 [follow-up]), respectively, of their residency year that measured knowledge (with a tool measuring biostatistics and research methodology knowledge), confidence, and attitude toward research. Research knowledge scores improved similarly from baseline to follow-up in the intervention and control groups: 11.8% and 11.3%, respectively (adjusted p=0.8). Research confidence improved significantly more in the intervention group,

with a 48% increase in confidence score from before to after residency completion, compared with a 15% increase in the control group (adjusted p=0.002). Residents in both the intervention and control groups expressed positive attitudes toward pharmacist-conducted research, with 100% and 87% of intervention and control residents, respectively (adjusted p=0.970), agreeing that pharmacist-conducted research is essential to driving pharmacy practice and expanding the roles of pharmacists. Conclusion: ASPIRE was not associated with greater research methodology knowledge but did significantly increase confidence in performing research.

Birch, D. G., Bennett, L. D., Duncan, J. L., Weleber, R. G., & Pennesi, M. E. (2016). Long-term follow-up of patients with retinitis pigmentosa (RP) receiving intraocular ciliary neurotrophic factor implants. *American Journal of Ophthalmology*,

PURPOSE: To evaluate the long-term efficacy of ciliary neurotrophic factor delivered via an intraocular encapsulated cell implant for the treatment of retinitis pigmentosa (RP). DESIGN: Long-term follow up of a multicenter, sham-controlled study. METHODS: Thirty-six patients at three CNTF4 sites were randomly assigned to receive a high- or low- dose implant in one eye and sham surgery in the fellow eye. The primary endpoint (change in visual field sensitivity at 12 months) has been reported previously.1 Here we report long-term visual acuity, visual field and optical coherence tomography (OCT) outcomes in 24 patients either retaining or explanting the device at 24 months relative to sham-treated eyes. RESULTS: Eyes retaining the implant showed significantly greater visual field loss from baseline than either explanted eyes or sham eyes through 42 months. By 60 months and continuing through 96 months, visual field loss was comparable among sham-treated eyes, eyes retaining the implant and explanted eyes, as was visual acuity and OCT macular volume. CONCLUSIONS: Over the short term, ciliary neurotrophic factor released continuously from an intra-vitreal implant lead to loss of total visual field sensitivity that was greater than the natural progression in the sham-treated eye. This additional loss of sensitivity related to the active implant was reversible when the implant was removed. Over the long term (60 - 96 months), there was no evidence of efficacy for visual acuity, visual field sensitivity or OCT measures of retinal structure.

Bishop, C. V., Hennebold, J. D., Kahl, C. A., & Stouffer, R. L. (2016). Knockdown of progesterone receptor (PGR) in macaque granulosa cells disrupts ovulation and progesterone production. *Biology of Reproduction*, *94*(5)

Adenoviral vectors (vectors) expressing short-hairpin RNAs complementary to macaque nuclear progesterone (P) receptor PGR mRNA (shPGR) or a nontargeting scrambled control (shScram) were used to determine the role PGR plays in ovulation/luteinization in rhesus monkeys. Nonluteinized granulosa cells collected from monkeys (n=4) undergoing controlled ovarian stimulation protocols were exposed to either shPGR, shScram, or no virus for 24 h; human chorionic gonadotropin (hCG) was then added to half of the wells to induce luteinization (luteinized granulosa cells [LGCs]; n = 4-6 wells/treatment/ monkey). Cells/media were collected 48, 72, and 120 h postvector for evaluation of PGR mRNA and P levels. Addition of hCG increased ($P < 0.05$) PGR mRNA and medium P levels in controls. However, a time-dependent decline ($P < 0.05$) in PGR mRNA and P occurred in shPGR vector groups. Injection of shPGR, but not shScram, vector into the preovulatory follicle 20 h before hCG administration during controlled ovulation protocols prevented follicle rupture in five of six monkeys as determined by laparoscopic evaluation, with a trapped oocyte confirmed in three of four follicles of excised ovaries. Injection of shPGR also prevented the rise in serum P levels following the hCG bolus compared to shScram ($P < 0.05$). Nuclear PGR immunostaining was undetectable in granulosa cells from shPGR-injected follicles, compared to intense staining in shScram controls. Thus, the nuclear PGR appears to mediate P action in the dominant follicle promoting ovulation in primates. In vitro and in vivo effects of PGR knockdown in LGCs also support the hypothesis that P enhances its own synthesis in the primate corpus luteum by promoting luteinization. © 2016 by the Society for the Study of Reproduction, Inc.

Bittel, A. M., Nickerson, A., Saldivar, I. S., Dolman, N. J., Nan, X., & Gibbs, S. L. (2016). Methodology for quantitative characterization of fluorophore photoswitching to predict superresolution microscopy image quality. *Scientific Reports*, *6*, 29687.

Single-molecule localization microscopy (SMLM) image quality and resolution strongly depend on the photoswitching properties of fluorophores used for sample labeling. Development of fluorophores with optimized photoswitching will considerably improve SMLM spatial and spectral

resolution. Currently, evaluating fluorophore photoswitching requires protein-conjugation before assessment mandating specific fluorophore functionality, which is a major hurdle for systematic characterization. Herein, we validated polyvinyl alcohol (PVA) as a single-molecule environment to efficiently quantify the photoswitching properties of fluorophores and identified photoswitching properties predictive of quality SMLM images. We demonstrated that the same fluorophore photoswitching properties measured in PVA films and using antibody adsorption, a protein-conjugation environment analogous to labeled cells, were significantly correlated to microtubule width and continuity, surrogate measures of SMLM image quality. Defining PVA as a fluorophore photoswitching screening platform will facilitate SMLM fluorophore development and optimal image buffer assessment through facile and accurate photoswitching property characterization, which translates to SMLM fluorophore imaging performance.

Bleich, M. R. (2011). The research imperative and the iom future of nursing: Strengthening nursing's contributions to leading change and advancing health. *Communicating Nursing Research, 44*, 3-11.

Bocalon, A. C., Mita, D., Natale, L. C., Pfeifer, C. S., & Braga, R. R. (2016). Polymerization stress of experimental composites containing random short glass fibers. *Dental Materials : Official Publication of the Academy of Dental Materials, 32*(9), 1079-1084.
OBJECTIVE: To test the null hypotheses that (1) the replacement of particles by short fibers does not affect polymerization stress (PS), flexural modulus (FM) or volumetric shrinkage (VS) of experimental composites and (2) PS is not affected by specimen thickness. METHODS: Three experimental composites were prepared, each containing similar mass fractions of BisGMA and TEGDMA and 60 vol% of fillers, being 0%, 3% or 6% constituted by 1.6-mm long glass fibers and the remaining by 1mum glass particles. PS (n=5) was tested in a high compliance system, using two specimen heights (1.5mm and 4.0mm). VS and maximum shrinkage rate were obtained in a mercury dilatometer (n=3). FM was tested in three-point bending (n=10). As an additional control, a commercial composite (Filtek Z250, 3M ESPE) was tested. Data were recorded 10min after the onset of photoactivation and analyzed by ANOVA/Tukey test (FM only) and Kruskal-Wallis (alpha: 5%). RESULTS: At both specimen heights, the composite with 3% of fibers

presented significantly higher PS than the controls (which showed similar PS values). Replacing 6% of particles by fibers did not increase PS significantly. FM was reduced in the presence of fibers, and 6% of fibers led to a decrease in VS. Shrinkage rate was not affected by the fibers. SIGNIFICANCE: Replacing 3vol% of particles by fibers resulted in significantly higher PS, which was associated to a decrease in FM compared to the control. PS was not affected by specimen height for any of the tested materials.

Boitz, J. M., Jardim, A., & Ullman, B. (2016). GMP reductase and genetic uncoupling of adenylate and guanylate metabolism in leishmania donovani parasites. *Molecular and Biochemical Parasitology*, Purine acquisition is an essential nutritional process for Leishmania. Although purine salvage into adenylate nucleotides has been investigated in detail, little attention has been focused on the guanylate branch of the purine pathway. To characterize guanylate nucleotide metabolism in Leishmania and create a cell culture model in which the pathways for adenylate and guanylate nucleotide synthesis can be genetically uncoupled for functional studies in intact cells, we created and characterized null mutants of L. donovani that were deficient in either GMP reductase alone (Deltagmpr) or in both GMP reductase and its paralog IMP dehydrogenase (Deltagmpr/Deltaimpdh). Whereas wild type parasites were capable of utilizing virtually any purine nucleobase/nucleoside, the Deltagmpr and Deltagmpr/Deltaimpdh null lines exhibited highly restricted growth phenotypes. The Deltagmpr single mutant could not grow in xanthine, guanine, or their corresponding nucleosides, while no purine on its own could support the growth of Deltagmpr/Deltaimpdh cells. Permissive growth conditions for the Deltagmpr/Deltaimpdh necessitated both xanthine, guanine, or the corresponding nucleosides, and additionally, a second purine that could serve as a source for adenylate nucleotide synthesis. Interestingly, GMPR, like its paralog IMPDH, is compartmentalized to the leishmanial glycosome, a process mediated by its COOH-terminal peroxisomal targeting signal. The restricted growth phenotypes displayed by the L. donovani Deltagmpr and Deltagmpr/Deltaimpdh null mutants confirms the importance of GMPR in the purine interconversion processes of this parasite.

Bone, W. P., Washington, N. L., Buske, O. J., Adams, D. R., Davis, J., Draper, D., et al. (2016). Computational evaluation of exome sequence data using human and model organism phenotypes

improves diagnostic efficiency. *Genetics in Medicine*, *18*(6), 608-617.

Purpose: Medical diagnosis and molecular or biochemical confirmation typically rely on the knowledge of the clinician. Although this is very difficult in extremely rare diseases, we hypothesized that the recording of patient phenotypes in Human Phenotype Ontology (HPO) terms and computationally ranking putative disease-associated sequence variants improves diagnosis, particularly for patients with atypical clinical profiles. Methods: Using simulated exomes and the National Institutes of Health Undiagnosed Diseases Program (UDP) patient cohort and associated exome sequence, we tested our hypothesis using Exomiser. Exomiser ranks candidate variants based on patient phenotype similarity to (i) known disease-gene phenotypes, (ii) model organism phenotypes of candidate orthologs, and (iii) phenotypes of protein-protein association neighbors. Results: Benchmarking showed Exomiser ranked the causal variant as the top hit in 97% of known disease-gene associations and ranked the correct seeded variant in up to 87% when detectable disease-gene associations were unavailable. Using UDP data, Exomiser ranked the causative variant(s) within the top 10 variants for 11 previously diagnosed variants and achieved a diagnosis for 4 of 23 cases undiagnosed by clinical evaluation. Conclusion: Structured phenotyping of patients and computational analysis are effective adjuncts for diagnosing patients with genetic disorders. © 2016 American College of Medical Genetics and Genomics.

Bonnemaison, M. L., Duffy, M. E., Mains, R. E., Vogt, S., Eipper, B. A., & Ralle, M. (2016). Copper, zinc and calcium: Imaging and quantification in anterior pituitary secretory granules. *Metallomics : Integrated Biometal Science*,

The anterior pituitary is specialized for the synthesis, storage and release of peptide hormones. The activation of inactive peptide hormone precursors requires a specific set of proteases and other post-translational processing enzymes. High levels of peptidylglycine alpha-amidating monooxygenase (PAM), an essential peptide processing enzyme, occur in the anterior pituitary. PAM, which converts glycine-extended peptides into amidated products, requires copper and zinc to support its two catalytic activities and calcium for structure. We used X-ray fluorescence microscopy on rat pituitary sections and inductively coupled plasma mass spectrometry on subcellular fractions prepared from rat anterior pituitary to localize and quantify copper, zinc and

calcium. X-ray fluorescence microscopy indicated that the calcium concentration in pituitary tissue was about 2.5 mM, 10-times more than zinc and 50-times more than copper. Although no higher than cytosolic levels, secretory granule levels of copper exceeded PAM levels by a factor of 10. Atp7a, which transports copper into the lumen of the secretory pathway, was enriched in endosomes and Golgi, not in secretory granules. If Atp7a transfers copper directly to PAM, this pH-dependent process is likely to occur in Golgi and endosomes.

Boukais, K., Bayles, R., Borges Lde, F., Louedec, L., Boulaftali, Y., Ho-Tin-Noe, B., et al. (2016). Uptake of plasmin-PN-1 complexes in early human atheroma. *Frontiers in Physiology*, *7*, 273. Zymogens are delivered to the arterial wall by radial transmural convection. Plasminogen can be activated within the arterial wall to produce plasmin, which is involved in evolution of the atherosclerotic plaque. Vascular smooth muscle cells (vSMCs) protect the vessels from proteolytic injury due to atherosclerosis development by highly expressing endocytic LDL receptor-related protein-1 (LRP-1), and by producing anti-proteases, such as Protease Nexin-1 (PN-1). PN-1 is able to form covalent complexes with plasmin. We hypothesized that plasmin-PN-1 complexes could be internalized via LRP-1 by vSMCs during the early stages of human atheroma. LRP-1 is also responsible for the capture of aggregated LDL in human atheroma. Plasmin activity and immunohistochemical analyses of early human atheroma showed that the plasminergic system is activated within the arterial wall, where intimal foam cells, including vSMCs and platelets, are the major sites of PN-1 accumulation. Both PN-1 and LRP-1 are overexpressed in early atheroma at both messenger and protein levels. Cell biology studies demonstrated an increased expression of PN-1 and tissue plasminogen activator by vSMCs in response to LDL. Plasmin-PN-1 complexes are internalized via LRP-1 in vSMCs, whereas plasmin alone is not. Tissue PN-1 interacts with plasmin in early human atheroma via two complementary mechanisms: plasmin inhibition and tissue uptake of plasmin-PN-1 complexes via LRP-1 in vSMCs. Despite this potential protective effect, plasminogen activation by vSMCs remains abnormally elevated in the intima in early stages of human atheroma.

Bourdette, D., & Patti, F. (2016). US health insurance is an obstacle to disease-modifying treatments in MS. *Neurology*, *87*(4), 346-347.

Bouska, A., Zhang, W., Gong, Q., Iqbal, J., Scuto, A., Vose, J., et al. (2016). Combined copy number and mutation analysis identifies oncogenic pathways associated with transformation of follicular lymphoma. *Leukemia*,

Follicular lymphoma (FL) is typically an indolent disease, but 30-40% of FL cases transform into an aggressive lymphoma (tFL) with a poor prognosis. To identify the genetic changes that drive this transformation, we sequenced the exomes of 12 cases with paired FL and tFL biopsies and identified 45 recurrently mutated genes in the FL-tFL data set and 39 in the tFL cases. We selected 496 genes of potential importance in transformation and sequenced them in 23 additional tFL cases. Integration of the mutation data with copy-number abnormality (CNA) data provided complementary information. We found recurrent mutations of miR-142, which has not been previously been reported to be mutated in FL/tFL. The genes most frequently mutated in tFL included KMT2D (MLL2), CREBBP, EZH2, BCL2 and MEF2B. Many recurrently mutated genes are involved in epigenetic regulation, the Janus-activated kinase-signal transducer and activator of transcription (STAT) or the nuclear factor-kappaB pathways, immune surveillance and cell cycle regulation or are TFs involved in B-cell development. Of particular interest are mutations and CNAs affecting S1P-activated pathways through S1PR1 or S1PR2, which likely regulate lymphoma cell migration and survival outside of follicles. Our custom gene enrichment panel provides high depth of coverage for the study of clonal evolution or divergence.Leukemia advance online publication, 8 July 2016; doi:10.1038/leu.2016.175.

Brookfield, K. F., Osmundson, S. S., Caughey, A. B., & Snowden, J. M. (2016). Does infection during pregnancy outside of the time of delivery increase the risk of cerebral palsy? *American Journal of Perinatology*,

Objective We sought to evaluate whether maternal antepartum infection (excluding chorioamnionitis) is associated with cerebral palsy (CP). Study Design This is a secondary analysis from a multicenter trial in women at risk of preterm delivery who received antenatal magnesium sulfate versus placebo. We compared the risk of CP in the children of women who had evidence of antepartum infection over the course of pregnancy to those women who had no evidence of antepartum infection during pregnancy. Results Within a cohort of 2,251 women who met our inclusion criteria, 1,350 women had no history of infection in pregnancy and 801 women

had a history of some type of antepartum infection during pregnancy. The incidence of CP was similar between the two groups (4.9 vs 5.0%; p = 0.917). After adjustment for maternal and obstetric confounders, we observed no significantly increased risk of CP among infants born to women with evidence of antepartum infection; (adjusted relative risk [aRR], 1.09 (0.72, 1.66); p = 0.68). Conclusion Compared with women with no evidence of antepartum infection during pregnancy, those women with infections excluding chorioamnionitis may not be at an increased risk of delivering an infant with CP.

Brower, A., Trefz, L., & Burns, C. (2016). In response. *Journal of Obstetric, Gynecologic, and Neonatal Nursing : JOGNN / NAACOG, 45*(2), 250-252.

Buena-Atienza, E., Ruther, K., Baumann, B., Bergholz, R., Birch, D., De Baere, E., et al. (2016). De novo intrachromosomal gene conversion from OPN1MW to OPN1LW in the male germline results in blue cone monochromacy. *Scientific Reports, 6*, 28253.

X-linked cone dysfunction disorders such as Blue Cone Monochromacy and X-linked Cone Dystrophy are characterized by complete loss (of) or reduced L- and M- cone function due to defects in the OPN1LW/OPN1MW gene cluster. Here we investigated 24 affected males from 16 families with either a structurally intact gene cluster or at least one intact single (hybrid) gene but harbouring rare combinations of common SNPs in exon 3 in single or multiple OPN1LW and OPN1MW gene copies. We assessed twelve different OPN1LW/MW exon 3 haplotypes by semi-quantitative minigene splicing assay. Nine haplotypes resulted in aberrant splicing of >/=20% of transcripts including the known pathogenic haplotypes (i.e. 'LIAVA', 'LVAVA') with absent or minute amounts of correctly spliced transcripts, respectively. De novo formation of the 'LIAVA' haplotype derived from an ancestral less deleterious 'LIAVS' haplotype was observed in one family with strikingly different phenotypes among affected family members. We could establish intrachromosomal gene conversion in the male germline as underlying mechanism. Gene conversion in the OPN1LW/OPN1MW genes has been postulated, however, we are first to demonstrate a de novo gene conversion within the lineage of a pedigree.

Bujalka, H., & Emery, B. (2016). Cellular mechanisms of adaptive myelination: Bridging the gap between animal studies and human cognition. *Cognitive Neuroscience, ,* 1-3.

Voelker and colleagues propose that we may illuminate learning-associated phenomena such as generalization by considering white matter plasticity. Consistent with this idea, human neuroimaging studies reveal learning-induced changes in adult white matter. Animal studies reveal that some forms of learning induce, and are dependent on, generation of new oligodendrocytes. Nevertheless, it remains unclear which alterations to myelin structure are most relevant to learning, and humans and rodents may profoundly differ in their capacity for oligodendrogenesis in adulthood. A full understanding of these issues will be critical to appreciating the role of adaptive myelination in human neuroplasticity.

Burchiel, K. J. (2016). Deep brain stimulation targets, technology, and trials: Two decades of progress. *Neurosurgery, 63 Suppl 1*, 6-9.

ABBREVIATIONS: AD, Alzheimer diseaseDBS, Deep brain stimulationFDA, Food and Drug AdministrationMER, Microelectrode recording.

Burchiel, K. J. (2016). Neurosurgical education: A new paradigm for curriculum, core, and subspecialty training. *Neurosurgery, 63 Suppl 1*, 88-90.

Burchiel, K. J. (2016). Trigeminal neuralgia: New evidence for origins and surgical treatment. *Neurosurgery, 63 Suppl 1*, 52-55.

Burnicka-Turek, O., Steimle, J. D., Huang, W., Felker, L., Kamp, A., Kweon, J., et al. (2016). Cilia gene mutations cause atrioventricular septal defects by multiple mechanisms. *Human Molecular Genetics,*

Atrioventricular septal defects (AVSDs) are a common severe form of congenital heart disease (CHD). In this study we identified deleterious non-synonymous mutations in two cilia genes, Dnah11 and Mks1, in independent N-ethyl-N-nitrosourea-induced mouse mutant lines with heritable recessive AVSDs by whole-exome sequencing. Cilia are required for left/right body axis determination and second heart field (SHF) Hedgehog (Hh) signaling, and we find that cilia mutations affect these requirements differentially. Dnah11avc 4 did not disrupt SHF Hh signaling and caused AVSDs only concurrently with heterotaxy, a left/right axis abnormality. In contrast, Mks1avc 6 disrupted SHF Hh signaling and caused AVSDs without heterotaxy. We performed

unbiased whole-genome SHF transcriptional profiling and found that cilia motility genes were not expressed in the SHF whereas cilia structural and signaling genes were highly expressed. SHF cilia gene expression predicted the phenotypic concordance between AVSDs and heterotaxy in mice and humans with cilia gene mutations. A two-step model of cilia action accurately predicted the AVSD/heterotaxyu phenotypic expression pattern caused by cilia gene mutations. We speculate that cilia gene mutations contribute to both syndromic and non-syndromic AVSDs in humans and provide a model that predicts the phenotypic consequences of specific cilia gene mutations.

Cambronne, X. A., Stewart, M. L., Kim, D., Jones-Brunette, A. M., Morgan, R. K., Farrens, D. L., et al. (2016). Biosensor reveals multiple sources for mitochondrial NAD(+). *Science (New York, N.Y.)*, *352*(6292), 1474-1477.

Nicotinamide adenine dinucleotide (NAD(+)) is an essential substrate for sirtuins and poly(adenosine diphosphate-ribose) polymerases (PARPs), which are NAD(+)-consuming enzymes localized in the nucleus, cytosol, and mitochondria. Fluctuations in NAD(+) concentrations within these subcellular compartments are thought to regulate the activity of NAD(+)-consuming enzymes; however, the challenge in measuring compartmentalized NAD(+) in cells has precluded direct evidence for this type of regulation. We describe the development of a genetically encoded fluorescent biosensor for directly monitoring free NAD(+) concentrations in subcellular compartments. We found that the concentrations of free NAD(+) in the nucleus, cytoplasm, and mitochondria approximate the Michaelis constants for sirtuins and PARPs in their respective compartments. Systematic depletion of enzymes that catalyze the final step of NAD(+) biosynthesis revealed cell-specific mechanisms for maintaining mitochondrial NAD(+) concentrations.

Carter, B. C., & Jahr, C. E. (2016). Postsynaptic, not presynaptic NMDA receptors are required for spike-timing-dependent LTD induction. *Nature Neuroscience*,

Long-term depression (LTD) between cortical layer 4 spiny stellate cells and layer 2/3 pyramidal cells requires the activation of NMDA receptors (NMDARs). In young rodents, this form of LTD has been repeatedly reported to require presynaptic NMDARs for its induction. Here we show that at

this synapse in the somatosensory cortex of 2- to 3-week-old rats and mice, postsynaptic, not presynaptic NMDARs are required for LTD induction. First, we find no evidence for functional NMDARs in L4 neuron axons using two-photon laser scanning microscopy and two-photon glutamate uncaging. Second, we find that genetic deletion of postsynaptic, but not presynaptic NMDARs prevents LTD induction. Finally, the pharmacology of the NMDAR requirement is consistent with a nonionic signaling mechanism.

Cary, R. P., Ray, S., Grayson, D. S., Painter, J., Carpenter, S., Maron, L., et al. (2016). Network structure among brain systems in adult ADHD is uniquely modified by stimulant administration. *Cerebral Cortex (New York, N.Y.: 1991)*,

Current research in connectomics highlights that self-organized functional networks or "communities" of cortical areas can be detected in the adult brain. This perspective may provide clues to mechanisms of treatment response in psychiatric conditions. Here we examine functional brain community topology based on resting-state fMRI in adult Attention-Deficit/Hyperactivity Disorder (ADHD; n = 22) and controls (n = 31). We sought to evaluate ADHD patterns in adulthood and their modification by short term stimulants administration. Participants with ADHD were scanned one or two weeks apart, once with medication and once without; comparison participants were scanned at one time-point. Functional connectivity was estimated from these scans and community detection applied to determine cortical network topology. Measures of change in connectivity profile were calculated via a graph measure, termed the Node Dissociation Index (NDI). Compared to controls, several cortical networks had atypical connectivity in adults with ADHD when withholding stimulants, as measured by NDI. In most networks stimulants significantly reduced, but did not eliminate, differences in the distribution of connections between key brain systems relative to the control sample. These findings provide an enriched model of connectivity in ADHD and demonstrate how stimulants may exert functional effects by altering connectivity profiles in the brain.

Caughey, A. B., & Valent, A. M. (2016). When to deliver women with diabetes in pregnancy? *American Journal of Perinatology*,

The prevalence of pregestational diabetes and the incidence of gestational diabetes have both

increased over recent years. One component of the management of diabetes in pregnancy is the timing of delivery in the late-preterm, early-term, or full-term periods. Recent guidance from the National Institute for Child Health and Human Development, Society for Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists has lacked specificity, for example, recommending delivery for women with pregestational diabetes with poorly controlled glucose levels to be from 34 to 39 weeks' gestation. This lack of specificity is predominant because of the large holes in existing data to guide clinical practice. This article reviews existing literature regarding diabetes in pregnancy and attempts to give an analytical framework and some clearer guidance around the timing of delivery.

Cauley, J. A., Barbour, K. E., Harrison, S. L., Cloonan, Y. K., Danielson, M. E., Ensrud, K. E., et al. (2016). Inflammatory markers and the risk of hip and vertebral fractures in men: The osteoporotic fractures in men (MrOS). *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*,

Cytokines play major roles in regulating bone remodeling, but their relationship to incident fractures in older men is uncertain. We tested the hypothesis that men with higher concentrations of pro-inflammatory markers have a higher risk of fracture. We used a case-cohort design and measured inflammatory markers in a random sample of 961 men and in men with incident fractures including 120 clinical vertebral, 117 hip, and 577 non-spine fractures; average follow-up 6.13 years (7.88 years for vertebral fractures). We measured interleukin (IL)-6, C-reactive protein (CRP), tumor necrosis factor alpha (TNFalpha), soluble receptors (SR) of IL-6 (IL-6SR) and TNF (TNFalphaSR1 and TNFalphaSR2), and IL-10. The risk of non-spine, hip, and clinical vertebral fracture was compared across quartiles (Q) of inflammatory markers using Cox proportional hazard models with tests for linear trend. In multivariable-adjusted models, men with the highest (Q4) TNFa cytokine concentrations and their receptors had a 2.0-4.2-fold higher risk of hip and clinical vertebral fracture than men with the lowest (Q1). Results were similar for all non-spine fractures, but associations were smaller. There was no association between CRP and IL-6SR and fracture. Men in the highest Q of IL-10 had a 49% lower risk of vertebral fracture compared with men in Q1. Among men with >/=3 inflammatory markers in the highest Q, the hazard ratio (HR) for hip fractures was 2.03 (95% confidence interval [CI] 1.11-3.71) and for

vertebral fracture 3.06 (1.66-5.63). The HRs for hip fracture were attenuated by 27%, 27%, and 15%, respectively, after adjusting for appendicular lean mass (ALM), disability, and bone density, suggesting mediating roles. ALM also attenuated the HR for vertebral fractures by 10%. There was no association between inflammation and rate of hip BMD loss. We conclude that inflammation may play an important role in the etiology of fractures in older men. (c) 2016 American Society for Bone and Mineral Research.

Cefalu, W. T., Boulton, A. J. M., Tamborlane, W. V., Moses, R. G., LeRoith, D., Greene, E. L., et al. (2016). Diabetes care: Lagniappe and seeing is believing! *Diabetes Care, 39*(7), 1069-1071.

Chadderdon, S. M., Belcik, J. T., Bader, L., Kievit, P., Grove, K. L., & Lindner, J. R. (2016). Vasoconstrictor eicosanoids and impaired microvascular function in inactive and insulin-resistant primates. *International Journal of Obesity (2005),*

The inability to augment capillary blood volume (CBV) in response to insulin or glucose is thought to contribute to insulin resistance (IR) by limiting glucose uptake in key storage sites. Understanding the mechanisms that contribute to impaired CBV augmentation early in the onset of IR may lead to new future therapies. We hypothesized that inactivity alters the balance of vasoactive eicosanoids and contributes to microvascular IR. In ten activity-restricted (AR) and six normal activity adult male rhesus macaques, contrast-enhanced ultrasound of skeletal muscle blood flow and CBV was performed at baseline and during intravenous glucose tolerance test (IVGTT). Plasma was analyzed for vasoconstrictor hydroxyeicosatetraenoic acids (HETEs) and the ratio of vasodilatory epoxyeicosatrienoic acids (EETs) to their less biologically active dihydroxyeicosatrienoic acids (DHETs) as an indirect measure of soluble epoxide hydrolase activity. AR primates were IR during IVGTT and had a 45% lower glucose-stimulated CBV response. Vasoconstrictor 18-HETE and 19-HETE and the DHET/EET ratio were markedly elevated in the AR group and correlated inversely with the CBV response. In addition, levels of 18-HETE and 19-HETE correlated directly with microvascular IR. We conclude that a shift toward increased eicosanoid vasoconstrictor tone correlates with abnormal skeletal muscle vascular recruitment and may contribute to IR.International Journal of Obesity advance online publication, 26 July 2016; doi:10.1038/ijo.2016.117.

Chalmers, J. R., Simpson, E., Apfelbacher, C. J., Thomas, K. S., von Kobyletzki, L., Schmitt, J., et al. (2016). Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *The British Journal of Dermatology, 175*(1), 69-79.

This article is a report of the fourth meeting of the Harmonising Outcome Measures for Eczema (HOME) initiative held in Malmo, Sweden on 23-24 April 2015 (HOME IV). The aim of the meeting was to achieve consensus over the preferred outcome instruments for measuring patient-reported symptoms and quality of life for the HOME core outcome set for atopic eczema (AE). Following presentations, which included data from systematic reviews, consensus discussions were held in a mixture of whole group and small group discussions. Small groups were allocated a priori to ensure representation of different stakeholders and countries. Decisions were voted on using electronic keypads. For the patient-reported symptoms, the group agreed by vote that itch, sleep loss, dryness, redness/inflamed skin and irritated skin were all considered essential aspects of AE symptoms. Many instruments for capturing patient-reported symptoms were discussed [including the Patient-Oriented SCOring Atopic Dermatitis index, Patient-Oriented Eczema Measure (POEM), Self-Administered Eczema Area and Severity Index, Itch Severity Scale, Atopic Dermatitis Quickscore and the Nottingham Eczema Severity Score] and, by consensus, POEM was selected as the preferred instrument to measure patient-reported symptoms. Further work is needed to determine the reliability and measurement error of POEM. Further work is also required to establish the importance of pain/soreness and the importance of collecting information regarding the intensity of symptoms in addition to their frequency. Much of the discussion on quality of life concerned the Dermatology Life Quality Index and Quality of Life Index for Atopic Dermatitis; however, consensus on a preferred instrument for measuring this domain could not be reached. In summary, POEM is recommended as the HOME core outcome instrument for measuring AE symptoms.

Chamine, I., & Oken, B. S. (2016). Aroma effects on physiologic and cognitive function following acute stress: A mechanism investigation. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*,

OBJECTIVE: Aromas may improve physiologic and cognitive function after stress, but associated

mechanisms remain unknown. This study evaluated the effects of lavender aroma, which is commonly used for stress reduction, on physiologic and cognitive functions. The contribution of pharmacologic, hedonic, and expectancy-related mechanisms of the aromatherapy effects was evaluated. METHODS: Ninety-two healthy adults (mean age, 58.0 years; 79.3% women) were randomly assigned to three aroma groups (lavender, perceptible placebo [coconut], and nonperceptible placebo [water] and to two prime subgroups (primed, with a suggestion of inhaling a powerful stress-reducing aroma, or no prime). Participants' performance on a battery of cognitive tests, physiologic responses, and subjective stress were evaluated at baseline and after exposure to a stress battery during which aromatherapy was present. Participants also rated the intensity and pleasantness of their assigned aroma. RESULTS: Pharmacologic effects of lavender but not placebo aromas significantly benefited post-stress performance on the working memory task ($F(2, 86) = 5.41$; $p = 0.006$). Increased expectancy due to positive prime, regardless of aroma type, facilitated post-stress performance on the processing speed task ($F(1, 87) = 8.31$; $p = 0.005$). Aroma hedonics (pleasantness and intensity) played a role in the beneficial lavender effect on working memory and physiologic function. CONCLUSIONS: The observable aroma effects were produced by a combination of mechanisms involving aroma-specific pharmacologic properties, aroma hedonic properties, and participant expectations. In the future, each of these mechanisms could be manipulated to produce optimal functioning.

Chan, R. V., Patel, S. N., Ryan, M. C., Jonas, K. E., Ostmo, S., Port, A. D., et al. (2015). The global education network for retinopathy of prematurity (gen-rop): Development, implementation, and evaluation of A novel tele-education system (an american ophthalmological society thesis). *Transactions of the American Ophthalmological Society, 113*, T21-T226.

PURPOSE: To describe the design, implementation, and evaluation of a tele-education system developed to improve diagnostic competency in retinopathy of prematurity (ROP) by ophthalmology residents. METHODS: A secure Web-based tele-education system was developed utilizing a repository of over 2,500 unique image sets of ROP. For each image set used in the system, a reference standard ROP diagnosis was established. Performance by ophthalmology residents (postgraduate years 2 to 4) from the United States and Canada in taking the ROP tele-education program was prospectively evaluated. Residents were presented with image-based

clinical cases of ROP during a pretest, posttest, and training chapters. Accuracy and reliability of ROP diagnosis (eg, plus disease, zone, stage, category) were determined using sensitivity, specificity, and the kappa statistic calculations of the results from the pretest and posttest. RESULTS: Fifty-five ophthalmology residents were provided access to the ROP tele-education program. Thirty-one ophthalmology residents completed the program. When all training levels were analyzed together, a statistically significant increase was observed in sensitivity for the diagnosis of plus disease, zone, stage, category, and aggressive posterior ROP (P<.05). Statistically significant changes in specificity for identification of stage 2 or worse (P=.027) and pre-plus (P=.028) were observed. CONCLUSIONS: A tele-education system for ROP education is effective in improving diagnostic accuracy of ROP by ophthalmology residents. This system may have utility in the setting of both healthcare and medical education reform by creating a validated method to certify telemedicine providers and educate the next generation of ophthalmologists.

Chang, A. L., Hoehn, R. S., Jernigan, P., Cox, D., Schreiber, M., & Pritts, T. A. (2016). Previous cryopreservation alters the natural history of the red blood cell storage lesion. *Shock*, BACKGROUND:: During storage, packed red blood cells (pRBCs) undergo a number of biochemical, metabolic and morphologic changes, collectively known as the "storage lesion". We aimed to determine the effect of cryopreservation on the red blood cell storage lesion compared to traditional 4?°C storage. METHODS:: Previously cryopreserved human packed red blood cells were compared to age matched never frozen packed red blood cells obtained from the local blood bank. The development of the red cell storage lesion was evaluated after 7, 14, 21, 28, and 42 days of storage at 4?°C in AS-3 storage medium. We measured physiological parameters including cell counts, lactic acid and potassium concentrations as well as signs of eryptosis including loss of phosphatidylserine (PS) asymmetry, microparticle production and osmotic fragility in hypotonic saline. RESULTS:: Compared to controls, previously cryopreserved pRBC at 7 days of storage in AS-3 showed lower red cell counts (3.7 vs 5.3?×?10^6?cells/uL, p(<0.01), hemoglobin (12.0 vs 16.5?g/dL, p?<?0.01), hematocrit (33.0 vs 46.5%, p?<?0.01), and pH (6.27 vs 6.72, p?<?0.01). Over 28 days of storage, storage cryopreserved pRBC developed increased cell free hemoglobin (0.7 vs 0.3?g/dL, p?<?0.01), greater PS exposure (10.1 vs 3.3%, p?<?0.01), and microparticle production (30,836 vs 1,802?MP/uL, p?<?0.01). Previously

cryopreserved cells were also less resistant to osmotic stress. CONCLUSION:: The red blood cell storage lesion is accelerated in previously cryopreserved pRBC after thawing. Biochemical deterioration of thawed and deglycerolized red cells suggests that storage time prior to transfusion should be limited in order to achieve similar risk profiles as never frozen standard liquid storage pRBC units. © 2016 by the Shock Society

Chen, J. K., Jacob, S. E., Nedorost, S. T., Hanifin, J. M., Simpson, E. L., Boguniewicz, M., et al. (2016). A pragmatic approach to patch testing atopic dermatitis patients: Clinical recommendations based on expert consensus opinion. *Dermatitis : Contact, Atopic, Occupational, Drug*, *27*(4), 186-192.

Allergic contact dermatitis (ACD) may complicate the clinical course of atopic dermatitis (AD), and patch testing remains the criterion standard for diagnosing ACD. To date, there have been no guidelines or consensus recommendations on when and how to patch test individuals with AD. Failure to patch test when appropriate may result in overlooking an important and potentially curable complicating comorbidity. In this article, we present consensus recommendations regarding when to perform patch testing in the AD patient, best practices, and common pitfalls. Patch testing should be considered in AD patients with dermatitis that fails to improve with topical therapy; with atypical/changing distribution of dermatitis, or pattern suggestive of ACD; with therapy-resistant hand eczema in the working population; with adult- or adolescent-onset AD; and/or before initiating systemic immunosuppressants for the treatment of dermatitis. A suggested patch testing algorithm for AD patients is provided.

Cheung, C. Y., Anderson, D. F., & Brace, R. A. (2016). Aquaporins in ovine amnion: Responses to altered amniotic fluid volumes and intramembranous absorption rates. *Physiological Reports*, *4*(14), 10.14814/phy2.12868.

Aquaporins (AQPs) are transmembrane channel proteins that facilitate rapid water movement across cell membranes. In amniotic membrane, the AQP-facilitated transfer of water across amnion cells has been proposed as a mechanism for amniotic fluid volume (AFV) regulation. To investigate whether AQPs modulate AFV by altering intramembranous absorption (IMA) rate, we tested the hypothesis that AQP gene expression in the amnion is positively correlated with IMA

rate during experimental conditions when IMA rate and AFV are modified over a wide range. The relative abundances of AQP1, AQP3, AQP8, AQP9, and AQP11 mRNA and protein were determined in the amnion of 16 late-gestation ovine fetuses subjected to 2 days of control conditions, urine drainage, urine replacement, or intraamniotic fluid infusion. AQP mRNA levels were determined by RT-qPCR and proteins by western immunoblot. Under control conditions, mRNA levels among the five AQPs differed more than 20-fold. During experimental treatments, mean IMA rate in the experimental groups ranged from 100 +/- 120 mL/day to 1370 +/- 270 mL/day. The mRNA levels of the five AQPs did not change from control and were not correlated with IMA rates. The protein levels of AQP1 were positively correlated with IMA rates (r(2) = 38%, P = 0.01) while the remaining four AQPs were not. These findings demonstrate that five AQPs are differentially expressed in ovine amnion. Our study supports the hypothesis that AQP1 may play a positive role in regulating the rate of fluid transfer across the amnion, thereby participating in the dynamic regulation of AFV.

Cheyney, M. (2016). Understanding recent home-birth research: An interview with drs. melissa cheyney and jonathan snowden. *The Journal of Perinatal Education*, *25*(2), 80-86.

In the past month, two new studies have been released-one in The New England Journal of Medicine (NEJM; Snowden et al., 2015) and the other in the Canadian Medical Association Journal (Hutton et al., 2015)-comparing out-of-hospital birth outcomes to hospital birth outcomes. These studies join a growing body of literature that consistently shows high rates of obstetric intervention in hospitals and also show low risk to neonates regardless of setting. However, the recent NEJM study found a small but statistically significant increase in risk for perinatal mortality for babies born out of hospital. Jeanette McCulloch of BirthSwell (http://www.birthswell.com) interviews Melissa Cheyney, PhD, CPM, LDM, medical anthropologist, chair of the Midwives Alliance Division of Research, and lead author on the largest study of outcomes for planned home births in the United States to date (Cheyney et al., 2014a), and Jonathan Snowden, PhD, epidemiologist and assistant professor in the Department of Obstetrics and Gynecology and School of Public Health at Oregon Health and Science University. Snowden is also the lead author of the recent NEJM study.

Cifu, A., & Prasad, V. (2016). Wearables, smartphones and novel anticoagulants: We will treat more atrial fibrillation, but will patients be better off? *Journal of General Internal Medicine*,

The widespread adoption of medical practices without a firm evidence base is common and the current growing enthusiasm for atrial fibrillation screening offers a real-time example of this phenomenon. Although no randomized trials supporting the utility of screening for atrial fibrillation exist, proponents suggest that such screening should be considered. Atrial fibrillation is a common condition that is often asymptomatic. It is also a condition associated with serious morbidity, primarily resulting from stroke. We practice at a time in which the ability to detect atrial fibrillation is becoming easier and treatments are becoming less onerous. Screening for atrial fibrillation may be beneficial but there is also a reasonable likelihood that its harms will outweigh it benefits. In this article we make the case that adopting this practice prior to data from randomized controlled trial would be a mistake. If screening for atrial fibrillation is adopted without such a robust evidence base we may well later discover that this course of action was wrong.

Clark, C. A., Cornell, R. F., Scott, E. C., Chung, J., & Costa, L. J. (2016). Management of relapsed and refractory multiple myeloma in modern times: Incorporating new agents into decision-making. *American Journal of Hematology*,

Although upfront treatment of multiple myeloma has become more effective, relapses are the norm, often driven by the emergence of a genetically divergent clone selected by the initial therapy. Recent trials have demonstrated the safety and efficacy of combination therapy also in the relapsed and refractory setting and supported the regulatory approval of several new agents including new proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. We provide a detailed summary of recent practice-changing trials in relapsed and refractory MM and share a practical approach to assimilate disease and patient-features into treatment decision. Am. J. Hematol., 2016. (c) 2016 Wiley Periodicals, Inc.

Cohen, D. J., Balasubramanian, B. A., Gordon, L., Marino, M., Ono, S., Solberg, L. I., et al. (2016). A national evaluation of a dissemination and implementation initiative to enhance primary care practice capacity and improve cardiovascular disease care: The ESCALATES study protocol.

Implementation Science : IS, *11*(1), 86-016-0449-8.

BACKGROUND: The Agency for Healthcare Research and Quality (AHRQ) launched the EvidenceNOW Initiative to rapidly disseminate and implement evidence-based cardiovascular disease (CVD) preventive care in smaller primary care practices. AHRQ funded eight grantees (seven regional Cooperatives and one independent national evaluation) to participate in EvidenceNOW. The national evaluation examines quality improvement efforts and outcomes for more than 1500 small primary care practices (restricted to those with fewer than ten physicians per clinic). Examples of external support include practice facilitation, expert consultation, performance feedback, and educational materials and activities. This paper describes the study protocol for the EvidenceNOW national evaluation, which is called Evaluating System Change to Advance Learning and Take Evidence to Scale (ESCALATES). METHODS: This prospective observational study will examine the portfolio of EvidenceNOW Cooperatives using both qualitative and quantitative data. Qualitative data include: online implementation diaries, observation and interviews at Cooperatives and practices, and systematic assessment of context from the perspective of Cooperative team members. Quantitative data include: practice-level performance on clinical quality measures (aspirin prescribing, blood pressure and cholesterol control, and smoking cessation; ABCS) collected by Cooperatives from electronic health records (EHRs); practice and practice member surveys to assess practice capacity and other organizational and structural characteristics; and systematic tracking of intervention delivery. Quantitative, qualitative, and mixed methods analyses will be conducted to examine how Cooperatives organize to provide external support to practices, to compare effectiveness of the dissemination and implementation approaches they implement, and to examine how regional variations and other organization and contextual factors influence implementation and effectiveness. DISCUSSION: ESCALATES is a national evaluation of an ambitious large-scale dissemination and implementation effort focused on transforming smaller primary care practices. Insights will help to inform the design of national health care practice extension systems aimed at supporting practice transformation efforts in the USA. CLINICAL TRIAL REGISTRATION: NCT02560428 (09/21/15).

Cook, M. R., Deal, S. B., Scott, J. M., Moren, A. M., & Kiraly, L. N. (2016). Teaching communication and supporting autonomy with a team-based operative simulator. *American Journal of Surgery*, BACKGROUND: Changing residency structure emphasizes the need for formal instruction on team leadership and intraoperative teaching skills. A high fidelity, multi-learner surgical simulation may offer opportunities for senior learners (SLs) to learn these skills while teaching technical skills to junior learners (JLs). METHODS: We designed and optimized a low-cost inguinal hernia model that paired JLs and SLs as an operative team. This was tested in 3 pilot simulations. Participants' feedback was analyzed using qualitative methods. RESULTS: JL feedback to SLs included the themes "guiding and instructing" and "allowing autonomy." Senior Learner feedback to JLs focused on "mechanics," "knowledge," and "perspective/flow." Both groups focused on "communication" and "professionalism." CONCLUSIONS: A multi-learner simulation can successfully meet the technical learning needs of JLs and the teaching and communication learning needs of SLs. This model of resident-driven simulation may illustrate future opportunities for operative simulation.

Costantino, G., Sun, B. C., Barbic, F., Bossi, I., Casazza, G., Dipaola, F., et al. (2016). Syncope clinical management in the emergency department: A consensus from the first international workshop on syncope risk stratification in the emergency department. *European Heart Journal, 37*(19), 1493-1498.

Cowan, N. G., & Hatch, T. R. (2016). Incidental finding in a renal transplant recipient allograft. *American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 16*(8), 2491-2493.

Coyner, A. S., Ryals, R. C., Ku, C. A., Fischer, C. M., Patel, R. C., Datta, S., et al. (2016). Retinal neuroprotective effects of flibanserin, an FDA-approved dual serotonin receptor agonist-antagonist. *PloS One, 11*(7), e0159776.
PURPOSE: To assess the neuroprotective effects of flibanserin (formerly BIMT-17), a dual 5-HT1A agonist and 5-HT2A antagonist, in a light-induced retinopathy model. METHODS: Albino BALB/c mice were injected intraperitoneally with either vehicle or increasing doses of flibanserin ranging from 0.75 to 15 mg/kg flibanserin. To assess 5-HT1A-mediated effects, BALB/c mice were

injected with 10 mg/kg WAY 100635, a 5-HT1A antagonist, prior to 6 mg/kg flibanserin and 5-HT1A knockout mice were injected with 6 mg/kg flibanserin. Injections were administered once immediately prior to light exposure or over the course of five days. Light exposure lasted for one hour at an intensity of 10,000 lux. Retinal structure was assessed using spectral domain optical coherence tomography and retinal function was assessed using electroretinography. To investigate the mechanisms of flibanserin-mediated neuroprotection, gene expression, measured by RT-qPCR, was assessed following five days of daily 15 mg/kg flibanserin injections. RESULTS: A five-day treatment regimen of 3 to 15 mg/kg of flibanserin significantly preserved outer retinal structure and function in a dose-dependent manner. Additionally, a single-day treatment regimen of 6 to 15 mg/kg of flibanserin still provided significant protection. The action of flibanserin was hindered by the 5-HT1A antagonist, WAY 100635, and was not effective in 5-HT1A knockout mice. Creb, c-Jun, c-Fos, Bcl-2, Cast1, Nqo1, Sod1, and Cat were significantly increased in flibanserin-injected mice versus vehicle-injected mice. CONCLUSIONS: Intraperitoneal delivery of flibanserin in a light-induced retinopathy mouse model provides retinal neuroprotection. Mechanistic data suggests that this effect is mediated through 5-HT1A receptors and that flibanserin augments the expression of genes capable of reducing mitochondrial dysfunction and oxidative stress. Since flibanserin is already FDA-approved for other indications, the potential to repurpose this drug for treating retinal degenerations merits further investigation.

Crane, N. A., Jenkins, L. M., Dion, C., Meyers, K. K., Weldon, A. L., Gabriel, L. B., et al. (2016). Comorbid anxiety increases cognitive control activation in major depressive disorder. *Depression and Anxiety*,

BACKGROUND: Major Depressive Disorder (MDD) and anxiety disorders often co-occur, with poorer treatment response and long-term outcomes. However, little is known about the shared and distinct neural mechanisms of comorbid MDD and anxiety (MDD+Anx). This study examined how MDD and MDD+Anx differentially impact cognitive control. METHODS: Eighteen MDD, 29 MDD+Anx, and 54 healthy controls (HC) completed the Parametric Go/No-Go (PGNG) during fMRI, including Target, Commission, and Rejection trials. RESULTS: MDD+Anx had more activation in the anterior dorsolateral prefrontal cortex, hippocampus, and caudate during Rejections, and inferior parietal lobule during correct Targets than MDD and HC. During

Rejections HC had greater activation in a number of cognitive control regions compared to MDD; in the posterior cingulate compared to MDD+Anx; and in the fusiform gyrus compared to all MDD. During Commissions HC had greater activation in the right inferior frontal gyrus than all MDD. MDD had more activation in the mid-cingulate, inferior parietal lobule, and superior temporal gyrus than MDD+Anx during Commissions. CONCLUSIONS: Despite similar performance, MDD and MDD+Anx showed distinct differences in neural mechanisms of cognitive control in relation to each other, as well as some shared differences in relation to HC. The results were consistent with our hypothesis of hypervigilance in MDD+Anx within the cognitive control network, but inconsistent with our hypothesis that there would be greater engagement of salience and emotion network regions. Comorbidity of depression and anxiety may cause increased heterogeneity in study samples, requiring further specificity in detection and measurement of intermediate phenotypes and treatment Targets.

Crawford, J. D., Chivukula, V. K., Haller, S., Vatankhah, N., Bohannan, C. J., Moneta, G. L., et al. (2016). Aortic outflow occlusion predicts rupture of abdominal aortic aneurysm. *Journal of Vascular Surgery*,

BACKGROUND: Current threshold recommendations for elective abdominal aortic aneurysm (AAA) repair are based solely on maximal AAA diameter. Peak wall stress (PWS) has been demonstrated to be a better predictor than AAA diameter of AAA rupture risk. However, PWS calculations are time-intensive, not widely available, and therefore not yet clinically practical. In addition, PWS analysis does not account for variations in wall strength between patients. We therefore sought to identify surrogate clinical markers of increased PWS and decreased aortic wall strength to better predict AAA rupture risk. METHODS: Patients treated at our institution from 2001 to 2014 for ruptured AAA (rAAA) were retrospectively identified and grouped into patients with small rAAA (maximum diameter 6 cm). Patients with large (>6 cm) non-rAAA were also identified sequentially from 2009 for comparison. Demographics, vascular risk factors, maximal aortic diameter, and aortic outflow occlusion (AOO) were recorded. AOO was defined as complete occlusion of the common, internal, or external iliac artery. Computational fluid dynamics and finite element analysis simulations were performed to calculate wall stress distributions and to extract PWS. RESULTS: We identified 61 patients with rAAA, of which 15 ruptured with AAA

diameter 60 mm (27% vs 8%; P = .047). Among all patients with rAAAs, those with AOO ruptured at smaller mean AAA diameters than in patients without AOO (62.1 +/- 11.8 mm vs 72.5 +/- 16.4 mm; P = .024). PWS calculations of a representative small rAAA and a large non-rAAA showed a substantial increase in PWS with AOO. CONCLUSIONS: We demonstrate that AOO, PAD, and COPD in AAA are associated with rAAAs at smaller diameters. AOO appears to increase PWS, whereas COPD and PAD may be surrogate markers of decreased aortic wall strength. We therefore recommend consideration of early, elective AAA repair in patients with AOO, PAD, or COPD to minimize risk of early rupture.

Crawford, J. D., Perrone, K. H., Jung, E., Mitchell, E. L., Landry, G. J., & Moneta, G. L. (2016). Arterial duplex for diagnosis of peripheral arterial emboli. *Journal of Vascular Surgery*,

BACKGROUND: Whether duplex ultrasound (DUS) imaging alone can be used to successfully plan revascularization for peripheral arterial embolism (PAE) is unknown. This study evaluated the utility of DUS imaging alone for the diagnosis and treatment of PAE. METHODS: Patients with cardiogenic PAE to the lower or upper extremities during a 20-year period were retrospectively evaluated. Patients with visceral or cerebral PAE were excluded. Diagnosis by DUS imaging alone was compared with contrast angiography (CA) or computed tomography angiography (CTA). Patient demographics, use of intraoperative CA, need for reintervention, length of revascularization procedure, and rate of fasciotomy and amputation were compared. Mean peak systolic velocity (PSV; cm/s) measured at the proximal, middle, and distal segment of each artery from the common femoral to the distal tibial arteries was also compared with surgical outcomes. RESULTS: We identified 203 extremities in 182 patients with PAE. Preoperative imaging was obtained in 89%, including DUS imaging alone (44%), CA (37%), and CTA (7%). DUS imaging was used more frequently than CA or CTA in women, older patients, patients with congestive heart failure, upper extremity PAE, and patients on antiplatelet agents preoperatively. Use of intraoperative CA, need for reintervention, rate of fasciotomy and limb loss, and hospital length of stay were similar between the two groups. No upper extremities required amputation. Patients with lower extremity emboli who underwent fasciotomy had lower mean PSVs than those free from fasciotomy at the popliteal (4 +/- 6 cm/s vs 31 +/- 62 cm/s; P = .03), anterior tibial (1 +/- 3 cm/s vs 10 +/- 16 cm/s; P = .004), and posterior tibial (2 +/- 3 cm/s vs 9 +/- 15 cm/s; P

= .03) arteries. The 30-day mortality for the series was 25% with a median follow-up of 7.4 months. The only predictor of 30-day mortality on multivariate analysis was tobacco use (odds ratio, 3.1; 95% confidence interval, 1.4-7.0). CONCLUSIONS: Surgical outcomes and survival for patients evaluated by preoperative DUS imaging alone for PAE are equivalent to patients evaluated with CA or CTA. PSVs in the tibiopopliteal arteries may predict the need for fasciotomy. Preoperative DUS imaging alone is sufficient for operative planning in patients with symptoms suggestive of PAE.

Crowson, M. G., Schulz, K., Parham, K., Vambutas, A., Witsell, D., Lee, W. T., et al. (2016). Meniere's disease: A CHEER database study of local and regional patient encounter and procedure patterns. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *155*(1), 15-21.

OBJECTIVE: (1) Integrate practice-based patient encounters using the Dartmouth Atlas Medicare database to understand practice treatments for Meniere's disease (MD). (2) Describe differences in the practice patterns between academic and community providers for MD. STUDY DESIGN: Practice-based research database review. SETTING: CHEER (Creating Healthcare Excellence through Education and Research) network academic and community providers. SUBJECTS AND METHODS: MD patient data were identified with ICD-9 and CPT codes. Demographics, unique visits, and procedures per patient were tabulated. The Dartmouth Atlas of Health Care was used to reference regional health care utilization. Statistical analysis included 1-way analyses of variance, bivariate linear regression, and Student's t tests, with significance set at $P < .05$. RESULTS: A total of 2071 unique patients with MD were identified from 8 academic and 10 community otolaryngology-head and neck surgery provider centers nationally. Average age was 56.5 years; 63.9% were female; and 91.4% self-reported white ethnicity. There was an average of 3.2 visits per patient. Western providers had the highest average visits per patient. Midwest providers had the highest average procedures per patient. Community providers had more visits per site and per patient than did academic providers. Academic providers had significantly more operative procedures per site ($P = .0002$) when compared with community providers. Health care service areas with higher total Medicare reimbursements per enrollee did not report significantly more operative procedures being performed. CONCLUSION: This is the first practice-based

clinical research database study to describe MD practice patterns. We demonstrate that academic otolaryngology-head and neck surgery providers perform significantly more operative procedures than do community providers for MD, and we validate these data with an independent Medicare spending database.

Cushing, T. A., Roberts, W. O., Hackett, P., Dexter, W. W., Brent, J. S., Young, C. C., et al. (2015). General medical considerations for the wilderness adventurer: Medical conditions that may worsen with or present challenges to coping with wilderness exposure. *Clinical Journal of Sport Medicine : Official Journal of the Canadian Academy of Sport Medicine, 25*(5), 396-403. Participation in wilderness and adventure sports is on the rise, and as such, practitioners will see more athletes seeking clearance to participate in these events. The purpose of this article is to describe specific medical conditions that may worsen or present challenges to the athlete in a wilderness environment.

Danilov, A. V., Lewis, L. D., Lansigan, F., Roudaia, L., Findley, D. L., Jones, S. Y., et al. (2016). A phase I dose-ranging study of bendamustine and rituximab in chronic lymphocytic leukemia patients with comorbidities. *British Journal of Haematology,*

Danilov, A. V., Li, H., Press, O. W., Shapira, I., Swinnen, L. J., Noy, A., et al. (2016). Feasibility of interim positron emission tomography (PET)-adapted therapy in HIV-positive patients with advanced hodgkin lymphoma (HL): A sub-analysis of SWOG S0816 phase 2 trial. *Leukemia & Lymphoma,* , 1-5.

DeConde, A. S., & Smith, T. L. (2016). Outcomes after frontal sinus surgery: An evidence-based review. *Otolaryngologic Clinics of North America, 49*(4), 1019-1033. Endoscopic sinus surgery is an effective intervention at improving quality of life for patients with medically refractory chronic rhinosinusitis. The evidence supporting frontal sinusotomy is limited to single institution case series. However, the data for Draf IIa frontal sinusotomy do demonstrate that most patients experience lasting frontal sinus patency on postoperative endoscopic examination and improvements in quality of life. Salvage endoscopic frontal sinus

surgery via a Draf III shows high rates of neo-ostium patency and subjective improvements in symptoms at a 2-year time point in case series.

Degoma, E. M., Ahmad, Z. S., O'Brien, E. C., Kindt, I., Shrader, P., Newman, C. B., et al. (2016). Treatment gaps in adults with heterozygous familial hypercholesterolemia in the united states. *Circulation: Cardiovascular Genetics, 9*(3), 240-249.

Background - Cardiovascular disease burden and treatment patterns among patients with familial hypercholesterolemia (FH) in the United States remain poorly described. In 2013, the FH Foundation launched the Cascade Screening for Awareness and Detection (CASCADE) of FH Registry to address this knowledge gap. Methods and Results - We conducted a cross-sectional analysis of 1295 adults with heterozygous FH enrolled in the CASCADE-FH Registry from 11 US lipid clinics. Median age at initiation of lipid-lowering therapy was 39 years, and median age at FH diagnosis was 47 years. Prevalent coronary heart disease was reported in 36% of patients, and 61% exhibited 1 or more modifiable risk factors. Median untreated low-density lipoprotein cholesterol (LDL-C) was 239 mg/dL. At enrollment, median LDL-C was 141 mg/dL; 42% of patients were taking high-intensity statin therapy and 45% received >1 LDL-lowering medication. Among FH patients receiving LDL-lowering medication(s), 25% achieved an LDL-C 1 LDL-lowering medication (1.80; 1.34-2.41). Conclusions - FH patients in the CASCADE-FH Registry are diagnosed late in life and often do not achieve adequate LDL-C lowering, despite a high prevalence of coronary heart disease and risk factors. These findings highlight the need for earlier diagnosis of FH and initiation of lipid-lowering therapy, more consistent use of guideline-recommended LDL-lowering therapy, and comprehensive management of traditional coronary heart disease risk factors. © 2016 American Heart Association, Inc.

DeGottardi, M. Q., Okoye, A. A., Vaidya, M., Talla, A., Konfe, A. L., Reyes, M. D., et al. (2016). Effect of anti-IL-15 administration on T cell and NK cell homeostasis in rhesus macaques. *Journal of Immunology (Baltimore, Md.: 1950), 197*(4), 1183-1198.

IL-15 has been implicated as a key regulator of T and NK cell homeostasis in multiple systems; however, its specific role in maintaining peripheral T and NK cell populations relative to other gamma-chain (gammac) cytokines has not been fully defined in primates. In this article, we

address this question by determining the effect of IL-15 inhibition with a rhesusized anti-IL-15 mAb on T and NK cell dynamics in rhesus macaques. Strikingly, anti-IL-15 treatment resulted in rapid depletion of NK cells and both CD4(+) and CD8(+) effector memory T cells (TEM) in blood and tissues, with little to no effect on naive or central memory T cells. Importantly, whereas depletion of NK cells was nearly complete and maintained as long as anti-IL-15 treatment was given, TEM depletion was countered by the onset of massive TEM proliferation, which almost completely restored circulating TEM numbers. Tissue TEM, however, remained significantly reduced, and most TEM maintained very high turnover throughout anti-IL-15 treatment. In the presence of IL-15 inhibition, TEM became increasingly more sensitive to IL-7 stimulation in vivo, and transcriptional analysis of TEM in IL-15-inhibited monkeys revealed engagement of the JAK/STAT signaling pathway, suggesting alternative gammac cytokine signaling may support TEM homeostasis in the absence of IL-15. Thus, IL-15 plays a major role in peripheral maintenance of NK cells and TEM However, whereas most NK cell populations collapse in the absence of IL-15, TEM can be maintained in the face of IL-15 inhibition by the activity of other homeostatic regulators, most likely IL-7.

Deguchi, H., Sinha, R. K., Marchese, P., Ruggeri, Z. M., Zilberman-Rudenko, J., McCarty, O. J., et al. (2016). Prothrombotic skeletal muscle myosin directly enhances prothrombin activation by binding factors xa and va. *Blood*,

To test the hypothesis that skeletal muscle myosins can directly influence blood coagulation and thrombosis, ex vivo studies of the effects of myosin on thrombogenesis in fresh human blood were conducted. Addition of myosin to blood augmented the thrombotic responses of human blood flowing over collagen-coated surfaces (300 s-1 shear rate). Perfusion of human blood over myosin-coated surfaces also caused fibrin and platelet deposition, evidencing myosin's thrombogenicity. Myosin markedly enhanced thrombin generation in both platelet rich plasma and platelet poor plasma, indicating that myosin promoted thrombin generation in plasma primarily independent of platelets. In purified reaction mixtures composed only of factor Xa, factor Va, prothrombin and calcium ions, myosin greatly enhanced prothrombinase activity. The Gla domain of factor Xa was not required for myosin's prothrombinase enhancement. When binding of purified clotting factors to immobilized-myosin was monitored using Bio-Layer

Interferometry, factors Xa and Va each showed favorable binding interactions. Factor Va reduced by 100-fold the apparent Kd of myosin for factor Xa (Kd ~ 0.48 nM), primarily by reducing koff, indicating formation of a stable ternary complex of myosin:Xa:Va. In studies to assess possible clinical relevance for this discovery, we found that anti-myosin antibodies inhibited thrombin generation in acute trauma patient plasmas more than in control plasmas (p=0.0004), implying myosin might contribute to acute trauma coagulopathy. We posit that myosin enhancement of thrombin generation could contribute either to promote hemostasis or to augment thrombosis risk with consequent implications for myosin's possible contributions to pathophysiology in the setting of acute injuries.

Deodhar, A., Dougados, M., Baeten, D., Wei, C., Geusens, P., Readie, A., et al. (2016). Effect of secukinumab on patient-reported outcomes in patients with active ankylosing spondylitis: A phase 3 randomized trial (MEASURE 1). *Arthritis & Rheumatology (Hoboken, N.J.)*,
OBJECTIVE: To evaluate the effect of secukinumab (interleukin-17A inhibitor) on patient-reported outcomes (PROs) in patients with active ankylosing spondylitis (AS). METHODS: In this phase 3 study, 371 patients received (1:1:1) intravenous secukinumab 10 mg/kg (baseline, weeks 2 and 4) followed by subcutaneous secukinumab 150 mg (IV-->150 mg) or 75 mg (IV-->75 mg) every 4 weeks or placebo. PROs included Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), BASDAI 50, short form-36 (SF-36) Physical (PCS) and Mental Component Scores (MCS), AS quality of life (ASQoL), Bath Ankylosing Spondylitis Functional Index (BASFI), EuroQoL-5-dimension health status questionnaire (EQ-5D), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Work Productivity and Activity Impairment-General Health questionnaire (WPAI-GH). RESULTS: At week 16, secukinumab IV-->150 mg or IV-->75 mg was associated with statistically and clinically significant improvements from baseline versus placebo in BASDAI (-2.3 for both regimens versus 0.6; P < 0.0001 and P < 0.001, respectively), SF-36 PCS (5.6 for both regimens versus 1.0; P < 0.0001 and P < 0.001, respectively), and ASQoL (-3.6, for both regimens versus -1.0; P < 0.0001 and P < 0.001, respectively). Clinically significant improvements in SF-36 MCS, BASFI, EQ-5D, and BASDAI 50 were observed with both secukinumab groups versus placebo at week 16; improvements were also observed in FACIT-F and WPAI-GH. All improvements were sustained through week 52. CONCLUSION: Secukinumab

provided significant and sustained improvements in patient-reported disease activity, health-related quality of life, and reduced functional impairment, fatigue, and impact of disease on work productivity in patients with active AS. This article is protected by copyright. All rights reserved.

DePasquale, N., Polenick, C. A., Hinde, J., Bray, J. W., Zarit, S. H., Moen, P., et al. (2016). Health behavior among men with multiple family roles: The moderating effects of perceived partner relationship quality. *American Journal of Men's Health*,

Men in the United States are increasingly involved in their children's lives and currently represent 40% of informal caregivers to dependent relatives or friends aged 18 years and older. Yet much more is known about the health effects of varying family role occupancies for women relative to men. The present research sought to fill this empirical gap by first comparing the health behavior (sleep duration, cigarette smoking, alcohol consumption, exercise, fast food consumption) of men who only occupy partner roles and partnered men who also fill father, informal caregiver, or both father and informal caregiver (i.e., sandwiched) roles. The moderating effects of perceived partner relationship quality, conceptualized here as partner support and strain, on direct family role-health behavior linkages were also examined. A secondary analysis of survey data from 366 cohabiting and married men in the Work, Family and Health Study indicated that men's multiple family role occupancies were generally not associated with health behavior. With men continuing to take on more family responsibilities, as well as the serious health consequences of unhealthy behavior, the implications of these null effects are encouraging - additional family roles can be integrated into cohabiting and married men's role repertoires with minimal health behavior risks. Moderation analysis revealed, however, that men's perceived partner relationship quality constituted a significant factor in determining whether multiple family role occupancies had positive or negative consequences for sleep duration, alcohol consumption, and fast food consumption. These findings are discussed in terms of their empirical and practical implications for partnered men and their families.

Derbew, M., Laytin, A. D., & Dicker, R. A. (2016). The surgical workforce shortage and successes in retaining surgical trainees in ethiopia: A professional survey. *Human Resources for Health*, *14*(Suppl 1), 29-016-0126-7.

BACKGROUND: Medical workforce shortages represent a major challenge in low- and middle-income countries, including those in Africa. Despite this, there is a dearth of information regarding the location and practice of African surgeons following completion of their training. In response to the call by the WHO Global Code of Practice on the International Recruitment of Health Personnel for a sound evidence base regarding patterns of practice and migration of the health workforce, this study describes the current place of residence, practice and setting of Ethiopian surgical residency graduates since commencement of their surgical training in Ethiopia or in Cuba. METHODS: This study presents data from a survey of all Ethiopian surgical residency training graduates since the programme's inception in 1985. RESULTS: A total of 348 Ethiopians had undergone surgical training in Ethiopia or Cuba since 1985; data for 327 (94.0 %) of these surgeons were collected and included in the study. The findings indicated that 75.8 % of graduates continued to practice in Ethiopia, with 80.9 % of these practicing in the public sector. Additionally, recent graduates were more likely to remain in Ethiopia and work within the public sector. The average total number of surgeons per million inhabitants in Ethiopia was approximately three and 48.0 % of Ethiopian surgeons practiced in Addis Ababa. CONCLUSIONS: Ethiopian surgeons are increasingly likely to remain in Ethiopia and to practice in the public sector. Nevertheless, Ethiopia continues to suffer from a drastic surgical workforce shortage that must be addressed through increased training capacity and strategies to combat emigration and attrition.

Desmarais, J., Beier, S., & Deodhar, A. (2016). Certolizumab pegol for treating axial spondyloarthritis. *Expert Opinion on Biological Therapy*, *16*(8), 1059-1064.

INTRODUCTION: Axial spondyloarthritis (axSpA) is a chronic inflammatory disease of the spine and sacroiliac (SI) joints. The spectrum of axSpA includes ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA). Evidence has supported the use of TNF alpha inhibitors (TNFi) in treating these diseases, with good efficacy and tolerable safety profiles. Certolizumab pegol (CZP) is an anti-TNF alpha (TNFa) agent with data to support its use in both AS and nr-axSpA. AREAS COVERED: The pharmacologic properties of CZP were reviewed. Data regarding the use and efficacy of CZP in axSpA were reviewed. Quality of life outcomes and safety profiles of CZP in axSpA patients were discussed as well. EXPERT OPINION: While there are several biologics with

evidence for improved outcomes in AS, there is less evidence for biologic medications that have good efficacy in nr-axSpA. CZP has good evidence of improved outcomes in terms of clinical efficacy, patient reported outcomes and imaging outcomes in both conditions, with a tolerable safety profile.

DeVoe, J. E., Barnes, K., Morris, C., Campbell, K., Morris-Singer, A., Westfall, J. M., et al. (2016). The personal doctoring manifesto: A perspective from the keystone IV conference. *Journal of the American Board of Family Medicine : JABFM, 29 Suppl 1*, S64-8.

The Keystone IV Conference was a touchstone moment for multigenerational conversations regarding our health care system and an opportunity to reconnect with the values of personal doctoring as a vocation. It inspired participants to renew commitments to relationships, healthy communities, and social change. Keystone IV was also a stark reminder of the need to rekindle family medicine's counterculture flame in today's tumultuous health care environment and reclaim the role of personal doctors in American society. Reimagining and reigniting the fire of personal relationship is today's counterculture movement for primary care. Personal doctors must heed the call for immediate action, which requires defining when relationships matter most in health care and understanding how to harness paradigm shifts in information technology, team-based care, and population health to strengthen, rather than undermine, personal doctoring. Simultaneously, we must also invent a new notion of personal doctoring that creates partnerships with patients and families to drive forward a social movement demanding health care focused on the whole person in the context of his or her community. Change will occur when patients insist on a personal doctoring approach as an essential priority for what they expect from the health care system-that anything less is unacceptable.

Dewland, T. A., Soliman, E. Z., Davis, B. R., Magnani, J. W., Yamal, J. M., Piller, L. B., et al. (2016). Effect of the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) on conduction system disease. *JAMA Internal Medicine, 176*(8), 1085-1092.

IMPORTANCE: Cardiac conduction abnormalities are associated with an increased risk for morbidity and mortality, and understanding factors that accelerate or delay conduction system disease could help to identify preventive and therapeutic strategies. Antifibrotic and anti-

inflammatory properties of angiotensin-converting enzyme inhibitors and treatment for hyperlipidemia may reduce the risk for incident conduction system disease. OBJECTIVE: To identify the effect of pharmacologic therapy randomization and clinical risk factors on the incidence of conduction system disease. DESIGN, SETTING, AND PARTICIPANTS: This secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) investigation acquired data from 623 North American centers. A total of 21004 ambulatory individuals 55 years or older with hypertension and at least 1 other cardiac risk factor were included in the analysis. INTERVENTIONS: Participants were randomly assigned to receive amlodipine besylate, lisinopril, or chlorthalidone. Individuals with elevated fasting low-density lipoprotein cholesterol levels were also randomized to pravastatin sodium vs usual care. MAIN OUTCOMES AND MEASURES: An electrocardiogram (ECG) was obtained at study enrollment and every 2 years of follow-up. The development of incident first-degree atrioventricular block, left anterior fascicular block, incomplete left bundle branch block (LBBB), LBBB, incomplete right bundle branch block (RBBB), RBBB, or intraventricular conduction delay was assessed by serial ECGs. RESULTS: The 21004 participants (11758 men [56.0%]; 9246 women [44.0%]; mean [SD] age, 66.5 [7.3] years) underwent a mean (SD) follow-up of 5.0 (1.2) years. Among the 1114 participants who developed any conduction defect, 389 developed LBBB, 570 developed RBBB, and 155 developed intraventricular conduction delay. Compared with chlorthalidone, randomization to lisinopril was associated with a significant 19% reduction in conduction abnormalities (hazard ratio [HR], 0.81; 95% CI, 0.69-0.95; P = .01). Treatment with amlodipine, however, was not associated with a significant difference in conduction outcome events (HR, 0.94; 95% CI, 0.81-1.09; P = .42). Similarly, pravastatin treatment was not associated with a reduced adjusted risk for incident disease compared with usual hyperlipidemia treatment (HR, 1.13; 95% CI, 0.95-1.35; P = .18). Increased age (HR, 1.47; 95% CI, 1.34-1.63; P < .001), male sex (HR, 0.59; 95% CI, 0.50-0.73; P < .001), white race (HR, 0.59; 95% CI, 0.50-0.70; P < .001), diabetes (HR, 1.23; 95% CI, 1.07-1.42; P = .003), and left ventricular hypertrophy (HR, 3.20; 95% CI, 2.61-3.94; P < .001) were also independently associated with increased risk for conduction system disease. CONCLUSIONS AND RELEVANCE: Incident conduction system disease is significantly reduced by lisinopril therapy and is independently associated with multiple clinical factors. Further studies are warranted to determine whether pharmacologic treatment affects

conduction abnormality outcomes, including pacemaker implantation. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00000542.

Dhruva, S. S., & Prasad, V. (2016). Application of medicare's new technology add-on payment program for blinatumomab. *JAMA Oncology*, *2*(2), 165-166.

Diemer, G. S., & Stedman, K. M. (2016). Modeling microvirus capsid protein evolution utilizing metagenomic sequence data. *Journal of Molecular Evolution*,

The Microviridae are increasingly becoming recognized as one of the most globally ubiquitous and highly diverse virus families, and as such, provide an advantageous model for studying virus evolution and adaptation. Here, we utilize microvirus sequences from diverse physiochemical environments, including novel sequences from a high-temperature acidic lake, to chart the outcome of natural selection in the main structural protein of the virus. Each icosahedral microvirus virion is composed of sixty identical capsid proteins that interact along twofold, threefold and fivefold symmetry axis interfaces to encapsidate a small, circular, single-stranded DNA genome. Viable assembly of the virus is guided by scaffolding proteins, which coordinate inter-subunit contacts between the capsid proteins. Structure-based analysis indicates that amino acid sequence conservation is predominantly localized to the twofold axis interface. While preservation of this quaternary interface appears to be essential, tertiary and secondary structural features of the capsid protein are permissive to considerable sequence variation.

Dixon, S. C., Nagle, C. M., Thrift, A. P., Pharoah, P. D., Pearce, C. L., Zheng, W., et al. (2016). Adult body mass index and risk of ovarian cancer by subtype: A mendelian randomization study. *International Journal of Epidemiology*,

BACKGROUND: Observational studies have reported a positive association between body mass index (BMI) and ovarian cancer risk. However, questions remain as to whether this represents a causal effect, or holds for all histological subtypes. The lack of association observed for serous cancers may, for instance, be due to disease-associated weight loss. Mendelian randomization (MR) uses genetic markers as proxies for risk factors to overcome limitations of observational studies. We used MR to elucidate the relationship between BMI and ovarian cancer, hypothesizing that genetically predicted BMI would be associated with increased risk of non-high grade serous

ovarian cancers (non-HGSC) but not HGSC. METHODS: We pooled data from 39 studies (14 047 cases, 23 003 controls) in the Ovarian Cancer Association Consortium. We constructed a weighted genetic risk score (GRS, partial F-statistic = 172), summing alleles at 87 single nucleotide polymorphisms previously associated with BMI, weighting by their published strength of association with BMI. Applying two-stage predictor-substitution MR, we used logistic regression to estimate study-specific odds ratios (OR) and 95% confidence intervals (CI) for the association between genetically predicted BMI and risk, and pooled these using random-effects meta-analysis. RESULTS: Higher genetically predicted BMI was associated with increased risk of non-HGSC (pooled OR = 1.29, 95% CI 1.03-1.61 per 5 units BMI) but not HGSC (pooled OR = 1.06, 95% CI 0.88-1.27). Secondary analyses stratified by behaviour/subtype suggested that, consistent with observational data, the association was strongest for low-grade/borderline serous cancers (OR = 1.93, 95% CI 1.33-2.81). CONCLUSIONS: Our data suggest that higher BMI increases risk of non-HGSC, but not the more common and aggressive HGSC subtype, confirming the observational evidence.

Dohare, P., Zia, M. T., Ahmed, E., Ahmed, A., Yadala, V., Schober, A. L., et al. (2016). AMPA-kainate receptor inhibition promotes neurologic recovery in premature rabbits with intraventricular hemorrhage. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *36*(11), 3363-3377.

Intraventricular hemorrhage (IVH) in preterm infants leads to cerebral inflammation, reduced myelination of the white matter, and neurological deficits. No therapeutic strategy exists against the IVH-induced white matter injury. AMPA-kainate receptor induced excitotoxicity contributes to oligodendrocyte precursor cell (OPC) damage and hypomyelination in both neonatal and adult models of brain injury. Here, we hypothesized that IVH damages white matter via AMPA receptor activation, and that AMPA-kainate receptor inhibition suppresses inflammation and restores OPC maturation, myelination, and neurologic recovery in preterm newborns with IVH. We tested these hypotheses in a rabbit model of glycerol-induced IVH and evaluated the expression of AMPA receptors in autopsy samples from human preterm infants. GluR1-GluR4 expressions were comparable between preterm humans and rabbits with and without IVH. However, GluR1 and GluR2 levels were significantly lower in the embryonic white matter and germinal matrix relative

to the neocortex in both infants with and without IVH. Pharmacological blockade of AMPA-kainate receptors with systemic NBQX, or selective AMPA receptor inhibition by intramuscular perampanel restored myelination and neurologic recovery in rabbits with IVH. NBQX administration also reduced the population of apoptotic OPCs, levels of several cytokines (TNFalpha, IL-beta, IL-6, LIF), and the density of Iba1(+) microglia in pups with IVH. Additionally, NBQX treatment inhibited STAT-3 phosphorylation, but not astrogliosis or transcription factors regulating gliosis. Our data suggest that AMPA-kainate receptor inhibition alleviates OPC loss and IVH-induced inflammation and restores myelination and neurologic recovery in preterm rabbits with IVH. Therapeutic use of FDA-approved perampanel treatment might enhance neurologic outcome in premature infants with IVH. SIGNIFICANCE STATEMENT: Intraventricular hemorrhage (IVH) is a major complication of prematurity and a large number of survivors with IVH develop cerebral palsy and cognitive deficits. The development of IVH leads to inflammation of the periventricular white matter, apoptosis and arrested maturation of oligodendrocyte precursor cells, and hypomyelination. Here, we show that AMPA-kainate receptor inhibition by NBQX suppresses inflammation, attenuates apoptosis of oligodendrocyte precursor cells, and promotes myelination as well as clinical recovery in preterm rabbits with IVH. Importantly, AMPA-specific inhibition by the FDA-approved perampanel, which unlike NBQX has a low side-effect profile, also enhances myelination and neurological recovery in rabbits with IVH. Hence, the present study highlights the role of AMPA-kainate receptor in IVH-induced white matter injury and identifies a novel strategy of neuroprotection, which might improve the neurological outcome for premature infants with IVH.

Dorrell, C., Schug, J., Canaday, P. S., Russ, H. A., Tarlow, B. D., Grompe, M. T., et al. (2016). Human islets contain four distinct subtypes of beta cells. *Nature Communications, 7*, 11756.
Human pancreatic islets of Langerhans contain five distinct endocrine cell types, each producing a characteristic hormone. The dysfunction or loss of the insulin-producing beta cells causes diabetes mellitus, a disease that harms millions. Until now, beta cells were generally regarded as a single, homogenous cell population. Here we identify four antigenically distinct subtypes of human beta cells, which we refer to as beta1-4, and which are distinguished by differential expression of ST8SIA1 and CD9. These subpopulations are always present in normal adult islets

and have diverse gene expression profiles and distinct basal and glucose-stimulated insulin secretion. Importantly, the beta cell subtype distribution is profoundly altered in type 2 diabetes. These data suggest that this antigenically defined beta cell heterogeneity is functionally and likely medically relevant.

Dotters-Katz, S. K., Humphrey, W. M., Senz, K. L., Lee, V. R., Shaffer, B. L., & Caughey, A. B. (2016). The effects of turner syndrome, 45,X on obstetric and neonatal outcomes: A retrospective cohort evaluation. *American Journal of Perinatology*,

Objective This study aims to evaluate the perinatal and neonatal outcomes associated with prenatal diagnosis of 45,X, both with and without fetal cardiac anomalies. Study Design A retrospective cohort of singleton pregnancies in California, 2005 to 2008, using vital statistics and International Classification of Diseases, Ninth Revision data, identifying prenatally diagnosed 45,X. Outcomes included preterm delivery, preeclampsia, intrauterine fetal demise (IUFD), cesarean section, small for gestational age (SGA), neonatal death, and infant death. Bivariate and multivariate analyses were used to compare pregnancies and neonates with and without 45,X. Prenatally diagnosed cardiac anomalies were also considered. Results Of the 2,029,000 deliveries, 138 had prenatally diagnosed 45,X. Out of these 138 deliveries, 22 had a prenatally diagnosed cardiac anomaly. Compared with unaffected pregnancies, those with fetal 45,X had higher rates of preterm delivery (19.5 vs. 9.9%, $p = 0.001$), cesarean section (44.2 vs. 30.2%, $p < 0.0001$), and SGA (21.5 vs. 6.3%, $p < 0.0001$). The affected cohort had no IUFDs. Neonatal death was 14.5 times higher in the 45,X cohort ($p < 0.0001$). Of only infants with cardiac anomalies, neonatal death was significantly more likely in those with 45,X ($p = 0.005$). In adjusted analysis, risk of SGA (< 3rd percentile), neonatal death, and infant death remained increased for infants with 45,X while controlling for fetal cardiac anomalies. Conclusion Prenatally diagnosed 45,X was associated with increased risk of cesarean section, and adverse neonatal outcomes, including mortality.

Doumouras, B. S., Alba, A. C., Foroutan, F., Burchill, L. J., Dipchand, A. I., & Ross, H. J. (2016). Outcomes in adult congenital heart disease patients undergoing heart transplantation: A systematic review and meta-analysis. *The Journal of Heart and Lung Transplantation : The*

Official Publication of the International Society for Heart Transplantation,

BACKGROUND: Studies assessing mortality and morbidity in adult transplant recipients with congenital heart disease (CHD) are limited. We conducted a systematic review and meta-analysis comparing post-transplant outcomes in these 2 populations. METHODS: After conducting an electronic database search, we selected studies evaluating mortality, cause-specific mortality, and risk of reoperation and dialysis in adult CHD vs non-CHD patients. We used random-effects models for the meta-analysis. RESULTS: Thirty-day mortality was significantly higher in CHD vs non-CHD patients (risk ratio [RR], 2.18; 95% confidence interval [CI], 1.62-2.93; I2 = 41%). This was influenced by increased mortality in Fontan/Glenn patients compared with non-CHD patients (RR, 3.3; 95% CI, 1.89-5.77; I2 = 0%). Mortality at 1 and 5 years was higher in the CHD population, although neither achieved statistical significance. Ten-year mortality was significantly lower in CHD patients (RR, 0.75; 95% CI, 0.60-0.95, I2 = 42%). Deaths caused by malignancy, infection, rejection, and cardiac allograft vasculopathy were decreased in CHD patients, although only death from malignancy achieved significance. Death secondary to primary graft failure, stroke, and hemorrhage was significantly higher in CHD patients. Risk of reoperation and dialysis were not statistically different between the 2 groups. CONCLUSIONS: Although adult CHD patients have higher early mortality, post-transplantation long-term survival is superior to non-CHD recipients. The challenge is to identify the CHD patients who will benefit from transplantation vs those who are higher risk.

Drake, M. G. (2016). TLR7 agonist-induced bronchodilation: Key mechanistic questions remain. *American Journal of Physiology.Lung Cellular and Molecular Physiology*, *311*(1), L177.

Drerup, C. M., Lusk, S., & Nechiporuk, A. (2016). Kif1B interacts with KBP to promote axon elongation by localizing a microtubule regulator to growth cones. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *36*(26), 7014-7026.

Delivery of proteins and organelles to the growth cone during axon extension relies on anterograde transport by kinesin motors. Though critical for neural circuit development, the mechanisms of cargo-specific anterograde transport during axon extension are only starting to be explored. Cargos of particular importance for axon outgrowth are microtubule modifiers, such as

SCG10 (Stathmin-2). SCG10 is expressed solely during axon extension, localized to growth cones, and essential for axon outgrowth; however, the mechanisms of SCG10 transport and activity were still debated. Using zebrafish mutants and in vivo imaging, we identified the Kif1B motor and its interactor Kif1 binding protein (KBP) as critical for SCG10 transport to axon growth cones and complete axon extension. Axon truncation in kbp(st23) mutants can be suppressed by SCG10 overexpression, confirming the direct relationship between decreased SCG10 levels and failed axon outgrowth. Live imaging revealed that the reduced levels of SCG10 in kbp(st23) mutant growth cones led to altered microtubule stability, defining the mechanistic basis of axon truncation. Thus, our data reveal a novel role for the Kif1B-KBP complex in the anterograde transport of SCG10, which is necessary for proper microtubule dynamics and subsequent axon extension. SIGNIFICANCE STATEMENT: Together, our data define the mechanistic underpinnings of failed axon outgrowth with loss of KBP or its associated motor, Kif1B. In addition, we provide conclusive evidence that this defect results from disruption of anterograde transport of SCG10. This is one of the first examples of a motor to be implicated in the essential transport of a discreet cargo necessary for axon extension. In addition, counter to previous in vitro and cell culture results, neither loss of the Kif1B motor nor KBP resulted in inhibition of mitochondrial transport. Altogether, our work links transport of SCG10 to the regulation of microtubule dynamics in the axon growth cone and enhances our understanding of this process during axon outgrowth.

Dufour, B. D., & McBride, J. L. (2016). Corticosterone dysregulation exacerbates disease progression in the R6/2 transgenic mouse model of huntington's disease. *Experimental Neurology*, *283*(Pt A), 308-317.

Huntington's disease (HD) is a genetic neurological disorder that causes severe and progressive motor, cognitive, psychiatric, and metabolic symptoms. There is a robust, significant elevation in circulating levels of the stress hormone, cortisol, in HD patients; however, the causes and consequences of this elevation are largely uncharacterized. Here, we evaluated whether elevated levels of corticosterone, the rodent homolog of cortisol, contributed to the development of symptomology in transgenic HD mice. Wild-type (WT) and transgenic R6/2 mice were given either 1) adrenalectomy with WT-level corticosterone replacement (10ng/ml), 2) adrenalectomy

with high HD-level corticosterone replacement (60ng/ml), or 3) sham surgery without replacement. R6/2 mice on HD-level replacement showed severe and rapid weight loss ($p<0.05$) and a shorter latency to death ($p<0.01$) relative to the HD mice on WT-level replacement. We further evaluated basal and stress-induced levels of circulating corticosterone in R6/2 mice throughout the course of their life. We found that R6/2 transgenic HD mice display a spontaneous elevation in circulating corticosterone levels that became significant at 10weeks of age. Furthermore, we identified significant dysregulation of circadian rhythmicity of corticosterone release measured over a 24h period compared to wild-type controls. Unexpectedly, we found that R6/2 transgenic mice show a blunted corticosterone response to restraint stress, compared to wild-type mice. Together, these data provide further evidence that HPA-axis activity is abnormal in R6/2 mice, and highlight the important role that cortisol plays in HD symptom development. Our findings suggest that cortisol-reducing therapeutics may be of value in improving HD patient quality of life.

Duringer, J., Fombonne, E., & Craig, M. (2016). No association between mycotoxin exposure and autism: A pilot case-control study in school-aged children. *Toxins*, *8*(7), 10.3390/toxins8070224. Evaluation of environmental risk factors in the development of autism spectrum disorder (ASD) is needed for a more complete understanding of disease etiology and best approaches for prevention, diagnosis, and treatment. A pilot experiment in 54 children (n = 25 ASD, n = 29 controls; aged 12.4 +/- 3.9 years) screened for 87 urinary mycotoxins via liquid chromatography-tandem mass spectrometry to assess current exposure. Zearalenone, zearalenone-4-glucoside, 3-acetyldeoxynivalenol, and altenuene were detected in 9/54 (20%) samples, most near the limit of detection. No mycotoxin/group of mycotoxins was associated with ASD-diagnosed children. To identify potential correlates of mycotoxin presence in urine, we further compared the nine subjects where a urinary mycotoxin was confirmed to the remaining 45 participants and found no difference based on the presence or absence of mycotoxin for age (t-test; $p = 0.322$), gender (Fisher's exact test; $p = 0.456$), exposure or not to selective serotonin reuptake inhibitors (Fisher's exact test; $p = 0.367$), or to other medications (Fisher's exact test; $p = 1.00$). While no positive association was found, more sophisticated sample preparation techniques and instrumentation, coupled with selectivity for a smaller group of

mycotoxins, could improve sensitivity and detection. Further, broadening sampling to in utero (mothers) and newborn-toddler years would cover additional exposure windows.

Eckstrom, E., Neal, M. B., Cotrell, V., Casey, C. M., McKenzie, G., Morgove, M. W., et al. (2016). An interprofessional approach to reducing the risk of falls through enhanced collaborative practice. *Journal of the American Geriatrics Society*,

Falls are the leading cause of accidental deaths in older adults and are a growing public health concern. The American Geriatrics Society (AGS) and British Geriatrics Society (BGS) published guidelines for falls screening and risk reduction, yet few primary care providers report following any guidelines for falls prevention. This article describes a project that engaged an interprofessional teaching team to support interprofessional clinical teams to reduce fall risk in older adults by implementing the AGS/BGS guidelines. Twenty-five interprofessional clinical teams with representatives from medicine, nursing, pharmacy, and social work were recruited from ambulatory, long-term care, hospital, and home health settings for a structured intervention: a 4-hour training workshop plus coaching for implementation for 1 year. The workshop focused on evidence-based strategies to decrease the risk of falls, including screening for falls; assessing gait, balance, orthostatic blood pressure, and other medical conditions; exercise including tai chi; vitamin D supplementation; medication review and reduction; and environmental assessment. Quantitative and qualitative data were collected using chart reviews, coaching plans and field notes, and postintervention structured interviews of participants. Site visits and coaching field notes confirmed uptake of the strategies. Chart reviews showed significant improvement in adoption of all falls prevention strategies except vitamin D supplementation. Long-term care facilities were more likely to address environmental concerns and add tai chi classes, and ambulatory settings were more likely to initiate falls screening. The intervention demonstrated that interprofessional practice change to target falls prevention can be incorporated into primary care and long-term care settings.

El-Assaad, I., Al-Kindi, S. G., Abraham, J., Sanatani, S., Bradley, D. J., Halsey, C., et al. (2016). Use of dofetilide in adult patients with atrial arrhythmias and congenital heart disease: A PACES collaborative study. *Heart Rhythm : The Official Journal of the Heart Rhythm Society*,

BACKGROUND: Arrhythmia management has become the major treatment challenge in patients with adult congenital heart disease (ACHD). OBJECTIVES: We sought to investigate the utility and safety profile of dofetilide for atrial arrhythmias in ACHD. METHODS: A retrospective chart review was performed. We included patients (age >/= 18) with CHD who had atrial fibrillation (AF) or intra atrial re-entrant tachycardia (IART) treated with dofetilide. RESULTS: We identified 64 patients with a mean age at initiation of 42 +/- 14 years. ACHD type included single ventricle (19), transposition of great arteries (14), atrial septal defect (9), tetralogy of Fallot (8), atrioventricular canal defect (5), mitral/aortic stenosis (7) and other (2). Thirty-five had AF and 29 had IART. A total of 3 patients had major inpatient adverse events: torsades de pointe (1), ventricular tachycardia (1) and QTc prolongation requiring discontinuation (1). Dofetilide was discontinued in one patient due to sinus node dysfunction and another patient discontinued therapy prior to discharge due to persistent arrhythmia. Of the patients who were discharged on dofetilide (n=59), 40 had adequate rhythm control and 19 had partial rhythm control. After a median follow up of 3 years, 29 patients remained on dofetilide and 2 patients died. Reasons for discontinuation included: waning effect (16), side effects (5), noncompliance (2), successful ablation (3), high cost (1) and unknown (1). CONCLUSION: Dofetilide remains a viable antiarrhythmic drug option in this challenging population. At 3 years, 49% remained on dofetilide. Close monitoring of renal function, concomitant medications and QTc interval is required.

Elmore, J. G., Cook, A. J., Bogart, A., Carney, P. A., Geller, B. M., Taplin, S. H., et al. (2016). Radiologists' interpretive skills in screening vs. diagnostic mammography: Are they related? *Clinical Imaging*, *40*(6), 1096-1103.

PURPOSE: This study aims to determine whether radiologists who perform well in screening also perform well in interpreting diagnostic mammography. MATERIALS AND METHODS: We evaluated the accuracy of 468 radiologists interpreting 2,234,947 screening and 196,164 diagnostic mammograms. Adjusting for site, radiologist, and patient characteristics, we identified radiologists with performance in the highest tertile and compared to those with lower performance. RESULTS: A moderate correlation was noted for radiologists' accuracy when interpreting screening versus their accuracy on diagnostic examinations: sensitivity

(rspearman=0.51, 95% CI: 0.22, 0.80; P=.0006) and specificity (rspearman=0.40, 95% CI: 0.30, 0.49; P<.0001). CONCLUSION: Different educational approaches to screening and diagnostic imaging should be considered.

Erkes, D. A., Xu, G., Daskalakis, C., Zurbach, K. A., Wilski, N. A., Moghbeli, T., et al. (2016). Intratumoral infection with murine cytomegalovirus synergizes with PD-L1 blockade to clear melanoma lesions and induce long-term immunity. *Molecular Therapy : The Journal of the American Society of Gene Therapy*,

Cytomegalovirus is an attractive cancer vaccine platform because it induces strong, functional CD8+ T-cell responses that accumulate over time and migrate into most tissues. To explore this, we used murine cytomegalovirus expressing a modified gp100 melanoma antigen. Therapeutic vaccination by the intraperitoneal and intradermal routes induced tumor infiltrating gp100-specific CD8+ T-cells, but provided minimal benefit for subcutaneous lesions. In contrast, intratumoral infection of established tumor nodules greatly inhibited tumor growth and improved overall survival in a CD8+ T-cell-dependent manner, even in mice previously infected with murine cytomegalovirus. Although murine cytomegalovirus could infect and kill B16F0s in vitro, infection was restricted to tumor-associated macrophages in vivo. Surprisingly, the presence of a tumor antigen in the virus only slightly increased the efficacy of intratumoral infection and tumor-specific CD8+ T-cells in the tumor remained dysfunctional. Importantly, combining intratumoral murine cytomegalovirus infection with anti-PD-L1 therapy was synergistic, resulting in tumor clearance from over half of the mice and subsequent protection against tumor challenge. Thus, while a murine cytomegalovirus-based vaccine was poorly effective against established subcutaneous tumors, direct infection of tumor nodules unexpectedly delayed tumor growth and synergized with immune checkpoint blockade to promote tumor clearance and long-term protection. Molecular Therapy (2016); doi:10.1038/mt.2016.121.

Falco, J. J., Thomas, A. J., Quin, X., Ashby, S., Mace, J. C., Deconde, A. S., et al. (2016). Lack of correlation between patient reported location and severity of facial pain and radiographic burden of disease in chronic rhinosinusitis. *International Forum of Allergy & Rhinology*,

BACKGROUND: Facial pain is a cardinal symptom of chronic rhinosinusitis (CRS) with significant

impacts on patient treatment selection, quality of life, and outcomes. The association between facial pain and CRS disease severity has not been systematically evaluated with validated, facial pain-specific questionnaires. Our objective was to measure pain location, severity, and interference in patients with CRS, and correlate these to the location and severity of radiographic evidence of disease. METHODS: Patients with CRS were enrolled into a prospective, cross-sectional study. Patients completed the Brief Pain Inventory Short Form, which is a validated and widely used tool that measures pain location, severity, and interference with daily activities of living. The Lund-Mackay (L-M) computed tomography (CT) scoring system was used to operationalize the radiographic location and severity of inflammation. Facial pain location, severity, and interference scores were correlated to paranasal sinus opacification scores. RESULTS: Consecutive patients with CRS with nasal polyps (CRSwNP; n = 37) and CRS without nasal polyps (CRSsNP; n = 46) were enrolled. No significant relationship was found between the location and severity of reported facial pain and radiographic findings of disease for patients with either CRSwNP or CRSsNP. There was no difference in pain location between patients with and without radiographic disease in a given sinus. CONCLUSION: Facial pain in CRS is not predicted by the radiographic extent of disease. The location and severity of facial pain reported by the patient is not a reliable marker of the anatomic location and severity of sinonasal inflammation. Pain location should not necessarily be relied upon for guiding targeted therapy.

Feldstein Ewing, S. W., Claus, E. D., Hudson, K. A., Filbey, F. M., Yakes Jimenez, E., Lisdahl, K. M., et al. (2016). Overweight adolescents' brain response to sweetened beverages mirrors addiction pathways. *Brain Imaging and Behavior*,

Many adolescents struggle with overweight/obesity, which exponentially increases in the transition to adulthood. Overweight/obesity places youth at risk for serious health conditions, including type 2 diabetes. In adults, neural substrates implicated in addiction (e.g., orbitofrontal cortex (OFC), striatum, amygdala, and ventral tegmental area) have been found to be relevant to risk for overweight/obesity. In this study, we examined three hypotheses to disentangle the potential overlap between addiction and overweight/obesity processing by examining (1) brain response to high vs. low calorie beverages, (2) the strength of correspondence between biometrics, including body mass index (BMI) and insulin resistance, and brain response and (3)

the relationship between a measure of food addiction and brain response using an established fMRI gustatory cue exposure task with a sample of overweight/obese youth (M age = 16.46; M BMI = 33.1). Greater BOLD response was observed across the OFC, inferior frontal gyrus (IFG), nucleus accumbens, right amygdala, and additional frontoparietal and temporal regions in neural processing of high vs. low calorie beverages. Further, BMI scores positively correlated with BOLD activation in the high calorie > low calorie contrast in the right postcentral gyrus and central operculum. Insulin resistance positively correlated with BOLD activation across the bilateral middle/superior temporal gyrus, left OFC, and superior parietal lobe. No relationships were observed between measures of food addiction and brain response. These findings support the activation of parallel addiction-related neural pathways in adolescents' high calorie processing, while also suggesting the importance of refining conceptual and neurocognitive models to fit this developmental period.

Ferracane, J. (2016). Mentoring and role modeling: The gifts that keep on giving. *Journal of Dental Research*, *95*(8), 845.

Fett, N. M., Fiorentino, D., & Werth, V. P. (2016). Practice and educational gaps in lupus, dermatomyositis, and morphea. *Dermatologic Clinics*, *34*(3), 243-250.
Patients with skin-predominant lupus erythematosus, dermatomyositis, and morphea should be evaluated, treated, and followed by dermatologists who can take primary responsibility for their care. Many academic centers have specialized centers with dermatologists who care for these patients. Patients with skin-predominant lupus erythematosus should be followed regularly with laboratory tests to detect significant systemic disease. Antibody tests can help determine the risks for individual patients. Patients with morphea rarely progress to systemic disease, but therapies can be helpful in treating and preventing progression of disease.

Fino, P. C., Nussbaum, M. A., & Brolinson, P. G. (2016). Locomotor deficits in recently concussed athletes and matched controls during single and dual-task turning gait: Preliminary results. *Journal of Neuroengineering and Rehabilitation*, *13*(1), 65-016-0177-y.
BACKGROUND: There is growing evidence that mild traumatic brain injury (concussion) can affect locomotor characteristics for prolonged periods of time even when physical signs and symptoms

are absent. While most locomotor deficits post-concussion have involved straight walking, turning gait has received little attention despite its pervasiveness in everyday locomotion and athletic competition. METHODS: This study longitudinally examined kinematic characteristics during preplanned turning in a small sample of recently concussed athletes (n = 4) and healthy matched control athletes (n = 4) to examine potential deficits during single and dual-task turning gait over the initial 6 weeks post-injury, with a one-year follow-up. Turning path kinematics (curvature, obstacle clearance, path length), stride kinematics (stride length, stride width, stride time), and inclination angles were calculated from motion capture of participants walking around an obstacle. RESULTS: Concussed athletes had larger dual-task costs in turning speed and stride time compared to healthy controls. After controlling for speed and turn curvature, recently concussed athletes increased their inclination towards the inside of the turn over time and decreased their stride time compared to controls indicating a prolonged recovery. Kinematic differences between groups were estimated to recover to healthy levels between 100 and 300 days post-injury, suggesting future prospective longitudinal studies should span 6-12 months post-injury. CONCLUSION: Turning gait should be included in future studies of concussion and may be a clinically useful tool. Future longitudinal studies should consider examining gait changes for up to 6-12 months post-injury.

Flynn, L., Ironside, P., Yedidia, M., Tanner, C. A., & Valiga, T. T. (2016). The national nursing education research network. *Journal of Nursing Education*, *55*(7), 363-364.

Focke, P. J., Hein, C., Hoffmann, B., Matulef, K., Bernhard, F., Dotsch, V., et al. (2016). Combining in vitro folding with cell free protein synthesis for membrane protein expression. *Biochemistry*, *55*(30), 4212-4219.

Cell free protein synthesis (CFPS) has emerged as a promising methodology for protein expression. While polypeptide production is very reliable and efficient using CFPS, the correct cotranslational folding of membrane proteins during CFPS is still a challenge. In this contribution, we describe a two-step protocol in which the integral membrane protein is initially expressed by CFPS as a precipitate followed by an in vitro folding procedure using lipid vesicles for converting the protein precipitate to the correctly folded protein. We demonstrate the feasibility of using this

approach for the K(+) channels KcsA and MVP and the amino acid transporter LeuT. We determine the crystal structure of the KcsA channel obtained by CFPS and in vitro folding to show the structural similarity to the cellular expressed KcsA channel and to establish the feasibility of using this two-step approach for membrane protein production for structural studies. Our studies show that the correct folding of these membrane proteins with complex topologies can take place in vitro without the involvement of the cellular machinery for membrane protein biogenesis. This indicates that the folding instructions for these complex membrane proteins are contained entirely within the protein sequence.

Francois, S., Sen, N., Mitton, B., Xiao, X., Sakamoto, K. M., & Arvin, A. (2016). Varicella-zoster virus activates CREB and inhibition of the pCREB-p300/CBP- interaction inhibits viral replication in vitro and skin pathogenesis in vivo. *Journal of Virology*,

Varicella zoster virus (VZV) is an alpha-herpesvirus that causes varicella upon primary infection and zoster upon reactivation from latency in sensory ganglion neurons. The replication of herpesviruses requires manipulation of cell signaling pathways. Notably, CREB, a factor involved in the regulation of several cellular processes, is activated upon infection of T cells with VZV. Here we report that VZV infection also induced CREB phosphorylation in fibroblasts and that XX-650-23, a newly identified inhibitor of the pCREB interaction with p300/CBP, restricted cell-cell spread of VZV in vitro CREB phosphorylation did not require the viral ORF47 or ORF 66 kinases encoded by VZV. Evaluating the biological relevance of these observations during VZV infection of human skin xenografts in the SCID mouse model of VZV pathogenesis showed both that pCREB was upregulated in infected skin and that treatment with XX-650-23 reduced infectious virus production and limited lesion formation compared to vehicle control. Thus, processes of CREB activation and p300/CBP binding are important for VZV skin infection and may be targeted for antiviral drug development. IMPORTANCE: Varicella zoster virus (VZV) is a common pathogen that causes chickenpox and shingles. As with all herpesviruses, the infection is acquired for life and the virus can periodically reactivate from latency. Although VZV infection is usually benign with few or no deleterious consequences, infection can be life-threatening in immunocompromised patients. Otherwise healthy elderly individuals who develop zoster as a consequence of viral reactivation are at risk for post-herpetic neuralgia (PHN), a painful and long

lasting complication. Current vaccines use a live attenuated virus that is usually safe but cannot be given to many immuno-deficient patients and retains the capacity to establish latency and reactivate, causing zoster. Antiviral drugs are effective against severe VZV infections but have little impact on PHN. A better understanding of virus-host cell interactions is relevant for developing improved therapies to safely interfere with cellular processes that are crucial for VZV pathogenesis.

Fujimoto, J., & Huang, D. (2016). Foreword: 25 years of optical coherence tomography. *Investigative Ophthalmology & Visual Science*, *57*(9), OCTi-OCTii.

Funk, T., Lim, Y., Kulungowski, A. M., Prok, L., Crombleholme, T. M., Choate, K., et al. (2016). Symptomatic congenital hemangioma and congenital hemangiomatosis associated with a somatic activating mutation in GNA11. *JAMA Dermatology*,
Importance: Congenital hemangiomas are uncommon benign vascular tumors that present fully formed at birth. They are rarely associated with transient hematologic abnormalities, which are typically less severe than the Kasabach-Merritt phenomenon associated with kaposiform hemangioendotheliomas. Congenital hemangiomas are typically solitary and have not been reported to occur in a multifocal, generalized pattern. Objective: To describe a male infant born with an unusual, large vascular mass complicated by anemia, thrombocytopenia, and disseminated intravascular coagulopathy, as well as innumerable small vascular papules in a generalized cutaneous distribution. Design, Setting, and Participant: This case report is a descriptive observation of the results of clinical, pathologic, and genetic studies performed in a single male infant observed for 2 years (May 2013 to June 2015) for vascular anomalies at a tertiary care referral center. Main Outcomes and Measures: Histopathologic, immunohistochemical, and genetic study results of tumor specimens and saliva. Results: Careful pathologic study of 3 tumor specimens revealed similar lobular proliferations of bland endothelial cells. Lesional vessels did not express GLUT1 or the lymphatic marker D2-40, whereas WT1 was expressed. A somatic c.A626C, p.Q209P mutation in the GNA11 gene was identified in tumoral tissue. Conclusions and Relevance: These findings support a unifying diagnosis of congenital hemangioma for these vascular tumors. To date, this is the first-reported case of a

hemangiomatosis presentation of congenital hemangioma. In addition to highlighting this novel phenotype, this case indicates the rare association of congenital hemangioma with hematologic abnormalities and verifies somatic activating mutations as the underlying cause of congenital hemangioma.

Furukawa, T. A., Salanti, G., Atkinson, L. Z., Leucht, S., Ruhe, H. G., Turner, E. H., et al. (2016). Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: Protocol for a network meta-analysis. *BMJ Open*, *6*(7), e010919-2015-010919.

INTRODUCTION: Many antidepressants are indicated for the treatment of major depression. Two network meta-analyses have provided the most comprehensive assessments to date, accounting for both direct and indirect comparisons; however, these reported conflicting interpretation of results. Here, we present a protocol for a systematic review and network meta-analysis aimed at updating the evidence base and comparing all second-generation as well as selected first-generation antidepressants in terms of efficacy and acceptability in the acute treatment of major depression. METHODS AND ANALYSIS: We will include all randomised controlled trials reported as double-blind and comparing one active drug with another or with placebo in the acute phase treatment of major depression in adults. We are interested in comparing the following active agents: agomelatine, amitriptyline, bupropion, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, trazodone, venlafaxine, vilazodone and vortioxetine. The main outcomes will be the proportion of patients who responded to or dropped out of the allocated treatment. Published and unpublished studies will be sought through relevant database searches, trial registries and websites; all reference selection and data extraction will be conducted by at least two independent reviewers. We will conduct a random effects network meta-analysis to synthesise all evidence for each outcome and obtain a comprehensive ranking of all treatments. To rank the various treatments for each outcome, we will use the surface under the cumulative ranking curve and the mean ranks. We will employ local as well as global methods to evaluate consistency. We will fit our model in a Bayesian framework using OpenBUGS, and produce results and various checks in Stata and R. We will also assess the quality of evidence

contributing to network estimates of the main outcomes with the GRADE framework. ETHICS AND DISSEMINATION: This review does not require ethical approval. PROSPERO REGISTRATION NUMBER: CRD42012002291.

Gao, S. S., Liu, L., Bailey, S. T., Flaxel, C. J., Huang, D., Li, D., et al. (2016). Quantification of choroidal neovascularization vessel length using optical coherence tomography angiography. *Journal of Biomedical Optics*, *21*(7), 76010.

Garver, J., Weber, L., Vela, E. M., Anderson, M., Warren, R., Merchlinsky, M., et al. (2016). Ectromelia virus disease characterization in the BALB/c mouse: A surrogate model for assessment of smallpox medical countermeasures. *Viruses*, *8*(7), 10.3390/v8070203.
In 2007, the United States- Food and Drug Administration (FDA) issued guidance concerning animal models for testing the efficacy of medical countermeasures against variola virus (VARV), the etiologic agent for smallpox. Ectromelia virus (ECTV) is naturally-occurring and responsible for severe mortality and morbidity as a result of mousepox disease in the murine model, displaying similarities to variola infection in humans. Due to the increased need of acceptable surrogate animal models for poxvirus disease, we have characterized ECTV infection in the BALB/c mouse. Mice were inoculated intranasally with a high lethal dose (125 PFU) of ECTV, resulting in complete mortality 10 days after infection. Decreases in weight and temperature from baseline were observed eight to nine days following infection. Viral titers via quantitative polymerase chain reaction (qPCR) and plaque assay were first observed in the blood at 4.5 days post-infection and in tissue (spleen and liver) at 3.5 days post-infection. Adverse clinical signs of disease were first observed four and five days post-infection, with severe signs occurring on day 7. Pathological changes consistent with ECTV infection were first observed five days after infection. Examination of data obtained from these parameters suggests the ECTV BALB/c model is suitable for potential use in medical countermeasures (MCMs) development and efficacy testing.

Geltzeiler, C. B., Tsikitis, V. L., Kim, J. S., Thomas, C. R.,Jr, Herzig, D. O., & Lu, K. C. (2016). Variation in the use of chemoradiotherapy for stage II and III anal cancer: Analysis of the national cancer data base. *Annals of Surgical Oncology*,

BACKGROUND: Treatment for anal canal cancer has evolved from radical operations to definitive chemoradiotherapy (CRT), which allows for sphincter preservation in most patients. OBJECTIVE: The aim of this study was to examine the use of CRT for patients with stage II and III anal cancer, among different patient demographics, geographic regions, and facility types. METHODS: Utilizing the National Cancer Data Base, we examined patients with stage II and III anal canal squamous cell carcinoma from 2003 to 2010. Via univariate analysis, we examined patterns of treatment by patient demographics, tumor characteristics, geographic region, and facility type (academic vs. community). A multivariable logistic regression model was built to evaluate differences in treatment patterns when adjusting by age, sex, race, comorbidities, and stage. RESULTS: A total of 12,801 patients were analyzed, of which 11,312 (88 %) received CRT. After adjusting for confounders, CRT was less likely to be administered to males [odds ratio (OR) 0.61, 95 % confidence interval (CI) 0.54-0.69], Black patients (OR 0.70, 95 % CI 0.59-0.83), and those with multiple comorbidities (OR 0.60, 95 % CI 0.51-0.72). CRT was not as widely utilized in the West (OR 0.74, 95 % CI 0.59-0.93), and patients treated in academic-based centers were less likely to receive CRT (OR 0.81, 95 % CI 0.72-0.92). Improved median overall survival was observed when CRT was utilized (p = 0.008). CONCLUSION: When controlling for age, sex, race, comorbidities, and stage, discrepancies in the use of CRT for anal cancer treatment exist between demographic subtypes, geographical regions, and facility types.

Gerhard, D. S., Clemons, P. A., Shamji, A. F., Hon, C., Wagner, B. K., Schreiber, S. L., et al. (2016). Transforming big data into cancer-relevant insight: An initial, multi-tier approach to assess reproducibility and relevance. *Molecular Cancer Research : MCR*,

The Cancer Target Discovery and Development (CTD2) Network was established to accelerate the transformation of "Big Data" into novel pharmacological targets, lead compounds, and biomarkers for rapid translation into improved patient outcomes. It rapidly became clear in this collaborative network that a key central issue was to define what constitutes sufficient computational or experimental evidence to support a biologically or clinically relevant finding. This manuscript represents a first attempt to delineate the challenges of supporting and confirming discoveries arising from the systematic analysis of large-scale data resources in a collaborative work environment and to provide a framework that would begin a community

discussion to resolve these challenges. The Network implemented a multi-Tier framework designed to substantiate the biological and biomedical relevance as well as the reproducibility of data and insights resulting from its collaborative activities. The same approach can be used by the broad scientific community to drive development of novel therapeutic and biomarker strategies for cancer.

Gerhardt, R. T., Glassberg, E., Holcomb, J. B., Mabry, R. L., Schreiber, M. B., & Spinella, P. C. (2016). Tactical study of care originating in the prehospital environment (tacscope): Acute traumatic coagulopathy on the contemporary battlefield. *Shock (Augusta, Ga.), 46*(3S Suppl 1), 104-107. BACKGROUND: Uncontrolled major hemorrhage and delayed evacuation remain substantial contributors to potentially survivable combat death, along with mission, environment, terrain, logistics, and hostile action. Life-saving interventions and the onset of acute traumatic coagulopathy (ATC) may also contribute. OBJECTIVE: Analyze US casualty records from the DoD Trauma Registry, using International Normalized Ratio (INR) of 1.5 for onset of ATC. METHODS: Retrospective cohort study from September 2007 to June 2011, inclusive. Independent variable was INR. Primary dependent variables were transfusion volume, massive transfusion (MT) defined as >10 units RBC/fresh whole blood in first 24 h, and 30-day survival. We used T test and chi-square analysis. Our IRB reviewed and exempted this study. RESULTS: In total, 8,913 cases were available. Fifty one percent had complete data with INR. Of excluded cases, 98.9% survived, average injury severity scales (ISS) was 7 (IQR 1-8), and less than 1% received MT. Among included cases, 98.5% survived, average ISS was 10 (IQR 2-14), average INR was 1.16 (CI95 1.14-1.17), and 2.7% received MT. There were 383 cases with ATC (8.4%). After stratification, we found that ATC cases were more likely to die (odds ratio (OR) 28, CI 16-48), receive MT (OR 9.6, CI 6.4-14.4), and were acidotic (pH 7.27 (7.24-7.31) vs. 7.38 (7.38-7.39)). Other significant differences included Injury Severity Score, Revised Trauma Score, blast mechanism, and penetrating injury. CONCLUSION: ATC is substantially associated with greater injury severity, MT, and mortality. Prehospital identification of MT casualties may expedite triage and evacuation, and enable remote damage control resuscitation to delay ATC onset and improve outcomes.

Gerstein, N. S., Young, A., Schulman, P. M., Stecker, E. C., & Jessel, P. M. (2016). Sedation in the electrophysiology laboratory: A multidisciplinary review. *Journal of the American Heart Association, 5*(6), 10.1161/JAHA.116.003629.

Geszvain, K., Smesrud, L., & Tebo, B. M. (2016). Identification of a third mn(II) oxidase enzyme in pseudomonas putida GB-1. *Applied and Environmental Microbiology, 82*(13), 3774-3782. The oxidation of soluble Mn(II) to insoluble Mn(IV) is a widespread bacterial activity found in a diverse array of microbes. In the Mn(II)-oxidizing bacterium Pseudomonas putida GB-1, two Mn(II) oxidase genes, named mnxG and mcoA, were previously identified; each encodes a multicopper oxidase (MCO)-type enzyme. Expression of these two genes is positively regulated by the response regulator MnxR. Preliminary investigation into putative additional regulatory pathways suggested that the flagellar regulators FleN and FleQ also regulate Mn(II) oxidase activity; however, it also revealed the presence of a third, previously uncharacterized Mn(II) oxidase activity in P. putida GB-1. A strain from which both of the Mn(II) oxidase genes and fleQ were deleted exhibited low levels of Mn(II) oxidase activity. The enzyme responsible was genetically and biochemically identified as an animal heme peroxidase (AHP) with domain and sequence similarity to the previously identified Mn(II) oxidase MopA. In the ΔfleQ strain, P. putida GB-1 MopA is overexpressed and secreted from the cell, where it actively oxidizes Mn. Thus, deletion of fleQ unmasked a third Mn(II) oxidase activity in this strain. These results provide an example of an Mn(II)-oxidizing bacterium utilizing both MCO and AHP enzymes. © 2016, American Society for Microbiology. All Rights Reserved.

Gordon, M. J., Raess, P. W., Young, K., Spurgeon, S. E., & Danilov, A. V. (2016). Ibrutinib is an effective treatment for B-cell prolymphocytic leukaemia. *British Journal of Haematology,*

Graff, J. N., Alumkal, J. J., Drake, C. G., Thomas, G. V., Redmond, W. L., Farhad, M., et al. (2016). Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. *Oncotarget,* While programmed cell death 1 (PD-1) inhibitors have shown clear anti-tumor efficacy in several solid tumors, prior results in men with metastatic castration resistant prostate cancer (mCRPC) showed no evidence of activity. Here we report unexpected antitumor activity seen in mCRPC patients treated with the anti-PD-1 antibody pembrolizumab. Patients with evidence of

progression on enzalutamide were treated with pembrolizumab 200 mg IV every 3 weeks for 4 doses; pembrolizumab was added to standard dose enzalutamide. Three of the first ten patients enrolled in this ongoing phase II trial experienced rapid prostate specific antigen (PSA) reductions to </= 0.2 ng/ml. Two of these three patients had measurable disease upon study entry; both achieved a partial response. There were three patients with significant immune-related adverse events. One had grade 2 myositis, one had grade 3 hypothyroidism, and one had grade 2 hypothyroidism. None of these patients had a response. Two of the three responders had a baseline tumor biopsy. Immunohistochemistry from those biopsies showed the presence of CD3+, CD8+, and CD163+ leukocyte infiltrates and PD-L1 expression. Genetic analysis of the two responders revealed markers of microsatellite instability in one. The surprising and robust responses seen in this study should lead to re-examination of PD-1 inhibition in prostate cancer.

Gray, J. W. (2016). PI3 kinase pathway mutations in human cancers. *JAMA Oncology*,

Gross, O. P., & von Gersdorff, H. (2016). Recycling at synapses. *Elife*, *5*, 10.7554/eLife.17692. Synaptic vesicles in rodent neurons are recycled using at least two distinct mechanisms.

Guydish, J., Tajima, B., Pramod, S., Le, T., Gubner, N. R., Campbell, B., et al. (2016). Use of multiple tobacco products in a national sample of persons enrolled in addiction treatment. *Drug and Alcohol Dependence*,

OBJECTIVE: To explore use of tobacco products in relationship to marketing exposure among persons in addiction treatment. METHOD: A random sample of treatment programs was drawn from the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN). Participants in each program completed surveys concerning use of tobacco products (N=1113). Exposure to tobacco marketing and counter-marketing, advertising receptivity, and perceived health risks of smoking were tested for their association with use of multiple tobacco products. RESULTS: Prevalence of combustible cigarette use was 77.9%. Weekly or greater use of other products was: e-cigarettes (17.7%), little filtered cigars (8.6%), smokeless tobacco (5.2%), and standard cigars (4.6%) with 24.4% using multiple tobacco products. Compared to single product users, multiple product users smoked more cigarettes per day (OR=1.03, 95% CI 1.01-1.05, p<0.001), were more likely to have tried to quit (OR=1.41, 95% CI 1.02-1.96, p=0.041), reported greater

daily exposure to advertising for products other than combustible cigarettes (OR=1.93, CI 1.35-2.75, p<0.001), and greater daily exposure to tobacco counter-marketing (OR=1.70, 95% CI: 1.09-2.63, p=0.019). CONCLUSION: Heavier smokers and those trying to quit may be more likely to use e-cigarettes, little filtered cigars, or smokeless tobacco and have greater susceptibility to their advertising. This highlights the importance of regulating advertising related to smoking cessation as their effectiveness for this purpose has not been demonstrated.

Hadad, N., Masser, D. R., Logan, S., Wronowski, B., Mangold, C. A., Clark, N., et al. (2016). Absence of genomic hypomethylation or regulation of cytosine-modifying enzymes with aging in male and female mice. *Epigenetics & Chromatin*, *9*, 30-016-0080-6. eCollection 2016.
BACKGROUND: Changes to the epigenome with aging, and DNA modifications in particular, have been proposed as a central regulator of the aging process, a predictor of mortality, and a contributor to the pathogenesis of age-related diseases. In the central nervous system, control of learning and memory, neurogenesis, and plasticity require changes in cytosine methylation and hydroxymethylation. Although genome-wide decreases in methylation with aging are often reported as scientific dogma, primary research reports describe decreases, increases, or lack of change in methylation and hydroxymethylation and their principle regulators, DNA methyltransferases and ten-eleven translocation dioxygenases in the hippocampus. Furthermore, existing data are limited to only male animals. RESULTS: Through examination of the hippocampus in young, adult, and old male and female mice by antibody-based, pyrosequencing, and whole-genome oxidative bisulfite sequencing methods, we provide compelling evidence that contradicts the genomic hypomethylation theory of aging. We also demonstrate that expression of DNA methyltransferases and ten-eleven translocation dioxygenases is not differentially regulated with aging or between the sexes, including the proposed cognitive aging regulator DNMT3a2. Using oxidative bisulfite sequencing that discriminates methylation from hydroxymethylation and by cytosine (CG and non-CG) context, we observe sex differences in average CG methylation and hydroxymethylation of the X chromosome, and small age-related differences in hydroxymethylation of CG island shores and shelves, and methylation of promoter regions. CONCLUSION: These findings clarify a long-standing misconception of the epigenomic

response to aging and demonstrate the need for studies of base-specific methylation and hydroxymethylation with aging in both sexes.

Hamilton, B. E., Woltjer, R. L., Prola-Netto, J., Nesbit, G. M., Gahramanov, S., Pham, T., et al. (2016). Ferumoxytol-enhanced MRI differentiation of meningioma from dural metastases: A pilot study with immunohistochemical observations. *Journal of Neuro-Oncology*,
Malignant dural neoplasms are not reliably distinguished from benign dural neoplasms with contrast-enhanced magnetic resonance imaging (MRI). MRI enhancement in central nervous system (CNS) diseases imaged with ferumoxytol has been attributed to intracellular uptake in macrophages rather than vascular leakage. We compared imaging to histopathology and immunohistochemistry in meningiomas and dural metastases having ferumoxytol-enhanced MRI (FeMRI) and gadolinium-enhanced MRI (GdMRI) in order to correlate enhancement patterns to macrophage presence and vascular state. All patients having extraaxial CNS tumors were retrospectively selected from one of two ongoing FeMRI studies. Enhancement was compared between GdMRI and FeMRI. Diagnoses were confirmed histologically and/or by characteristic imaging. Tumor and vascular histology was reviewed. Immunohistochemical staining for CD68 (a macrophage marker), Connexin-43 (Cx43) (a marker of normal gap junctions), and smooth muscle actin (SMA) as a marker of vascularity, was performed in seven study cases with available tissue. Immunohistochemistry was performed on archival material from 33 subjects outside of the current study as controls: 20 WHO grade I cases of meningioma and 13 metastatic tumors. Metastases displayed marked delayed enhancement on FeMRI, similar to GdMRI. Four patients with dural metastases and one patient with meningioma showed similar enhancement on FeMRI and GdMRI. Five meningiomas with typical enhancement on GdMRI lacked enhancement on FeMRI. Enhancement on FeMRI was better associated with decreased Cx43 expression than intralesional macrophages. These pilot data suggest that FeMRI may better differentiate metastatic disease from meningiomas than GdMRI, and that differences in tumor vasculature rather than macrophage presence could underlie differences in contrast enhancement.

Han, P. K. J., Dieckmann, N. F., Holt, C., Gutheil, C., & Peters, E. (2016). Factors affecting physicians' intentions to communicate personalized prognostic information to cancer patients at the end of

life: An experimental vignette study. *Medical Decision Making, 36*(6), 703-713.

Purpose. To explore the effects of personalized prognostic information on physicians' intentions to communicate prognosis to cancer patients at the end of life, and to identify factors that moderate these effects. Methods. A factorial experiment was conducted in which 93 family medicine physicians were presented with a hypothetical vignette depicting an end-stage gastric cancer patient seeking prognostic information. Physicians' intentions to communicate prognosis were assessed before and after provision of personalized prognostic information, while emotional distress of the patient and ambiguity (imprecision) of the prognostic estimate were varied between subjects. General linear models were used to test the effects of personalized prognostic information, patient distress, and ambiguity on prognostic communication intentions, and potential moderating effects of 1) perceived patient distress, 2) perceived credibility of prognostic models, 3) physician numeracy (objective and subjective), and 4) physician aversion to risk and ambiguity. Results. Provision of personalized prognostic information increased prognostic communication intentions ($P < 0.001$, $\eta 2 = 0.38$), although experimentally manipulated patient distress and prognostic ambiguity had no effects. Greater change in communication intentions was positively associated with higher perceived credibility of prognostic models ($P = 0.007$, $\eta 2 = 0.10$), higher objective numeracy ($P = 0.01$, $\eta 2 = 0.09$), female sex ($P = 0.01$, $\eta 2 = 0.08$), and lower perceived patient distress ($P = 0.02$, $\eta 2 = 0.07$). Intentions to communicate available personalized prognostic information were positively associated with higher perceived credibility of prognostic models ($P = 0.02$, $\eta 2 = 0.09$), higher subjective numeracy ($P = 0.02$, $\eta 2 = 0.08$), and lower ambiguity aversion ($P = 0.06$, $\eta 2 = 0.04$). Conclusions. Provision of personalized prognostic information increases physicians' prognostic communication intentions to a hypothetical end-stage cancer patient, and situational and physician characteristics moderate this effect. More research is needed to confirm these findings and elucidate the determinants of prognostic communication at the end of life. © Society for Medical Decision Making.

Hanifin, J. M. (2016). New drugs for atopic dermatitis may provide clues to basic mechanisms of itch and inflammation. *Journal of the American Academy of Dermatology,*

Hare, A. Q., & Rich, P. (2016). Clinical and educational gaps in diagnosis of nail disorders. *Dermatologic Clinics, 34*(3), 269-273.

Dermatologists care for skin, hair, and nails, yet many dermatologists find nail disorders challenging. Practice gaps in knowledge, skill, and attitude in clinical practice and resident education are sometimes impediments to timely medical and surgical diagnosis of nail disorders. Limited resident exposure to diagnosis and management of complicated nail disorders and lack of experience performing diagnostic and surgical procedures impairs progress toward surmounting these gaps.

Hart, R. A., DePasse, J. M., & Daniels, A. H. (2016). Failure to launch: What the rejection of lumbar total disk replacement tells us about american spine surgery. *Clinical Spine Surgery,*

STUDY DESIGN: Spine surgeon survey. OBJECTIVE: The objective was to investigate the failure of widespread adoption of lumbar total disk replacement (L-TDR) in the United States. SUMMARY OF BACKGROUND DATA: L-TDR has been available for use in the United States since 2005. L-TDR has not gained wide acceptance as a treatment for degenerative disk disease despite substantial investments in product development and positive results in randomized controlled trials. METHODS: Estimates of the number of L-TDR procedures performed in the United States from 2005 to 2010 were calculated using the Nationwide Inpatient Sample database. Insurance policies were assessed for L-TDR coverage through Internet search. Finally, an 18-question survey regarding surgeons' opinions toward L-TDR was distributed to the members of North American Spine Society. RESULTS: The estimated number of primary L-TDR procedures performed in the United States decreased from 3650 in 2005 to 1863 in 2010, whereas revision L-TDR procedures increased from 420 to 499. Of 14 major insurers, 11 (78.6%) do not cover L-TDR. In total, 613 spine surgeons responded to the survey. Over half of respondents (51.1%, 313/612) have performed L-TDR, although only 44.6% (136/305) of initial adopters currently perform the surgery. However, 81.5% (106/130) of those currently performing L-TDR have been satisfied with the results. When asked about their perceptions of L-TDR, 65.0% (367/565) indicated a lack of insurance coverage for L-TDR in their region, 54.9% (310/565) worry about long-term complications, and 52.7% (298/565) worry about the technical challenges of revision. CONCLUSIONS: Despite early enthusiasm for L-TDR, wide adoption has not occurred. A primary

reason for this failure seems to be a lack of insurance coverage, despite intermediate-term clinical success. In addition, surgeons continue to express concerns regarding long-term outcomes and the technical difficulties of revision. This case study of a failed surgical innovation may signal increasing involvement of payers in clinical decision-making and may be instructive to surgeons, policymakers, and manufacturers.

Hayama, T., Yamaguchi, T., Kato-Itoh, M., Ishii, Y., Mizuno, N., Umino, A., et al. (2016). Practical selection methods for rat and mouse round spermatids without DNA staining by flow cytometric cell sorting. *Molecular Reproduction and Development*, *83*(6), 488-496.

Round spermatid injection (ROSI) into unfertilized oocytes enables a male with a severe spermatogenesis disorder to have children. One limitation of the application of this technique in the clinic is the identification and isolation of round spermatids from testis tissue. Here we developed an efficient and simple method to isolate rodent haploid round spermatids using flow cytometric cell sorting, based on DNA content (stained with Hoechst 33342 or Dye Cycle Violet) or by cell diameter and granularity (forward and side scatter). ROSI was performed with round spermatids selected by flow cytometry, and we obtained healthy offspring from unstained cells. This non-invasive method could therefore be an effective option for breeding domestic animals and human male infertility treatment. Mol. Reprod. Dev. 83: 488–496, 2016. © 2016 Wiley Periodicals, Inc. © 2016 Wiley Periodicals, Inc.

Henry, J. A., Griest, S., Austin, D., Helt, W., Gordon, J., Thielman, E., et al. (2016). Tinnitus screener: Results from the first 100 participants in an epidemiology study. *American Journal of Audiology*, *25*(2), 153-160.

Purpose: In the Noise Outcomes in Servicemembers Epidemiology Study, Veterans recently separated from the military undergo comprehensive assessments to initiate longterm monitoring of their auditory function. We developed the Tinnitus Screener, a four-item algorithmic instrument that determines whether tinnitus is present and, if so, whether it is constant or intermittent, or whether only temporary tinnitus has been experienced. Predictive validity data are presented for the first 100 Noise Outcomes in Servicemembers Epidemiology Study participants. Method: The Tinnitus Screener was administered to participants by telephone. In

lieu of a gold standard for determining tinnitus presence, the predictive validity of the tinnitus category assigned to participants on the basis of the Screener results was assessed when the participants attended audiologic testing. Results: Of the 100 participants, 67 screened positive for intermittent or constant tinnitus. Three were categorized as "temporary" tinnitus only, and 30 were categorized as "no tinnitus." Tinnitus categorization was predictively valid with 96 of the 100 participants. Conclusions: These results provide preliminary evidence that the Screener may be suitable for quickly determining essential parameters of reported tinnitus. We have since revised the instrument to differentiate acute from chronic tinnitus and to identify occasional tinnitus. We are also obtaining measures that will enable assessment of its test-retest reliability.

Henry, J. A., Stewart, B. J., Griest, S., Kaelin, C., Zaugg, T. L., & Carlson, K. (2016). Multisite randomized controlled trial to compare two methods of tinnitus intervention to two control conditions. *Ear and Hearing*,

OBJECTIVES: In this four-site clinical trial, we evaluated whether tinnitus masking (TM) and tinnitus retraining therapy (TRT) decreased tinnitus severity more than the two control groups: an attention-control group that received tinnitus educational counseling (and hearing aids if needed; TED), and a 6-month-wait-list control (WLC) group. The authors hypothesized that, over the first 6 months of treatment, TM and TRT would decrease tinnitus severity in Veterans relative to TED and WLC, and that TED would decrease tinnitus severity relative to WLC. The authors also hypothesized that, over 18 months of treatment, TM and TRT would decrease tinnitus severity relative to TED. Treatment effectiveness was hypothesized not to be different across the four sites. DESIGN: Across four Veterans affairs medical center sites, N = 148 qualifying Veterans who experienced sufficiently bothersome tinnitus were randomized into one of the four groups. The 115 Veterans assigned to TM (n = 42), TRT (n = 34), and TED (n = 39) were considered immediate-treatment subjects; they received comparable time and attention from audiologists. The 33 Veterans assigned to WLC were, after 6 months, randomized to receive delayed treatment in TM, TRT, or TED. Assessment of outcomes took place using the Tinnitus Handicap Inventory (THI) at 0, 3, 6, 12, and 18 months. RESULTS: Results of a repeated measures analysis of variance using an intention-to-treat approach showed that the tinnitus severity of Veterans

receiving TM, TRT, and TED significantly decreased ($p < 0.05$) relative to Veterans in the WLC group at 3 months (effect sizes = 0.44, 0.52, and 0.27, respectively) and at 6 months (effect sizes = 0.52, 0.56, and 0.40, respectively). Analyses comparing effectiveness of TM, TRT, and TED over 18 months revealed that the three conditions were not significantly different, but that tinnitus severity in the combined groups significantly decreased ($p < 0.01$) from baseline to 3 months (5.6 THI points) and from 3 to 6 months (3.7 THI points). With respect to clinically significant change, about half of Veterans who received TM (55%), TRT (59%), or TED (46%) showed strong or modest improvement on the THI by 18 months. Without treatment, the WLC group did not show significant change. Treatment effectiveness did not differ by study site. CONCLUSIONS: Audiologists who provided interventions to Veterans with bothersome tinnitus in the regular clinic setting were able to significantly reduce tinnitus severity over 18 months using TM, TRT, and TED approaches. These results suggest that TM, TRT, and TED, when implemented as in this trial, will provide effectiveness that is relatively similar by 6 months and beyond.

Herting, M. M., Keenan, M. F., & Nagel, B. J. (2016). Aerobic fitness linked to cortical brain development in adolescent males: Preliminary findings suggest a possible role of BDNF genotype. *Frontiers in Human Neuroscience, 10*, 327.

Aerobic exercise has been shown to impact brain structure and cognition in children and adults. Exercise-induced activation of a growth protein known as brain derived neurotrophic factor (BDNF) is thought to contribute to such relationships. To date, however, no study has examined how aerobic fitness relates to cortical brain structure during development and if BDNF genotype moderates these relationships. Using structural magnetic resonance imaging (MRI) and FreeSurfer, the current study examined how aerobic fitness relates to volume, thickness, and surface area in 34 male adolescents, 15 to 18 years old. Moreover, we examined if the val66met BDNF genotype moderated these relationships. We hypothesized that aerobic fitness would relate to greater thickness and volumes in frontal, parietal, and motor regions, and that these relationships would be less robust in individuals carrying a Met allele, since this genotype leads to lower BDNF expression. We found that aerobic fitness positively related to right rostral middle frontal cortical volume in all adolescents. However, results also showed BDNF genotype moderated the relationship between aerobic fitness and bilateral medial precuneus surface area,

with a positive relationship seen in individuals with the Val/Val allele, but no relationship detected in those adolescents carrying a Met allele. Lastly, using self-reported levels of aerobic activity, we found that higher-fit adolescents showed larger right medial pericalcarine, right cuneus and left precuneus surface areas as compared to their low-fit peers. Our findings suggest that aerobic fitness is linked to cortical brain development in male adolescents, and that more research is warranted to determine how an individual's genes may influence these relationships.

Hickey, R. D., Mao, S. A., Glorioso, J., Elgilani, F., Amiot, B., Chen, H., et al. (2016). Curative ex vivo liver-directed gene therapy in a pig model of hereditary tyrosinemia type 1. *Science Translational Medicine, 8*(349), 349ra99.

We tested the hypothesis that ex vivo hepatocyte gene therapy can correct the metabolic disorder in fumarylacetoacetate hydrolase-deficient (Fah(-/-)) pigs, a large animal model of hereditary tyrosinemia type 1 (HT1). Recipient Fah(-/-) pigs underwent partial liver resection and hepatocyte isolation by collagenase digestion. Hepatocytes were transduced with one or both of the lentiviral vectors expressing the therapeutic Fah and the reporter sodium-iodide symporter (Nis) genes under control of the thyroxine-binding globulin promoter. Pigs received autologous transplants of hepatocytes by portal vein infusion. After transplantation, the protective drug 2-(2-nitro-4-trifluoromethylbenzyol)-1,3 cyclohexanedione (NTBC) was withheld from recipient pigs to provide a selective advantage for expansion of corrected FAH(+) cells. Proliferation of transplanted cells, assessed by both immunohistochemistry and noninvasive positron emission tomography imaging of NIS-labeled cells, demonstrated near-complete liver repopulation by gene-corrected cells. Tyrosine and succinylacetone levels improved to within normal range, demonstrating complete correction of tyrosine metabolism. In addition, repopulation of the Fah(-/-) liver with transplanted cells inhibited the onset of severe fibrosis, a characteristic of nontransplanted Fah(-/-) pigs. This study demonstrates correction of disease in a pig model of metabolic liver disease by ex vivo gene therapy. To date, ex vivo gene therapy has only been successful in small animal models. We conclude that further exploration of ex vivo hepatocyte genetic correction is warranted for clinical use.

Hill-Burns, E. M., Ross, O. A., Wissemann, W. T., Soto-Ortolaza, A. I., Zareparsi, S., Siuda, J., et al. (2016). Identification of genetic modifiers of age-at-onset for familial parkinson's disease. *Human Molecular Genetics,*

Parkinson's disease (PD) is the most common cause of neurodegenerative movement disorder and the second most common cause of dementia. Genes are thought to have a stronger effect on age-at-onset of PD than on risk, yet there has been a phenomenal success in identifying risk loci but not age-at-onset modifiers. We conducted a genome-wide study for age-at-onset. We analysed familial and non-familial PD separately, per prior evidence for strong genetic effect on age-at-onset in familial PD. GWAS was conducted in 431 unrelated PD individuals with at least one affected relative (familial PD) and 1544 non-familial PD from the NeuroGenetics Research Consortium (NGRC); an additional 737 familial PD and 2363 non-familial PD were used for replication. In familial PD, two signals were detected and replicated robustly: one mapped to LHFPL2 on 5q14.1 (PNGRC = 3E-8, PReplication = 2E-5, PNGRC + Replication = 1E-11), the second mapped to TPM1 on 15q22.2 (PNGRC = 8E-9, PReplication = 2E-4, PNGRC + Replication = 9E-11). The variants that were associated with accelerated onset had low frequencies (<0.02). The LHFPL2 variant was associated with earlier onset by 12.33 [95% CI: 6.2; 18.45] years in NGRC, 8.03 [2.95; 13.11] years in replication, and 9.79 [5.88; 13.70] years in the combined data. The TPM1 variant was associated with earlier onset by 15.30 [8.10; 22.49] years in NGRC, 9.29 [1.79; 16.79] years in replication, and 12.42 [7.23; 17.61] years in the combined data. Neither LHFPL2 nor TPM1 was associated with age-at-onset in non-familial PD. LHFPL2 (function unknown) is overexpressed in brain tumours. TPM1 encodes a highly conserved protein that regulates muscle contraction, and is a tumour-suppressor gene.

Hoak, D. A., & Lutsep, H. L. (2016). Management of symptomatic intracranial stenosis. *Current Cardiology Reports, 18*(9), 83-016-0762-5.

Intracranial atherosclerotic disease is a common cause of stroke worldwide, causing approximately 10 % of strokes in the USA and up to 50 % in Asian populations. Recurrent stroke risks are particularly high in those with a stenosis of 70 % or more and a recent transient ischemic attack or stroke. Warfarin has been associated with higher major hemorrhage rates and no reduction of recurrent stroke compared to aspirin in patients with symptomatic intracranial

stenosis. After early trials showed the feasibility of stenting, two randomized trials compared stenting plus medical management to medical management alone in symptomatic intracranial stenosis. Stenting was linked with increased risk and showed no benefit in any subpopulation of patients. Aggressive medical management in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was associated with half the risk of stroke compared to that in similar patients in a previous symptomatic intracranial stenosis trial after adjustment of confounding characteristics. Aggressive medical management comprises risk factor control, including a target systolic blood pressure <140 mmHg, a low density lipoprotein <70 mg/dL, hemoglobin A1C <7.0 %, and lifestyle management that incorporates exercise, smoking cessation and weight management, and the use of antithrombotics.

Horti, A. G., Wang, Y., Minn, I. L., Lan, X., Wang, J., Koehler, R., et al. (2016). 18F-FNDP for PET imaging of soluble epoxide hydrolase (sEH). *Journal of Nuclear Medicine : Official Publication, Society of Nuclear Medicine*,

Soluble epoxide hydrolase is a bifunctional enzyme located within cytosol and peroxisomes that converts epoxides to the corresponding diols and hydrolyzes phosphate monoesters. It serves to inactivate epoxyeicosatrienoic acids (EETs), which have vasoactive and anti-inflammatory properties. Inhibitors of sEH are pursued as agents to mitigate neuronal damage after stroke. We developed N-(3,3-diphenylpropyl)-6-[18F]fluoronicotinamide ([18F]FNDP), which proved highly specific for imaging of sEH in the mouse and non-human primate brain with PET. METHODS: [18F]FNDP was synthesized from the corresponding bromo-precursor. sEH inhibitory activity of [18F]FNDP was measured using the sEH Inhibitor Screening Assay Kit. Biodistribution was undertaken in CD-1 mice. Binding specificity was assayed in CD-1 and sEH knock-out mice and Papio anubis (baboon) through pre-treatment with an sEH inhibitor to block sEH binding. Dynamic PET imaging with arterial blood sampling was performed in baboon with regional tracer binding quantified using distribution volume (VT). Metabolism of [18F]FNDP in baboon was assessed using high performance liquid chromatography. RESULTS: [18F]FNDP (Ki = 1.73 nM) was synthesized in one step in radiochemical yield of 14 +/- 7% (non-decay-corrected, n = 6), specific radioactivity in the range of 888 - 3,774 GBq/mmol (24,000 - 102,000 mCi/micromol)

and in radiochemical purity > 99%. In CD-1 mice regional uptake followed the pattern of striatum > cortex > hippocampus > cerebellum, consistent with the known brain distribution of sEH, with 5.2 percent injected dose per gram of tissue at peak uptake. Blockade of 80-90% was demonstrated in all brain regions. Minimal radiotracer uptake was present in sEH-KO mice. PET baboon brain distribution paralleled that seen in mouse with marked blockade (95%) noted in all regions indicating sEH-mediated uptake of [18F]FNDP. Two hydrophilic metabolites were identified with 30% parent compound present at 90 min post-injection in baboon plasma. CONCLUSION: [18F]FNDP can be synthesized in suitable radiochemical yield and high specific radioactivity and purity using an automatic radiosynthesis module. In vivo imaging experiments demonstrated that [18F]FNDP targeted sEH in murine and non-human primate brain specifically. [18F]FNDP is a promising PET radiotracer likely to be useful for understanding the role of sEH in a variety of conditions affecting the central nervous system.

Hostetler, C. M., Phillips, T. J., & Ryabinin, A. E. (2016). Methamphetamine consumption inhibits pair bonding and hypothalamic oxytocin in prairie voles. *PloS One*, *11*(7), e0158178. Methamphetamine (MA) abuse has been linked to violence, risk-taking behaviors, decreased sexual inhibition, and criminal activity. It is important to understand mechanisms underlying these drug effects for prevention and treatment of MA-associated social problems. Previous studies have demonstrated that experimenter-administered amphetamine inhibits pair bonding and increases aggression in monogamous prairie voles. It is not currently known whether similar effects on social behaviors would be obtained under conditions during which the drug is voluntarily (actively) administered. The current study investigated whether MA drinking affects pair bonding and what neurocircuits are engaged. In Experiment 1, we exposed male and female voles to 4 days each of 20 and 40 mg/L MA under a continuous 2-bottle choice (2BC) procedure. Animals were housed either singly or in mesh-divided cages with a social partner. Voles consumed MA in a drinking solution, but MA drinking was not affected by either sex or housing condition. In Experiment 2, we investigated whether MA drinking disrupts social bonding by measuring aggression and partner preference formation following three consecutive days of 18-hour/day access to 100 mg/L MA in a 2BC procedure. Although aggression toward a novel opposite-sex animal was not affected by MA exposure, partner preference was inhibited in MA

drinking animals. Experiment 3 examined whether alterations in hypothalamic neuropeptides provide a potential explanation for the inhibition of partner preference observed in Experiment 2. MA drinking led to significant decreases in oxytocin, but not vasopressin, in the paraventricular nucleus of the hypothalamus. These experiments are the first investigation into how voluntary pre-exposure to MA affects the development of social attachment in a socially monogamous species and identify potential neural circuits involved in these effects.

Howard, L. E., De Hoedt, A. M., Aronson, W. J., Kane, C. J., Amling, C. L., Cooperberg, M. R., et al. (2016). Do skeletal-related events predict overall survival in men with metastatic castration-resistant prostate cancer? *Prostate Cancer and Prostatic Diseases*,

BACKGROUND: Skeletal-related events (SREs) including pathologic fracture, spinal cord compression, radiation to bone and surgery to bone, are common in men with bone metastatic castration-resistant prostate cancer (mCRPC). Men with mCRPC are at high risk of death. Whether SREs predict mortality is unclear. We tested the association between SREs and overall survival (OS) in a multiethnic cohort with bone mCRPC, controlling for key covariates unavailable in claims data such as bone pain, number of bone metastases and PSA doubling time (PSADT). METHODS: We collected data on 233 men diagnosed with nonmetastatic castration-resistant prostate cancer (CRPC) in 2000-2013 at two Veterans Affairs hospitals who later progressed to bone metastases. First occurrence of SRE and OS were collected from the medical records. Cox models were used to test the association between SRE and OS, treating SRE as a time-dependent variable. We adjusted for age, year, race, treatment center, biopsy Gleason, primary treatment to the prostate, PSA, PSADT, months from androgen deprivation therapy to CRPC, months from CRPC to metastasis and number of bone metastases at initial bone metastasis diagnosis. In a secondary analysis, we also adjusted for bone pain. RESULTS: During follow-up, 88 (38%) patients had an SRE and 198 (85%) died. After adjusting for risk factors, SRE was associated with increased mortality (hazard ratio (HR)=1.67; 95% confidence interval (CI) 1.22-2.30; P=0.001). When bone pain was added to the model, the association of SREs and OS was attenuated, but remained significant (HR=1.42; 95% CI 1.01-1.99; P=0.042). CONCLUSIONS: SREs are associated with increased mortality in men with bone mCRPC. Further studies on the

impact of preventing SREs to increase survival are warranted.Prostate Cancer and Prostatic Diseases advance online publication, 5 July 2016; doi:10.1038/pcan.2016.26.

Hu, Z., Mao, J. H., Curtis, C., Huang, G., Gu, S., Heiser, L., et al. (2016). Genome co-amplification upregulates a mitotic gene network activity that predicts outcome and response to mitotic protein inhibitors in breast cancer. *Breast Cancer Research : BCR, 18*(1), 70-016-0728-y. BACKGROUND: High mitotic activity is associated with the genesis and progression of many cancers. Small molecule inhibitors of mitotic apparatus proteins are now being developed and evaluated clinically as anticancer agents. With clinical trials of several of these experimental compounds underway, it is important to understand the molecular mechanisms that determine high mitotic activity, identify tumor subtypes that carry molecular aberrations that confer high mitotic activity, and to develop molecular markers that distinguish which tumors will be most responsive to mitotic apparatus inhibitors. METHODS: We identified a coordinately regulated mitotic apparatus network by analyzing gene expression profiles for 53 malignant and non-malignant human breast cancer cell lines and two separate primary breast tumor datasets. We defined the mitotic network activity index (MNAI) as the sum of the transcriptional levels of the 54 coordinately regulated mitotic apparatus genes. The effect of those genes on cell growth was evaluated by small interfering RNA (siRNA). RESULTS: High MNAI was enriched in basal-like breast tumors and was associated with reduced survival duration and preferential sensitivity to inhibitors of the mitotic apparatus proteins, polo-like kinase, centromere associated protein E and aurora kinase designated GSK462364, GSK923295 and GSK1070916, respectively. Co-amplification of regions of chromosomes 8q24, 10p15-p12, 12p13, and 17q24-q25 was associated with the transcriptional upregulation of this network of 54 mitotic apparatus genes, and we identify transcription factors that localize to these regions and putatively regulate mitotic activity. Knockdown of the mitotic network by siRNA identified 22 genes that might be considered as additional therapeutic targets for this clinically relevant patient subgroup. CONCLUSIONS: We define a molecular signature which may guide therapeutic approaches for tumors with high mitotic network activity.

Huang, X., Jin, M., Chen, Y. X., Wang, J., Zhai, K., Chang, Y., et al. (2016). ERP44 inhibits human lung cancer cell migration mainly via IP3R2. *Aging*, *8*(6), 1276-1286.

Cancer cell migration is involved in tumour metastasis. However, the relationship between calcium signalling and cancer migration is not well elucidated. In this study, we used the human lung adenocarcinoma A549 cell line to examine the role of endoplasmic reticulum protein 44 (ERP44), which has been reported to regulate calcium release inside of the endoplasmic reticulum (ER), in cell migration. We found that the inositol 1,4,5-trisphosphate receptors (IP3Rs/ITPRs) inhibitor 2-APB significantly inhibited A549 cell migration by inhibiting cell polarization and pseudopodium protrusion, which suggests that Ca2+ is necessary for A549 cell migration. Similarly, the overexpression of ERP44 reduced intracellular Ca2+ release via IP3Rs, altered cell morphology and significantly inhibited the migration of A549 cells. These phenomena were primarily dependent on IP3R2 because wound healing in A549 cells with IP3R2 rather than IP3R1 or IP3R3 siRNA was markedly inhibited. Moreover, the overexpression of ERP44 did not affect the migration of the human neuroblastoma cell line SH-SY5Y, which mainly expresses IP3R1. Based on the above observations, we conclude that ERP44 regulates A549 cell migration mainly via an IP3R2-dependent pathway.

Hunter, J. G. (2016). Editor's note. *World Journal of Surgery*, , 1.

Hyun, H. K., & Ferracane, J. L. (2016). Influence of biofilm formation on the optical properties of novel bioactive glass-containing composites. *Dental Materials : Official Publication of the Academy of Dental Materials*, *32*(9), 1144-1151.

OBJECTIVE: Bioactive glass (BAG) has been suggested as a possible additive for dental restorative materials because of its antimicrobial effect and potential for promoting apatite formation in body fluids. The purpose of this study was to investigate the effects of bacterial biofilm on the change of colorimetric value and translucency of novel BAG-containing composites having different initial surface roughness. METHODS: Composites with 72wt% total filler load were prepared by replacing 15% of the silanized Sr glass with BAG (65 mol % Si; 4% P; 31% Ca), BAG-F (61% Si; 31% Ca; 4% P; 3% F; 1% B), or silanized silica. Light-cured discs of 2-mm thickness (n=10/group) were divided into 4 different surface roughness subgroups produced by

wet polishing with 600 and then up to 1200, 2400, or 4000 grit SiC. CIE L*a*b* were measured and the color difference and translucency parameter (TP) were calculated before and after incubating in media with or without a Streptococcus mutans (UA 159) biofilm for 2 wks (no agitation). Results were analyzed using ANOVA/Tukey's test (alpha=0.05). RESULTS: All the color differences for BAG and BAG-F composite showed significant decreases with bacterial biofilm compared to media-only. The mean TP (SD) of BAG and BAG-F composite before aging [10.0 (2.8) and 8.5 (1.4)] was higher than that of the control composite [4.9 (0.8)], while the change in TP with aging was greater compared to the control with or without bacteria. BAG-F composites with the smoothest surfaces showed a greater decrease in TP under bacterial biofilm compared to the BAG composite. SIGNIFICANCE: Highly polished dental composites containing bioactive glass additives may become slightly rougher and show reduced translucency when exposed to bacterial biofilms, but do not discolor any more than control composites that do not contain the BAG.

Inaba, K., Byerly, S., Bush, L. D., Martin, M. J., Martin, D., Peck, K. A., et al. (2016). Cervical spinal clearance: A prospective western trauma association multi-institutional trial. *The Journal of Trauma and Acute Care Surgery*,

BACKGROUND: For blunt trauma patients who have failed the NEXUS low-risk criteria, the adequacy of CT as the definitive imaging modality for clearance remains controversial. The purpose of this study was to prospectively evaluate the accuracy of CT for the detection of clinically significant C-spine injury. METHODS: Prospective multicenter observational study (09/2013-03/2015), at 18 North American Trauma Centers. All adult (>/=18yo) blunt trauma patients underwent a structured clinical examination. NEXUS failures underwent a CT of the C-spine with clinical follow up to discharge. The primary outcome measure was sensitivity and specificity of CT for clinically significant injuries requiring surgical stabilization, halo or cervical-thoracic orthotic (CTO) placement using the gold standard of final diagnosis at the time of discharge, incorporating all imaging and operative findings. RESULTS: 10,765 patients met inclusion criteria, 489 (4.5%) were excluded (previous spinal instrumentation or outside hospital transfer). 10,276 patients [4,660 (45.3%) unevaluable/distracting injuries, 5,040 (49.0%) midline C-spine tenderness, 576 (5.6%) neurologic symptoms] were prospectively enrolled: mean age 48.1yo (range 18-110), SBP 138 (SD 26), median GCS 15 (IQR 14,15), ISS 9 (IQR

4,16). Overall, 198 (1.9%) had a clinically significant C-spine injury requiring surgery [153 (1.5%)] or halo [25 (0.2%)] or CTO [20 (0.2%)]. The sensitivity and specificity for clinically significant injury was 98.5% and 91.0% with a NPV of 99.97%. There were 3 (0.03%) false negative CT scans that missed a clinically significant injury, all had a focal neurologic abnormality on their index clinical examination consistent with central cord syndrome and 2 of 3 had severe degenerative disease. CONCLUSIONS: For patients requiring acute imaging for their C-spine after blunt trauma, CT was effective for ruling out clinically significant injury with a sensitivity of 98.5%. For patients with an abnormal neurologic exam as the trigger for imaging, there is a small but clinically significant incidence of a missed injury and further imaging with MRI is warranted. LEVEL OF EVIDENCE: Level II, Diagnostic Tests or Criteria.

Ito, M. K., & Santos, R. D. (2016). PCSK9 inhibition with monoclonal antibodies: Modern management of hypercholesterolemia. *Journal of Clinical Pharmacology*,

Current guidelines for hypercholesterolemia treatment emphasize lifestyle modification and lipid-modifying therapy to reduce the risk for cardiovascular disease. Statins are the primary class of agents used for the treatment of hypercholesterolemia. Although statins are effective for many patients, they fail to achieve optimal reduction in lipids for some patients, including those who have or are at high risk for cardiovascular disease. The PCSK9 gene was identified in the past decade as a potential therapeutic target for the management of patients with hypercholesterolemia. Pharmacologic interventions to decrease PCSK9 levels are in development, with the most promising approach using monoclonal antibodies that bind to PCSK9 in the plasma. Two monoclonal antibodies, alirocumab and evolocumab, have recently been approved for the treatment of hypercholesterolemia, and a third one, bococizumab, is in phase 3 clinical development. All 3 agents achieve significant reductions in levels of low-density lipoprotein cholesterol, as well as reductions in non-high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a). Long-term outcome trials are under way to determine the sustained efficacy, safety, and tolerability of PCSK9 inhibitors and whether this novel class of agents decreases the risk for major cardiovascular events in patients on lipid-modifying therapy. Available data suggest that PCSK9 inhibitors provide a robust reduction in atherogenic cholesterol levels with a good safety profile, especially for patients who fail to obtain an optimal clinical response to statin

therapy, those who are statin intolerant or have contraindications to statin therapy, and those with familial hypercholesterolemia. © 2016, The American College of Clinical Pharmacology.

Iturria-Medina, Y., Sotero, R. C., Toussaint, P. J., Mateos-Pérez, J. M., Evans, A. C., Weiner, M. W., et al. (2016). Early role of vascular dysregulation on late-onset alzheimer's disease based on multifactorial data-driven analysis. *Nature Communications, 7*

Multifactorial mechanisms underlying late-onset Alzheimer's disease (LOAD) are poorly characterized from an integrative perspective. Here spatiotemporal alterations in brain amyloid-β deposition, metabolism, vascular, functional activity at rest, structural properties, cognitive integrity and peripheral proteins levels are characterized in relation to LOAD progression. We analyse over 7,700 brain images and tens of plasma and cerebrospinal fluid biomarkers from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Through a multifactorial data-driven analysis, we obtain dynamic LOAD-abnormality indices for all biomarkers, and a tentative temporal ordering of disease progression. Imaging results suggest that intra-brain vascular dysregulation is an early pathological event during disease development. Cognitive decline is noticeable from initial LOAD stages, suggesting early memory deficit associated with the primary disease factors. High abnormality levels are also observed for specific proteins associated with the vascular system's integrity. Although still subjected to the sensitivity of the algorithms and biomarkers employed, our results might contribute to the development of preventive therapeutic interventions.

Jacob, R. L., Geddes, J., McCartney, S., & Burchiel, K. J. (2016). Cost analysis of awake versus asleep deep brain stimulation: A single academic health center experience. *Journal of Neurosurgery, 124*(5), 1517-1523.

Objective The objective of this study was to compare the cost of deep brain stimulation (DBS) performed awake versus asleep at a single US academic health center and to compare costs across the University HealthSystem Consortium (UHC) Clinical Database. Methods Inpatient and outpatient demographic and hospital financial data for patients receiving a neurostimulator lead implant (from the first quarter of 2009 to the second quarter of 2014) were collected and analyzed. Inpatient charges included those associated with International Classification of

Diseases, Ninth Revision (ICD-9) procedure code 0293 (implantation or replacement of intracranial neurostimulator lead). Outpatient charges included all preoperative charges ? 30 days prior to implant and all postoperative charges ? 30 days after implant. The cost of care based on reported charges and a cost-to-charge ratio was estimated. The UHC database was queried (January 2011 to March 2014) with the same ICD-9 code. Procedure cost data across like hospitals (27 UHC hospitals) conducting similar DBS procedures were compared. Results Two hundred eleven DBS procedures (53 awake and 158 asleep) were performed at a single US academic health center during the study period. The average patient age (± SD) was 65 ± 9 years old and 39% of patients were female. The most common primary diagnosis was Parkinson's disease (61.1%) followed by essential and other forms of tremor (36%). Overall average DBS procedure cost was 39,152 ± 5340. Asleep DBS cost 38,850 ± 4830, which was not significantly different than the awake DBS cost of 40,052 ± 6604. The standard deviation for asleep DBS was significantly lower (p ? 0.05). In 2013, the median cost for a neurostimulator implant lead was 34,052 at UHC-affiliated hospitals that performed at least 5 procedures a year. At Oregon Health & Science University, the median cost was 17,150 and the observed single academic health center cost for a neurostimulator lead implant was less than the expected cost (ratio 0.97). Conclusions In this single academic medical center cost analysis, DBS performed asleep was associated with a lower cost variation relative to the awake procedure. Furthermore, costs compared favorably to UHC-affiliated hospitals. While asleep DBS is not yet standard practice, this center exclusively performs asleep DBS at a lower cost than comparable institutions. © AANS, 2016.

Jacobs, J., Bleier, B. S., Hopkins, C., Hwang, P., Poetker, D., Schlosser, R., et al. (2016). Response to: The "RACE" national database for recurrent acute rhinosinusitis may need a relook. *International Forum of Allergy & Rhinology*,

Jensen, J. T., Hanna, C., Yao, S., Thompson, E., Bauer, C., & Slayden, O. D. (2016). Transcervical administration of polidocanol foam prevents pregnancy in female baboons. *Contraception*, BACKGROUND: Our objective was to conduct a pilot study to determine if transcervical administration of polidocanol foam (PF) with or without doxycycline or benzalkonium chloride

(BZK) would prevent pregnancy in baboons. METHODS: In study phase 1, adult cycling baboons underwent a hysterosalpingogram to evaluate tubal patency prior to transcervical infusion of 20 mL of 5% PF followed by 1 mL of saline containing 100 mg doxycycline (5%/doxy; n=5), 3% PF plus doxycycline (3%/doxy; n=4), 3% PF with 0.01% BZK (3%/BZK; n=4) or no additional treatment (control; n=9). Immediately following treatment, animals received intramuscular depot medroxyprogesterone acetate (DMPA, 2 mg/kg) to suppress cyclicity during healing and were then socially housed with males of proven fertility. The primary outcome was pregnancy within six cycles of resumption of menses (efficacy phase 1). During study phase 2, PF-treated females from study phase 1 contributed additional cycles (6-8) of exposure (efficacy phase 2), and 5 control females who had recovered from medical abortion (after study phase 1 pregnancy) were subsequently treated with 5% PF (with DMPA) and exposed to breeding (efficacy phase 1; n=3 six cycles, n=2 five cycles). RESULTS: All females resumed normal menstrual cycles and mating activity after DMPA. During efficacy phase 1, 7/9 (78%) control females became pregnant. In contrast, fewer pregnancies occurred in PF-treated females: 5% PF 0/5 (0%), 5%/doxy 1/5 (20%), 3%/doxy 1/4 (25%) and 3%/BZK 1/4 (25%). During efficacy phase 2, only one additional pregnancy occurred (3%/BZK). CONCLUSIONS: A single transcervical treatment with 5% PF prevented pregnancy in most baboons. Cotreatment with doxycycline or BZK did not improve results. IMPLICATIONS: Transcervical intrauterine administration of PF resulted in a high rate of tubal occlusion with prevention of pregnancy; refinements are needed to increase the contraceptive rate following a single treatment to near 100%.

Jones, D., Hansen, M., Van Otterloo, J., Dickinson, C., & Guise, J. M. (2016). Emergency medical services provider pediatric adverse event rate varies by call origin pediatric emergency care. *Pediatric Emergency Care*,

OBJECTIVE: Emergency medical services providers may be called to a variety of sites to transport pediatric patients, whether it be a scene call for initial evaluation and care, a clinic for transportation of a patient who has been assessed by medical providers, or a hospital where assessment and stabilization have already begun. We hypothesize that there may be a direct relationship between adverse event rates and adverse event severity in transports from less medically stabilizing origins. METHODS: Emergency medical services records of all critical

pediatric transports in an urban Oregon county in 2011 were reviewed and abstracted using a standardized tool. From this, UNSEMs (unintended injury, near miss, suboptimal action, error, management complication) were determined, and the potential severity of the issue was assessed. Then, UNSEMs were compared with the origin of transport using logistic regression. RESULTS: Four hundred ninety records were abstracted: 59 hospital transports, 48 clinic transports, and 384 scene transports. Furthermore, UNSEMs were noted in 24 hospital transports (40.7%), 33 clinic transports (68.8%), and 263 scene transports (68.5%). Severe UNSEMs were reported on 0 hospital transports (0.0%), 12 clinic transports (25.0%), and 65 scene transports (16.9%). The odds ratio of UNSEM occurrence from a hospital compared with nonmedical scenes was 0.35 (95% confidence interval, 0.20-0.60), and the odds ratio of a severe UNSEM from a hospital compared with nonmedical scenes was 0.09 (95% confidence interval, 0.01-0.63). CONCLUSIONS: In conclusion, UNSEMs involving the emergency medical services care of children are more likely to occur when transport originates from a clinic or scene compared with a hospital.

Jonkman, N. H., Westland, H., Trappenburg, J. C. A., Groenwold, R. H. H., Bischoff, E. W. M. A., Bourbeau, J., et al. (2016). Characteristics of effective self-management interventions in patients with COPD: Individual patient data meta-analysis. *European Respiratory Journal, 48*(1), 55-68. It is unknown whether heterogeneity in effects of self-management interventions in patients with chronic obstructive pulmonary disease (COPD) can be explained by differences in programme characteristics. This study aimed to identify which characteristics of COPD self-management interventions are most effective. Systematic search in electronic databases identified randomised trials on self-management interventions conducted between 1985 and 2013. Individual patient data were requested for meta-analysis by generalised mixed effects models. 14 randomised trials were included (67% of eligible), representing 3282 patients (75% of eligible). Univariable analyses showed favourable effects on some outcomes for more planned contacts and longer duration of interventions, interventions with peer contact, without log keeping, without problem solving, and without support allocation. After adjusting for other programme characteristics in multivariable analyses, only the effects of duration on all-cause hospitalisation remained. Each month increase in intervention duration reduced risk of all-cause hospitalisation (time to event

hazard ratios 0.98, 95% CI 0.97-0.99; risk ratio (RR) after 6 months follow-up 0.96, 95% CI 0.92-0.99; RR after 12 months follow-up 0.98, 95% CI 0.96-1.00). Our results showed that longer duration of self-management interventions conferred a reduction in all-cause hospitalisations in COPD patients. Other characteristics are not consistently associated with differential effects of self-management interventions across clinically relevant outcomes.

Kahi, C. J., & Lieberman, D. (2016). Family history of colorectal adenomas: Taking the methodological bull by the horns. *Gastroenterology*, *150*(3), 550-552.

Kaplan, J. S., Mohr, C., Hostetler, C. M., Ryabinin, A. E., Finn, D. A., & Rossi, D. J. (2016). Alcohol suppresses tonic GABAA receptor currents in cerebellar granule cells in the prairie vole: A neural signature of high-alcohol-consuming genotypes. *Alcoholism, Clinical and Experimental Research*, *40*(8), 1617-1626.

BACKGROUND: Evidence indicates that the cerebellum plays a role in genetic predilection to excessive alcohol (ethanol [EtOH]) consumption in rodents and humans, but the molecular mechanisms mediating such predilection are not understood. We recently determined that EtOH has opposite actions (enhancement or suppression) on tonic GABAA receptor (GABAA R) currents in cerebellar granule cells (GCs) in low- and high-EtOH-consuming rodents, respectively, and proposed that variation in GC tonic GABAA R current responses to EtOH contributes to genetic variation in EtOH consumption phenotype. METHODS: Voltage-clamp recordings of GCs in acutely prepared slices of cerebellum were used to evaluate the effect of EtOH on GC tonic GABAA R currents in another high-EtOH-consuming rodent, prairie voles (PVs). RESULTS: EtOH (52 mM) suppressed the magnitude of the tonic GABAA R current in 57% of cells, had no effect in 38% of cells, and enhanced the tonic GABAA R current in 5% of cells. This result is similar to GCs from high-EtOH-consuming C57BL/6J (B6) mice, but it differs from the enhancement of tonic GABAA R currents by EtOH in low-EtOH-consuming DBA/2J (D2) mice and Sprague Dawley (SD) rats. EtOH suppression of tonic GABAA R currents was not affected by the sodium channel blocker, tetrodotoxin (500 nM), and was independent of the frequency of phasic GABAA R-mediated currents, suggesting that suppression is mediated by postsynaptic actions on GABAA Rs, rather

than a reduction of GABA release. Finally, immunohistochemical analysis of neuronal nitric oxide synthase (nNOS; which can mediate EtOH enhancement of GABA release) demonstrated that nNOS expression in the GC layer of PV cerebellum was similar to the levels seen in B6 mice, both being significantly reduced relative to D2 mice and SD rats. CONCLUSIONS: Combined, these data highlight the GC GABAA R response to EtOH in another species, the high-EtOH-consuming PV, which correlates with EtOH consumption phenotype and further implicates the GC GABAA R system as a contributing mechanism to high EtOH consumption.

Kappus, M., Diamond, S., Hurt, R. T., & Martindale, R. (2016). Intestinal failure: New definition and clinical implications. *Current Gastroenterology Reports, 18*(9), 48-016-0525-x.
Intestinal failure (IF) is a state in which the nutritional demands of the body are not met by the gastrointestinal absorptive surface. It is a long-recognized complication associated with short bowel syndrome, which results in malabsorption after significant resection of the intestine for many reasons or functional dysmotility. Etiologies have included Crohn's disease, vascular complications, and the effects of radiation enteritis, as well as the effects of intestinal obstruction, dysmotility, or congenital defects. While IF has been long-recognized, it has historically not been uniformly defined, which has made both recognition and management challenging. This review examines the previous definitions of IF as well as the newer definition and classification of IF and how it is essential to IF clinical guidelines.

Kar, S. P., Beesley, J., Amin Al Olama, A., Michailidou, K., Tyrer, J., Kote-Jarai, Z., et al. (2016). Genome-wide meta-analyses of breast, ovarian, and prostate cancer association studies identify multiple new susceptibility loci shared by at least two cancer types. *Cancer Discovery*,
Breast, ovarian, and prostate cancers are hormone-related and may have a shared genetic basis, but this has not been investigated systematically by genome-wide association (GWA) studies. Meta-analyses combining the largest GWA meta-analysis data sets for these cancers totaling 112,349 cases and 116,421 controls of European ancestry, all together and in pairs, identified at $P < 10\text{-}8$ seven new cross-cancer loci: three associated with susceptibility to all three cancers (rs17041869/2q13/BCL2L11; rs7937840/11q12/INCENP; rs1469713/19p13/GATAD2A), two breast and ovarian cancer risk loci (rs200182588/9q31/SMC2; rs8037137/15q26/RCCD1), and

two breast and prostate cancer risk loci (rs5013329/1p34/NSUN4; rs9375701/6q23/L3MBTL3). Index variants in five additional regions previously associated with only one cancer also showed clear association with a second cancer type. Cell-type-specific expression quantitative trait locus and enhancer-gene interaction annotations suggested target genes with potential cross-cancer roles at the new loci. Pathway analysis revealed significant enrichment of death receptor signaling genes near loci with P < 10-5 in the three-cancer meta-analysis. SIGNIFICANCE: We demonstrate that combining large-scale GWA meta-analysis findings across cancer types can identify completely new risk loci common to breast, ovarian, and prostate cancers. We show that the identification of such cross-cancer risk loci has the potential to shed new light on the shared biology underlying these hormone-related cancers. Cancer Discov; 6(9); 1-16. (c)2016 AACR.

Kathpalia, P., Bhatia, A., Robertazzi, S., Ahn, J., Cohen, S. M., Sontag, S., et al. (2015). Indwelling peritoneal catheters in patients with cirrhosis and refractory ascites. *Internal Medicine Journal*, *45*(10), 1026-1031.

BACKGROUND: The prevalence of spontaneous bacterial peritonitis (SBP) in hospitalised cirrhotics with ascites is 10-30%. Treatment for refractory ascites includes paracenteses, transjugular intrahepatic portosystemic shunt or drain placement; the latter is discouraged due to a perceived infection risk. AIM: This study aimed to evaluate the risk of bacterial peritonitis (BP) with peritoneal drains in patients with Child-Pugh class B or C cirrhosis and determine their impact on survival. METHODS: We conducted a retrospective review of end-stage liver disease (ESLD) patients with non-malignant, refractory ascites who had peritoneal drains placed for >/=3 days at Loyola University between 1999 and 2009. Cell counts were performed at drain placement and within 72 h. BP was defined as ascitic polymorphonuclear neutrophils >250/mm(3) . Univariate analysis assessed the association between demographics, laboratory markers and development of BP. Kaplan-Meier curve estimates by infection were constructed and survival distributions were compared using log-rank statistic. RESULTS: There were 227 drain placements during the study period. Twenty-two per cent were diagnosed with BP (12% had SBP at drain placement; 10% developed BP within 72 h). There was no association between BP and baseline characteristics. Patients who developed BP within 72 h of drain placement had 50% mortality at 5 months compared with 50 months in those without infection (log-rank P </=

0.003). CONCLUSION: In ESLD patients who received an indwelling peritoneal catheter, there was 10% risk of developing BP and significant mortality increase. Though placing drains is not the mainstay of treatment for refractory ascites, we confirm the theoretical adverse risk of peritoneal drains on infection and survival in cirrhotics.

Kazanci, H. O., & Jacques, S. L. (2016). Diffuse light tomography to detect blood vessels using Tikhonov regularization. *3rd International Symposium on Optics and Biophotonics, SFM 2015 and 7th Finnish-Russian Photonics and Laser Symposium, PALS 2015*, , *9917.*

Detection of blood vessels within light-scattering tissues involves detection of subtle shadows as blood absorbs light. These shadows are diffuse but measurable by a set of source-detector pairs in a spatial array of sources and detectors on the tissue surface. The measured shadows can reconstruct the internal position(s) of blood vessels. The tomographic method involves a set of Ns sources and Nd detectors such that Nsd = Ns x Nd source-detector pairs produce Nsd measurements, each interrogating the tissue with a unique perspective, i.e., a unique region of sensitivity to voxels within the tissue. This tutorial report describes the reconstruction of the image of a blood vessel within a soft tissue based on such source-detector measurements, by solving a matrix equation using Tikhonov regularization. This is not a novel contribution, but rather a simple introduction to a well-known method, demonstrating its use in mapping blood perfusion. © 2016 SPIE.

Keller, F. S., & Kaufman, J. A. (2016). Obituary. *Cardiovascular and Interventional Radiology, 39*(9), 1227-1228.

Kellogg, M., Liang, C. W., & Liebeskind, D. S. (2016). Sudden neurologic deficit. *Handbook of Clinical Neurology, 136*, 857-872.

Clinicians treating sudden neurologic deficit are being faced with an increasing number of available imaging modalities. In this chapter we discuss a general approach to acute neuroimaging and weigh the considerations that determine which modality or modalities should be utilized.

Khan, A. R., Chuhutin, A., Wiborg, O., Kroenke, C. D., Nyengaard, J. R., Hansen, B., et al. (2016). Biophysical modeling of high field diffusion MRI demonstrates micro-structural aberration in chronic mild stress rat brain. *Neuroimage*,

Depression is one of the leading causes of disability worldwide. Immense heterogeneity in symptoms of depression causes difficulty in diagnosis, and to date, there are no established biomarkers or imaging methods to examine depression. Unpredictable chronic mild stress (CMS) induced anhedonia is considered to be a realistic model of depression in studies of animal subjects. Stereological and neuronal tracing techniques have demonstrated persistent remodeling of microstructure in hippocampus, prefrontal cortex and amygdala of CMS brains. Recent developments in diffusion MRI (d-MRI) analyses, such as neurite density and diffusion kurtosis imaging (DKI), are able to capture microstructural changes and are considered to be robust tools in preclinical and clinical imaging. The present study utilized d-MRI analyzed with a neurite density model and the DKI framework to investigate microstructure in the hippocampus, prefrontal cortex, caudate putamen and amygdala regions of CMS rat brains by comparison to brains from normal controls. To validate findings of CMS induced microstructural alteration, histology was performed to determine neurite, nuclear and astrocyte density. d-MRI based neurite density and tensor-based mean kurtosis (MKT) were significantly higher, while mean diffusivity (MD), extracellular diffusivity (Deff) and intra-neurite diffusivity(DL) were significantly lower in the amygdala of CMS rat brains. Deff was also significantly lower in the hippocampus and caudate putamen in stressed groups. Histological neurite density corroborated the d-MRI findings in the amygdala and reductions in nuclear and astrocyte density further buttressed the d-MRI results. The present study demonstrated that the d-MRI based neurite density and MKT can reveal specific microstructural changes in CMS rat brains and these parameters might have value in clinical diagnosis of depression and for evaluation of treatment efficacy.

Kho, A. T., Sharma, S., Davis, J. S., Spina, J., Howard, D., McEnroy, K., et al. (2016). Circulating MicroRNAs: Association with lung function in asthma. *PloS One*, *11*(6), e0157998.

BACKGROUND: MicroRNAs are key transcriptional and network regulators previously associated with asthma susceptibility. However, their role in relation to asthma severity has not been delineated. OBJECTIVE: We hypothesized that circulating microRNAs could serve as biomarkers of

changes in lung function in asthma patients. METHODS: We isolated microRNAs from serum samples obtained at randomization for 160 participants of the Childhood Asthma Management Program. Using a TaqMan microRNA array containing 754 microRNA primers, we tested for the presence of known asthma microRNAs, and assessed the association of the individual microRNAs with lung function as measured by FEV1/FVC, FEV1% and FVC%. We further tested the subset of FEV1/FVC microRNAs for sex-specific and lung developmental associations. RESULTS: Of the 108 well-detected circulating microRNAs, 74 (68.5%) had previously been linked to asthma susceptibility. We found 22 (20.3%), 4 (3.7%) and 8 (7.4%) microRNAs to be associated with FEV1/FVC, FEV1% and FVC%, respectively. 8 (of 22) FEV1/FVC, 3 (of 4) FEV1% and 1 (of 8) FVC% microRNAs had functionally validated target genes that have been linked via genome wide association studies to asthma and FEV1 change. Among the 22 FEV1/FVC microRNAs, 9 (40.9%) remain associated with FEV1/FVC in boys alone in a sex-stratified analysis (compared with 3 FEV1/FVC microRNAs in girls alone), 7 (31.8%) were associated with fetal lung development, and 3 (13.6%) in both. Ontology analyses revealed enrichment for pathways integral to asthma, including PPAR signaling, G-protein coupled signaling, actin and myosin binding, and respiratory system development. CONCLUSIONS: Circulating microRNAs reflect asthma biology and are associated with lung function differences in asthmatics. They may represent biomarkers of asthma severity.

Kim, J. H., Collins-McMillen, D., Caposio, P., & Yurochko, A. D. (2016). Viral binding-induced signaling drives a unique and extended intracellular trafficking pattern during infection of primary monocytes. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(31), 8819-8824.

We initiated experiments to examine the infection of monocytes postentry. New data show that human cytomegalovirus (HCMV) DNA is detected in the nucleus beginning only at 3 d postinfection in monocytes, compared with 30 min postinfection in fibroblasts and endothelial cells, suggesting that HCMV nuclear translocation in monocytes is distinct from that seen in other cell types. We now show that HCMV is initially retained in early endosomes and then moves sequentially to the trans-Golgi network (TGN) and recycling endosomes before nuclear translocation. HCMV is retained initially as a mature particle before deenvelopment in recycling

endosomes. Disruption of the TGN significantly reduced nuclear translocation of viral DNA, and HCMV nuclear translocation in infected monocytes was observed only when correct gH/gL/UL128-131/integrin/c-Src signaling occurred. Taken together, our findings show that viral binding of the gH/gL/UL128-131 complex to integrins and the ensuing c-Src signaling drive a unique nuclear translocation pattern that promotes productive infection and avoids viral degradation, suggesting that it represents an additional viral evasion/survival strategy.

Kinast, R. M., Akula, K. K., Debarber, A. E., Barker, G. T., Gardiner, S. K., Whitson, E., et al. (2016). The degradation of mitomycin C under various storage methods. *Journal of Glaucoma*, *25*(6), 477-481.

Purpose: To compare the effects of common pharmacy preparation and storage conditions on the stability of mitomycin C (MMC) in solution. Methods: We used C18 reversed-phase high-performance liquid chromatography to determine the stability of 0.4 mg/mL MMC solutions, and liquid chromatography-electrospray ionization-mass spectrometry to identify degradation products. Conditions compared were: compounding and storage by refrigeration (1 and 2 wk), freezing (23 d), shipment "on-ice" (1 mo frozen followed by 1-wk refrigeration), and immediately compounding dry powder (Mitosol; Mobius Therapeutics LLC). We tested 3 samples for each storage method when samples reached room temperature (time 0), and then 1, 4, and 24 hours later. We used MMC peak area as a percentage of total (MMC plus degradants) area detected with high-performance liquid chromatography as a measure of stability. Results: We assessed MMC stability for 5 preparation and storage methods at 4 timepoints (with n=3 per timepoint). At time 0, we found similar stabilities for MMC (F=0.72, P=0.599) between all 5 storage methods: 1-week refrigerated (97.9±0.2%), dry powder (97.5±0.3%), 2-week refrigerated (96.9±0.2%), 23-day frozen (96.7±3.1%), and shipment on-ice (96.0±1.2%). However, MMC demonstrated significant degradation over a 24-hour period with 2-week refrigeration (95.7±0.3%, β=-0.1%/h, P<0.001) and shipment on-ice (93.1±1.8%, β=-0.1%/h, P=0.013). We identified small amounts (<3.2%) of 2 degradants, cis-hydroxymitosene and trans-hydroxymitosene, across all samples. Conclusions: The different preparation and storage methods of MMC showed similar stability when used immediately upon reaching room temperature. However, degradation of MMC

occurred with further storage at room temperature. The clinical implication of small amounts of MMC degradants is unclear. © 2015 Wolters Kluwer Health, Inc.

King, V., & Nettleton, W. (2016). Intermittent inhaled corticosteroid therapy for mild persistent asthma in children and adults. *American Family Physician, 94*(1), 21-22.

Ko, A. L., Ozpinar, A., Raskin, J. S., Magill, S. T., Raslan, A. M., & Burchiel, K. J. (2016). Correlation of preoperative MRI with the long-term outcomes of dorsal root entry zone lesioning for brachial plexus avulsion pain. *Journal of Neurosurgery, 124*(5), 1470-1478.

Obj ective Lesioning of the dorsal root entry zone (DREZotomy) is an effective treatment for brachial plexus avulsion (BPA) pain. The role of preoperative assessment with MRI has been shown to be unreliable for determining affected levels; however, it may have a role in predicting pain outcomes. Here, DREZotomy outcomes are reviewed and preoperative MRI is examined as a possible prognostic factor. Methods?A retrospective review was performed of an institutional database of patients who had undergone brachial plexus DREZ procedures since 1995. Preoperative MRI was examined to assess damage to the DREZ or dorsal horn, as evidenced by avulsion of the DREZ or T2 hyperintensity within the spinal cord. Phone interviews were conducted to assess the long-term pain outcomes. Results?Between 1995 and 2012, 27 patients were found to have undergone cervical DREZ procedures for BPA. Of these, 15 had preoperative MR images of the cervical spine available for review. The outcomes were graded from 1 to 4 as poor (no significant relief), good (more than 50% pain relief), excellent (more than 75% pain relief), or pain free, respectively. Overall, DREZotomy was found to be a safe, efficacious, and durable procedure for relief of pain due to BPA. The initial success rate was 73%, which declined to 66% at a median follow-up time of 62.5 months. Damage to the DREZ or dorsal horn was significantly correlated with poorer outcomes ($p = 0.02$). The average outcomes in patients without MRI evidence of DREZ or dorsal horn damage was significantly higher than in patients with such damage (3.67 vs 1.75, t-test; $p = 0.001$). A longer duration of pain prior to operation was also a significant predictor of treatment success ($p = 0.004$). Con clusions?Overall, the DREZotomy procedure has a 66% chance of achieving meaningful pain relief on longterm follow-

up. Successful pain relief is associated with the lack of damage to the DREZ and dorsal horn on preoperative MRI. © AANS, 2016.

Kolivras, A., Thompson, N., & Thompson, C. (2016). Loss of cytokeratin-15 (CK15) expression is not specific for lichen planopilaris (LPP). *Journal of the American Academy of Dermatology*, *75*(2), 428-429.

Kosasih, H. J., Last, K., Rogerson, F. M., Golub, S. B., Gauci, S. J., Russo, V. C., et al. (2016). A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) forms catalytically active oligomers. *The Journal of Biological Chemistry*, *291*(7), 3197-3208.
The metalloproteinase ADAMTS-5 (A disintegrin and metalloproteinase with thrombospondin motifs) degrades aggrecan, a proteoglycan essential for cartilage structure and function. ADAMTS-5 is the major aggrecanase in mouse cartilage, and is also likely to be the major aggrecanase in humans. ADAMTS-5 is a multidomain enzyme, but the function of the C-terminal ancillary domains is poorly understood. We show that mutant ADAMTS-5 lacking the catalytic domain, but with a full suite of ancillary domains inhibits wild type ADAMTS activity, in vitro and in vivo, in a dominant-negative manner. The data suggest that mutant ADAMTS-5 binds to wild type ADAMTS-5; thus we tested the hypothesis that ADAMTS-5 associates to form oligomers. Co-elution, competition, and in situ PLA experiments using full-length and truncated recombinant ADAMTS-5 confirmed that ADAMTS-5 molecules interact, and showed that the catalytic and disintegrin-like domains support these intermolecular interactions. Cross-linking experiments revealed that recombinant ADAMTS-5 formed large, reduction-sensitive oligomers with a nominal molecular mass of approximately 400 kDa. The oligomers were unimolecular and proteolytically active. ADAMTS-5 truncates comprising the disintegrin and/or catalytic domains were able to competitively block full-length ADAMTS-5-mediated aggrecan cleavage, measured by production of the G1-EGE(373) neoepitope. These results show that ADAMTS-5 oligomerization is required for full aggrecanase activity, and they provide evidence that blocking oligomerization inhibits ADAMTS-5 activity. The data identify the surface provided by the catalytic and disintegrin-like domains of ADAMTS-5 as a legitimate target for the design of aggrecanase inhibitors.

Kurland, B. F., Peterson, L. M., Lee, J. H., Schubert, E. K., Currin, E. R., Link, J. M., et al. (2016). Estrogen receptor binding (FES PET) and glycolytic activity (FDG PET) predict progression-free survival on endocrine therapy in patients with ER+ breast cancer. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

PURPOSE: 18F-fluoroestradiol (FES) positron emission tomography (PET) scans measure regional estrogen binding, and 18F-fluorodeoxyglucose (FDG) PET measures tumor glycolytic activity. We examined quantitative and qualitative imaging biomarkers of progression-free survival in breast cancer patients receiving endocrine therapy. EXPERIMENTAL DESIGN: Ninety patients with breast cancer from an estrogen receptor positive, HER2-negative primary tumor underwent FES PET and FDG PET scans prior to endocrine therapy (63% aromatase inhibitor, 22% aromatase inhibitor and fulvestrant, 15% other). Eighty-four had evaluable data for progression-free survival prediction. RESULTS: Recursive partitioning with fivefold internal cross-validation used both FES PET and FDG PET measures to classify patients into three distinct response groups. FDG PET identified 24 patients (29%) with low FDG uptake, suggesting indolent tumors. These patients had a median progression-free survival of 26.1 months (95% confidence interval 11.2-49.7). Of patients with more FDG-avid tumors, 50 (59%) had high average FES uptake, and 10 (12%) had low average FES uptake. These groups had median progression-free survival of 7.9 (5.6-11.8) and 3.3 months (1.4-not evaluable), respectively. Patient and tumor features did not replace or improve the PET measures' prediction of progression-free survival. Prespecified endocrine resistance classifiers identified in smaller cohorts did not individually predict progression-free survival. CONCLUSION: A wide range of therapy regimens are available for treatment of ER+ metastatic breast cancer, but no guidelines are established for sequencing these therapies. FDG PET and FES PET may help guide the timing of endocrine therapy and selection of targeted and/or cytotoxic chemotherapy. A multicenter trial is ongoing for external validation.

Kurvers, R. H., Herzog, S. M., Hertwig, R., Krause, J., Carney, P. A., Bogart, A., et al. (2016). Boosting medical diagnostics by pooling independent judgments. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(31), 8777-8782.

Collective intelligence refers to the ability of groups to outperform individual decision makers when solving complex cognitive problems. Despite its potential to revolutionize decision making

in a wide range of domains, including medical, economic, and political decision making, at present, little is known about the conditions underlying collective intelligence in real-world contexts. We here focus on two key areas of medical diagnostics, breast and skin cancer detection. Using a simulation study that draws on large real-world datasets, involving more than 140 doctors making more than 20,000 diagnoses, we investigate when combining the independent judgments of multiple doctors outperforms the best doctor in a group. We find that similarity in diagnostic accuracy is a key condition for collective intelligence: Aggregating the independent judgments of doctors outperforms the best doctor in a group whenever the diagnostic accuracy of doctors is relatively similar, but not when doctors' diagnostic accuracy differs too much. This intriguingly simple result is highly robust and holds across different group sizes, performance levels of the best doctor, and collective intelligence rules. The enabling role of similarity, in turn, is explained by its systematic effects on the number of correct and incorrect decisions of the best doctor that are overruled by the collective. By identifying a key factor underlying collective intelligence in two important real-world contexts, our findings pave the way for innovative and more effective approaches to complex real-world decision making, and to the scientific analyses of those approaches.

Lagasse, L. L., Conradt, E., Karalunas, S. L., Dansereau, L. M., Butner, J. E., Shankaran, S., et al. (2016). Transactional relations between caregiving stress, executive functioning, and problem behavior from early childhood to early adolescence. *Development and Psychopathology, 28*(3), 743-756.

Developmental psychopathologists face the difficult task of identifying the environmental conditions that may contribute to early childhood behavior problems. Highly stressed caregivers can exacerbate behavior problems, while children with behavior problems may make parenting more difficult and increase caregiver stress. Unknown is: (a) how these transactions originate, (b) whether they persist over time to contribute to the development of problem behavior and (c) what role resilience factors, such as child executive functioning, may play in mitigating the development of problem behavior. In the present study, transactional relations between caregiving stress, executive functioning, and behavior problems were examined in a sample of 1,388 children with prenatal drug exposures at three developmental time points: early childhood

(birth to age 5), middle childhood (ages 6 to 9), and early adolescence (ages 10 to 13). Transactional relations differed between caregiving stress and internalizing versus externalizing behavior. Targeting executive functioning in evidence-based interventions for children with prenatal substance exposure who present with internalizing problems and treating caregiving psychopathology, depression, and parenting stress in early childhood may be particularly important for children presenting with internalizing behavior.

Leapman, M. S., Freedland, S. J., Aronson, W. J., Kane, C. J., Terris, M. K., Walker, K., et al. (2016). Pathologic and biochemical outcomes among african-american and caucasian men with low-risk prostate cancer in the SEARCH database: Implications for active surveillance candidacy. *The Journal of Urology*,

BACKGROUND: Racial disparities in the incidence and risk profile of prostate cancer (PCa) at diagnosis among African-American (AA) men are well reported, however it remains unclear whether AA race is independently associated with adverse outcomes among men with clinical low risk disease. METHODS: We conducted a retrospective analysis among 895 men with clinical low risk PCa treated with radical prostatectomy within the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Associations between AA versus Caucasian race with pathologic biochemical recurrence outcomes were examined using chi-square, logistic regression, log-rank, and Cox proportional hazards analyses. RESULTS: We identified 355 AA and 540 Caucasian men with low-risk tumors within the SEARCH cohort followed for a median of 6.3 years. Following adjustment for relevant covariates, AA race was not significantly associated with pathological upgrade (OR 1.33, p=0.12), major upgrade (OR 0.58, p=0.10), upstaging (OR 1.09, p=0.73), or positive surgical margins (OR 1.04, p=0.81). The 5-year recurrence-free survival rates were 73.4% for AA and 78.4% for Caucasian men (log-rank p=0.18). In a Cox proportional hazards analysis model, AA race was not significantly associated with BCR (HR 1.11, p=0.52). CONCLUSIONS: In a cohort of clinical low-risk patients treated with prostatectomy within an equal access health system with a high representation of AA men, we observed no significant differences in the rates of pathologic upgrade, upstage or biochemical recurrence. These data support continued use of AS in AA. Upgrading and upstaging remain concerning possibilities for all men regardless of race.

Lee, J. C., Su, S. Y., Changou, C. A., Yang, R. S., Tsai, K. S., Collins, M. T., et al. (2016). Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. *Modern Pathology : An Official Journal of the United States and Canadian Academy of Pathology, Inc,*

Phosphaturic mesenchymal tumors typically cause paraneoplastic osteomalacia, chiefly as a result of FGF23 secretion. In a prior study, we identified FN1-FGFR1 fusion in 9 of 15 phosphaturic mesenchymal tumors. In this study, a total of 66 phosphaturic mesenchymal tumors and 7 tumors resembling phosphaturic mesenchymal tumor but without known phosphaturia were studied. A novel FN1-FGF1 fusion gene was identified in two cases without FN1-FGFR1 fusion by RNA sequencing and cross-validated with direct sequencing and western blot. Fluorescence in situ hybridization analyses revealed FN1-FGFR1 fusion in 16 of 39 (41%) phosphaturic mesenchymal tumors and identified an additional case with FN1-FGF1 fusion. The two fusion genes were mutually exclusive. Combined with previous data, the overall prevalence of FN1-FGFR1 and FN1-FGF1 fusions was 42% (21/50) and 6% (3/50), respectively. FGFR1 immunohistochemistry was positive in 82% (45/55) of phosphaturic mesenchymal tumors regardless of fusion status. By contrast, 121 cases of potential morphologic mimics (belonging to 13 tumor types) rarely expressed FGFR1, the main exceptions being solitary fibrous tumors (positive in 40%), chondroblastomas (40%), and giant cell tumors of bone (38%), suggesting a possible role for FGFR1 immunohistochemistry in the diagnosis of phosphaturic mesenchymal tumor. With the exception of one case reported in our prior study, none of the remaining tumors resembling phosphaturic mesenchymal tumor had either fusion type or expressed significant FGFR1. Our findings provide insight into possible mechanisms underlying the pathogenesis of phosphaturic mesenchymal tumor and imply a central role of the FGF1-FGFR1 signaling pathway. The novel FN1-FGF1 protein is expected to be secreted and serves as a ligand that binds and activates FGFR1 to achieve an autocrine loop. Further study is required to determine the functions of these fusion proteins.Modern Pathology advance online publication, 22 July 2016; doi:10.1038/modpathol.2016.137.

Lee, W. T., Witsell, D. L., Parham, K., Shin, J. J., Chapurin, N., Pynnonen, M. A., et al. (2016). Tonsillectomy bleed rates across the CHEER practice research network: Pursuing guideline

adherence and quality improvement. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *155*(1), 28-32.

OBJECTIVES: (1) Compare postoperative bleeding in the CHEER network (Creating Healthcare Excellence through Education and Research) among age groups, diagnoses, and practice types. (2) Report the incidence of bleeding by individual CHEER practice site based on practice guidelines. STUDY DESIGN: Retrospective data collection database review of the CHEER network based on ICD-9 and CPT codes related to tonsillectomy patients. SETTING: Multisite practice-based network. SUBJECTS AND METHODS: A total of 8347 subjects underwent tonsillectomy as determined by procedure code within the retrospective data collection database, and 107 had postoperative hemorrhage. These subjects had demographic information and related diagnoses based on the CPT and ICD-9 codes collected. Postoperative ICD-9 and CPT codes were used to identify patients who also had postoperative bleed. Variables included age (/=12 years), diagnoses (infectious vs noninfectious), and practice type (community vs academic). Statistical analysis included multivariate logistic regression variables predictive of postoperative bleeding, with P /=12 years old had a significantly increased bleed rate when compared with the younger group (odds ratio, 5.98; 95% confidence interval: 3.79-9.44; P < .0001). There was no significant difference in bleed rates when practices or diagnoses were compared. CONCLUSION: A site descriptor database built to expedite clinical research can be used for practice assessment and quality improvement. These data were also useful to identify patient risk factors for posttonsillectomy bleed.

Leitenberger, J. J., & Golden, S. K. (2016). Reconstruction after full-thickness loss of the antihelix, scapha, and triangular fossa. *Dermatologic Surgery*, *42*(7), 893-896.

Levy, J. M., Mace, J. C., Rudmik, L., Soler, Z. M., & Smith, T. L. (2016). Low 22-item sinonasal outcome test scores in chronic rhinosinusitis: Why do patients seek treatment? *The Laryngoscope*,

OBJECTIVES/HYPOTHESIS: Patients with chronic rhinosinusitis (CRS) who experience minimal reductions in quality of life (QoL) may present for treatment despite QoL scores comparable to controls without CRS. This study seeks to identify cofactors influencing patients with CRS and low

22-item Sinonasal Outcome Test (SNOT-22) scores to seek care. STUDY DESIGN: Prospective, multicenter, observational cohort. METHODS: Patients with CRS were enrolled between April 2011 and September 2015. Patients with sinonasal mucocele or unilateral sinus opacification were excluded. Control subjects without CRS were enrolled for comparison. Low-SNOT CRS was defined as a SNOT-22 score /= 20, n = 641; controls without CRS, n = 95) were enrolled. Low SNOT scores were identified in 6% of subjects with CRS. After adjustment, low-SNOT CRS and control groups without CRS reported similar baseline average SNOT-22 total scores (P = .879). Unexpectedly, compared to controls, low-SNOT CRS patients had significantly better average psychological (2.1 +/- 2.3 vs. 5.8 +/- 6.0; P = .030) and sleep dysfunction (2.7 +/- 3.4 vs. 6.0 +/- 5.2; P = .016) scores. Fourteen of 38 (37%) low-SNOT patients elected to undergo endoscopic sinus surgery (ESS), with a significantly lower likelihood of reporting a minimal clinically important difference (MCID) when compared to high-SNOT patients (43% vs. 82%; P < .001) after a mean follow-up of approximately 15 months. CONCLUSIONS: Low-SNOT CRS patients represent an outlier population for which measures of QoL fail to identify factors influencing the decision to seek treatment. Low-SNOT CRS patients electing ESS have a decreased likelihood of reporting MCIDs following ESS. Further study is required to identify novel factors associated with treatment-seeking behavior in this population. LEVEL OF EVIDENCE: 3B Laryngoscope, 2016.

Lewandowski Holley, A., Wilson, A. C., Cho, E., & Palermo, T. M. (2016). Clinical phenotyping of youth with new-onset musculoskeletal pain: A controlled cohort study. *The Clinical Journal of Pain*, OBJECTIVES: The course of pediatric musculoskeletal pain from acute to chronic has not been well described and there is limited understanding of how to identify individuals with new-onset pain who may be predisposed to developing persisting symptoms. Thus, the purpose of this study was to describe the clinical phonotype of treatment-seeking youth with new-onset musculoskeletal pain compared with youth with and without chronic pain. Further, we tested predictors of pain-related disability and pain sensitivity in the new-onset pain sample. METHODS: Participants were 191 youth, ages 10 to 17 years, representing 3 cohorts (new-onset musculoskeletal pain, chronic musculoskeletal pain, and a comparison group without chronic pain). Participants completed questionnaire measures of pain characteristics, psychological

functioning, sleep, and pain-related disability. They also attended a laboratory visit to complete an experimental pain assessment using heat and cold stimuli to assess pain sensitivity and conditioned pain modulation. RESULTS: Findings revealed youth with new-onset musculoskeletal pain had a distinct clinical phenotype where symptoms of pain and disability were in the mid-range between those of youth with diagnosed chronic musculoskeletal pain and youth in the community without chronic pain. Linear regressions within the new-onset pain sample demonstrated poorer sleep quality and higher pain fear predicted greater pain-related disability, and pain catastrophizing predicted cold pressor sensitivity. DISCUSSION: Clinical phenotyping of youth with new-onset musculoskeletal pain highlights factors relevant to the pain experience. Future research can examine the roles of these variables in predicting longitudinal risk for chronic pain and disability.

Leyro, T. M., Crew, E. E., Bryson, S. W., Lembke, A., Bailey, S. R., Prochaska, J. J., et al. (2016). Retrospective analysis of changing characteristics of treatment-seeking smokers: Implications for further reducing smoking prevalence. *BMJ Open*, *6*(6), e010960-2015-010960.
OBJECTIVE: The goal of the current study was to empirically compare successive cohorts of treatment-seeking smokers who enrolled in randomised clinical trials in a region of the USA characterised by strong tobacco control policies and low smoking prevalence, over the past three decades. DESIGN: Retrospective treatment cohort comparison. SETTING: Data were collected from 9 randomised clinical trials conducted at Stanford University and the University of California, San Francisco, between 1990 and 2013. PARTICIPANTS: Data from a total of 2083 participants were included (Stanford, n=1356; University of California San Francisco, n=727). PRIMARY AND SECONDARY OUTCOMES: One-way analysis of variance and covariance, chi(2) and logistic regression analyses were used to examine relations between nicotine dependence, cigarettes per day, depressive symptoms and demographic characteristics among study cohorts. RESULTS: Similar trends were observed at both settings. When compared to earlier trials, participants in more recent trials smoked fewer cigarettes, were less nicotine-dependent, reported more depressive symptoms, were more likely to be male and more likely to be from a minority ethnic/racial group, than those enrolled in initial trials (all p's<0.05). Analysis of covariances revealed that cigarettes per day, nicotine dependence and current depressive symptom scores

were each significantly related to trial (all p's<0.001). CONCLUSIONS: Our findings suggest that more recent smoking cessation treatment-seeking cohorts in a low prevalence region were characterised by less smoking severity, more severe symptoms of depression and were more likely to be male and from a minority racial/ethnic group.

L'Hommedieu, C. E., Gera, J. J., Rupp, G., Salin, J. W., Cox, J. S., & Duwelius, P. J. (2016). Impact of anterior vs posterior approach for total hip arthroplasty on post-acute care service utilization. *The Journal of Arthroplasty*,

BACKGROUND: Controversy exists as to which surgical approach is best for total hip arthroplasty (THA). Previous studies suggested that the tissue-sparing anterior approach should result in a more rapid recovery requiring fewer postacute services, ultimately decreasing overall episodic cost. The purpose of this cross-sectional study was to determine if any significant differences exist between the anterior vs posterior approaches on postacute care service utilization, readmissions, or episodic cost. METHODS: Claims data from 26,773 Medicare fee-for-service beneficiaries receiving elective THAs (Medical Severity-Diagnosis Related Groups (MS-DRGs) 469/470) were analyzed. Claims data were collected from the 2-year period, January 2013 through December 2014. The posterior surgical approach was performed on 23,653 patients while 3120 patients received the anterior approach. RESULTS: Data analysis showed negligible effect sizes in postacute care service utilization, readmission rate, and cost between the surgical approaches for elective THA (MS-DRG 469 and 470). Average THA total episode cost was negligibly higher for procedures using the anterior approach compared to the posterior approach ($22,517 and $22,068, respectively). Statistically significant differences were observed in inpatient rehab and home health cost and service utilization. However, the effect sizes of these comparisons are negligible when accounting for the large sample size. All other comparisons showed minimal and statistically insignificant variation. CONCLUSION: The results indicate that surgical approach alone is not the primary driver of postacute care service utilization, quality outcomes, or cost. Other factors such as physician-led patient-focused care pathways, care coordination, rapid rehabilitation protocols, perioperative pain management protocols, and patient education are integral for effective patient care.

Li, M. H., Leng, T., Feng, X. C., Yang, T., Simon, R. P., & Xiong, Z. G. (2016). Modulation of acid-sensing ion channel 1a by intracellular pH and its role in ischemic stroke. *The Journal of Biological Chemistry*,

An important contributor to brain ischemia is known to be extracellular acidosis, which activates acid-sensing ion channels (ASICs), a family of proton-gated sodium channels. Lines of evidence suggest that targeting ASICs may lead to novel therapeutic strategies for stroke. Investigations of the role of ASICs in ischemic brain injury have naturally focused on the role of extracellular pH in ASIC activation. By contrast, intracellular pH (pHi) has received little attention. This is a significant gap in our understanding since the ASIC response to extracellular pH is modulated by pHi: activation of ASICs by extracellular protons is paradoxically enhanced by intracellular alkalosis. Our previous studies show that acidosis-induced cell injury in in vitro models is attenuated by intracellular acidification. However, whether pHi affects ischemic brain injury in vivo is completely unknown. Furthermore, while ASICs in native neurons are composed of different subunits characterized by distinct electrophysiological/pharmacological properties, the subunit-dependent modulation of ASIC activity by pHi has not be investigated. Using a combination of in vitro and in vivo ischemic brain injury models, electrophysiological, biochemical, and molecular biological approaches, we show that the intracellular alkalizing agent quinine potentiates, whereas the intracellular acidifying agent propionate inhibits, oxygen-glucose deprivation induced cell injury in vitro and brain ischemia-induced infarct volume in vivo. Moreover, we find that the potentiation of ASICs by quinine depends on the presence of the ASIC1a, ASIC2a subunits, but not ASIC1b, ASIC3 subunits. Furthermore, we have determined the amino acids in ASIC1a that are involved in the modulation of ASICs by pHi.

Lin, A. E., Karnis, M. F., Calderwood, L., Crenshaw, M., Bhatt, A., Souter, I., et al. (2016). Proposal for a national registry to monitor women with turner syndrome seeking assisted reproductive technology. *Fertility and Sterility*, *105*(6), 1446-1448.

Lin, C., Mollon, B., Scott, C., Brady, P., Axelrod, T. S., & Jenkinson, R. J. (2016). Intrathoracic glenohumeral dislocation without fracture of the humerus. *JBJS Case Connector*, *6*(1)

Case: A fifty-three-year-old man presented with an intrathoracic glenohumeral dislocation

(ITGHD) and associated hemothorax, rib fracture, massive rotator cuff tear, and axillary nerve palsy following an ice hockey injury. Treatment consisted of closed reduction and staged open rotator cuff repair. Despite a substantial injury, the patient recovered nearly normal use of the arm two years postoperatively. Conclusion: ITGHD is an extremely rare entity. This injury should be managed by a multidisciplinary team with anticipation of associated thoracic and vascular injuries. In cases with repairable pathology (e.g., an acute rotator cuff tear), good functional outcomes can be obtained.

Lin, C. A., Bhandari, M., Guyatt, G., Walter, S. D., Schemitsch, E. H., Swiontkowski, M., et al. (2016). Does participation in a randomized clinical trial change outcomes? an evaluation of patients not enrolled in the SPRINT trial. *Journal of Orthopaedic Trauma, 30*(3), 156-161.

Objectives: To determine the extent to which knowledge from clinical trial protocols is transferred to nonparticipating patients. Design: Retrospective review of prospectively collected data from a large clinical trial. Setting: Six level-1 international trauma centers. Methods: We compared rates and timing of reoperation in a subset of patients enrolled in the Study to Prospectively evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) to concurrent patients who were eligible but not enrolled. This was a retrospective review of prospectively collected trial data. The records of 6 of the original SPRINT centers were searched for non-SPRINT patients who underwent intramedullary nailing of a closed tibial fracture. The rate and timing of reoperation were compared. A $P < 0.05$ was considered significant. Results: One hundred fourteen non-SPRINT patients were compared with 328 patients enrolled in SPRINT from those same sites. There were 7 reoperations (6.1%) in non-SPRINT patients versus 18 (5.2%) in SPRINT patients [odds ratio (OR) 1.19, 95% confidence interval (CI) 0.41 to 3.13; P 0.811]. There was no difference in the time to reoperation between the SPRINT and non-SPRINT patients (6.2 vs. 6.8 months, 95% CI of the difference -3.8 to 2.6; P 0.685) or in the proportion of patients who underwent reoperation before 6 months (29% vs. 43%; OR 1.75; 95% CI 0.18 to 15.41; P 0.647). Conclusions: Patients not enrolled in SPRINT had similarly low rates of reoperation for nonunion, and the average time to reoperation for both groups was longer than 6 months. A 6-month waiting period may have allowed slow-to-heal fractures adequate time to heal, thereby

reducing the rate of diagnosis of nonunion. As such, this waiting period could contribute to lower-than-expected reoperation rates for nonunion. It is possible that clinical trials may beneficially influence the care of nonenrolled patients. © Copyright 2016 Wolters Kluwer Health, Inc. All rights reserved.

Liu, J. J., Jones, J. S., & Rao, P. K. (2016). Urinalysis in the evaluation of hematuria. *Jama, 315*(24), 2726-2727.

Liu, N. T., Salinas, J., Fenrich, C. A., Serio-Melvin, M. L., Kramer, G. C., Driscoll, I. R., et al. (2016). Predicting the proportion of full thickness involvement for any given burn size based on burn resuscitation volumes. *The Journal of Trauma and Acute Care Surgery*,
INTRODUCTION: The depth of burn has been an important factor often overlooked when estimating the total resuscitation fluid needed for early burn care. The goal of this study was to determine the degree to which full thickness (FT) involvement impacted overall 24-hour burn resuscitation volumes. METHODS: We performed a retrospective review of patients admitted to our burn intensive care unit from December 2007 to April 2013, with significant burns who required resuscitation using our computerized decision support system for burn fluid resuscitation. We defined the degree of FT involvement as FT Index (FTI = percentage of FT injury/percentage of total body surface area burned [%FT/%TBSA]) and compared variables on actual 24-hour fluid resuscitation volumes overall as well as for any given burn size. RESULTS: A total of 203 patients admitted to our burn center during the study period were included in the analysis. Mean age and weight were 47 +/- 19 years and 87 +/- 18 kg, respectively. Mean %TBSA was 41 +/- 20 with a mean %FT of 18 +/- 24. As %TBSA, %FT, and FTI increased, so did actual 24-hour fluid resuscitation volumes respectively (ml/kg). However, increase in FTI did not result in increased volume indexed to burn size (ml/kg/%TBSA). This was true even when patients with inhalation injury were excluded. Further investigation revealed that as %TBSA increased, %FT increased nonlinearly (quadratic polynomial) (R=0.994). CONCLUSIONS: Total burn size as well as FT burn size were both highly correlated with increased 24-hour fluid resuscitation volumes. However, FTI did not correlate with a corresponding increase in resuscitation volumes for any given burn size, even when patients with inhalation injury were

excluded. Thus, there is insufficient data to presume that those who receive more volume at any given burn size are likely to be mostly full thickness or vice versa. This was influenced by a relatively low sample size at each 10%TBSA increment and larger burn sizes disproportionately having more FT burns. A more robust sample size may elucidate this relationship better. LEVEL OF EVIDENCE: Level IV Therapeutic/Care Management. FUNDING: U.S. Army Combat Casualty Care Research Program.

Lo, D. M., Flaxel, C. J., & Fawzi, A. A. (2016). Macular effects of silicone oil tamponade: Optical coherence tomography findings during and after silicone oil removal. *Current Eye Research*, , 1-6.

OBJECTIVE: To investigate retinal morphologic changes during silicone oil tamponade and after its removal using spectral domain OCT (SD-OCT) imaging. MATERIALS AND METHODS: Retrospective review of 12 patients who underwent silicone oil tamponade for repair of retinal detachments. Macular OCT scans and volumetric thickness maps were examined qualitatively and quantitatively. RESULTS: Volumetric OCT revealed two distinct patterns during silicone oil: macular thickening (Group A) and macular thinning (Group B). In Group A, mean foveal thickness (507 +/- 169 microm vs. 407 +/- 163 microm, p = 0.003) and mean macular volume (11.6 +/- 2.4 mm3 vs. 9.9 +/- 1.5 mm3) were significantly increased during tamponade compared to post-oil removal. Group B had significantly decreased mean foveal thickness (210 +/- 38 microm vs. 276 +/- 58 microm, p = 0.009) and macular volume (7.3 +/- 1.8 mm3 vs. 8.4 +/- 1.8 mm3) during tamponade. Importantly, resolution of macular changes occurred without further intervention and was associated with improved visual acuity in both groups. CONCLUSION: Our series suggests that when faced with unexplained macular edema or macular thinning during tamponade, silicone oil removal alone can achieve resolution of these structural changes.

Lowensohn, R. I., Stadler, D. D., & Naze, C. (2016). Current concepts of maternal nutrition. *Obstetrical & Gynecological Survey*, *71*(7), 413-426.

BACKGROUND: A nutrient-rich maternal diet before and during pregnancy is associated with improved fetal health, more appropriate birth weight, and increased rates of maternal and infant survival. Physicians need a better understanding of the role of diet in shaping fetal outcomes. Given this background, we reviewed and summarized articles on maternal nutrition found in

MEDLINE since 1981, written in English, and limited to human subjects. FOR THE OFFSPRING: Maternal diets high in sugar and fat lead to an increased incidence of metabolic syndrome, diabetes, and cardiovascular disease later in life. Folic acid should be supplemented prior to conception and continued through at least the first 28 days of fetal life to prevent neural tube defects, and vitamin C should be given to women who smoke to lower the incidence of asthma and wheezing in the children. Iodine deficiency is increasing, and iodine should be included in prenatal supplements. If the maternal hemoglobin is 7 g/dL or more, there is no evidence that iron supplementation is needed. Fish intake during pregnancy is protective against atopic outcomes, whereas high-meat diets contribute to elevated adult blood pressure and hypersecretion of cortisol. FOR THE MOTHER: Calcium supplementation lowers the risk of preeclampsia and hypertensive disease in pregnancy. CONCLUSIONS: Given the limits of our current knowledge, a diet rich in whole grains, fruits, vegetables, and selected fish is desirable for the best outcomes. Diets high in sugar and fat lead to higher rates of diabetes, metabolic syndrome, and cardiovascular disease. Folic acid, iodine, and calcium in all pregnant women and vitamin C in smokers are the only supplements so far shown to be of value for routine use. The physician treating a pregnant woman should be ready to advise a healthy diet for the benefit of the fetus.

Loyo, M., Gerecci, D., Mace, J. C., Barnes, M., Liao, S., & Wang, T. D. (2016). Modifications to the butterfly graft used to treat nasal obstruction and assessment of visibility. *JAMA Facial Plastic Surgery*,

Importance: Graft visibility in the supratip region has been the main criticism of the butterfly graft. Because of the graft location, slightly unfavorable supratip fullness can occur, resulting in patient dissatisfaction with the cosmetic result. Objective: To describe the clinical outcomes and visibility of the butterfly graft after technique modifications. Design, Setting, and Participants: In this retrospective review of adults who had undergone primary or secondary rhinoplasty with butterfly grafting from July 1, 2013, through July 31, 2014, at a tertiary care center at an academic institution, an operative log and photographs were reviewed in an effort to analyze outcomes of butterfly graft use in rhinoplasty. Main Outcomes and Measures: Nasal obstruction and visibility of the butterfly graft. Results: Thirty-four patients were included in the case series

(mean [SD] age, 46 [19.4] years; 23 women and 11 men). The mean (SD) length of the graft was 3.4 (0.5) cm, and the mean (SD) width was 0.9 (0.2) cm. A significant decrease was found in the Nasal Obstruction Symptoms Evaluation score after surgery (mean [SD] preoperative score, 69 [17]; mean [SD] postoperative score, 23 [24]; P < .001). In regard to appearance, 25 patients (74%) rated their appearance as improved or no changes, 6 (18%) as minimally worse, and 1 (3%) as much worse. Fifty-nine observers participated in the masked survey for the study. When the graft was present, observers detected it 59.7% (282 of 472 answers) of the time. When the graft was not present, its presence was suspected 36.5% (237 of 649 answers) of the time. Conclusions and Relevance: The modified butterfly graft is a longer and thinner graft than the originally described butterfly graft. It is still an effective tool in the treatment of nasal obstruction with acceptable visibility. In most cases, it is difficult for health care professionals to identify the presence of the graft. Level of Evidence: 4.

Ma, H., Marti Gutierrez, N., Morey, R., Van Dyken, C., Kang, E., Hayama, T., et al. (2016). Incompatibility between nuclear and mitochondrial genomes contributes to an interspecies reproductive barrier. *Cell Metabolism*,

Vertebrate cells carry two different genomes, nuclear (nDNA) and mitochondrial (mtDNA), both encoding proteins involved in oxidative phosphorylation. Because of the extensive interactions, adaptive coevolution of the two genomes must occur to ensure normal mitochondrial function. To investigate whether incompatibilities between these two genomes could contribute to interspecies reproductive barriers, we performed reciprocal mtDNA replacement (MR) in zygotes between widely divergent Mus m. domesticus (B6) and conplastic Mus m. musculus (PWD) mice. Transfer of MR1 cybrid embryos (B6nDNA-PWDmtDNA) supported normal development of F1 offspring with reduced male fertility but unaffected reproductive fitness in females. Furthermore, donor PWD mtDNA was faithfully transmitted through the germline into F2 and F3 generations. In contrast, reciprocal MR2 (PWDnDNA-B6mtDNA) produced high embryonic loss and stillborn rates, suggesting an association between mitochondrial function and infertility. These results strongly suggest that functional incompatibility between nuclear and mitochondrial genomes contributes to interspecies reproductive isolation in mammals.

Ma, J. X., Tang, M., Wang, L., Weikert, M. P., Huang, D., & Koch, D. D. (2016). Comparison of newer IOL power calculation methods for eyes with previous radial keratotomy. *Investigative Ophthalmology & Visual Science*, *57*(9), OCT162-8.

PURPOSE: To evaluate the accuracy of the optical coherence tomography-based (OCT formula) and Barrett True K (True K) intraocular lens (IOL) calculation formulas in eyes with previous radial keratotomy (RK). METHODS: In 95 eyes of 65 patients, using the actual refraction following cataract surgery as target refraction, the predicted IOL power for each method was calculated. The IOL prediction error (PE) was obtained by subtracting the predicted IOL power from the implanted IOL power. The arithmetic IOL PE and median refractive PE were calculated and compared. RESULTS: All formulas except the True K produced hyperopic IOL PEs at 1 month, which decreased at >/=4 months (all P /=4 months. The Average produced significantly smaller refractive PE than did the double-K Holladay 1 at 1 month ($P < 0.05$). There were no significant differences in refractive PEs among formulas at 4 months. CONCLUSIONS: The OCT formula and True K were comparable to the double-K Holladay 1 method on the ASCRS (American Society of Cataract and Refractive Surgery) calculator. The Average IOL power on the ASCRS calculator may be considered when selecting the IOL power. Further improvements in the accuracy of IOL power calculation in RK eyes are desirable.

Madden, C. J., & Morrison, S. F. (2016). A high-fat diet impairs cooling-evoked brown adipose tissue activation via a vagal afferent mechanism. *American Journal of Physiology.Endocrinology and Metabolism*, *311*(2), E287-92.

In dramatic contrast to rats on a control diet, rats maintained on a high-fat diet (HFD) failed to activate brown adipose tissue (BAT) during cooling despite robust increases in their BAT activity following direct activation of their BAT sympathetic premotor neurons in the raphe pallidus. Cervical vagotomy or blockade of glutamate receptors in the nucleus of the tractus solitarii (NTS) reversed the HFD-induced inhibition of cold-evoked BAT activity. Thus, a HFD does not prevent rats from mounting a robust, centrally driven BAT thermogenesis; however, a HFD does alter a vagal afferent input to NTS neurons, thereby preventing the normal activation of BAT thermogenesis to cooling. These results, paralleling the absence of cooling-evoked glucose

uptake in the BAT of obese humans, reveal a neural mechanism through which consumption of a HFD contributes to reduced energy expenditure and thus to weight gain.

Mafi, J. N., & Edwards, S. T. (2016). How can we improve the efficiency of specialty care? *Journal of General Internal Medicine*,

Maggiore, R. J. (2016). Locally advanced head and neck cancer in either the older or the vulnerable adult: Making the case for a team-based, "gero-centric" approach. *Journal of Geriatric Oncology*, Multidisciplinary, team-based care goes hand in hand with geriatric oncology paradigms for caring for older adults with cancer. Team-based care was the central theme for the 2015 SIOG Annual Meeting. Team-based approaches to the evaluation and management of older adults with different cancer types, including head and neck cancer, were presented. This review aims to summarize the salient points of that presentation, including a synthesis of recent multidisciplinary, "gero-centric" research efforts to improve the care for older adults with more advanced stages of head and neck cancer.

Mailankody, S., & Prasad, V. (2016). Implications of proposed medicare reforms to counteract high cancer drug prices. *Jama*, *316*(3), 271-272.

Mailankody, S., & Prasad, V. (2016). Thinking systematically about the off-label use of cancer drugs and combinations for patients who have exhausted proven therapies. *The Oncologist*,

Mann, L., Siman, F. M., Downs, M., Sun, C. J., de Hernandez, B. U., Garcia, M., et al. (2016). Reducing the impact of immigration enforcement policies to ensure the health of north carolinians: Statewide community-level recommendations. *North Carolina Medical Journal*, *77*(4), 240-246.

BACKGROUND: Research indicates that fear of immigration enforcement among Latinos in North Carolina results in limited access to and utilization of health services and negative health consequences. This project developed recommendations to mitigate the public health impact of immigration enforcement policies in North Carolina. METHODS: Our community-based participatory research partnership conducted 6 Spanish-language report-backs (an approach to

sharing, validating, and interpreting data) and 3 bilingual forums with community members and public health leaders throughout North Carolina. The goals of these events were to discuss the impact of immigration enforcement on Latino health and develop recommendations to increase health services access and utilization. Findings from the report-backs and forums were analyzed using grounded theory to identify and refine common recommendations. RESULTS: A total of 344 people participated in the report-backs and forums. Eight recommendations emerged: increase knowledge among Latinos about local health services; build capacity to promote policy changes; implement system-level changes among organizations providing health services; train lay health advisors to help community members navigate systems; share Latinos' experiences with policy makers; reduce transportation barriers; increase schools' support of Latino families; and increase collaboration among community members, organizations, health care providers, and academic researchers. LIMITATIONS: Representatives from 16 of 100 North Carolina counties participated. These 16 counties represent geographically diverse regions, and many of these counties have large Latino populations. CONCLUSIONS: Immigration enforcement is a public health issue. Participants proposed developing new partnerships, identifying strategies, and implementing action steps for carrying out recommendations to reduce negative health outcomes among Latinos in North Carolina.

Markway, B. D., Cho, H., Anderson, D. E., Holden, P., Ravi, V., Little, C. B., et al. (2016). Reoxygenation enhances tumour necrosis factor alpha-induced degradation of the extracellular matrix produced by chondrogenic cells. *European Cells & Materials*, *31*, 425-439.

Mesenchymal stem cells (MSCs) have been considered as a potential source for cell-based therapies in arthritic diseases for both their chondrogenic and anti-inflammatory properties. Thus, we examined how MSC-based neocartilage responds to tumour necrosis factor alpha (TNF-alpha) compared to articular chondrocyte (AC)-based neocartilage. Since oxygen tension is altered in arthritic joints, we also examined how increased oxygen tension influences this process. Monolayer-expanded healthy human ACs and bone marrow MSCs were cultured in chondrogenic medium in three-dimensional culture under hypoxia. They were then exposed to TNF-alpha under hypoxic or increased oxygen tension. We found no inherent anti-inflammatory potential of MSC-derived neocartilage as it pertains to the enzymes studied here: more degradative enzymes were

upregulated by TNF-alpha in MSCs than in ACs, regardless of the oxygen tension. MSCs were also more sensitive to reoxygenation during TNF-alpha exposure, as indicated by increased proteoglycan loss, increased aggrecanase-generated metabolites, and further upregulation of the major aggrecanases, ADAMTS4 and ADAMTS5. There was also evidence of matrix metalloproteinase (MMP)-mediated aggrecan interglobular domain cleavage and type II collagen loss in response to TNF-alpha in both MSCs and ACs, but more MMPs were further upregulated by reoxygenation in MSCs than in ACs. Our study provides further evidence that consideration of oxygen tension is essential for studying cartilage degradation; for example, neocartilage produced from MSCs may be more sensitive to the negative effects of repeated hypoxia/reoxygenation events than AC-derived neocartilage. Consideration of the differences in responses may be important for cell-based therapies and selection of adjunctive chondroprotective agents.

McKenna, K. M., Hashimoto, D. A., Maguire, M. S., & Bynum, W. E.,4th. (2016). The missing link: Connection is the key to resilience in medical education. *Academic Medicine : Journal of the Association of American Medical Colleges*,

Awareness of the risks of burnout, depression, learner mistreatment, and suboptimal learning environments is increasing in academic medicine. A growing wellness and resilience movement has emerged in response to these disturbing trends; however, efforts to address threats to physician resilience have often emphasized strategies to improve life outside of work, with less attention paid to the role of belonging and connection at work. In this Commentary the authors propose that connection to colleagues, patients, and profession is fundamental to medical learners' resilience, highlighting "social resilience" as a key factor in overall well-being. They outline three specific forces that drive disconnection in medical education: the impact of shift work, the impact of the electronic medical record, and the impact of "work-life balance." Finally, the authors propose ways to overcome these forces in order to build meaningful connection and enhanced resilience in a new era of medicine.

Medler, T. R., Craig, J. M., Fiorillo, A. A., Feeney, Y. B., Harrell, J. C., & Clevenger, C. V. (2016). HDAC6 deacetylates HMGN2 to regulate Stat5a activity and breast cancer growth. *Molecular*

Cancer Research : MCR,

Stat5a is a transcription factor utilized by several cytokine/hormone receptor signaling pathways that promotes transcription of genes associated with proliferation, differentiation, and survival of cancer cells. However, there are currently no clinically approved therapies that directly target Stat5a, despite ample evidence that it contributes to breast cancer pathogenesis. Here, deacetylation of the Stat5a coactivator and chromatin remodeling protein HMGN2 on lysine residue K2 by HDAC6 promotes Stat5a-mediated transcription and breast cancer growth. HDAC6 inhibition both in vitro and in vivo enhances HMGN2 acetylation with a concomitant reduction in Stat5a-mediated signaling, resulting in an inhibition of breast cancer growth. Furthermore, HMGN2 is highly acetylated at K2 in normal human breast tissue, but is deacetylated in primary breast tumors and lymph node metastases, suggesting that targeting HMGN2 deacetylation is a viable treatment for breast cancer. Together, these results reveal a novel mechanism by which HDAC6 activity promotes the transcription of Stat5a target genes and demonstrate utility of HDAC6 inhibition for breast cancer therapy. IMPLICATIONS: HMGN2 deacetylation enhances Stat5a transcriptional activity, thereby regulating prolactin-induced gene transcription and breast cancer growth.

Menard, M. T., Farber, A., Assmann, S. F., Choudhry, N. K., Conte, M. S., Creager, M. A., et al. (2016). Design and rationale of the best endovascular versus best surgical therapy for patients with critical limb ischemia (BEST-CLI) trial. *Journal of the American Heart Association*, *5*(7), 10.1161/JAHA.116.003219.

BACKGROUND: Critical limb ischemia (CLI) is increasing in prevalence, and remains a significant source of mortality and limb loss. The decision to recommend surgical or endovascular revascularization for patients who are candidates for both varies significantly among providers and is driven more by individual preference than scientific evidence. METHODS AND RESULTS: The Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia (BEST-CLI) Trial is a prospective, randomized, multidisciplinary, controlled, superiority trial designed to compare treatment efficacy, functional outcomes, quality of life, and cost in patients undergoing best endovascular or best open surgical revascularization. Approximately 140 clinical sites in the United States and Canada will enroll 2100 patients with CLI who are candidates for

both treatment options. A pragmatic trial design requires consensus on patient eligibility by at least 2 investigators, but leaves the choice of specific procedural strategy within the assigned revascularization approach to the individual treating investigator. Patients with suitable single-segment of saphenous vein available for potential bypass will be randomized within Cohort 1 (n=1620), while patients without will be randomized within Cohort 2 (n=480). The primary efficacy end point of the trial is Major Adverse Limb Event-Free Survival. Key secondary end points include Re-intervention and Amputation-Free-Survival and Amputation Free-Survival. CONCLUSIONS: The BEST-CLI trial is the first randomized controlled trial comparing endovascular therapy to open surgical bypass in patients with CLI to be carried out in North America. This landmark comparative effectiveness trial aims to provide Level I data to clarify the appropriate role for both treatment strategies and help define an evidence-based standard of care for this challenging patient population. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02060630.

Minko, I. G., Jacobs, A. C., de Leon, A. R., Gruppi, F., Donley, N., Harris, T. M., et al. (2016). Catalysts of DNA strand cleavage at Apurinic/Apyrimidinic sites. *Scientific Reports*, *6*, 28894. Apurinic/apyrimidinic (AP) sites are constantly formed in cellular DNA due to instability of the glycosidic bond, particularly at purines and various oxidized, alkylated, or otherwise damaged nucleobases. AP sites are also generated by DNA glycosylases that initiate DNA base excision repair. These lesions represent a significant block to DNA replication and are extremely mutagenic. Some DNA glycosylases possess AP lyase activities that nick the DNA strand at the deoxyribose moiety via a beta- or beta,delta-elimination reaction. Various amines can incise AP sites via a similar mechanism, but this non-enzymatic cleavage typically requires high reagent concentrations. Herein, we describe a new class of small molecules that function at low micromolar concentrations as both beta- and beta,delta-elimination catalysts at AP sites. Structure-activity relationships have established several characteristics that appear to be necessary for the formation of an iminium ion intermediate that self-catalyzes the elimination at the deoxyribose ring.

Miura, L. N., Srikantom, S. V., & Schenck, J. (2016). Double fixation: Bilateral bisphosphonate-related hip fractures. *The American Journal of Medicine*,

Moe, E. L., Dobek, J., Nail, L., Wipfli, B., & Winters-Stone, K. M. (2016). Influence of structured resistance training on daily physical activity energy expenditure in breast cancer survivors: 1878 board #30 june 2, 3: 30 PM - 5: 00 PM. *Medicine and Science in Sports and Exercise*, *48*(5 Suppl 1), 515-516.

Morasco, B. J., Greaves, D. W., Lovejoy, T. I., Turk, D. C., Dobscha, S. K., & Hauser, P. (2016). Development and preliminary evaluation of an integrated cognitive-behavior treatment for chronic pain and substance use disorder in patients with the hepatitis C virus. *Pain Medicine (Malden, Mass.)*,

OBJECTIVE: Individuals with the hepatitis C virus (HCV) have high rates of both chronic pain and substance use disorder (SUD). Despite high comorbidity, there are limited data available on effective methods of treatment for co-occurring chronic pain and SUD. In this study, we sought to develop and conduct preliminary testing of an integrated cognitive-behavior therapy (CBT) for chronic pain and SUD in patients with HCV. DESIGN: Descriptive, including pretreatment, posttreatment, and follow-up testing. SETTING AND PATIENTS: Outpatient clinic as part of one VA Medical Center. PARTICIPANTS: Veterans with chronic pain, SUD, and HCV. INTERVENTION: Eight-session integrated group CBT for chronic pain and SUD in patients with HCV. METHODS: Participants completed standardized measures of pain, function, depression severity, and alcohol and substance use at baseline, post-treatment, and 3-month follow-up. RESULTS: Generalized estimating equations identified improvements in pain interference, reducing cravings for alcohol and other substances, and decreasing past-month alcohol and substance use. The proportion of participants who met diagnostic criteria for current SUD demonstrated a four-fold decrease over the course of the study from 24% at baseline to 15% at post-treatment and 6% at 3-month follow-up. On response to a global impression of change, 94% of participants noted improvement from baseline. CONCLUSIONS: Results from this pilot study suggest that a customized CBT for patients with both chronic pain and SUD (CBT-cp.sud) may be beneficial in improving important

pain and addiction-related outcomes in patients with HCV. Larger scale investigations of this intervention appear warranted.

Morgan, T. K. (2016). Impact of obesity on uteroplacental immunology and placental pathology. *Neoreviews, 17*(2), e70-e79.

Obesity is a growing problem. Currently 1 in 3 reproductive-age women is obese. This is significant because obesity is associated with an increased risk of gestational diabetesmellitus (GDM), pretermbirth, fetal growth abnormalities, preeclampsia, and stillbirth. Obesity alone increases the risk of stillbirth by threefold, whereas GDM increases this risk to approximately 10-fold. How obesity and GDM affect placental and fetal growth are beginning to be understood, but the underlying pathophysiology leading to bad pregnancy outcomes is essentially unknown. This review will discuss the effects of obesity and GDM on fetoplacental growth, the histopathologic features seen in these placentas, how obesity may affect uterine spiral artery remodeling, and why this leads to placental insufficiency. New insights suggest that abnormal regulation of maternal T cells and uterine natural killer cells may be important in the disease process, but much more research is needed.

Morrison, J., & Kaufman, J. (2016). Vascular access tracking system: A web-based clinical tracking tool for identifying catheter related blood stream infections in interventional radiology placed central venous catheters. *Journal of Digital Imaging,*

Vascular access is invaluable in the treatment of hospitalized patients. Central venous catheters provide a durable and long-term solution while saving patients from repeated needle sticks for peripheral IVs and blood draws. The initial catheter placement procedure and long-term catheter usage place patients at risk for infection. The goal of this project was to develop a system to track and evaluate central line-associated blood stream infections related to interventional radiology placement of central venous catheters. A customized web-based clinical database was developed via open-source tools to provide a dashboard for data mining and analysis of the catheter placement and infection information. Preliminary results were gathered over a 4-month period confirming the utility of the system. The tools and methodology employed to develop the

vascular access tracking system could be easily tailored to other clinical scenarios to assist in quality control and improvement programs.

Morrison, J. J., Kharoti, Y., & Farsad, K. (2016). Exsanguinating aortoesophageal fistula: A herculean effort. *Journal of Vascular and Interventional Radiology : JVIR*, *27*(8), 1226-1227.

Moss, A. H., Zive, D. M., Falkenstine, E. C., Fromme, E. K., & Tolle, S. W. (2016). Physician orders for life-sustaining treatment medical intervention orders and in-hospital death rates: Comparable patterns in two state registries. *Journal of the American Geriatrics Society*,

Muirhead, C. A., Sanford, J. N., McCullar, B. G., Nolt, D., & MacDonald, K. D. (2016). One center's guide to outpatient management of pediatric cystic fibrosis acute pulmonary exacerbation. *Clinical Medicine Insights.Pediatrics*, *10*, 57-65.

Cystic fibrosis (CF) is a chronic disorder characterized by acute pulmonary exacerbations that comprise increased cough, chest congestion, increased mucus production, shortness of breath, weight loss, and fatigue. Typically, severe episodes are treated in the inpatient setting and include intravenous antimicrobials, airway clearance therapy, and nutritional support. Children with less-severe findings can often be managed as outpatients with oral antimicrobials and increased airway clearance therapy at home without visiting the specialty CF center to begin treatment. Selection of specific antimicrobial agents is dependent on pathogens found in surveillance culture, activity of an agent in patients with CF, and the unique physiology of these patients. In this pediatric review, we present our practice for defining acute pulmonary exacerbation, deciding treatment location, initiating treatment either in-person or remotely, determining the frequency of airway clearance, selecting antimicrobial therapy, recommending timing for follow-up visit, and recognizing and managing treatment failures.

Mukherjee, A., Alzhanov, D., & Rotwein, P. (2016). Defining human insulin-like growth factor 1 gene regulation. *American Journal of Physiology.Endocrinology and Metabolism*, , ajpendo.00212.2016.

Growth hormone (GH) plays an essential role in controlling somatic growth and in regulating multiple physiological processes in humans and other species. Insulin-like growth factor 1 (IGF1), a conserved secreted 70-amino acid peptide, is a critical mediator of many of the biological

effects of GH. Previous studies have demonstrated that GH rapidly and potently promotes IGF1 gene expression in rodents and in some other mammals through the transcription factor Stat5b, leading to accumulation of IGF1 mRNAs and production of IGF1. Despite this progress, very little is known about how GH or other trophic factors control human IGF1 gene expression, in large part because of the absence of any cellular model systems that robustly express IGF1. Here we have addressed mechanisms of regulation of human IGF1 by GH after generating cell lines in which the IGF1 chromosomal locus has been incorporated into a mouse cell line. Using these cells we find that physiological levels of GH rapidly stimulate human IGF1 gene transcription, and identify several potential transcriptional enhancers in chromatin that bind Stat5b in a GH-regulated way. Each of the putative enhancers also activates a human IGF1 gene promoter in reconstitution experiments in the presence of the GH receptor, Stat5b, and GH. We thus have developed a novel experimental platform that now may be used to determine how human IGF1 gene expression is controlled under different physiological and pathological conditions.

Mungall, C. J., Washington, N. L., Nguyen-Xuan, J., Condit, C., Smedley, D., Kohler, S., et al. (2015). Use of model organism and disease databases to support matchmaking for human disease gene discovery. *Human Mutation, 36*(10), 979-984.

The Matchmaker Exchange application programming interface (API) allows searching a patient's genotypic or phenotypic profiles across clinical sites, for the purposes of cohort discovery and variant disease causal validation. This API can be used not only to search for matching patients, but also to match against public disease and model organism data. This public disease data enable matching known diseases and variant-phenotype associations using phenotype semantic similarity algorithms developed by the Monarch Initiative. The model data can provide additional evidence to aid diagnosis, suggest relevant models for disease mechanism and treatment exploration, and identify collaborators across the translational divide. The Monarch Initiative provides an implementation of this API for searching multiple integrated sources of data that contextualize the knowledge about any given patient or patient family into the greater biomedical knowledge landscape. While this corpus of data can aid diagnosis, it is also the beginning of research to improve understanding of rare human diseases.

Nakamura, Y. K., Metea, C., Karstens, L., Asquith, M., Gruner, H., Moscibrocki, C., et al. (2016). Gut microbial alterations associated with protection from autoimmune uveitis. *Investigative Ophthalmology & Visual Science*, *57*(8), 3747-3758.

PURPOSE: To investigate the contribution of the gut microbiota to the pathogenesis of uveitis. METHODS: Experimental autoimmune uveitis (EAU) in B10.RIII mice was induced using interphotoreceptor binding protein peptide. Mice were treated with oral or intraperitoneal (IP) antibiotics. Effector (Teff) and regulatory (Treg) T lymphocytes were identified using flow cytometry; 16S rRNA gene sequencing and qPCR were performed on gastrointestinal (GI) contents. RESULTS: Broad-spectrum (four antibiotics given simultaneously) oral, but not IP, antibiotics reduced mean uveitis clinical scores significantly compared with water-treated animals (0.5 vs. 3.0, P 0.99 for IP). Both oral metronidazole (P = 0.02) and vancomycin (P < 0.0001) alone decreased inflammation, whereas neomycin (P = 0.7) and ampicillin (P = 0.4) did not change mean uveitis scores. Oral broad-spectrum antibiotics increased Tregs in the GI lamina propria of EAU animals at 1 week, and in extraintestinal lymphoid tissues later, whereas Teff and inflammatory cytokines were reduced. 16S sequencing of GI contents revealed altered microbiota in immunized mice compared with nonimmunized mice, and microbial diversity clustering in EAU mice treated with uveitis-protective antibiotics. Experimental autoimmune uveitis mice also demonstrated gut microbial diversity clustering associated with clinical score severity. CONCLUSIONS: Oral antibiotics modulate the severity of inducible EAU by increasing Tregs in the gut and extraintestinal tissues, as well as decreasing effector T cells and cytokines. 16S sequencing suggests that there may be protective and, conversely, potentially uveitogenic, gut microbiota. These findings may lead to a better understanding of how uveitis can be treated or prevented by modulating the gut microbiome.

Neuendorf, R., Harding, A., Stello, N., Hanes, D., & Wahbeh, H. (2016). Depression and anxiety in patients with inflammatory bowel disease: A systematic review. *Journal of Psychosomatic Research*, *87*, 70-80.

OBJECTIVE: An increasing number of studies have been conducted to look at anxiety and depression in IBD; however, there is no clear consensus on the prevalence of anxiety and depression in this population. The objective of this systematic review was to compile the existing

data on the prevalence of all mood and anxiety disorders in Inflammatory Bowel Disease patients. METHODS: A series of comprehensive literature searches of Medline, Cochrane Library, PsycINFO, CINAHL, Embase, AMED, and ProQuest Dissertations were performed through March 2014. Inclusion criteria included peer-reviewed, published scientific articles that reported a measurement of mood or anxiety among IBD patients. Only studies with adults (>/=18years old) and with more than 10 patients were included. Methodological quality was assessed for all included studies. RESULTS: 171 articles were identified with a total of 158,371 participants. Pooled prevalence estimate for anxiety disorders was 20.5% [4.9%, 36.5%] and 35.1% [30.5, 39.7%] for symptoms of anxiety. IBD patients in active disease had higher prevalence of anxiety of 75.6% [65.5%, 85.7%] compared to disease remission. Pooled prevalence of depression disorders was 15.2% [9.9%, 20.5%] and was 21.6% [18.7%, 24.3%] for symptoms of depression. The prevalence of depressive symptoms was higher in Crohn's disease (25.3% [20.7%, 30.0%]) compared to UC, and higher with active disease (40.7% [31.1%, 50.3%]) compared to IBD patients in remission. CONCLUSION: Results from this systematic review indicate that patients with IBD have about a 20% prevalence rate of anxiety and a 15% prevalence rate of depression.

Neunert, C., Despotovic, J., Haley, K., Lambert, M. P., Nottage, K., Shimano, K., et al. (2016). Thrombopoietin receptor agonist use in children: Data from the pediatric ITP consortium of north america ICON2 study. *Pediatric Blood and Cancer, 63*(8), 1407-1413.

Background: Data on second-line treatment options for pediatric patients with immune thrombocytopenia (ITP) are limited. Thrombopoietin receptor agonists (TPO-RA) provide a nonimmunosuppressive option for children who require an increased platelet count. Procedure: We performed a multicenter retrospective study of pediatric ITP patients followed at ITP Consortium of North America (ICON) sites to characterize TPO-RA use. Results: Seventy-nine children had a total of 87 treatments (28 eltrombopag, 43 romiplostim, and eight trialed on both). The majority had primary ITP (82%) and most (60.8%) had chronic ITP. However, 22% had persistent ITP and 18% had newly diagnosed ITP. During the first 3 months of treatment, 89% achieved a platelet count ≥ 50 × 109/l (86% romiplostim, 81% eltrombopag, P = 0.26) at least once in the absence of rescue therapy. The average time to a response was 6.4 weeks for

romiplostim and 7.0 weeks for eltrombopag (P = 0.83). Only 40% of patients demonstrated a stable response with consistent dosing over time. An intermittent response with constant dose titration was seen in 15%, and an initial response that waned to no response was seen in 13%. Significant adverse events were minimal with the exception of two patients with thrombotic events and one who developed a neutralizing antibody. Conclusions: Our results demonstrate that TPO-RA agents are being used in children with ITP of varying duration and severity. The response was similar to clinical trials, but the sustainability of response varied. Future studies need to focus on the ideal timing and rationale for these medications in pediatric patients.

Nguyen, K. T., Vittinghoff, E., Dewland, T. A., Mandyam, M. C., Stein, P. K., Soliman, E. Z., et al. (2016). Electrocardiographic predictors of incident atrial fibrillation. *The American Journal of Cardiology*,

Atrial fibrillation (AF) is likely secondary to multiple different pathophysiological mechanisms that are increasingly but incompletely understood. Motivated by the hypothesis that 3 previously described electrocardiographic predictors of AF identify distinct AF mechanisms, we sought to determine if these electrocardiographic findings independently predict incident disease. Among Cardiovascular Health Study participants without prevalent AF, we determined whether left anterior fascicular block (LAFB), a prolonged QTC, and atrial premature complexes (APCs) each predicted AF after adjusting for each other. We then calculated the attributable risk in the exposed for each electrocardiographic marker. LAFB and QTC intervals were assessed on baseline 12-lead electrocardiogram (n = 4,696). APC count was determined using 24-hour Holter recordings obtained in a random subsample (n = 1,234). After adjusting for potential confounders and each electrocardiographic marker, LAFB (hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.1 to 3.9, p = 0.023), a prolonged QTC (HR 2.5, 95% CI 1.4 to 4.3, p = 0.002), and every doubling of APC count (HR 1.2, 95% CI 1.1 to 1.3, p <0.001) each remained independently predictive of incident AF. The attributable risk of AF in the exposed was 35% (95% CI 13% to 52%) for LAFB, 25% (95% CI 0.6% to 44%) for a prolonged QTC, and 34% (95% CI 26% to 42%) for APCs. In conclusion, in a community-based cohort, 3 previously established

electrocardiogram-derived AF predictors were each independently associated with incident AF, suggesting that they may represent distinct mechanisms underlying the disease.

Nguyen-Truong, C. K. (2011). Translation team approach: Psychometrics of a vietnamese pap testing survey. *Communicating Nursing Research, 44*, 73-80.

Nielsen, A. (2016). Concept-based learning in clinical experiences: Bringing theory to clinical education for deep learning. *Journal of Nursing Education, 55*(7), 365-371.
Background: Concept-based learning is used increasingly in nursing education to support the organization, transfer, and retention of knowledge. Concept-based learning activities (CBLAs) have been used in clinical education to explore key aspects of the patient situation and principles of nursing care, without responsibility for total patient care. The nature of best practices in teaching and the resultant learning are not well understood. Method: The purpose of this multiple-case study research was to explore and describe concept-based learning in the context of clinical education in inpatient settings. Four clinical groups (each a case) were observed while they used CBLAs in the clinical setting. Results: Major findings include that concept-based learning fosters deep learning, connection of theory with practice, and clinical judgment. Strategies used to support learning, major teaching-learning foci, and preconditions for concept-based teaching and learning will be described. Conclusion: Concept-based learning is promising to support integration of theory with practice and clinical judgment through application experiences with patients. © SLACK Incorporated.

Nielsen, J. S., Sally, M., Mullins, R. J., Slater, M., Groat, T., Gao, X., et al. (2016). Bicarbonate and mannitol treatment for traumatic rhabdomyolysis revisited. *American Journal of Surgery,*
BACKGROUND: A rhabdomyolysis protocol (RP) with mannitol and bicarbonate to prevent acute renal dysfunction (ARD, creatinine >2.0 mg/dL) remains controversial. METHODS: Patients with creatine kinase (CK) greater than 2,000 U/L over a 10-year period were identified. Shock, Injury Severity Score, massive transfusion, intravenous contrast exposure, and RP use were evaluated. RP was initiated for a CK greater than 10,000 U/L (first half of the study) or greater than 20,000 U/L (second half). Multivariable analyses were used to identify predictors of ARD and the independent effect of the RP. RESULTS: Seventy-seven patients were identified, 24 (31%)

developed ARD, and 4 (5%) required hemodialysis. After controlling for other risk factors, peak CK greater than 10,000 U/L (odds ratio 8.6, P = .016) and failure to implement RP (odds ratio 5.7, P = .030) were independent predictors of ARD. Among patients with CK greater than 10,000, ARD developed in 26% of patients with the RP versus 70% without it (P = .008). CONCLUSION: Reduced ARD was noted with RP. A prospective controlled study is still warranted.

Noble, M. J., Decker, S. L., & Zane Horowitz, B. (2016). Inhalational mercury toxicity from artisanal gold extraction reported to the oregon poison center, 2002-2015. *Clinical Toxicology (Philadelphia, Pa.)*, , 1-5.

CONTEXT: Mercury exposure has been described among small-scale gold mining communities in developing countries, but reports of inhalational mercury toxicity among home gold extractors in the US remain uncommon. OBJECTIVE: We sought to identify inhalational mercury exposures and toxicity among artisanal gold extractors. METHODS: This is an observational case series of a single Poison Center database from 2002-2015. We review all cases of "mercury" or "mercury inhalation" exposures, with detailed description of a recent representative case. RESULTS: Nine cases were reported, with patients' ages ranging 32-81 years. Eight (89%) patients were male. Seven of eight (88%) patients with acute exposures reported pulmonary symptoms consistent with mercury vapor inhalation such as dyspnea and cough; two (29%) patients had severe toxicity requiring intubation. Four of six (67%) patients had markedly elevated whole blood mercury concentrations up to 346 mcg/L; each received a different chelation regimen. Four (44%) patients used methamphetamines at the time of their exposure. The case report describes a patient with elevated mercury concentrations who required intubation for hypoxic respiratory failure. He received chelation therapy based on chelator availability, with decreasing 24-hour urine mercury concentrations. The house where he was exposed remains uninhabitable from elevated ambient mercury vapor concentrations. CONCLUSION: Artisanal gold extraction may be associated with inhalational mercury toxicity, including elevated blood mercury concentrations and acute hypoxic lung injury requiring intubation.

Noelck, N., Papak, J., Freeman, M., Paynter, R., Low, A., Motu'apuaka, M., et al. (2016). Effectiveness of left atrial appendage exclusion procedures to reduce the risk of stroke: A systematic review of

the evidence. *Circulation.Cardiovascular Quality and Outcomes*, *9*(4), 395-405.

BACKGROUND: Atrial fibrillation is an important cause of cardioembolic stroke. Oral anticoagulants (OAC) reduce stroke risk but increase the risk of serious bleeding. Left atrial appendage (LAA) procedures have been developed to isolate the LAA from circulating blood flow, as an alternative to OAC. We conducted a systematic review of the benefits and harms of surgical and percutaneous LAA exclusion procedures. METHODS AND RESULTS: We searched multiple data sources, including Ovid MEDLINE, Cochrane, and Embase, through January 7, 2015. Of 2567 citations, 20 primary studies met prespecified inclusion criteria. We abstracted data on patient characteristics, stroke, mortality, and adverse effects. We assessed study quality and graded the strength of evidence using published criteria. Trials found low-strength evidence that percutaneous LAA exclusion confers similar risks of stroke and mortality as continued OAC, but this evidence was limited to the Watchman device in patients eligible for long-term OAC. Observational studies found moderate-strength evidence of serious harms with a variety of percutaneous LAA procedures. There is low-strength evidence that surgical LAA exclusion does not add significant harm during heart surgery for another indication, but evidence on stroke reduction is insufficient. CONCLUSIONS: There is limited evidence that the Watchman device may be noninferior to long-term OAC in selected patients. Data on effectiveness of LAA exclusion devices is lacking in patients ineligible for long-term OAC. Percutaneous LAA devices are associated with high rates of procedure-related harms. Although surgical LAA exclusion during heart surgery does not seem to add incremental harm, there is insufficient evidence of benefit.

Norris, P., Hill, H., Morton, K., & Jacob, S. E. (2016). Majantol is a relevant fragrance allergy in adolescent children. *Dermatitis : Contact, Atopic, Occupational, Drug*, *27*(4), 233-234.

Olson, R., Wipfli, B., Thompson, S. V., Elliot, D. L., Anger, W. K., Bodner, T., et al. (2016). Weight control intervention for truck drivers: The SHIFT randomized controlled trial, united states. *American Journal of Public Health*, , e1-e9.

OBJECTIVES: To evaluate the effectiveness of the Safety and Health Involvement For Truckers (SHIFT) intervention with a randomized controlled design. METHODS: The multicomponent intervention was a weight-loss competition supported with body weight and behavioral self-

monitoring, computer-based training, and motivational interviewing. We evaluated intervention effectiveness with a cluster-randomized design involving 22 terminals from 5 companies in the United States in 2012 to 2014. Companies were required to provide interstate transportation services and operate at least 2 larger terminals. We randomly assigned terminals to intervention or usual practice control conditions. We assessed participating drivers (n = 452) at baseline and 6 months. RESULTS: In an intent-to-treat analysis, the postintervention difference between groups in mean body mass index change was 1.00 kilograms per meters squared (P < .001; intervention = -0.73; control = +0.27). Behavioral changes included statistically significant improvements in fruit and vegetable consumption and physical activity. CONCLUSIONS: Results establish the effectiveness of a multicomponent and remotely administered intervention for producing significant weight loss among commercial truck drivers. (Am J Public Health. Published online ahead of print July 26, 2016: e1-e9. doi:10.2105/AJPH.2016.303262).

Orwoll, E. (2016). Passing the baton--harnessing the full value of older scientists. *The New England Journal of Medicine*, *374*(26), 2514-2517.

Outcalt, S. D., Nicolaidis, C., Bair, M. J., Myers, L. J., Miech, E. J., & Matthias, M. S. (2016). A qualitative examination of pain centrality among veterans of iraq and afghanistan conflicts. *Pain Medicine (Malden, Mass.)*,

OBJECTIVE: Centrality of pain refers to the degree to which a patient views chronic pain as integral to his or her life or identity. The purpose of this study was to gain a richer understanding of pain centrality from the perspective of patients who live with chronic pain. METHODS: Face-to-face interviews were conducted with 26 Veterans with chronic and disabling musculoskeletal pain after completing a stepped care intervention within a randomized controlled trial. Qualitative data were analyzed using an immersion/crystallization approach. We evaluated the role centrality plays in Veterans' lives and examined whether and how their narratives differ when centrality either significantly decreases or increases after participation in a stepped care intervention for chronic pain. RESULTS: Our data identified three emergent themes that characterized pain centrality: 1) control, 2) acceptance, and 3) preoccupation. We identified five characteristics that distinguished patients' changes in centrality from baseline: 1) biopsychosocial viewpoint, 2)

activity level, 3) pain communication, 4) participation in managing own pain, and 5) social support. CONCLUSIONS: This study highlights centrality of pain as an important construct to consider within the overall patient experience of chronic pain.

Ozburn, A. R., Purohit, K., Parekh, P. K., Kaplan, G. N., Falcon, E., Mukherjee, S., et al. (2016). Functional implications of the CLOCK3111T/C single-nucleotide polymorphism. *Frontiers in Psychiatry*, *7*(APR)

Circadian rhythm disruptions are prominently associated with bipolar disorder (BD). Circadian rhythms are regulated by the molecular clock, a family of proteins that function together in a transcriptional-translational feedback loop. The CLOCK protein is a key transcription factor of this feedback loop, and previous studies have found that manipulations of the Clock gene are sufficient to produce manic-like behavior in mice (1). The CLOCK 3111T/C single-nucleotide polymorphism (SNP; rs1801260) is a genetic variation of the human CLOCK gene that is significantly associated with increased frequency of manic episodes in BD patients (2). The 3111T/C SNP is located in the 3'-untranslated region of the CLOCK gene. In this study, we sought to examine the functional implications of the human CLOCK 3111T/C SNP by transfecting a mammalian cell line (mouse embryonic fibroblasts isolated from Clock-/- knockout mice) with pcDNA plasmids containing the human CLOCK gene with either the T or C SNP at position 3111. We then measured circadian gene expression over a 24-h time period. We found that the CLOCK3111C SNP resulted in higher mRNA levels than the CLOCK 3111T SNP. Furthermore, we found that Per2, a transcriptional target of CLOCK, was also more highly expressed with CLOCK 3111C expression, indicating that the 3'-UTR SNP affects the expression, function, and stability of CLOCK mRNA.

Paller, A. S., Tom, W. L., Lebwohl, M. G., Blumenthal, R. L., Boguniewicz, M., Call, R. S., et al. (2016). Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology*,

BACKGROUND: Additional topical treatments for atopic dermatitis (AD) are needed that provide relief while minimizing risks. OBJECTIVE: We sought to assess the efficacy and safety of

crisaborole ointment, a phosphodiesterase 4 inhibitor, in two phase III AD studies (AD-301: NCT02118766; AD-302: NCT02118792). METHODS: Two identically designed, vehicle-controlled, double-blind studies enrolled and randomly assigned (2:1, crisaborole:vehicle) patients aged 2 years or older with an Investigator's Static Global Assessment (ISGA) score of mild or moderate for twice-daily application for 28 days. The primary end point was ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline. Additional analyses included time to success in ISGA score, percentage of patients achieving clear/almost clear, reduction in severity of AD signs, and time to improvement in pruritus. RESULTS: More crisaborole- than vehicle-treated patients achieved ISGA score success (clear/almost clear with >/=2-grade improvement; AD-301: 32.8% vs 25.4%, P = .038; AD-302: 31.4% vs 18.0%, P < .001), with a greater percentage with clear/almost clear (51.7% vs 40.6%, P = .005; 48.5% vs 29.7%, P < .001). Crisaborole-treated patients achieved success in ISGA score and improvement in pruritus earlier than those treated with vehicle (both P </= .001). Treatment-related adverse events were infrequent and mild to moderate in severity. LIMITATIONS: Short study duration was a limitation. CONCLUSIONS: Crisaborole demonstrated a favorable safety profile and improvement in all measures of efficacy, including overall disease severity, pruritus, and other signs of AD.

Palmer, A. D., Newsom, J. T., & Rook, K. S. (2016). How does difficulty communicating affect the social relationships of older adults? an exploration using data from a national survey. *Journal of Communication Disorders, 62*, 131-146.

Healthy social relationships are important for maintaining mental and physical health in later life. Less social support, smaller social networks, and more negative social interactions have been linked to depression, poorer immune functioning, lower self-rated health, increased incidence of disease, and higher mortality. Overwhelming evidence suggests that communication disorders adversely affect social relationships. Much less is known about whether some or all aspects of social relationships are negatively affected by a communication disorder. The relative impact of a communication disorder on social relationships, as compared to other kinds of disability, is also poorly understood. Data were analyzed from a representative national sample of community-dwelling adults aged 65 and older living in the continental United States (n=742). Results from

multiple regressions indicated that difficulty communicating was significantly associated with several parameters of social relationships even after controlling for age, gender, partnership status, health, functional limitations, and visual impairment. Communication difficulty was a significant predictor of smaller social network size, fewer positive social exchanges, less frequent participation in social activities, and higher levels of loneliness, but was not a significant predictor of negative social exchanges. These findings suggest that communication disorders may place older adults at increased risk for mental and physical health problems because of social isolation, reduced social participation, and higher rates of loneliness. In addition, it appears that communication disorders may have a greater impact on positive, rather than negative, aspects of social relationships. LEARNING OUTCOMES: As a result of this activity, the following learning outcomes will be realized: Readers will be able to (1) describe changes in the social relationships of older adults that occur as part of normal aging, (2) identify the aspects of social relationships that were significantly impacted by a communication difficulty, and (3) discuss possible reasons for these findings including potential clinical implications.

Pandi-Perumal, S. R., BaHammam, A. S., Ojike, N. I., Akinseye, O. A., Kendzerska, T., Buttoo, K., et al. (2016). Melatonin and human cardiovascular disease. *Journal of Cardiovascular Pharmacology and Therapeutics*,

The possible therapeutic role of melatonin in the pathophysiology of coronary artery disorder (CAD) is increasingly being recognized. In humans, exogenous melatonin has been shown to decrease nocturnal hypertension, improve systolic and diastolic blood pressure, reduce the pulsatility index in the internal carotid artery, decrease platelet aggregation, and reduce serum catecholamine levels. Low circulating levels of melatonin are reported in individuals with CAD, arterial hypertension, and congestive heart failure. This review assesses current literature on the cardiovascular effects of melatonin in humans. It can be concluded that melatonin deserves to be considered in clinical trials evaluating novel therapeutic interventions for cardiovascular disorders.

Pardanaud, L., Pibouin-Fragner, L., Dubrac, A., English, I., Mathivet, T., Brunet, I., et al. (2016). Sympathetic innervation promotes arterial fate by enhancing endothelial ERK. *Circulation Research*,

RATIONALE: Arterial endothelial cells are morphologically, functionally and molecularly distinct from those found in veins and lymphatic vessels. How arterial fate is acquired during development and maintained in adult vessels is incompletely understood. OBJECTIVE: We set out to identify factors that promote arterial endothelial cell fate in vivo. METHODS AND RESULTS: We developed a functional assay allowing us to monitor and manipulate arterial fate in vivo, using arteries isolated from quails that are grafted into the coelom of chick embryos. Endothelial cells migrate out from the grafted artery and their colonization of host arteries and/or veins is quantified. Here we show that sympathetic innervation promotes arterial endothelial cell fate in vivo. Removal of sympathetic nerves decreases arterial fate and leads to colonization of veins, while exposure to sympathetic nerves or norepinephrine imposes arterial fate. Mechanistically, sympathetic nerves increase endothelial ERK activity via adrenergic alpha1 and alpha2 receptors. CONCLUSIONS: These findings show that sympathetic innervation promotes arterial endothelial fate and may lead to novel approaches to improve arterialization in human disease.

Parham, K., Chapurin, N., Schulz, K., Shin, J. J., Pynnonen, M. A., Witsell, D. L., et al. (2016). Thyroid disease and surgery in CHEER: The nation's otolaryngology-head and neck surgery practice-based network. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery, 155*(1), 22-27.

OBJECTIVES: (1) Describe thyroid-related diagnoses and procedures in Creating Healthcare Excellence through Education and Research (CHEER) across academic and community sites. (2) Compare management of malignant thyroid disease across these sites. (3) Provide practice-based data related to flexible laryngoscopy vocal fold assessment before and after thyroid surgery based on the American Academy of Otolaryngology-Head and Neck Surgery Foundation's clinical practice guidelines. STUDY DESIGN: Review of retrospective data collection (RDC) database of the CHEER network using ICD-9 and CPT codes related to thyroid conditions. SETTING: Multisite practice-based network. SUBJECTS AND METHODS: There were 3807 thyroid patients (1392 malignant, 2415 benign) with 10,160 unique visits identified from 1 year of patient data in the RDC. Analysis was performed for identified cohort of patients using demographics, site characteristics, and diagnostic and procedural distribution. RESULTS: Mean number of patients with thyroid disease per site was 238 (range, 23-715). In community

practices, 19% of patients with thyroid disease had cancer versus 45% in the academic setting (P < .001). While academic sites manage more cancer patients, community sites are also surgically treating thyroid cancer and performed more procedures per cancer patient (4.2 vs 3.5, P < .001). Vocal fold function was assessed by flexible laryngoscopy in 34.0% of preoperative patients and in 3.7% postoperatively. CONCLUSION: This is the first overview of malignant and benign thyroid disease through CHEER. It shows how the RDC can be used alone and with national guidelines to inform of clinical practice patterns in academic and community sites. This demonstrates the potential for future thyroid-related studies utilizing the otolaryngology-head and neck surgery practice-based research network.

Parikh, R. B., & Prasad, V. (2016). Blood-based screening for colon cancer: A disruptive innovation or simply a disruption? *Jama, 315*(23), 2519-2520.

Park, J. W., Liu, M. C., Yee, D., Yau, C., van 't Veer, L. J., Symmans, W. F., et al. (2016). Adaptive randomization of neratinib in early breast cancer. *The New England Journal of Medicine, 375*(1), 11-22.

BACKGROUND: The heterogeneity of breast cancer makes identifying effective therapies challenging. The I-SPY 2 trial, a multicenter, adaptive phase 2 trial of neoadjuvant therapy for high-risk clinical stage II or III breast cancer, evaluated multiple new agents added to standard chemotherapy to assess the effects on rates of pathological complete response (i.e., absence of residual cancer in the breast or lymph nodes at the time of surgery). METHODS: We used adaptive randomization to compare standard neoadjuvant chemotherapy plus the tyrosine kinase inhibitor neratinib with control. Eligible women were categorized according to eight biomarker subtypes on the basis of human epidermal growth factor receptor 2 (HER2) status, hormone-receptor status, and risk according to a 70-gene profile. Neratinib was evaluated against control with regard to 10 biomarker signatures (prospectively defined combinations of subtypes). The primary end point was pathological complete response. Volume changes on serial magnetic resonance imaging were used to assess the likelihood of such a response in each patient. Adaptive assignment to experimental groups within each disease subtype was based on Bayesian probabilities of the superiority of the treatment over control. Enrollment in the experimental

group was stopped when the 85% Bayesian predictive probability of success in a confirmatory phase 3 trial of neoadjuvant therapy reached a prespecified threshold for any biomarker signature ("graduation"). Enrollment was stopped for futility if the probability fell to below 10% for every biomarker signature. RESULTS: Neratinib reached the prespecified efficacy threshold with regard to the HER2-positive, hormone-receptor-negative signature. Among patients with HER2-positive, hormone-receptor-negative cancer, the mean estimated rate of pathological complete response was 56% (95% Bayesian probability interval [PI], 37 to 73%) among 115 patients in the neratinib group, as compared with 33% among 78 controls (95% PI, 11 to 54%). The final predictive probability of success in phase 3 testing was 79%. CONCLUSIONS: Neratinib added to standard therapy was highly likely to result in higher rates of pathological complete response than standard chemotherapy with trastuzumab among patients with HER2-positive, hormone-receptor-negative breast cancer. (Funded by QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.).

Patel, J. J., Rosenthal, M. D., Miller, K. R., Codner, P., Kiraly, L., & Martindale, R. G. (2016). The critical care obesity paradox and implications for nutrition support. *Current Gastroenterology Reports, 18*(9), 45-016-0519-8.

Obesity is a leading cause of preventable death worldwide. The prevalence of obesity has been increasing and is associated with an increased risk for other co-morbidities. In the critical care setting, nearly one third of patients are obese. Obese critically ill patients pose significant physical and on-physical challenges to providers, including optimization of nutrition therapy. Intuitively, obese patients would have worse critical care-related outcome. On the contrary, emerging data suggests that critically ill obese patients have improved outcomes, and this phenomenon has been coined "the obesity paradox." The purposes of this review will be to outline the historical views and pathophysiology of obesity and epidemiology of obesity, describe the challenges associated with obesity in the intensive care unit setting, review critical care outcomes in the obese, define the obesity-critical care paradox, and identify the challenges and role of nutrition support in the critically ill obese patient.

Pearson, Y. E., Lund, A. W., Lin, A., Ng, C. P., Alsuwaidi, A., Azzeh, S., et al. (2016). Non-invasive single cell biomechanical analysis using live imaging datasets. *Journal of Cell Science*,

The physiological state of a cell is governed by a multitude of processes and can be described by a combination of mechanical, spatial, and temporal properties. Quantifying cell dynamics at multiple scales is essential for comprehensive studies of cellular function, and remains a challenge via traditional end-point assays. We introduce an efficient, non-invasive computational tool that takes, time-lapse images as input to automatically detect, segment, and analyze unlabeled live cells; the program then outputs kinematic cellular shape and migration parameters, while simultaneously measuring cellular stiffness and viscosity. We demonstrate the program's capabilities by testing it on human mesenchymal stem cells (huMSC) induced to differentiate towards osteoblastic (huOB) lineage, and T-lymphocyte cells (T cells) of naive and stimulated phenotypes. The program detected relative cellular stiffness differences in huMSC and huOB comparable to studies that utilize atomic force microscopy; it further distinguished naive from stimulated T cells, based on characteristics necessary to invoke an immune response. In summary, we introduce an integrated tool to decipher spatiotemporal and intracellular dynamics of cells, providing a new and alternative approach for cell characterization.

Peckham, J. L., Block, R., Buchanan, M., & Pommier, S. (2016). Unspoken ink: A structured, creative writing workshop for adolescents and young adult cancer patients as a psychosocial intervention. *Journal of Adolescent and Young Adult Oncology*,

Pendyal, A. (2016). What they don't teach you. *Journal of General Internal Medicine*,

Pendyal, A., & Gelow, J. M. (2016). Cardiohepatic interactions: Implications for management in advanced heart failure. *Heart Failure Clinics*, *12*(3), 349-361.

Liver disease is a common sequela of heart failure and can range from mild reversible liver injury to hepatic fibrosis and, in its most severe form, cardiac cirrhosis. Hepatic fibrosis and cirrhosis due to chronic heart failure have important implications for prognosis, medication management, mechanical circulatory support, and heart transplantation. This article reviews the current understanding of liver disease in heart failure and provides a framework for approaching liver disease in the advanced heart failure population.

Permuth, J. B., Pirie, A., Ann Chen, Y., Lin, H. Y., Reid, B. M., Chen, Z., et al. (2016). Exome genotyping arrays to identify rare and low frequency variants associated with epithelial ovarian cancer risk. *Human Molecular Genetics,*

Rare and low frequency variants are not well covered in most germline genotyping arrays and are understudied in relation to epithelial ovarian cancer (EOC) risk. To address this gap, we used genotyping arrays targeting rarer protein-coding variation in 8,165 EOC cases and 11,619 controls from the international Ovarian Cancer Association Consortium (OCAC). Pooled association analyses were conducted at the variant and gene level for 98,543 variants directly genotyped through two exome genotyping projects. Only common variants that represent or are in strong linkage disequilibrium (LD) with previously-identified signals at established loci reached traditional thresholds for exome-wide significance (P P>/=5.0 x10 - 7) were detected for rare and low-frequency variants at 16 novel loci. Four rare missense variants were identified (ACTBL2 rs73757391 (5q11.2), BTD rs200337373 (3p25.1), KRT13 rs150321809 (17q21.2) and MC2R rs104894658 (18p11.21)), but only MC2R rs104894668 had a large effect size (OR = 9.66). Genes most strongly associated with EOC risk included ACTBL2 (PAML = 3.23 x 10 - 5; PSKAT-o = 9.23 x 10 - 4) and KRT13 (PAML = 1.67 x 10 - 4; PSKAT-o = 1.07 x 10 - 5), reaffirming variant-level analysis. In summary, this large study identified several rare and low-frequency variants and genes that may contribute to EOC susceptibility, albeit with possible small effects. Future studies that integrate epidemiology, sequencing, and functional assays are needed to further unravel the unexplained heritability and biology of this disease.

Petersen, J., Kaye, J., Jacobs, P. G., Quinones, A., Dodge, H., Arnold, A., et al. (2016). Longitudinal relationship between loneliness and social isolation in older adults: Results from the cardiovascular health study. *Journal of Aging and Health, 28*(5), 775-795.

Objective: To understand the longitudinal relationship between loneliness and isolation. Method: Participants included 5,870 adults 65 years and older (M = 72.89 ± 5.59 years) from the first 5 years of the Cardiovascular Health Study. Loneliness was assessed using a dichotomized loneliness question. Social isolation was assessed using six items from the Lubben Social Network Scale. Yearly life events were included to assess abrupt social network changes. Mixed effects logistic regression was employed to analyze the relationship between isolation and loneliness.

Results: Higher levels of social isolation were associated with higher odds of loneliness, as was an increase (from median) in level of social isolation. Life events such as a friend dying were also associated with increased odds of loneliness. Discussion: These results suggest that average level of isolation and increases in the level of isolation are closely tied to loneliness, which has implications for future assessment or monitoring of loneliness in older adult populations. © The Author(s) 2015.

Pflibsen, L., Stang, K. A., Sconce, M. D., Wilson, V. B., Hood, R. L., Meshul, C. K., et al. (2015). Executive function deficits and glutamatergic protein alterations in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of parkinson's disease. *Journal of Neuroscience Research*, *93*(12), 1849-1864.

Changes in executive function are at the root of most cognitive problems associated with Parkinson's disease. Because dopaminergic treatment does not necessarily alleviate deficits in executive function, it has been hypothesized that dysfunction of neurotransmitters/systems other than dopamine (DA) may be associated with this decrease in cognitive function. We have reported decreases in motor function and dopaminergic/glutamatergic biomarkers in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Parkinson's mouse model. Assessment of executive function and dopaminergic/glutamatergic biomarkers within the limbic circuit has not previously been explored in our model. Our results show progressive behavioral decline in a cued response task (a rodent model for frontal cortex cognitive function) with increasing weekly doses of MPTP. Although within the dorsolateral (DL) striatum mice that had been given MPTP showed a 63% and 83% loss of tyrosine hydroxylase and dopamine transporter expression, respectively, there were no changes in the nucleus accumbens or medial prefrontal cortex (mPFC). Furthermore, dopamine-1 receptor and vesicular glutamate transporter (VGLUT)-1 expression increased in the mPFC following DA loss. There were significant MPTP-induced decreases and increases in VGLUT-1 and VGLUT-2 expression, respectively, within the DL striatum. We propose that the behavioral decline following MPTP treatment may be associated with a change not only in cortical-cortical (VGLUT-1) glutamate function but also in striatal DA and glutamate (VGLUT-1/VGLUT-2) input.

Pierce, M., & Scottoline, B. (2016). Neonatal McCune-albright syndrome with survival beyond two years. *American Journal of Medical Genetics.Part A*,

McCune-Albright syndrome (MAS) is a rare disease resulting from a somatic, mosaic mutation of GNAS1 encoding the Gs alpha subunit of the G-protein coupled membrane receptor responsible for multiple hormonal signaling cascades. We present a patient with neonatal MAS who initially presented with neonatal diabetes and concern for congenital cardiac disease, and subsequently was found to have significant ACTH-independent neonatal Cushing syndrome. Her course included multi-system organ involvement, although she initially did not have obvious findings consistent with the MAS classic triad of cafe-au-lait macules, fibrous dysplasia, or peripheral precocious puberty. After medical and surgical treatment, she remains the only reported survivor of neonatal MAS. This clinical report alerts clinicians to the possibility of this disease in neonates with non-classical endocrine and non-endocrine manifestations of MAS, and demonstrates that this very early presentation is potentially survivable. (c) 2016 Wiley Periodicals, Inc.

Piker, E. G., Schulz, K., Parham, K., Vambutas, A., Witsell, D., Tucci, D., et al. (2016). Variation in the use of vestibular diagnostic testing for patients presenting to otolaryngology clinics with dizziness. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *155*(1), 42-47.

OBJECTIVE: We used a national otolaryngology practice-based research network database to characterize the utilization of vestibular function testing in patients diagnosed with dizziness and/or a vestibular disorder. STUDY DESIGN: Database review. SETTING: The Creating Healthcare Excellence through Education and Research (CHEER) practice-based research network of academic and community providers SUBJECTS AND METHODS: Dizzy patients in the CHEER retrospective database were identified through ICD-9 codes; vestibular testing procedures were identified with CPT codes. Demographics and procedures per patient were tabulated. Analysis included number and type of vestibular tests ordered, stratified by individual clinic and by practice type (community vs academic). Chi-square tests were performed to assess if the percentage of patients receiving testing was statistically significant across clinics. A logistic regression model was used to examine the association between receipt of testing and being tested on initial visit. RESULTS: A total of 12,468 patients diagnosed with dizziness and/or a

vestibular disorder were identified from 7 community and 5 academic CHEER network clinics across the country. One-fifth of these patients had at least 1 vestibular function test. The percentage of patients tested varied widely by site, from 3% to 72%; academic clinics were twice as likely to test. Initial visit vestibular testing also varied, from 0% to 96% of dizzy patients, and was 15 times more likely in academic clinics. CONCLUSION: There is significant variation in use and timing of vestibular diagnostic testing across otolaryngology clinics. The CHEER network research database does not contain outcome data. These results illustrate the critical need for research that examines outcomes as related to vestibular testing.

Pina, M. M., & Cunningham, C. L. (2016). Involvement of ventral tegmental area ionotropic glutamate receptors in the expression of ethanol-induced conditioned place preference. *Behavioural Brain Research*, *313*, 23-29.

The ventral tegmental area (VTA) is a well-established neural substrate of reward-related processes. Activity within this structure is increased by the primary and conditioned rewarding effects of abused drugs and its engagement is heavily reliant on excitatory input from structures upstream. In the case of drug seeking, it is thought that exposure to drug-associated cues engages glutamatergic VTA afferents that signal directly to dopamine cells, thereby triggering this behavior. It is unclear, however, whether glutamate input to VTA is directly involved in ethanol-associated cue seeking. Here, the role of intra-VTA ionotropic glutamate receptor (iGluR) signaling in ethanol-cue seeking was evaluated in DBA/2J mice using an ethanol conditioned place preference (CPP) procedure. Intra-VTA iGluRs alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR)/kainate and N-methyl-d-aspartate (NMDAR) were blocked during ethanol CPP expression by co-infusion of antagonist drugs 6,7-dinitroquinoxaline-2,3-dione (DNQX; AMPA/kainate) and d-(-)-2-Amino-5-phosphonopentanoic acid (AP5; NMDA). Compared to aCSF, bilateral infusion of low (1 DNQX+100 AP5ng/side) and high (5 DNQX+500 AP5ng/side) doses of the AMPAR and NMDAR antagonist cocktail into VTA blocked ethanol CPP expression. This effect was site specific, as DNQX/AP5 infusion proximal to VTA did not significantly impact CPP expression. An increase in activity was found at the high but not low dose of DNQX/AP5. These findings demonstrate that activation of iGluRs within the VTA is necessary for ethanol-associated cue seeking, as measured by CPP.

Pitekova, B., Ravi, S., Shah, S. V., Mladosievicova, B., Heitner, S., & Ferencik, M. (2016). The role of imaging with cardiac computed tomography in cardio-oncology patients. *Current Cardiology Reports*, *18*(9), 87-016-0768-z.

Cardiovascular diseases and cancer represent the two most common causes of morbidity and mortality in industrialized countries. With the increase in long-term survival of cancer patients, cardiovascular diseases are the leading cause of mortality for many cancer survivors. In this article, we will review the most common cardiovascular toxicities of cancer therapies and will describe the role of cardiac CT in the detection and monitoring of cardiovascular disease. While there is limited evidence for the use of CT imaging in cancer patients, we will discuss the utility of cardiac CT in the detection and management of coronary artery disease, pericardial and valvular heart disease.

Prior, S., Miousse, I. R., Nzabarushimana, E., Pathak, R., Skinner, C., Kutanzi, K. R., et al. (2016). Densely ionizing radiation affects DNA methylation of selective LINE-1 elements. *Environmental Research*, *150*, 470-481.

Long Interspersed Nucleotide Element 1 (LINE-1) retrotransposons are heavily methylated and are the most abundant transposable elements in mammalian genomes. Here, we investigated the differential DNA methylation within the LINE-1 under normal conditions and in response to environmentally relevant doses of sparsely and densely ionizing radiation. We demonstrate that DNA methylation of LINE-1 elements in the lungs of C57BL6 mice is dependent on their evolutionary age, where the elder age of the element is associated with the lower extent of DNA methylation. Exposure to 5-aza-2'-deoxycytidine and methionine-deficient diet affected DNA methylation of selective LINE-1 elements in an age- and promoter type-dependent manner. Exposure to densely IR, but not sparsely IR, resulted in DNA hypermethylation of older LINE-1 elements, while the DNA methylation of evolutionary younger elements remained mostly unchanged. We also demonstrate that exposure to densely IR increased mRNA and protein levels of LINE-1 via the loss of the histone H3K9 dimethylation and an increase in the H3K4 trimethylation at the LINE-1 5'-untranslated region, independently of DNA methylation. Our findings suggest that DNA methylation is important for regulation of LINE-1 expression under

normal conditions, but histone modifications may dictate the transcriptional activity of LINE-1 in response to exposure to densely IR.

Protopsaltis, T., Bronsard, N., Soroceanu, A., Henry, J. K., Lafage, R., Smith, J., et al. (2016). Cervical sagittal deformity develops after PJK in adult thoracolumbar deformity correction: Radiographic analysis utilizing a novel global sagittal angular parameter, the CTPA. *European Spine Journal : Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*,
PURPOSE: To describe reciprocal changes in cervical alignment after adult spinal deformity (ASD) correction and subsequent development of proximal junctional kyphosis (PJK). This study also investigated these changes using two novel global sagittal angular parameters, cervical-thoracic pelvic angle (CTPA) and the T1 pelvic angle (TPA). METHODS: Multicenter, retrospective consecutive case series of ASD patients undergoing thoracolumbar three-column osteotomy (3CO) with fusion to the pelvis. Radiographs were analyzed at baseline and 1 year post-operatively. Patients were substratified into upper thoracic (UT; UIV T6 and above) and lower thoracic (LT; UIV below T6). PJK was defined by >10 degrees angle between UIV and UIV + 2 and >10 degrees change in the angle from baseline to post-op. RESULTS: PJK developed in 29 % (78 of 267) of patients. CTPA was linearly correlated with cervical plumbline (CPL) as a measure of cervical sagittal alignment ($R = 0.826$, $p < 0.001$). PJK patients had significantly greater post-operative CTPA and SVA than patients without PJK (NPJK) ($p = 0.042$; $p = 0.021$). For UT ($n = 141$) but not LT ($n = 136$), PJK patients at 1 year had larger CTPA (4.9 degrees vs. 3.7 degrees , $p = 0.015$) and CPL (5.1 vs. 3.8 cm, $p = 0.022$) than NPJK patients, despite similar corrections in PT and PI-LL. CONCLUSIONS: The prevalence of PJK was 29 % at 1 year follow-up. CTPA, which correlates with CPL as a global analog of cervical sagittal balance, and TPA describe relative proportions of cervical and thoracolumbar deformities. Patients who develop PJK in the upper thoracic spine after thoracolumbar 3CO also develop concomitant cervical sagittal deformity, with increases in CPL and CTPA.

Puckett, C., & Mudd, J. O. (2016). Tailoring therapies in advanced heart failure. *Heart Failure Clinics*, *12*(3), 375-384.

Heart failure effects millions of people throughout the world and is a growing epidemic with a significant impact on the economics and systems of care delivery. The goal of therapy in advanced heart failure is to improve quality of life and prolong survival. Standard medical therapies may require tailoring as advanced therapies are considered in the context of patient and caregiver goals. The aim of this review is to summarize concepts for tailored medical therapy and monitoring in advanced heart failure and discuss the importance of tailoring systems of care and shared decision making in advanced heart failure.

Quinn, C., & Karam, C. (2016). Utility of pediatric nerve biopsy in tertiary care referral. *Pediatric Neurology Briefs, 30*(3), 20-30-3-3.

Investigators from Mayo Clinic in Rochester, MN, report the utility of nerve biopsy as a diagnostic tool in their institution.

Ray, A., Williams, M. A., Meek, S. M., Bowen, R. C., Grossmann, K. F., Andtbacka, R. H., et al. (2016). A phase I study of intratumoral ipilimumab and interleukin-2 in patients with advanced melanoma. *Oncotarget*,

PURPOSE: Intratumoral interleukin-2 (IL-2) is effective but does not generate systemic immunity. Intravenous ipilimumab produces durable clinical response in a minority of patients, with potentially severe toxicities. Circulating anti-tumor T cells activated by ipilimumab may differ greatly from tumor-infiltrating lymphocytes activated by intratumoral ipilimumab in phenotypes and functionality. The objective of this study was to primarily assess the safety of intratumoral ipilimumab/IL-2 combination and to obtain data on clinical efficacy. RESULTS: There was no dose limiting toxicity. While local response of injected lesions was observed in 67% patients (95% CI, 40%-93%), an abscopal response was seen in 89% (95% CI, 68%-100%). The overall response rate and clinical benefit rate by immune-related response criteria (irRC) was 40% (95% CI, 10%-70%) and 50% (95% CI, 19%-81%), respectively. Enhanced systemic immune response was observed in most patients and correlated with clinical responses. EXPERIMENTAL DESIGN: Twelve patients with unresectable stages III/IV melanoma were enrolled. A standard 3+3 design was employed to assess highest tolerable intratumoral dose of ipilimumab and IL-2 based on toxicity during the first three weeks. Escalated doses of ipilimumab was injected into only one lesion

weekly for eight weeks in cohorts of three patients. A fixed dose of IL-2 was injected three times a week into the same lesion for two weeks, followed by two times a week for six weeks. CONCLUSIONS: Intratumoral injection with the combination of ipilimumab/IL-2 is well tolerated and generates responses in both injected and non-injected lesions in the majority of patients.

Redmond, W. L., & Linch, S. N. (2016). Combinatorial immunotherapeutic approaches to restore the function of anergic tumor-reactive cytotoxic CD8+ T cells. *Human Vaccines & Immunotherapeutics*, , 1-4.
Numerous preclinical studies have demonstrated that combination immunotherapy can significantly reduce tumor growth and improve overall survival as compared to monotherapy. Furthermore, dual CTLA-4/PD-1 checkpoint blockade recently received FDA-approval for patients with metastatic melanoma, becoming the first combination immunotherapy to garner this designation in a rapidly evolving field. Despite this progress, the majority of patients do not respond to treatment, underscoring the critical need for more effective therapies. We have been investigating the mechanisms by which combination immunotherapy with an OX40 agonist plus CTLA-4 checkpoint blockade augments effector T cell responses to elicit anti-tumor immunity. Surprisingly, this approach failed to eradicate well-established tumors, in part due to the induction of anergy in cytotoxic CD8+ T cells. Further work revealed that anergic CD8+ T cells could be rescued by combining a dendritic cell-targeted vaccine with combination immunotherapy. Taken together, these data suggest that novel combinatorial immunotherapeutic strategies incorporating a vaccination strategy may be needed to generate effective anti-tumor responses in the majority of patients with metastatic disease.

Rieckmann, T., Moore, L. A., Croy, C. D., Novins, D. K., & Aarons, G. (2016). A national study of american indian and alaska native substance abuse treatment: Provider and program characteristics. *Journal of Substance Abuse Treatment*, *68*, 46-56.
American Indians and Alaska Natives (AIANs) experience major disparities in accessing quality care for mental health and substance use disorders. There are long-standing concerns about access to and quality of care for AIANs in rural and urban areas including the influence of staff and organizational factors, and attitudes toward evidence-based treatment for addiction. We

conducted the first national survey of programs serving AIAN communities and examined workforce and programmatic differences between clinics located in urban/suburban (n=50) and rural (n=142) communities. We explored the correlates of openness toward using evidence-based treatments (EBTs). Programs located in rural areas were significantly less likely to have nurses, traditional healing consultants, or ceremonial providers on staff, to consult outside evaluators, to use strategic planning to improve program quality, to offer pharmacotherapies, pipe ceremonies, and cultural activities among their services, and to participate in research or program evaluation studies. They were significantly more likely to employ elders among their traditional healers, offer AA-open group recovery services, and collect data on treatment outcomes. Greater openness toward EBTs was related to a larger clinical staff, having addiction providers, being led by directors who perceived a gap in access to EBTs, and working with key stakeholders to improve access to services. Programs that provided early intervention services (American Society of Addiction Medicine level 0.5) reported less openness. This research provides baseline workforce and program level data that can be used to better understand changes in access and quality for AIAN over time.

Ring, K. L., Bruegl, A. S., Allen, B. A., Elkin, E. P., Singh, N., Hartman, A. R., et al. (2016). Germline multi-gene hereditary cancer panel testing in an unselected endometrial cancer cohort. *Modern Pathology : An Official Journal of the United States and Canadian Academy of Pathology, Inc*, Hereditary endometrial carcinoma is associated with germline mutations in Lynch syndrome genes. The role of other cancer predisposition genes is unclear. We aimed to determine the prevalence of cancer predisposition gene mutations in an unselected endometrial carcinoma patient cohort. Mutations in 25 genes were identified using a next-generation sequencing-based panel applied in 381 endometrial carcinoma patients who had undergone tumor testing to screen for Lynch syndrome. Thirty-five patients (9.2%) had a deleterious mutation: 22 (5.8%) in Lynch syndrome genes (three MLH1, five MSH2, two EPCAM-MSH2, six MSH6, and six PMS2) and 13 (3.4%) in 10 non-Lynch syndrome genes (four CHEK2, one each in APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, NBN, PTEN, and RAD51C). Of 21 patients with deleterious mutations in Lynch syndrome genes with tumor testing, 2 (9.5%) had tumor testing results suggestive of sporadic cancer. Of 12 patients with deleterious mutations in MSH6 and PMS2, 10 were diagnosed at age

>50 and 8 did not have a family history of Lynch syndrome-associated cancers. Patients with deleterious mutations in non-Lynch syndrome genes were more likely to have serous tumor histology (23.1 vs 6.4%, P=0.02). The three patients with non-Lynch syndrome deleterious mutations and serous histology had mutations in BRCA2, BRIP1, and RAD51C. Current clinical criteria fail to identify a portion of actionable mutations in Lynch syndrome and other hereditary cancer syndromes. Performance characteristics of tumor testing are sufficiently robust to implement universal tumor testing to identify patients with Lynch syndrome. Germline multi-gene panel testing is feasible and informative, leading to the identification of additional actionable mutations.Modern Pathology advance online publication, 22 July 2016; doi:10.1038/modpathol.2016.135.

Robinson, J. D., & Jagsi, R. (2016). Physician-patient communication-an actionable target for reducing overly aggressive care near the end of life. *JAMA Oncology*,

Rodrigues, S. A., Jr., Chemin, P., Piaia, P. P., & Ferracane, J. L. (2015). Surface roughness and gloss of actual composites as polished with different polishing systems. *Operative Dentistry, 40*(4), 418-429.

Objective: This in vitro study evaluated the effect of polishing with different polishing systems on the surface roughness and gloss of commercial composites. Methods: One hundred disk-shaped specimens (10 mm in diameter ×2 mm thick) were made with Filtek P-90, Filtek Z350 XT, Opallis, and Grandio. The specimens were manually finished with #400 sandpaper and polished by a single operator using three multistep systems (Superfix, Diamond Pro, and Sof-lex), one two-step system (Polidores DFL), and one one-step system (Enhance), following the manufacturer's instructions. The average surface roughness (lm) was measured with a surface profilometer (TR 200 Surface Roughness Tester), and gloss was measured using a small-area glossmeter (Novo- Curve, Rhopoint Instrumentation, East Sussex, UK). Data were analyzed by two-way analysis of variance and Tukey's test (α=0.05). Results: Statistically significant differences in surface roughness were identified by varying the polishing systems (p,<0.0001) and by the interaction between polishing system and composite (p,<0.0001). Pairwise comparisons revealed higher surface roughness for Grandio when polished with Sof-Lex and

Filtek Z250 and Opallis when polished with Enhance. Gloss was influenced by the composites (p, <0.0001), the polishing systems (p, <0.0001), and the interaction between them (p, <0.0001). The one-step system, Enhance, produced the lowest gloss for all composites. Conclusions: Surface roughness and gloss were affected by composites and polishing systems. The inter-action between both also influenced these surface characteristics, meaning that a single polishing system will not behave similarly for all composites. The multistep systems produced higher gloss, while the one-step system produced the highest surface roughness and the lowest gloss of all. © Operative Dentistry.

Ross, A. M., Lee, C. S., & Lutsep, H. (2016). Influence of gender and age on the peripheral immune response in stroke. *Journal of Cardiovascular Nursing, 31*(4), 331-335.

Background: Women and men have unique stroke risk factors and can experience different poststroke infections. Objective: The aim of this study is to determine the influence of gender, age, and risk factors on the peripheral immune response in stroke/transient ischemic attack (TIA). Method: A total of 192 adult acute stroke/TIA cases were analyzed for age, gender, risk factors for stroke/TIA, and white blood cell with differential count. χ 2 Test and analysis of variance were conducted to test for differences between genders and age groups related to stroke risk factors and the immune response. Growth modeling was used to test for trended differences in the immune response. Results: Women were 4 years older than men; fewer women had strokes in the younger age group (<79 years) and more men currently smoked. Trended lymphocyte percentages for the young and old (slope, P =.04; pattern, P =.02) and admission monocyte percentages by gender were significantly different (P =.01). Conclusions: Age influenced trended lymphocyte numbers and gender influenced monocyte percentage on admission. © 2016 Wolters Kluwer Health, Inc.

Rugo, H. S., Olopade, O. I., DeMichele, A., Yau, C., van 't Veer, L. J., Buxton, M. B., et al. (2016). Adaptive randomization of veliparib-carboplatin treatment in breast cancer. *The New England Journal of Medicine, 375*(1), 23-34.

BACKGROUND: The genetic and clinical heterogeneity of breast cancer makes the identification of effective therapies challenging. We designed I-SPY 2, a phase 2, multicenter, adaptively

randomized trial to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match experimental regimens with responding cancer subtypes. We report results for veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, combined with carboplatin. METHODS: In this ongoing trial, women are eligible for participation if they have stage II or III breast cancer with a tumor 2.5 cm or larger in diameter; cancers are categorized into eight biomarker subtypes on the basis of status with regard to human epidermal growth factor receptor 2 (HER2), hormone receptors, and a 70-gene assay. Patients undergo adaptive randomization within each biomarker subtype to receive regimens that have better performance than the standard therapy. Regimens are evaluated within 10 biomarker signatures (i.e., prospectively defined combinations of biomarker subtypes). Veliparib-carboplatin plus standard therapy was considered for HER2-negative tumors and was therefore evaluated in 3 signatures. The primary end point is pathological complete response. Tumor volume changes measured by magnetic resonance imaging during treatment are used to predict whether a patient will have a pathological complete response. Regimens move on from phase 2 if and when they have a high Bayesian predictive probability of success in a subsequent phase 3 neoadjuvant trial within the biomarker signature in which they performed well. RESULTS: With regard to triple-negative breast cancer, veliparib-carboplatin had an 88% predicted probability of success in a phase 3 trial. A total of 72 patients were randomly assigned to receive veliparib-carboplatin, and 44 patients were concurrently assigned to receive control therapy; at the completion of chemotherapy, the estimated rates of pathological complete response in the triple-negative population were 51% (95% Bayesian probability interval [PI], 36 to 66%) in the veliparib-carboplatin group versus 26% (95% PI, 9 to 43%) in the control group. The toxicity of veliparib-carboplatin was greater than that of the control. CONCLUSIONS: The process used in our trial showed that veliparib-carboplatin added to standard therapy resulted in higher rates of pathological complete response than standard therapy alone specifically in triple-negative breast cancer. (Funded by the QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.).

Sahn, D. J. (2016). Meet our editorial board member. *Current Medical Imaging Reviews*, *12*(3), 157-158.

Sakai, L. Y., Keene, D. R., Renard, M., & De Backer, J. (2016). FBN1: The disease-causing gene for marfan syndrome and other genetic disorders. *Gene*,

FBN1 encodes the gene for fibrillin-1, a structural macromolecule that polymerizes into microfibrils. Fibrillin microfibrils are morphologically distinctive fibrils, present in all connective tissues and assembled into tissue-specific architectural frameworks. FBN1 is the causative gene for Marfan syndrome, an inherited disorder of connective tissue whose major features include tall stature and arachnodactyly, ectopia lentis, and thoracic aortic aneurysm and dissection. More than one thousand individual mutations in FBN1 are associated with Marfan syndrome, making genotype-phenotype correlations difficult. Moreover, mutations in specific regions of FBN1 can result in the opposite features of short stature and brachydactyly characteristic of Weill-Marchesani syndrome and other acromelic dysplasias. How can mutations in one molecule result in disparate clinical syndromes? Current concepts of the fibrillinopathies require an appreciation of tissue-specific fibrillin microfibril microenvironments and the collaborative relationship between the structures of fibrillin microfibril networks and biological functions such as regulation of growth factor signaling.

Sakata, K. K., Stephenson, L. S., Mulanax, A., Bierman, J., Mcgrath, K., Scholl, G., et al. (2016). Professional and interprofessional differences in electronic health records use and recognition of safety issues in critically ill patients. *Journal of Interprofessional Care*, , 1-7.

During interprofessional intensive care unit (ICU) rounds each member of the interprofessional team is responsible for gathering and interpreting information from the electronic health records (EHR) to facilitate effective team decision-making. This study was conducted to determine how each professional group reviews EHR data in preparation for rounds and their ability to identify patient safety issues. Twenty-five physicians, 29 nurses, and 20 pharmacists participated. Individual participants were given verbal and written sign-out and then asked to review a simulated record in our institution's EHR, which contained 14 patient safety items. After reviewing the chart, subjects presented the patient and the number of safety items recognised was recorded. About 40%, 30%, and 26% of safety issues were recognised by physicians, nurses, and pharmacists, respectively ($p = 0.0006$) and no item recognised 100% of the time. There was little overlap between the three groups with only 50% of items predicted to be

recognised 100% of the time by the team. Differential recognition was associated with marked differences in EHR use, with only 3/152 EHR screens utilised by all three groups and the majority of screens used exclusively only by one group. There were significant and non-overlapping differences in individual profession recognition of patient safety issues in the EHR. Preferential identification of safety issues by certain professional groups may be attributed to differences in EHR use. Future studies will be needed to determine if shared decision-making during rounds can improve recognition of safety issues.

Samuels, M. H., Kolobova, I., Smeraglio, A., Niederhausen, M., Janowsky, J. S., & Schuff, K. G. (2016). Effect of thyroid function variations within the laboratory reference range on health status, mood, and cognition in levothyroxine-treated subjects. *Thyroid : Official Journal of the American Thyroid Association*,

BACKGROUND: There has been recent debate within the thyroid field regarding whether current upper limits of the thyrotropin (TSH) reference range should be lowered. This debate can be better informed by investigation of whether variations in thyroid function within the reference range have clinical effects. One important target organ for thyroid hormone is the brain, but little is known about variations in neurocognitive measures within the reference range for thyroid function. METHODS: This was a cross-sectional study of 132 otherwise healthy hypothyroid subjects receiving chronic replacement therapy with levothyroxine (LT4) who had TSH levels across the full span of the laboratory reference range (0.34-5.6 mU/L). Subjects underwent detailed tests of health status, mood, and cognitive function, with an emphasis on memory and executive functions. RESULTS: Subjects with low-normal (2.5 mU/L) TSH levels did not differ on most tests of health status, mood, or cognitive function, and there were no correlations between TSH, free T4, or free T3 levels and most outcomes. There was, however, a suggestion that thyroid function affected performance on the Iowa Gambling Task, which mimics real life decision-making. Subjects with low-normal TSH levels made more advantageous decisions than those with high-normal TSH levels. CONCLUSIONS: Variations in thyroid function within the laboratory reference range do not appear to have clinically relevant effects on health status, mood, or memory in LT4 treated subjects. However, decision making, which encompasses many

executive functions, may be affected. Unless further studies strengthen this finding, these data do not support narrowing the TSH reference range.

Sasaki, T., Hanisch, F. G., Deutzmann, R., Sakai, L. Y., Sakuma, T., Miyamoto, T., et al. (2016). Functional consequence of fibulin-4 missense mutations associated with vascular and skeletal abnormalities and cutis laxa. *Matrix Biology : Journal of the International Society for Matrix Biology*,

Fibulin-4 is a 60kDa calcium binding glycoprotein that has an important role in development and integrity of extracellular matrices. It interacts with elastin, fibrillin-1 and collagen IV as well as with lysyl oxidases and is involved in elastogenesis and cross-link formation. To date, several mutations in the fibulin-4 gene (FBLN4/EFEMP2) are known in patients whose major symptoms are vascular deformities, aneurysm, cutis laxa, joint laxity, or arachnodactyly. The pathogenetic mechanisms how these mutations translate into the clinical phenotype are, however, poorly understood. In order to elucidate these mechanisms, we expressed fibulin-4 mutants recombinantly in HEK293 cells, purified the proteins in native forms and analyzed alterations in protein synthesis, secretion, matrix assembly, and interaction with other proteins in relation to wild type fibulin-4. Our studies show that different mutations affect these properties in multiple ways, resulting in fibulin-4 deficiency and/or impaired ability to form elastic fibers. The substitutions E126K and C267Y impaired secretion of the protein, but not mRNA synthesis. Furthermore, the E126K mutant showed less resistance to proteases, reduced binding to collagen IV and fibrillin-1, as well as to LTBP1s and LTBP4s. The A397T mutation introduced an extra O-glycosylation site and deleted binding to LTBP1s. We show that fibulin-4 binds stronger than fibulin-3 and -5 to LTBP1s, 3, and 4s, and to the lysyl oxidases LOX and LOXL1; the binding of fibulin-4 to the LOX propeptide was strongly reduced by the mutation E57K. These findings show that different mutations in the fibulin-4 gene result in different molecular defects affecting secretion rates, protein stability, LOX-induced cross-linking, or binding to other ECM components and molecules of the TGF-beta pathway, and thus illustrate the complex role of fibulin-4 in connective tissue assembly.

Scherber, R. M., Kosiorek, H. E., Senyak, Z., Dueck, A. C., Clark, M. M., Boxer, M. A., et al. (2016). Comprehensively understanding fatigue in patients with myeloproliferative neoplasms. *Cancer*, *122*(3), 477-485.

BACKGROUND: Patients with myeloproliferative neoplasms (MPNs) experience a high persistence, prevalence, and severity of fatigue. There is currently only limited information regarding factors that contribute to fatigue in patients with MPNs. METHODS: A 70-item, Internet-based survey regarding fatigue was developed by MPN investigators and patients/advocates and hosted by the Mayo Clinic Survey Research Center. RESULTS: Fatigue was found to be prevalent and severe among international survey respondents (1788 respondents). Higher body mass index (P 2 on the Patient Health Questionnaire, indicating a high probability of depression. Higher Brief Fatigue Inventory score, Myeloproliferative Neoplasm Total Symptom Score, and individual symptom items were all associated with a higher likelihood of depressive symptoms (P<.0001). CONCLUSIONS: The management of fatigue should be multifactorial, with a comprehensive assessment and treatment plan to address all modifiable fatigue etiologies. Patients with MPNs likely have a higher prevalence of mood disturbances compared with the general population, suggesting the need to assess and intervene in this domain.

Scott, J. R., Deeken, C. R., Martindale, R. G., & Rosen, M. J. (2016). Evaluation of a fully absorbable poly-4-hydroxybutyrate/absorbable barrier composite mesh in a porcine model of ventral hernia repair. *Surgical Endoscopy*,

BACKGROUND: The objective of this study was to evaluate the mechanical and histological properties of a fully absorbable poly-4-hydroxybutyrate/absorbable barrier composite mesh (Phasix ST) compared to partially absorbable (Ventralight ST), fully absorbable (Phasix), and biologically derived (Strattice) meshes in a porcine model of ventral hernia repair. METHODS: Bilateral abdominal surgical defects were created in twenty-four Yucatan pigs, repaired with intraperitoneal (Phasix ST, Ventralight ST) or retromuscular (Phasix, Strattice) mesh, and evaluated at 12 and 24 weeks (n = 6 mesh/group/time point). RESULTS: Prior to implantation, Strattice demonstrated significantly higher (p 0.05). Phasix mesh/repair strength was significantly greater than Strattice ($p < 0.001$) at 12 and 24 weeks, and Ventralight ST mesh/repair strength was significantly greater than Phasix ST mesh ($p < 0.05$) at 24 weeks. At

12 and 24 weeks, Phasix ST and Ventralight ST were associated with mild inflammation and minimal-mild fibrosis/neovascularization, with no significant differences between groups. At both time points, Phasix was associated with minimal-mild inflammation/fibrosis and mild neovascularization. Strattice was associated with minimal inflammation/fibrosis, with minimal neovascularization at 12 weeks, which increased to mild by 24 weeks. Strattice exhibited significantly less neovascularization than Phasix at 12 weeks and significantly greater inflammation at 24 weeks due to remodeling. CONCLUSIONS: Phasix ST demonstrated mechanical and histological properties comparable to partially absorbable (Ventralight ST) and fully resorbable (Phasix) meshes at 12 and 24 weeks in this model. Data also suggest that fully absorbable meshes with longer-term resorption profiles may provide improved mechanical and histological properties compared to biologically derived scaffolds.

Seifer, D. B., Tal, O., Wantman, E., Edul, P., & Baker, V. L. (2016). Prognostic indicators of assisted reproduction technology outcomes of cycles with ultralow serum antimullerian hormone: A multivariate analysis of over 5,000 autologous cycles from the society for assisted reproductive technology clinic outcome reporting system database for 2012-2013. *Fertility and Sterility*, *105*(2), 385-93.e3.

OBJECTIVE: To assess cycle outcomes when antimullerian hormone (AMH) is ultralow (</=0.16 ng/mL) and to determine which parameters contribute to the probability of cycle cancellation and/or outcome. DESIGN: Retrospective analysis. SETTING: Not applicable. PATIENT(S): 5,087 (7.3%) fresh and 243 (1.5%) thawed cycles with ultralow AMH values. INTERVENTION(S): Linear and logistic regression, comparison with age-matched cycles with normal AMH concentrations. MAIN OUTCOME MEASURE(S): Cancellation rate; number of retrieved oocytes, embryos, transferred embryos, and cryopreserved embryos; clinical pregnancy, live-birth, and multiple birth rates. RESULT(S): The total cancellation rate per cycle start for fresh cycles was 54%. Of these, 38.6% of the cycles were canceled before retrieval, and 3.3% of cycles obtained no oocytes at time of retrieval. Of all retrieval attempts, 50.7% had three oocytes or fewer retrieved, and 25.1% had no embryo transfer. The live-birth rates were 9.5% per cycle start. Cycles with ultralow AMH levels compared with age-matched normal AMH cycles demonstrated more than a fivefold greater pre-retrieval cancellation rate, a twofold less live-birth rate per cycle

and a 4.5-fold less embryo cryopreservation rate. CONCLUSION(S): Refusing treatment solely on the basis of ultralow AMH levels is not advisable, but patients should be counseled appropriately about the prognostic factors for cancellation and outcomes.

Shah, V., Bellantone, R. A., & Taft, D. R. (2016). Evaluating the potential for delivery of irinotecan via the buccal route: Physicochemical characterization and in vitro permeation assessment across porcine buccal mucosa. *Aaps Pharmscitech*,

Irinotecan (CPT-11) is used to treat advanced colorectal cancer as an intravenous therapy. Depending on pH, CPT-11 exists in either a lactone (active) or carboxylate (inactive) form, or both. In this investigation, the feasibility for systemic delivery of CPT-11 through the buccal route was evaluated. Permeation of CPT-11 across porcine buccal mucosa was studied in vitro using side-by-side flow through diffusion cells at 37 degrees C. Experiments were performed over a pH range from 4 to 9, and the permeability of both the lactone and carboxylate forms of CPT-11 was measured. CPT-11 steady state flux was determined over a range of donor concentrations at pH 4 (0.5, 1, 5, 10, 15, 20 mg/ml) and pH 6.8 (0.5, 5, 10 mg/ml). Steady state flux increased linearly with increasing donor concentration of CPT-11 at pH 4 (r 2 = 0.9935) and at pH 6.8 (r 2 = 0.9886). CPT-11 permeability was independent of pH, although the distribution coefficient increased with increasing pH. Estimates of permeability for the lactone and carboxylate forms were 4.16 x 10-5 cm/s and 2.6 x 10-5 cm/s, respectively. These calculated permeability values were in agreement with the in vitro experimental data. Overall, CPT-11 was found to permeate through porcine buccal mucosa via passive diffusion. CPT-11 permeability was independent of pH, suggesting that the compound was transported mainly via a paracellular route. Overall, the results of this research suggest that the buccal route is a potential extravascular mode of delivery for CPT-11.

Shayman, C. S., Middaugh, J. L., & Hullar, T. E. (2016). Taste disturbance due to cochlear implant stimulation. *Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology*,

OBJECTIVE: To characterize stimulation of taste fibers in the facial nerve following cochlear implantation. PATIENT: A 34-year old presented with reversible dysgeusia following activation of

a cochlear implant. INTERVENTION: Reprogramming targeted to specific offending electrodes reduced symptom intensity. Computed tomography demonstrated dehiscence of the bone separating the labyrinthine segment of the facial nerve and the basal turn of the cochlea in proximity to the electrode array. RESULTS: Dysgeusia was attributed to stimulation of taste fibers in the facial nerve by electrodes 13 to 16 of the cochlear implant array located in the superior-most portion of the basal turn. CONCLUSIONS: Dysgeusia following cochlear implant activation has not previously been reported. This likely results from stimulation of taste fibers through dehiscence of the bone separating the labyrinthine segment of the Fallopian canal and the basal turn of the cochlea. While in some cases of apparent dehiscence there may be thin bone present, recognition of this potential anatomic feature may influence the choice of which ear and which electrode design to implant.

Sinha, A., Nagel, C. L., Thomas, E., Schmidt, W. P., Torondel, B., Boisson, S., et al. (2016). Assessing latrine use in rural india: A cross-sectional study comparing reported use and passive latrine use monitors. *The American Journal of Tropical Medicine and Hygiene*,

Although large-scale programs, like India's Total Sanitation Campaign (TSC), have improved latrine coverage in rural settings, evidence suggests that actual use is suboptimal. However, the reliability of methods to assess latrine use is uncertain. We assessed the reliability of self-reported use, the standard method, by comparing survey-based responses against passive latrine use monitors (PLUMs) through a cross-sectional study among 292 households in 25 villages in rural Odisha, India, which recently received individual household latrines under the TSC. PLUMs were installed for 2 weeks and householders responded to surveys about their latrine use behavior. Reported use was compared with PLUM results using Bland-Altman (BA) plots and concordance statistics. Reported use was higher than corresponding PLUM-recorded events across the range of comparisons. The mean reported "usual" daily events per household (7.09, 95% confidence interval [CI] = 6.51, 7.68) was nearly twice that of the PLUM-recorded daily average (3.62, 95% CI = 3.29, 3.94). There was poor agreement between "usual" daily latrine use and the average daily PLUM-recorded events (rhoc = 0.331, 95% CI = 0.242, 0.427). Moderate agreement (rhoc = 0.598, 95% CI = 0.497, 0.683) was obtained when comparing daily reported use during the previous 48 hours with the average daily PLUM count. Self-reported

latrine use, though already suggesting suboptimal adoption, likely exaggerates the actual level of uptake of latrines constructed under the program. Where reliance on self-reports is used, survey questions should focus on the 48 hours prior to the date of the survey rather than asking about "usual" latrine use behavior.

Slater, J. K., Braverman, M. T., & Meath, T. (2016). Patient satisfaction with a hospital's arts-enhanced environment as a predictor of the likelihood of recommending the hospital. *Arts and Health*, , 1-14.

Background: A multi-component arts initiative was instituted at a non-metropolitan, five-hospital healthcare system. This study examined whether patients' satisfaction with the hospital arts-enhanced environment was associated with their likelihood to recommend the hospital. Methods: A survey was mailed to a random sample of patients who had been discharged from the five hospitals between 2010 and 2012. Survey items included standard HCAHPS and other questions. Logistic regression was used to identify predictors of patients' likelihood to recommend. Results: Patients' ratings of the hospital's arts environment significantly predicted their likelihood to recommend. Other predictors included demographic variables, provider characteristics, and room conditions. Conclusions: This is one of the first studies to demonstrate that patients' positive experiences with an arts-enhanced hospital environment are statistically predictive of a higher likelihood of recommending the hospital to others. Modest investment to develop an arts-enhanced environment is recommended for boosting HCAHPS scores and maximizing Medicare reimbursement rates.

Slayden, O. D., Lee, D. O., Yao, S., & Jensen, J. T. (2016). Polidocanol induced tubal occlusion in nonhuman primates: Immunohistochemical detection of collagen I-V. *Contraception*,

OBJECTIVE: Intrauterine administration of polidocanol foam (PF) can create fallopian tube occlusion in nonhuman primates (NHPs). The objective of this study was to determine if PF induced tubal obstructions contain collagen in the extracellular matrix. STUDY DESIGN: We compared tissues samples of the intramural fallopian tube obtained from previous studies evaluating the effects of intrauterine infusion of 5% polidocanol foam 2-12weeks after treatment. Serial sections of the intramural portion of the fallopian tube obtained from representative

treated (rhesus macaques n=7; baboon n=11) and untreated control (macaque n=3; baboon n=5) animals were stained with hematoxylin and eosin (H&E) to identify tubal occlusion, and by immunohistochemistry for collagen I (Col-I), Col-III, and Col IV. Descriptive results are summarized. RESULTS: Control animals exhibited histologically normal fallopian tubal epithelium with no staining for Col-1, light staining for Col-III and V in the lamina propria, and Col- IV distributed evenly in the extracellular matrix of the lamina propria. Treatment with PF resulted in acute tissue damage confined to the intramural tube; no epithelial damage or occlusion occurred in the tubal isthmus or ampulla. Blockade of the intramural tube demonstrated fibrosis with the epithelium replaced with extracellular matrix that stained strongly for Col- I, III, IV, and V. Col-II was undetectable. CONCLUSION: Tubal blockage induced by PF resulted in loss of normal epithelium and accumulation of collagen I, III, IV, and V at the site of obstruction. The presence of dense collagen staining supports the hypothesis that PF infusion creates lasting tubal obstructions. IMPLICATIONS: This study demonstrates that polidocanol foam-induced tubal occlusion results in deposition of collagens suggesting the potential for a more lasting blockade. The structural nature of this occlusion supports the development of intrauterine administration of polidocanol foam as a nonsurgical method of permanent contraception.

Smith, T. L., Singh, A., Luong, A., Ow, R. A., Shotts, S. D., Sautter, N. B., et al. (2016). Randomized controlled trial of a bioabsorbable steroid-releasing implant in the frontal sinus opening. *The Laryngoscope*,

OBJECTIVES/HYPOTHESIS: To assess safety and efficacy of a steroid-releasing implant in improving surgical outcomes when placed in the frontal sinus opening (FSO) following endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis (CRS). STUDY DESIGN: Prospective, multicenter, randomized, blinded trial using an intrapatient control design. METHODS: Eighty adult (>/= 18 years) CRS patients who underwent successful bilateral frontal sinusotomy were randomized to receive a steroid-releasing implant in one FSO, whereas the contralateral control side received no implant. All patients received standard postoperative care. Endoscopic evaluations recorded at 30-days postendoscopic sinus surgery (ESS) were graded real time by clinical investigators and by an independent, blinded sinus surgeon to assess the need for postoperative interventions in the FSO. RESULTS: Implants were successfully placed in all 80

frontal sinuses, resulting in 100% implant delivery success. At 30-days post-ESS, steroid-releasing implants provided a statistically significant (P = 0.0070) reduction in the need for postoperative interventions compared to surgery alone by an independent reviewer, representing 38% relative reduction. Clinical investigators reported statistically significant reduction in this measure at 30 days (P < 0.0001) and 90 days (P = 0.0129). Clinical investigators also reported a 55.6% reduction in the need for oral steroid interventions (P = 0.0015), 75% reduction in the need for surgical interventions (P = 0.0225), 16.7% reduction in inflammation score, 54.3% reduction in restenosis rate (P = 0.0002), and 32.2% greater diameter of FSO (P < 0.0001) on treated sides compared to control at 30 days. No implant-related adverse events were reported. CONCLUSION: This study demonstrates the efficacy of steroid-releasing implants in improving outcomes of frontal sinus surgery. LEVEL OF EVIDENCE: 1b. Laryngoscope, 2016.

Smulders, K., Dale, M. L., Carlson-Kuhta, P., Nutt, J. G., & Horak, F. B. (2016). Pharmacological treatment in parkinson's disease: Effects on gait. *Parkinsonism & Related Disorders*,
Gait impairments are a hallmark of Parkinson's disease (PD), both as early symptom and an important cause of disability later in the disease course. Although levodopa has been shown to improve gait speed and step length, the effect of dopamine replacement therapy on other aspects of gait is less well understood. In fact, falls are not reduced and some aspects of postural instability during gait are unresponsive to dopaminergic treatment. Moreover, many medications other than dopaminergic agents, can benefit or impair gait in people with PD. We review the effects of pharmacological interventions used in PD on gait, discriminating, whenever possible, among effects on four components of everyday mobility: straight walking, gait initiation, turning, gait adaptability. Additionally, we summarize the effects on freezing of gait. There is substantial evidence for improvement of spatial characteristics of simple, straight-ahead gait with levodopa and levodopa-enhancing drugs. Recent work suggests that drugs aiming to enhance the acetylcholine system might improve gait stability measures. There is a lack of well-designed studies to evaluate effects on more complex, but highly relevant walking abilities such as turning and making flexible adjustments to gait. Finally, paucity in the literature exists on detrimental effects of drugs used in PD that are known to worsen gait and postural stability in the elderly population.

Snowden, J. M., Rodriguez, M. I., Jackson, S. D., & Marcus, J. L. (2016). Preexposure prophylaxis and patient centeredness: A call for holistically protecting and promoting the health of gay men. *American Journal of Men's Health, 10*(5), 353-358.

Preexposure prophylaxis has transformed HIV prevention, becoming widespread in communities of gay and bisexual men in the developed world in a short time. There is a broad concern that preexposure prophylaxis will discourage condom use among gay men (i.e., "risk compensation"). This commentary argues for broadening the focus on gay men's health beyond sexual health to address the holistic health and well-being of gay men. Gay men may benefit from being offered candid, nonjudgmental health promotion/HIV prevention messages not requiring condom use for anal sex. Lessons can be drawn from the family planning movement, which has undergone a similar shift in focus. The principle of patient centeredness supports such a shift in gay men's health toward the goal of providing men with the knowledge to evaluate various prevention approaches according to the specifics of their life circumstances and health needs. Bringing more nuance to discussions of sexual risk and sexual pleasure could facilitate more universally healthy attitudes regarding sex among gay men, in turn enabling healthier decisions more compatible with men's own values and preferences.

Spencer, D. C., Sun, F. T., Brown, S. N., Jobst, B. C., Fountain, N. B., Wong, V. S., et al. (2016). Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. *Epilepsia,*

OBJECTIVE: Previous studies reporting circadian patterns of epileptiform activity and seizures are limited by (1) short-term recording in an epilepsy monitoring unit (EMU) with altered antiepileptic drugs (AEDs) and sleep, or (2) subjective seizure diary reports. We studied circadian patterns using long-term ambulatory intracranial recordings captured by the NeuroPace RNS System. METHODS: Retrospective study of RNS System trial participants with stable detection parameters over a continuous 84-day period. We analyzed all detections and long device-detected epileptiform events (long episodes) and defined a subset of subjects in whom long episodes represented electrographic seizures (LE-SZ). Spectrum resampling determined the dominant frequency periodicity and cosinor analysis identified significant circadian peaks in detected activity. Chi-square analysis was used to compare subjects grouped by region of seizure onset.

RESULTS: In the 134 subjects, detections showed a strongly circadian and uniform pattern irrespective of region of onset that peaked during normal sleep hours. In contrast, long episodes and LE-SZ patterns varied by region. Neocortical regions had a monophasic, nocturnally dominant rhythm, whereas limbic regions showed a more complex pattern and diurnal peak. Rhythms in some individual limbic subjects were best fit by a dual oscillator (circadian + ultradian) model. SIGNIFICANCE: Epileptiform activity has a strong 24 h periodicity with peak nocturnal occurrence. Limbic and neocortical epilepsy show divergent circadian influences. These findings confirm that circadian patterns of epileptiform activity vary by seizure-onset zone, with implications for treatment and safety, including SUDEP.

Spencer, P. S., Kitara, D. L., Gazda, S. K., & Winkler, A. S. (2016). Nodding syndrome: 2015 international conference report and gulu accord. *Eneurologicalsci*, *3*, 80-83.
Nodding syndrome is a pediatric epileptic encephalopathy of apparent environmental origin that was first described in Tanzania, with recent epidemics in South Sudan and Uganda. Following a brief description of the medical geography, setting and case definition of this progressive brain disorder, we report recent advances relating to etiology, diagnosis and treatment described in papers given at the 2nd International Conference on Nodding Syndrome held in July 2015 in Gulu, Uganda. The target audience for this report includes: anthropologists, entomologists, epileptologists, health care workers, helminthologists, medical researchers, neuroepidemiologists, neurologists, neuroscientists, neuropathologists, nurses, nutritional scientists, primary health care physicians, psychiatrists, public health practitioners, toxicologists, and virologists. © 2016 The Authors

Spindel, E. R., & McEvoy, C. T. (2016). Reply: Why pregnant women should avoid any form of nicotine during pregnancy: An elastin-based perspective. *American Journal of Respiratory and Critical Care Medicine*, *194*(2), 247-248.

Steffens, N. M., Tucholka, J. L., Nabozny, M. J., Schmick, A. E., Brasel, K. J., & Schwarze, M. L. (2016). Engaging patients, health care professionals, and community members to improve preoperative decision making for older adults facing high-risk surgery. *JAMA Surgery*,
Importance: Older patients are at greater risk for postoperative complications, yet they are less

likely than younger patients to ask questions about surgery. Objective: To design an intervention to improve preoperative decision making and manage postoperative expectations. Design, Setting, and Participants: A Patient and Family Advisory Council (PFAC) was created to help identify preoperative decisional needs. The PFAC included 4 men and women who had previous experience with high-risk surgery as older patients or their family members; the PFAC met monthly at a local library from May 2014 to April 2015 to examine findings from a prior qualitative study and to integrate themes with PFAC members' experiences. Patient observations included 91 recorded conversations between patients and surgeons and 61 patient interviews before and after surgery. The PFAC members and other stakeholders evaluated 118 publicly available questions and selected 12 corresponding to identified needs to generate a question prompt list (QPL). Three focus groups, including 31 community members from diverse backgrounds, were conducted at community centers in Madison and Milwaukee, Wisconsin, to refine the QPL. A clinical pilot with 42 patients considering surgery was conducted in one outpatient surgical clinic in Madison. Main Outcomes and Measures: Generation of a QPL to address patients' preoperative informational and decisional needs. Results: Through exploration of qualitative data, the PFAC noted 3 critical problems. Patients and family members believed surgery had to be done, were surprised that postoperative recovery was difficult, and lacked knowledge about the perioperative use of advance directives. The PFAC identified a need for more information and decisional support during preoperative conversations that included clarification of treatment options, setting postoperative expectations, and advance care planning. The following 3 question prompt categories arose: "Should I have surgery?" "What should I expect if everything goes well?" and "What happens if things go wrong?" The final list included 11 questions within these domains, was understandable in English and Spanish, and was acceptable to patients in the clinic. Conclusions and Relevance: Through direct engagement of stakeholders, a QPL was created to address core decisional and informational needs of surgical patients. Future testing will evaluate whether this list can be used to improve patient engagement and reduce postoperative regret and conflict about postoperative treatments.

Stenzel, P., Sauer, D., & Andersen, P. (2016). Ciliated squamous cell carcinoma of the tonsil. *International Journal of Surgical Pathology*,

Stock, R., Hall, J., Chang, A. M., & Cohen, D. (2016). Physicians' early perspectives on oregon's coordinated care organizations. *Healthcare (Amsterdam, Netherlands)*, *4*(2), 92-97.

BACKGROUND: Through development of Coordinated Care Organizations (CCOs), Oregon's version of the Accountable Care Organization (ACO) for Medicaid beneficiaries, Oregon is redesigning the healthcare system delivering care to some of its most vulnerable citizens. While clinicians are central to healthcare transformation, little is known about the impact on their role. The aim of this study was to understand the current and perceived effect CCO-related changes have on Oregon physicians' professional and personal lives. METHODS: This qualitative observational study involved semi-structured interviews, conducted between March and October, 2013, of twenty-two purposively selected physicians who varied in years of practice, gender, employment status, specialty, and geographic location from three different CCOs. A grounded theory approach was used to analyze data. RESULTS: Physicians expressed uncertainty and ambiguity about the CCO model, reporting minor financial changes in the first year, but anticipating future reimbursement changes; new team-based care roles and responsibilities, accountability for quality incentive measures; and effects of CCO implementation on their personal lives. To meet CCO model changes and requirements, physicians requested collegial networking, team-based care training, and data system and information technology support for undergoing health system transformation. CONCLUSIONS: Although perhaps not immediate, healthcare reform can have a real and perceived impact on physicians' professional and personal lives. IMPLICATIONS: Attention to the impact of healthcare reform on physicians' personal and professional lives is important to ensure strategies are implemented to maintain a viable workforce, professional satisfaction, financial sustainability, and quality of care.

Stone, A. L., & Wilson, A. C. (2016). Transmission of risk from parents with chronic pain to offspring: An integrative conceptual model. *Pain*,

Offspring of parents with chronic pain are at increased risk for pain and adverse mental and physical health outcomes (Higgins et al, 2015). Although the association between chronic pain in parents and offspring has been established, few studies have addressed why or how this relation occurs. Identifying mechanisms for the transmission of risk that leads to the development of chronic pain in offspring is important for developing preventive interventions targeted to decrease

risk for chronic pain and related outcomes (eg, disability and internalizing symptoms). This review presents a conceptual model for the intergenerational transmission of chronic pain from parents to offspring with the goal of setting an agenda for future research and the development of preventive interventions. Our proposed model highlights 5 potential mechanisms for the relation between parental chronic pain and pediatric chronic pain and related adverse outcomes: (1) genetics, (2) alterations in early neurobiological development, (3) pain-specific social learning, (4), general parenting and family health, and (5) exposure to stressful environment. In addition, the model presents 3 potential moderators for the relation between parent and child chronic pain: (1) the presence of chronic pain in a second parent, (2) timing, course, and location of parental chronic pain, and (3) offspring's characteristics (ie, sex, developmental stage, race or ethnicity, and temperament). Such a framework highlights chronic pain as inherently familial and intergenerational, opening up avenues for new models of intervention and prevention that can be family centered and include at-risk children.

Stoner, M. C., Calligaro, K. D., Chaer, R. A., Dietzek, A. M., Farber, A., Guzman, R. J., et al. (2016). Reporting standards of the society for vascular surgery for endovascular treatment of chronic lower extremity peripheral artery disease: Executive summary. *Journal of Vascular Surgery*, *64*(1), 227-228.

Recommended reporting standards for lower extremity ischemia were last published by the Society for Vascular Surgery in 1997. Since that time, there has been a proliferation of endovascular therapies for the treatment of chronic peripheral arterial disease. The purpose of this document is to clarify and update these standards, specifically for reports on endovascular treatment. The document is divided into sections: Claudication Reporting, Critical Limb Ischemia Reporting, Preintervention Assessment and Nonanatomic Treatment, Intervention, Outcome Measures - Procedural, Outcome Measures - Disease Specific, and Complications. © Copyright 2016 by the Society for Vascular Surgery. Published by Elsevier Inc.

Stream, G., DeVoe, J. E., Hughes, L. S., & Phillips, R. L.,Jr. (2016). Accelerating momentum toward improved health for patients and populations: Family medicine as a disruptive innovation-A perspective from the keystone IV conference. *Journal of the American Board of Family Medicine :*

JABFM, 29 Suppl 1, S60-3.

This paper was prepared in follow up to the G. Gayle Stephens Keystone IV Conference by authors who attended the conference and are also members of the Family Medicine for America's Health board of directors (FMAHealth.org). It connects the aspirations of the current strategic and communications efforts of FMAHealth with the ideas developed at the conference. The FMAHealth project is sponsored by 8 national family medicine organizations and seeks to build on the work of the original Future of Family Medicine project. Among its objectives are a robust family physician workforce practicing in a continually improving medical home model, supported by a comprehensive payment model sufficient to sustain the medical home and enable the personal physician relationship with patients.

Strong, A. L., Nauta, A. C., & Kuang, A. A. (2015). Local wound care for primary cleft lip repair: Treatment and outcomes with use of topical hydrogen peroxide. *Wounds : A Compendium of Clinical Research and Practice, 27*(12), 319-326.

OBJECTIVES: This study highlights and validates a peroxide-based wound healing strategy for treatment of surgically closed facial wounds in a pediatric population. The authors identified pediatric patients undergoing primary cleft lip repair as a specific population to evaluate the outcomes of such a protocol. Through analysis of defined outcome measures, a reliable and reproducible protocol for postoperative wound care following primary cleft lip repair with favorable results is described. METHODS: This retrospective study analyzes wound healing outcomes in pediatric patients undergoing primary cleft lip repair from 2006 to 2011 at a tertiary academic center. The wound healing protocol was used in both primary unilateral and bilateral repairs. One hundred fortysix patients between the ages of 0 and 4 years underwent primary cleft lip repair and cleft rhinoplasty by a single, fellowship-trained craniofacial surgeon. Postoperatively, wounds were treated with half-strength hydrogen peroxide and bacitracin, as well as scar massage. Incisional dehiscence, hypertrophic scar formation, discoloration, infection, and reoperation were studied. Outcomes were evaluated in light of parent compliance, demographics, preoperative nasoalveolar molding (PNAM), and diagnosis. RESULTS: The authors identified 146 patients for inclusion in this study. There was no wound or incisional dehiscence. One hundred twenty-four patients demonstrated favorable cosmetic outcome. Only 3 (2%) of

patients who developed suboptimal outcomes underwent secondary surgical revision (> 1 year after surgery). Demographic differences were not statistically significant, and PNAM treatment did not influence outcomes. CONCLUSION: These data validate the use of halfstrength hydrogen peroxide and bacitracin as part of a wound healing strategy in pediatric incisional wounds. The use of hydrogen peroxide produced comparable outcomes to previously published studies utilizing other wound healing strategies and, therefore, these study findings support the further use of this regimen for this particular population.

Sullivan, D. R., Mongoue-Tchokote, S., Mori, M., Goy, E., & Ganzini, L. (2016). Randomized, double-blind, placebo controlled study of methylphenidate for the treatment of depression in SSRI-treated cancer patients receiving palliative care. *Psycho-Oncology*,

OBJECTIVE: To determine the effectiveness of methylphenidate for depression treatment in advanced cancer patients. METHODS: An 18-day randomized, double-blind, placebo-controlled clinical trial of methylphenidate for treatment of depression in selective serotonin reuptake inhibitor (SSRI)-treated patients with advanced cancer in hospice or receiving palliative care. The primary outcome was depression remission, defined as a >/=50% reduction in score on the Montgomery-Asberg Depression Rating Scale. RESULTS: Among 47 enrolled participants, 35 were randomized. At study day 18, 85% of the methylphenidate and 60% of the placebo group were in depression remission (p = 0.22). Mean time to depression remission was 10.3 days [standard error (SE) 1.8] in the methylphenidate and 8.1 (SE 1.3) in the placebo group (p = 0.48). The mean baseline score for the Hospital Anxiety and Depression Scale (HADS) was 10.4 in each group and decreased by 3.6 (SE 1.1) in the methylphenidate and 2.3 (SE 1.2) in the placebo group (p = 0.51) by day 18. Once in remission, 1 methylphenidate and 5 placebo participants relapsed to depression (p = 0.18). There was no difference in mortality between the groups during the trial. Trial results were limited by small sample size attributed to difficulties in recruiting terminally ill patients. CONCLUSIONS: This trial failed to demonstrate that methylphenidate treatment in SSRI-treated patients had a significant effect on depression remission in advanced cancer patients. This study underscores the difficulties in conducting trials for symptom management in patients with shortened life expectancy.

Sureshchandra, S., Rais, M., Stull, C., Grant, K., & Messaoudi, I. (2016). Transcriptome profiling reveals disruption of innate immunity in chronic heavy ethanol consuming female rhesus macaques. *PloS One*, *11*(7), e0159295.

It is well established that heavy ethanol consumption interferes with the immune system and inflammatory processes, resulting in increased risk for infectious and chronic diseases. However, these processes have yet to be systematically studied in a dose and sex-dependent manner. In this study, we investigated the impact of chronic heavy ethanol consumption on gene expression using RNA-seq in peripheral blood mononuclear cells isolated from female rhesus macaques with daily consumption of 4% ethanol available 22hr/day for 12 months resulting in average ethanol consumption of 4.3 g/kg/day (considered heavy drinking). Differential gene expression analysis was performed using edgeR and gene enrichment analysis using MetaCore. We identified 1106 differentially expressed genes, meeting the criterion of >/= two-fold change and p-value </= 0.05 in expression (445 up- and 661 down-regulated). Pathway analysis of the 879 genes with characterized identifiers showed that the most enriched gene ontology processes were "response to wounding", "blood coagulation", "immune system process", and "regulation of signaling". Changes in gene expression were seen despite the lack of differences in the frequency of any major immune cell subtype between ethanol and controls, suggesting that heavy ethanol consumption modulates gene expression at the cellular level rather than altering the distribution of peripheral blood mononuclear cells. Collectively, these observations provide mechanisms to explain the higher incidence of infection, delay in wound healing, and increase in cardiovascular disease seen in subjects with Alcohol use disorder.

Teo, A. R., Andrea, S. B., Sakakibara, R., Motohara, S., Matthieu, M. M., & Fetters, M. D. (2016). Brief gatekeeper training for suicide prevention in an ethnic minority population: A controlled intervention. *BMC Psychiatry*, *16*(1), 211-016-0924-4.

BACKGROUND: Suicide is a critical public health problem around the globe. Asian populations are characterized by elevated suicide rates and a tendency to seek social support from family and friends over mental health professionals. Gatekeeper training programs have been developed to train frontline individuals in behaviors that assist at-risk individuals in obtaining mental health treatment. The purpose of this study is to assess the efficacy of a brief, multi-component

gatekeeper intervention in promoting suicide prevention in a high-risk Asian community in the United States. METHODS: We adapted an evidence-based gatekeeper training into a two-hour, multi-modal and interactive event for Japanese-Americans and related stakeholders. Then we evaluated the intervention compared to an attention control using mixed methods. RESULTS: A sample of 106 community members participated in the study. Intervention participants (n = 85) showed significant increases in all three types of intended gatekeeper behavior, all four measures of self-efficacy, and both measures of social norms relevant to suicide prevention, while the control group (n = 48) showed no significant improvements. Additional results showed significantly higher satisfaction and no adverse experiences associated with the gatekeeper training. The separate collection of qualitative data, and integration with the quantitative survey constructs confirmed and expanded understanding about the benefits of the intervention. CONCLUSIONS: A brief, multi-modal gatekeeper training is efficacious in promoting positive gatekeeper behaviors and self-efficacy for suicide prevention in an at-risk ethnic minority population of Japanese Americans.

Thayer, E. K., Rathkey, D., Miller, M. F., Palmer, R., Mejicano, G. C., Pusic, M., et al. (2016). Applying the institutional review board data repository approach to manage ethical considerations in evaluating and studying medical education. *Medical Education Online, 21*, 32021.
ISSUE: Medical educators and educational researchers continue to improve their processes for managing medical student and program evaluation data using sound ethical principles. This is becoming even more important as curricular innovations are occurring across undergraduate and graduate medical education. Dissemination of findings from this work is critical, and peer-reviewed journals often require an institutional review board (IRB) determination. APPROACH: IRB data repositories, originally designed for the longitudinal study of biological specimens, can be applied to medical education research. The benefits of such an approach include obtaining expedited review for multiple related studies within a single IRB application and allowing for more flexibility when conducting complex longitudinal studies involving large datasets from multiple data sources and/or institutions. In this paper, we inform educators and educational researchers on our analysis of the use of the IRB data repository approach to manage ethical considerations as part of best practices for amassing, pooling, and sharing data for educational research,

evaluation, and improvement purposes. IMPLICATIONS: Fostering multi-institutional studies while following sound ethical principles in the study of medical education is needed, and the IRB data repository approach has many benefits, especially for longitudinal assessment of complex multi-site data.

Tilden, E. L., Caughey, A. B., Lee, C. S., & Emeis, C. (2016). The effect of childbirth self-efficacy on perinatal outcomes. *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing, 45*(4), 465-480.

Objective: To synthesize and critique the quantitative literature on measuring childbirth self-efficacy and the effect of childbirth self-efficacy on perinatal outcomes. Data Sources: Eligible studies were identified through searches of MEDLINE, CINAHL, Scopus, and Google Scholar databases. Study Selection: Published research articles that used a tool explicitly intended to measure childbirth self-efficacy and that examined outcomes within the perinatal period were included. All articles were in English and were published in peer-reviewed journals. Data Extraction: First author, country, year of publication, reference and definition of childbirth self-efficacy, measurement of childbirth self-efficacy, sample recruitment and retention, sample characteristics, study design, interventions (with experimental and quasiexperimental studies), and perinatal outcomes were extracted and summarized. Data Synthesis: Of 619 publications, 23 studies published between 1983 and 2015 met inclusion criteria and were critiqued and synthesized in this review. Conclusion: There is overall consistency in how childbirth self-efficacy is defined and measured among studies, which facilitates comparison and synthesis. Our findings suggest that increased childbirth self-efficacy is associated with a wide variety of improved perinatal outcomes. Moreover, there is evidence that childbirth self-efficacy is a psychosocial factor that can be modified through various efficacy-enhancing interventions. Future researchers will be able to build knowledge in this area through (a) use of experimental and quasiexperimental design, (b) recruitment and retention of more diverse samples, (c) explicit reporting of definitions of terms (e.g., high risk), (d) investigation of interventions that increase childbirth self-efficacy during pregnancy, and (e) investigation about how childbirth self-efficacy-enhancing interventions might lead to decreased active labor pain and suffering. Exploratory research should continue to examine the potential association between higher prenatal childbirth

self-efficacy and improved early parenting outcomes. © 2016 AWHONN, the Association of Women's Health, Obstetric and Neonatal Nurses.

Toyoda, K., & Tebo, B. M. (2016). Kinetics of mn(II) oxidation by spores of the marine bacillus sp. SG-1. *Geochimica Et Cosmochimica Acta, 189*, 58-69.

The kinetics of Mn(II) oxidation by spores of the marine Bacillus sp. SG-1 was measured under controlled conditions of the initial Mn(II) concentration, spore concentration, chemical speciation, pH, O2, and temperature. Mn(II) oxidation experiments were performed with spore concentrations ranging from 0.7 to 11 × 109 spores/L, a pH range from 5.8 to 8.1, temperatures between 4 and 58 °C, a range of dissolved oxygen from 2 to 270 μM, and initial Mn(II) concentrations from 1 to 200 μM. The Mn(II) oxidation rates were directly proportional to the spore concentrations over these ranges of concentration. The Mn(II) oxidation rate increased with increasing initial Mn(II) concentration to a critical concentration, as described by the Michaelis-Menten model (Km = ca. 3 μM). Whereas with starting Mn(II) concentrations above the critical concentration, the rate was almost constant in low ionic solution (I = 0.05, 0.08). At high ionic solution (I = 0.53, 0.68), the rate was inversely correlated with Mn(II) concentration. Increase in the Mn(II) oxidation rate with the dissolved oxygen concentration followed the Michaelis-Menten model (Km = 12-19 μM DO) in both a HEPES-buffered commercial drinking (soft) water and in artificial and natural seawater. Overall, our results suggest that the mass transport limitations of Mn(II) ions due to secondary Mn oxide products accumulating on the spores cause a significant decrease of the oxidation rate at higher initial Mn(II) concentration on a spore basis, as well as in more concentrated ionic solutions. The optimum pH for Mn(II) oxidation was approximately 7.0 in low ionic solutions (I = 0.08). The high rates at the alkaline side (pH > 7.5) may suggest a contribution by heterogeneous reactions on manganese bio-oxides. The effect of temperature on the Mn(II) oxidation rate was studied in three solutions (500 mM NaCl, ASW, NSW solutions). Thermal denaturation occurred at 58 °C and spore germination was evident at 40 °C in all three solutions. The activation energies calculated from the Arrhenius plots are consistent with the observation that Ca ions stimulate the Mn(II) oxidation rate. © 2016 Elsevier Ltd.

Trovato, M., Maurano, F., D'Apice, L., Costa, V., Sartorius, R., Cuccaro, F., et al. (2016). E2 multimeric scaffold for vaccine formulation: Immune response by intranasal delivery and transcriptome profile of E2-pulsed dendritic cells. *BMC Microbiology*, *16*(1), 152-016-0772-x. BACKGROUND: The E2 multimeric scaffold represents a powerful delivery system able to elicit robust humoral and cellular immune responses upon systemic administrations. Here recombinant E2 scaffold displaying the third variable loop of HIV-1 Envelope gp120 glycoprotein was administered via mucosa, and the mucosal and systemic immune responses were analysed. To gain further insights into the molecular mechanisms that orchestrate the immune response upon E2 vaccination, we analysed the transcriptome profile of dendritic cells (DCs) exposed to the E2 scaffold with the aim to define a specific gene expression signature for E2-primed immune responses. RESULTS: The in vivo immunogenicity and the potential of E2 scaffold as a mucosal vaccine candidate were investigated in BALB/c mice vaccinated via the intranasal route. Fecal and systemic antigen-specific IgA antibodies, cytokine-producing CD4(+) and CD8(+) cells were induced assessing the immunogenicity of E2 particles via intranasal administration. The cytokine analysis identified a mixed T-helper cell response, while the systemic antibody response showed a prevalence of IgG1 isotype indicative of a polarized Th2-type immune response. RNA-Sequencing analysis revealed that E2 scaffold up-regulates in DCs transcriptional regulators of the Th2-polarizing cell response, defining a type 2 DC transcriptomic signature. CONCLUSIONS: The current study provides experimental evidence to the possible application of E2 scaffold as antigen delivery system for mucosal immunization and taking advantages of genome-wide approach dissects the type of response induced by E2 particles.

Troxell, M. L., & Higgins, J. P. (2016). Renal cell carcinoma in kidney allografts: Histologic types, including biphasic papillary carcinoma. *Human Pathology*,
Kidney transplant recipients are at increased risk of malignancy, with about 5% incidence of cancer in native end-stage kidneys. Carcinoma in the renal allograft is far less common. Prior studies have demonstrated a propensity for renal cell carcinomas of papillary subtypes in end stage kidneys, and perhaps in allograft kidneys, but most allograft studies lack detailed pathologic review and predate the current classification system. We reviewed our experience with renal carcinoma in kidney allografts at 2 academic centers applying the ISUP classification,

informed by immunohistochemistry. The incidence of renal allograft carcinoma was about 0.26% in our population. Of 12 allograft carcinomas, 6 were papillary (50%), 4 clear cell (33%) and one each clear cell (tubulo) papillary and chromophobe. Two of the papillary carcinomas had distinctive biphasic glomeruloid architecture matching the newly named "Biphasic Squamoid Alveolar" pattern and were difficult to classify on core biopsies. The two cell types had different immunophenotypes in our hands (eosinophilic cells: RCC-/CK HMW+/cyclin D1+; clear cells: RCC+/CK HMW negative to weak/cyclin D1-). None of the patients experienced cancer recurrences or metastasis. Our study confirms the predilection for papillary renal cell carcinomas in kidney allografts, and highlights the occurrence of rare morphologic variants. Larger studies are needed with careful pathologic review, which has been lacking in the literature.

Tshala-Katumbay, D. D., Ngombe, N. N., Okitundu, D., David, L., Westaway, S. K., Boivin, M. J., et al. (2016). Cyanide and the human brain: Perspectives from a model of food (cassava) poisoning. *Annals of the New York Academy of Sciences*,

Threats by fundamentalist leaders to use chemical weapons have resulted in renewed interest in cyanide toxicity. Relevant insights may be gained from studies on cyanide mass intoxication in populations relying on cyanogenic cassava as the main source of food. In these populations, sublethal concentrations (up to 80 mumol/l) of cyanide in the blood are commonplace and lead to signs of acute toxicity. Long-term toxicity signs include a distinct and irreversible spastic paralysis, known as konzo, and cognition deficits, mainly in sequential processing (visual-spatial analysis) domains. Toxic culprits include cyanide (mitochondrial toxicant), thiocyanate (AMPA-receptor chaotropic cyanide metabolite), cyanate (protein-carbamoylating cyanide metabolite), and 2-iminothiazolidine-4-carboxylic acid (seizure inducer). Factors of susceptibility include younger age, female gender, protein-deficient diet, and, possibly, the gut functional metagenome. The existence of uniquely exposed and neurologically affected populations offers invaluable research opportunities to develop a comprehensive understanding of cyanide toxicity and test or validate point-of-care diagnostic tools and treatment options to be included in preparedness kits in response to cyanide-related threats.

Tukey, M. H., Clark, J. A., Bolton, R., Kelley, M. J., Slatore, C. G., Au, D. H., et al. (2016). Readiness for implementation of lung cancer screening: A national survey of VA pulmonologists. *Annals of the American Thoracic Society*,

RATIONALE: To mitigate the potential harms of screening, professional societies recommend that lung cancer screening be conducted in multidisciplinary programs with the capacity to provide comprehensive care from screening through pulmonary nodule evaluation to treatment of screen-detected cancers. The degree to which this standard can be met at the national level is unknown. OBJECTIVES: To assess the readiness of clinical facilities in a national healthcare system for implementation of comprehensive lung cancer screening programs, as compared to the ideal described in policy recommendations. METHODS: Cross-sectional, self-administered survey of staff pulmonologists in pulmonary outpatient clinics in Veterans Health Administration (VA) facilities. MEASUREMENTS AND MAIN RESULTS: The facility-level response rate was 84.1% (106 of 126 facilities with pulmonary clinics). 88.7% of facilities showed favorable provider perceptions of the evidence for lung cancer screening and 73.6% of facilities had favorable provider-perceived local context for screening implementation. All elements of the policy-recommended infrastructure for comprehensive screening programs were present in 36 of 106 (34.0%) facilities; the most common deficiencies were on-site PET scanners or radiation oncology services. Overall, 26.5% of VA facilities were ideally prepared for lung cancer screening implementation (44.1% if the policy recommendations for on-site PET scanners and radiation oncology services were waived). CONCLUSIONS: Many facilities may be less than ideally positioned for implementation of comprehensive lung cancer screening programs. To ensure safe, effective screening, hospitals may need to invest resources or coordinate care with facilities that can offer comprehensive care for screening through downstream evaluation and treatment of screen-detected cancers.

Usher, C. (2016). Here/In this issue and There/Abstract thinking: Drawing from different disciplines. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(7), 533-534.

Vaaga, C. E., & Westbrook, G. L. (2016). Parallel processing of afferent olfactory sensory information. *The Journal of Physiology*,

KEY POINTS: The functional synaptic connectivity between olfactory receptor neurons and principal cells within the olfactory bulb is not well understood. One view suggests that mitral cells, the primary output neuron of the olfactory bulb, are solely activated by feedforward excitation. Using focal, single glomerular stimulation, we demonstrate that mitral cells receive direct, monosynaptic input from olfactory receptor neurons. Compared to external tufted cells, mitral cells have a prolonged afferent-evoked EPSC, which serves to amplify the synaptic input. The properties of presynaptic glutamate release from olfactory receptor neurons are similar between mitral and external tufted cells. Our data suggest that afferent input enters the olfactory bulb in a parallel fashion. ABSTRACT: Primary olfactory receptor neurons terminate in anatomically and functionally discrete cortical modules known as olfactory bulb glomeruli. The synaptic connectivity and postsynaptic responses of mitral and external tufted cells within the glomerulus may involve both direct and indirect components. For example, it has been suggested that sensory input to mitral cells is indirect through feedforward excitation from external tufted cells. We also observed feedforward excitation of mitral cells with weak stimulation of the olfactory nerve layer; however, focal stimulation of an axon bundle entering an individual glomerulus revealed that mitral cells receive monosynaptic afferent inputs. Although external tufted cells had a 4.1-fold larger peak EPSC amplitude, integration of the evoked currents showed that the synaptic charge was 5-fold larger in mitral cells, reflecting the prolonged response in mitral cells. Presynaptic afferents onto mitral and external tufted cells had similar quantal amplitude and release probability, suggesting that the larger peak EPSC in external tufted cells was the result of more synaptic contacts. The results of the present study indicate that the monosynaptic afferent input to mitral cells depends on the strength of odorant stimulation. The enhanced spiking that we observed in response to brief afferent input provides a mechanism for amplifying sensory information and contrasts with the transient response in external tufted cells. These parallel input paths may have discrete functions in processing olfactory sensory input.

Van Voorhis, W. C., Adams, J. H., Adelfio, R., Ahyong, V., Akabas, M. H., Alano, P., et al. (2016). Open source drug discovery with the malaria box compound collection for neglected diseases and beyond. *PLoS Pathogens, 12*(7), e1005763.

A major cause of the paucity of new starting points for drug discovery is the lack of interaction

between academia and industry. Much of the global resource in biology is present in universities, whereas the focus of medicinal chemistry is still largely within industry. Open source drug discovery, with sharing of information, is clearly a first step towards overcoming this gap. But the interface could especially be bridged through a scale-up of open sharing of physical compounds, which would accelerate the finding of new starting points for drug discovery. The Medicines for Malaria Venture Malaria Box is a collection of over 400 compounds representing families of structures identified in phenotypic screens of pharmaceutical and academic libraries against the Plasmodium falciparum malaria parasite. The set has now been distributed to almost 200 research groups globally in the last two years, with the only stipulation that information from the screens is deposited in the public domain. This paper reports for the first time on 236 screens that have been carried out against the Malaria Box and compares these results with 55 assays that were previously published, in a format that allows a meta-analysis of the combined dataset. The combined biochemical and cellular assays presented here suggest mechanisms of action for 135 (34%) of the compounds active in killing multiple life-cycle stages of the malaria parasite, including asexual blood, liver, gametocyte, gametes and insect ookinete stages. In addition, many compounds demonstrated activity against other pathogens, showing hits in assays with 16 protozoa, 7 helminths, 9 bacterial and mycobacterial species, the dengue fever mosquito vector, and the NCI60 human cancer cell line panel of 60 human tumor cell lines. Toxicological, pharmacokinetic and metabolic properties were collected on all the compounds, assisting in the selection of the most promising candidates for murine proof-of-concept experiments and medicinal chemistry programs. The data for all of these assays are presented and analyzed to show how outstanding leads for many indications can be selected. These results reveal the immense potential for translating the dispersed expertise in biological assays involving human pathogens into drug discovery starting points, by providing open access to new families of molecules, and emphasize how a small additional investment made to help acquire and distribute compounds, and sharing the data, can catalyze drug discovery for dozens of different indications. Another lesson is that when multiple screens from different groups are run on the same library, results can be integrated quickly to select the most valuable starting points for subsequent medicinal chemistry efforts.

Ventral Hernia Outcome Collaborative, Mitchell, T. O., Holihan, J. L., Askenasy, E. P., Greenberg, J. A., Keith, J. N., et al. (2016). Do risk calculators accurately predict surgical site occurrences? *The Journal of Surgical Research, 203*(1), 56-63.

INTRODUCTION: Current risk assessment models for surgical site occurrence (SSO) and surgical site infection (SSI) after open ventral hernia repair (VHR) have limited external validation. Our aim was to determine (1) whether existing models stratify patients into groups by risk and (2) which model best predicts the rate of SSO and SSI. METHODS: Patients who underwent open VHR and were followed for at least 1 mo were included. Using two data sets-a retrospective multicenter database (Ventral Hernia Outcomes Collaborative) and a single-center prospective database (Prospective)-each patient was assigned a predicted risk with each of the following models: Ventral Hernia Risk Score (VHRS), Ventral Hernia Working Group (VHWG), Centers for Disease Control and Prevention Wound Class, and Hernia Wound Risk Assessment Tool (HW-RAT). Patients in the Prospective database were also assigned a predicted risk from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). Areas under the receiver operating characteristic curve (area under the curve [AUC]) were compared to assess the predictive accuracy of the models for SSO and SSI. Pearson's chi-square was used to determine which models were able to risk-stratify patients into groups with significantly differing rates of actual SSO and SSI. RESULTS: The Ventral Hernia Outcomes Collaborative database (n = 795) had an overall SSO and SSI rate of 23% and 17%, respectively. The AUCs were low for SSO (0.56, 0.54, 0.52, and 0.60) and SSI (0.55, 0.53, 0.50, and 0.58). The VHRS (P = 0.01) and HW-RAT (P < 0.01) significantly stratified patients into tiers for SSO, whereas the VHWG (P < 0.05) and HW-RAT (P < 0.05) stratified for SSI. In the Prospective database (n = 88), 14% and 8% developed an SSO and SSI, respectively. The AUCs were low for SSO (0.63, 0.54, 0.50, 0.57, and 0.69) and modest for SSI (0.81, 0.64, 0.55, 0.62, and 0.73). The ACS-NSQIP (P < 0.01) stratified for SSO, whereas the VHRS (P < 0.01) and ACS-NSQIP (P < 0.05) stratified for SSI. In both databases, VHRS, VHWG, and Centers for Disease Control and Prevention overestimated risk of SSO and SSI, whereas HW-RAT and ACS-NSQIP underestimated risk for all groups. CONCLUSIONS: All five existing predictive models have limited ability to risk-stratify patients and accurately assess risk of SSO. However, both the VHRS and ACS-NSQIP demonstrate modest success in identifying patients at risk for SSI. Continued model refinement is needed to improve

the two highest performing models (VHRS and ACS-NSQIP) along with investigation to determine whether modifications to perioperative management based on risk stratification can improve outcomes.

Villasana, L. E., Weber, S., Akinyeke, T., & Raber, J. (2016). Genotype differences in anxiety and fear learning and memory of WT and ApoE4 mice associated with enhanced generation of hippocampal reactive oxygen species. *Journal of Neurochemistry*,

Apolipoprotein E (apoE), involved in cholesterol and lipid metabolism, also influences cognitive function and injury repair. In humans, apoE is expressed in three isoforms. E4 is a risk factor for age-related cognitive decline and Alzheimer's disease, particularly in women. E4 might also be a risk factor for developing behavioral and cognitive changes following 56 Fe irradiation, a component of the space environment astronauts are exposed to during missions. These changes might be related to enhanced generation of reactive oxygen species (ROS). In this study, we compared the behavioral and cognitive performance of sham-irradiated and irradiated wild-type (WT) mice and mice expressing the human E3 or E4 isoforms, and assessed the generation of ROS in hippocampal slices from these mice. E4 mice had greater anxiety-like and conditioned fear behaviors than WT mice, and these genotype differences were associated with greater levels of ROS in E4 than WT mice. The greater generation of ROS in the hippocampus of E4 than WT mice might contribute to their higher anxiety levels and enhanced fear conditioning. In E4, but not wild-type, mice, PMA-treated hippocampal slices showed more DHE oxidation in sham-irradiated than irradiated mice and hippocampal HO-1 levels were higher in irradiated than sham-irradiated E4 mice. This article is protected by copyright. All rights reserved.

Volpicelli-Daley, L. A., Abdelmotilib, H., Liu, Z., Stoyka, L., Daher, J. P., Milnerwood, A. J., et al. (2016). G2019S-LRRK2 expression augments alpha-synuclein sequestration into inclusions in neurons. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *36*(28), 7415-7427.

Pathologic inclusions define alpha-synucleinopathies that include Parkinson's disease (PD). The most common genetic cause of PD is the G2019S LRRK2 mutation that upregulates LRRK2 kinase activity. However, the interaction between alpha-synuclein, LRRK2, and the formation of alpha-

synuclein inclusions remains unclear. Here, we show that G2019S-LRRK2 expression, in both cultured neurons and dopaminergic neurons in the rat substantia nigra pars compact, increases the recruitment of endogenous alpha-synuclein into inclusions in response to alpha-synuclein fibril exposure. This results from the expression of mutant G2019S-LRRK2, as overexpression of WT-LRRK2 not only does not increase formation of inclusions but reduces their abundance. In addition, treatment of primary mouse neurons with LRRK2 kinase inhibitors, PF-06447475 and MLi-2, blocks G2019S-LRRK2 effects, suggesting that the G2019S-LRRK2 potentiation of inclusion formation depends on its kinase activity. Overexpression of G2019S-LRRK2 slightly increases, whereas WT-LRRK2 decreases, total levels of alpha-synuclein. Knockdown of total alpha-synuclein with potent antisense oligonucleotides substantially reduces inclusion formation in G2019S-LRRK2-expressing neurons, suggesting that LRRK2 influences alpha-synuclein inclusion formation by altering alpha-synuclein levels. These findings support the hypothesis that G2019S-LRRK2 may increase the progression of pathological alpha-synuclein inclusions after the initial formation of alpha-synuclein pathology by increasing a pool of alpha-synuclein that is more susceptible to forming inclusions. SIGNIFICANCE STATEMENT: alpha-Synuclein inclusions are found in the brains of patients with many different neurodegenerative diseases. Point mutation, duplication, or triplication of the alpha-synuclein gene can all cause Parkinson's disease (PD). The G2019S mutation in LRRK2 is the most common known genetic cause of PD. The interaction between G2019S-LRRK2 and alpha-synuclein may uncover new mechanisms and targets for neuroprotection. Here, we show that expression of G2019S-LRRK2 increases alpha-synuclein mobility and enhances aggregation of alpha-synuclein in primary cultured neurons and in dopaminergic neurons of the substantia nigra pars compacta, a susceptible brain region in PD. Potent LRRK2 kinase inhibitors, which are being developed for clinical use, block the increased alpha-synuclein aggregation in G2019S-LRRK2-expressing neurons. These results demonstrate that alpha-synuclein inclusion formation in neurons can be blocked and that novel therapeutic compounds targeting this process by inhibiting LRRK2 kinase activity may slow progression of PD-associated pathology.

Vranas, K. C., & Kerlin, M. P. (2016). ICU physician workflow: Inside the balloon. *Critical Care Medicine*, *44*(8), 1607-1608.

Waddell, E. N., Sacks, R., Farley, S. M., & Johns, M. (2016). Point-of-sale tobacco marketing to youth in new york state. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*,

PURPOSE: To assess youth exposure to menthol versus nonmenthol cigarette advertising, we examined whether menthol cigarette promotions are more likely in neighborhoods with relatively high youth populations. METHODS: We linked 2011 New York State Retail Advertising Tobacco Survey observational data with U.S. Census and American Community Survey demographic data. Multivariable models assessed the relationship between neighborhood youth population and point-of-sale cigarette promotions for three brands of cigarettes, adjusting for neighborhood demographic characteristics including race/ethnicity and poverty. RESULTS: Menthol cigarette point-of-sale marketing was more likely in neighborhoods with higher proportions of youth, adjusting for presence of nonmenthol brand marketing, neighborhood race/ethnicity, neighborhood poverty, and urban geography. CONCLUSIONS: Data from the 2011 Retail Advertising Tobacco Study linked to block level census data clearly indicate that price reduction promotions for menthol cigarettes are disproportionately targeted to youth markets in New York State.

Waqar, S. N., Bonomi, P. D., Govindan, R., Hirsch, F. R., Riely, G. J., Papadimitrakopoulou, V., et al. (2016). Clinician perspectives on current issues in lung cancer drug development. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*,

Recent advances in molecularly targeted therapy and immunotherapy offer a glimmer of hope for potentially realizing the dream of personalized therapy for lung cancer. This article highlights current questions in clinical trial design, enrollment strategies and patient focused drug development, with particular emphasis on unique issues in trials of targeted therapy and immunotherapy.

Warren, J. B., & Wiggins, N. (2016). Shared decision making in neonatal quality improvement. *The Journal of Perinatal & Neonatal Nursing*, *30*(3), 237-239.

Since the Institute of Medicine published Crossing the Quality Chasm in 2001, healthcare systems

have become more focused on improving the quality of healthcare delivery. At Oregon Health & Science University and Doernbecher Children's Hospital, we recognize the need to take an interprofessional, team-based approach to improving the care we provide to our current and future patients. We describe here an ongoing quality improvement project in the Doernbecher Neonatal Intensive Care Unit (NICU), with specific attention to the factors we believe have contributed to the implementation and early success of the project. These factors include the history of quality improvement work in our NICU and in the field of neonatology, the "dyad leadership" structure under which we operate in our NICU, and our developing understanding of the concept of "team intelligence." These elements have led to the formation of a team that can practice shared decision making and work as one to realize a shared goal.

Warren, M. (2016). Abdominal massage may decrease gastric residual volumes and abdominal circumference in critically ill patients. *Evidence-Based Nursing, 19*(3), 76.

Warren, R. L., Ramamoorthy, S., Ciganovic, N., Zhang, Y., Wilson, T. M., Petrie, T., et al. (2016). Minimal basilar membrane motion in low-frequency hearing. *Proceedings of the National Academy of Sciences of the United States of America, 113*(30), E4304-10.

Low-frequency hearing is critically important for speech and music perception, but no mechanical measurements have previously been available from inner ears with intact low-frequency parts. These regions of the cochlea may function in ways different from the extensively studied high-frequency regions, where the sensory outer hair cells produce force that greatly increases the sound-evoked vibrations of the basilar membrane. We used laser interferometry in vitro and optical coherence tomography in vivo to study the low-frequency part of the guinea pig cochlea, and found that sound stimulation caused motion of a minimal portion of the basilar membrane. Outside the region of peak movement, an exponential decline in motion amplitude occurred across the basilar membrane. The moving region had different dependence on stimulus frequency than the vibrations measured near the mechanosensitive stereocilia. This behavior differs substantially from the behavior found in the extensively studied high-frequency regions of the cochlea.

Watson, J. J., Pati, S., & Schreiber, M. A. (2016). Plasma transfusion: History, current realities and novel improvements. *Shock (Augusta, Ga.)*,

Traumatic hemorrhage is the leading cause of preventable death after trauma. Early transfusion of plasma and balanced transfusion have been shown to optimize survival, mitigate the acute coagulopathy of trauma and restore the endothelial glycocalyx. There are a myriad of plasma formulations available worldwide including: fresh frozen plasma, thawed plasma, liquid plasma, plasma frozen within 24 hours and lyophilized plasma. Significant equipoise exists in the literature regarding the optimal plasma formulation. Lyophilized plasma is a freeze dried formulation that was originally developed in the 1930's and used by the American and British military in WW II. It was subsequently discontinued due to risk of disease transmission from pooled donors. Recently there has been significant research focusing on optimizing reconstitution of lyophilized plasma. Findings show sterile water buffered with ascorbic acid results in decreased blood loss with suppression of systemic inflammation. We are now beginning to realize the creation of a plasma-derived formulation that rapidly produces the associated benefits without logistical or safety constraints. This review will highlight the history of plasma, detail the various types of plasma formulations currently available, their pathophysiological effects and impacts of storage on coagulation factors in vitro and in vivo, novel concepts and future directions.

Wei, D., Osman, C., Dukhovny, D., Romley, J., Hall, M., Chin, S., et al. (2016). Cost consciousness among physicians in the neonatal intensive care unit. *Journal of Perinatology : Official Journal of the California Perinatal Association*,

OBJECTIVE: The objectives of this study were (1) to describe the prevalence and correlates of cost consciousness among physician providers in neonatology and (2) to describe knowledge of cost of common medications, laboratory/imaging evaluations, hospitalization costs and reimbursements. STUDY DESIGN: A 54-item survey was administered to members of the Section on Neonatal-Perinatal Medicine of the American Academy of Pediatrics. RESULTS: Of the 602 participants, 37% reported cost consciousness in decision making. Adjusting for years in practice, gender, training level, type of practice setting and region of practice, formalized education about costs was associated with increased cost consciousness in practice (adjusted odds ratio (AOR): 3.4; 95% confidence interval (CI): 1.2 to 9.8). Working in a private practice setting was also

associated with increased cost consciousness when ordering laboratory (AOR: 3.0; (95% CI: 1.2 to 7.6)) or imaging tests (AOR: 2.0; 95% CI: 1.0 to 4.8). CONCLUSIONS: We found variation in knowledge of cost. Formal education about costs and working in a private practice setting were associated with increased cost consciousness.Journal of Perinatology advance online publication, 28 July 2016; doi:10.1038/jp.2016.117.

Winett, L., Wallack, L., Richardson, D., Boone-Heinonen, J., & Messer, L. (2016). A framework to address challenges in communicating the developmental origins of health and disease. *Current Environmental Health Reports, 3*(3), 169-177.

Findings from the field of Developmental Origins of Health and Disease (DOHaD) suggest that some of the most pressing public health problems facing communities today may begin much earlier than previously understood. In particular, this body of work provides evidence that social, physical, chemical, environmental, and behavioral influences in early life play a significant role in establishing vulnerabilities for chronic disease later in life. Further, because this work points to the importance of adverse environmental exposures that cluster in population groups, it suggests that existing opportunities to intervene at a population level may need to refocus their efforts "upstream" to sufficiently combat the fundamental causes of disease. To translate these findings into improved public health, however, the distance between scientific discovery and population application will need to be bridged by conversations across a breadth of disciplines and social roles. And importantly, those involved will likely begin without a shared vocabulary or conceptual starting point. The purpose of this paper is to support and inform the translation of DOHaD findings from the bench to population-level health promotion and disease prevention, by: (1) discussing the unique communication challenges inherent to translation of DOHaD for broad audiences, (2) introducing the First-hit/Second-hit Framework with an epidemiologic planning matrix as a model for conceptualizing and structuring communication around DOHaD, and (3) discussing the ways in which patterns of communicating DOHaD findings can expand the range of solutions considered and encourage discussion of population-level solutions in relation to one another, rather than in isolation.

Winthrop, K. L., Silverfield, J., Racewicz, A., Neal, J., Lee, E. B., Hrycaj, P., et al. (2016). The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Annals of the Rheumatic Diseases, 75*(4), 687-695.

OBJECTIVE: To evaluate tofacitinib's effect upon pneumococcal and influenza vaccine immunogenicity. METHODS: We conducted two studies in patients with rheumatoid arthritis using the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) and the 2011-2012 trivalent influenza vaccine. In study A, tofacitinib-naive patients were randomised to tofacitinib 10 mg twice daily or placebo, stratified by background methotrexate and vaccinated 4 weeks later. In study B, patients already receiving tofacitinib 10 mg twice daily (with or without methotrexate) were randomised into two groups: those continuing ('continuous') or interrupting ('withdrawn') tofacitinib for 2 weeks, and then vaccinated 1 week after randomisation. In both studies, titres were measured 35 days after vaccination. Primary endpoints were the proportion of patients achieving a satisfactory response to pneumococcus (twofold or more titre increase against six or more of 12 pneumococcal serotypes) and influenza (fourfold or more titre increase against two or more of three influenza antigens). RESULTS: In study A (N=200), fewer tofacitinib patients (45.1%) developed satisfactory pneumococcal responses versus placebo (68.4%), and pneumococcal titres were lower with tofacitinib (particularly with methotrexate). Similar proportions of tofacitinib-treated and placebo-treated patients developed satisfactory influenza responses (56.9% and 62.2%, respectively), although fewer tofacitinib patients (76.5%) developed protective influenza titres (>/=1:40 in two or more of three antigens) versus placebo (91.8%). In study B (N=183), similar proportions of continuous and withdrawn patients had satisfactory responses to PPSV-23 (75.0% and 84.6%, respectively) and influenza (66.3% and 63.7%, respectively). CONCLUSIONS: Among patients starting tofacitinib, diminished responsiveness to PPSV-23, but not influenza, was observed, particularly in those taking concomitant methotrexate. Among existing tofacitinib users, temporary drug discontinuation had limited effect upon influenza or PPSV-23 vaccine responses. TRIAL REGISTRATION NUMBERS: NCT01359150, NCT00413699.

Woods, G. N., Huang, M. H., Cawthon, P. M., Laughlin, G. A., Schousboe, J. T., McDaniels-Davidson, C., et al. (2016). SHBG, sex steroids and kyphosis in older men: The MrOS study. *Journal of*

Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research,

Accentuated kyphosis is associated with adverse health outcomes including falls and fractures. Low bone density is a risk factor for hyperkyphosis, and each vertebral fracture adds roughly 4 degrees to forward spine curvature. Sex steroids, in particular low bioavailable estradiol and high SHBG, are associated with bone loss and high SHBG is associated with vertebral fractures in older men. We therefore hypothesized that low bioavailable estradiol and high SHBG would be associated with worse kyphosis. To test this hypothesis, we examined the cross-sectional associations between individual bioavailable sex hormones and SHBG with radiographically assessed kyphosis. Participants included 1500 men aged 65 and older from the Osteoporotic Fractures in Men (MrOS) Study, in whom baseline measures of kyphosis and sex hormones were available. Modified Cobb angle of kyphosis, calculated from T4 through T12, was assessed from supine lateral spine radiographs. Serum total estradiol and total testosterone were measured by mass spectrometry, and bioavailable sex steroids were calculated from mass action equations. After adjustment for age and other confounding variables, no association was found between bioavailable estradiol or testosterone and Cobb angle, either when kyphosis was analyzed as a continuous variable or dichotomized into highest vs. lower three quartiles. In linear regression models adjusted for age and clinic site, there was a significant association between SHBG and kyphosis (parameter estimate = 0.76 per SD increase, p = 0.01). In the fully adjusted model, this association was weakened and of only borderline statistical significance (parameter estimate = 0.61 per SD, p = 0.05). Logistic models demonstrated similar findings. Although associated with bone loss, we did not demonstrate that low bioavailable estradiol translates into worse kyphosis in older men. High SHBG is associated with bone loss and vertebral fractures. Our results suggest that high SHBG may also be a risk factor for hyperkyphosis.

Wright, M. H., Farooqui, S. M., White, A. R., & Greene, A. C. (2016). Production of manganese oxide nanoparticles by shewanella species. *Applied and Environmental Microbiology*,

Several species of the bacterial genus Shewanella are well known dissimilatory reducers of manganese under anaerobic conditions. In fact, Shewanella oneidensis is one of the most studied

of all metal reducing bacteria. In the current study, a number of Shewanella strains were tested for manganese oxidizing capacity under aerobic conditions. All were able to oxidize Mn(II) and produce solid dark brown manganese oxides. S. loihica strain PV-4 was the strongest oxidizer, producing oxides at rates of 20.3 mg/L/day and oxidizing Mn(II) concentrations of up to 9 mM. In contrast, S. oneidensis MR-1 was the weakest oxidizer tested, producing 4.4 mg/L/day of oxide and oxidizing up to 4 mM Mn(II). Analysis of products from the strongest oxidizers, S. loihica PV-4 and S. putrefaciens CN-32, revealed finely grained nano-sized and poorly crystalline oxide particles with identical Mn oxidation states of 3.86. The biogenic manganese oxide products could subsequently be reduced within 2 days by all of the Shewanella strains when culture conditions were made anoxic and an appropriate nutrient (lactate) was added. While Shewanella species have been detected as part of manganese oxidizing consortia in natural environments previously, the current study is the first clear instance of manganese reducing Shewanella species being able to oxidize manganese in aerobic cultures. IMPORTANCE: Members of the genus Shewanella are well known as dissimilatory manganese reducing bacteria. This study shows for the first time that a number of species from Shewanella are also capable of manganese oxidation under aerobic conditions. Characterisation of the products of the two most efficient oxidizers, S. loihica and S. putrefaciens revealed a finely grained nano-sized oxide. By changing culture conditions, the manganese oxide products could be subsequently reduced by the same bacteria. The ability of Shewanella species to both oxidize and reduce manganese indicates that the genus plays a significant role overall geochemical cycling of manganese. Due to the high affinity of manganese oxides for binding other metals, these bacteria may also contribute to the immobilization and release of other metals in the environment.

Wyatt, R., Anderson-Drevs, K., & Van Male, L. M. (2016). Workplace violence in health care: A critical issue with a promising solution. *Jama*,

Xiao, L., Ohayon, D., McKenzie, I. A., Sinclair-Wilson, A., Wright, J. L., Fudge, A. D., et al. (2016). Rapid production of new oligodendrocytes is required in the earliest stages of motor-skill learning. *Nature Neuroscience*,

We identified mRNA encoding the ecto-enzyme Enpp6 as a marker of newly forming

oligodendrocytes, and used Enpp6 in situ hybridization to track oligodendrocyte differentiation in adult mice as they learned a motor skill (running on a wheel with unevenly spaced rungs). Within just 2.5 h of exposure to the complex wheel, production of Enpp6-expressing immature oligodendrocytes was accelerated in subcortical white matter; within 4 h, it was accelerated in motor cortex. Conditional deletion of myelin regulatory factor (Myrf) in oligodendrocyte precursors blocked formation of new Enpp6+ oligodendrocytes and impaired learning within the same approximately 2-3 h time frame. This very early requirement for oligodendrocytes suggests a direct and active role in learning, closely linked to synaptic strengthening. Running performance of normal mice continued to improve over the following week accompanied by secondary waves of oligodendrocyte precursor proliferation and differentiation. We concluded that new oligodendrocytes contribute to both early and late stages of motor skill learning.

Yang, Y. F., Sun, Y. Y., Acott, T. S., & Keller, K. E. (2016). Effects of induction and inhibition of matrix cross-linking on remodeling of the aqueous outflow resistance by ocular trabecular meshwork cells. *Scientific Reports*, *6*, 30505.

The trabecular meshwork (TM) tissue controls drainage of aqueous humor from the anterior chamber of the eye primarily by regulating extracellular matrix (ECM) remodeling by matrix metalloproteinases (MMPs). Glaucomatous TM tissue is stiffer than age-matched controls, which may be due to alterations in ECM cross-linking. In this study, we used genipin or beta-aminopropionitrile (BAPN) agents to induce or inhibit matrix cross-linking, respectively, to investigate the effects on outflow resistance and ECM remodeling. Treatment with BAPN increased outflow rates in perfused human and porcine anterior segments, whereas genipin reduced outflow. Using a fluorogenic peptide assay, MMP activity was increased with BAPN treatment, but reduced with genipin treatment. In genipin-treated TM cells, Western immunoblotting showed a reduction of active MMP2 and MMP14 species and the presence of TIMP2-MMP14 higher molecular weight complexes. BAPN treatment increased collagen type I mRNA and protein levels, but genipin reduced the levels of collagen type I, tenascin C, elastin and versican. CD44 and fibronectin levels were unaffected by either treatment. Collectively, our results show that matrix cross-linking has profound effects on outflow resistance and ECM

composition and are consistent with the emerging paradigm that the stiffer the ECM, the lower the aqueous outflow facility through the TM.

Yao, R., Park, B. Y., & Caughey, A. B. (2016). The effects of maternal obesity on perinatal outcomes among those born small for gestational age. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* , 1-17. BACKGROUND: Maternal obesity has been associated with higher birth weight. Small for gestational age (SGA) neonates born to obese women may be associated with pathological growth with increased neonatal complications. METHODS: This was a retrospective cohort study of all non-anomalous singleton neonates born in Texas from 2006-2011. Analyses were limited to births between 34 and 42 weeks gestation with birth weight </=10th percentile. Results were stratified by maternal pre-pregnancy BMI class. The risk for stillbirth, neonatal death, neonatal intensive care unit (NICU) admission and 5 minute Apgar scores <7 were estimated for each obesity class and compared to the normal weight group. Multivariable logistic regression analyses were performed to control for potential confounding variables. RESULTS: The rate of stillbirth was 1.4/1,000 births for normal weight women, and 2.9/1,000 among obese women ($p < 0.001$, aOR: 1.83 [1.43, 2.34]). The rate of neonatal deaths among normal weight women was 4.3/1,000 births, whereas among obese women it was 4.7/1,000 ($p = 0.94$, aOR: 1.10 [0.92, 1.30]). A dose-dependent relationship between maternal obesity and stillbirths was seen, but not for other neonatal outcomes. CONCLUSION: Among SGA neonates, maternal pre-pregnancy obesity was associated with increased risks for stillbirth, NICU admission and low Apgar scores but not neonatal death.

Yarmohammadi, A., Zangwill, L. M., Diniz-Filho, A., Suh, M. H., Manalastas, P. I., Fatehee, N., et al. (2016). Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. *Investigative Ophthalmology & Visual Science, 57*(9), OCT451-9. PURPOSE: The purpose of this study was to compare retinal nerve fiber layer (RNFL) thickness and optical coherence tomography angiography (OCT-A) retinal vasculature measurements in healthy, glaucoma suspect, and glaucoma patients. METHODS: Two hundred sixty-one eyes of

164 healthy, glaucoma suspect, and open-angle glaucoma (OAG) participants from the Diagnostic Innovations in Glaucoma Study with good quality OCT-A images were included. Retinal vasculature information was summarized as a vessel density map and as vessel density (%), which is the proportion of flowing vessel area over the total area evaluated. Two vessel density measurements extracted from the RNFL were analyzed: (1) circumpapillary vessel density (cpVD) measured in a 750-mum-wide elliptical annulus around the disc and (2) whole image vessel density (wiVD) measured over the entire image. Areas under the receiver operating characteristic curves (AUROC) were used to evaluate diagnostic accuracy. RESULTS: Age-adjusted mean vessel density was significantly lower in OAG eyes compared with glaucoma suspects and healthy eyes. (cpVD: 55.1 +/- 7%, 60.3 +/- 5%, and 64.2 +/- 3%, respectively; P < 0.001; and wiVD: 46.2 +/- 6%, 51.3 +/- 5%, and 56.6 +/- 3%, respectively; P < 0.001). For differentiating between glaucoma and healthy eyes, the age-adjusted AUROC was highest for wiVD (0.94), followed by RNFL thickness (0.92) and cpVD (0.83). The AUROCs for differentiating between healthy and glaucoma suspect eyes were highest for wiVD (0.70), followed by cpVD (0.65) and RNFL thickness (0.65). CONCLUSIONS: Optical coherence tomography angiography vessel density had similar diagnostic accuracy to RNFL thickness measurements for differentiating between healthy and glaucoma eyes. These results suggest that OCT-A measurements reflect damage to tissues relevant to the pathophysiology of OAG.

Yassine, H. N., Rawat, V., Mack, W. J., Quinn, J. F., Yurko-Mauro, K., Bailey-Hall, E., et al. (2016). The effect of APOE genotype on the delivery of DHA to cerebrospinal fluid in alzheimer's disease. *Alzheimer's Research & Therapy*, *8*, 25-016-0194-x.

BACKGROUND: Apolipoprotein E (APOE) varepsilon4 and low cerebrospinal fluid (CSF) amyloid-beta42 (Abeta42) levels are predictors for developing Alzheimer's disease (AD). The results of several studies indicate an interaction between docosahexaenoic acid (DHA) consumption and cognitive outcomes by APOE genotype. Our objective in the present study was to examine whether APOE varepsilon4 genotype and low CSF Abeta42 levels were associated with reduced delivery of DHA to CSF in the Alzheimer's Disease Cooperative Study-sponsored DHA clinical trial. METHODS: Phospholipid DHA was assayed in the plasma of 384 participants and CSF of 70 participants at baseline. Forty-four of the 70 participants completed the 18-month follow-up visit

after allocation to placebo (n = 15) or DHA (n = 29). Plasma and CSF DHA levels, CSF Abeta42, Tau, and phosphorylated Tau were measured at baseline and after the 18-month intervention. Participants were divided into tertiles based on baseline Abeta42 CSF levels. To assess DHA delivery across the blood-brain barrier, the ratio of CSF to plasma DHA levels was calculated. RESULTS: At baseline, there were no significant differences between CSF or plasma phospholipid DHA levels by CSF Abeta42 tertiles or varepsilon4 status. After 18 months of DHA supplementation, participants at the lowest Abeta42 tertile had significantly lower CSF DHA levels ($p = 0.01$) and lower CSF-to-plasma DHA ratios ($p = 0.05$) compared to the other tertiles. Baseline CSF Abeta42 levels were significantly lower in varepsilon4 carriers than in varepsilon4 noncarriers ($p = 0.01$). Participants carrying the varepsilon4 allele (n = 25) demonstrated a less pronounced increase in CSF DHA level compared with noncarriers (n = 4), with a possible interaction effect between treatment and APOE genotype ($p = 0.07$). CONCLUSIONS: APOE varepsilon4 allele and lower CSF Abeta42 levels were associated with less transport of DHA to CSF. Brain amyloid pathology may limit the delivery of DHA to the brain in AD. TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT00440050 . Registered on 22 Feb 2007.

Yedinak, C. G., Cetas, I., Ozpinar, A., McCartney, S., Dogan, A., & Fleseriu, M. (2016). Dopamine agonist therapy induces significant recovery of HPA axis function in prolactinomas independent of tumor size: A large single center experience. *Endocrine*,

Our objective was to compare prevalence and rates of recovery of hypothalamic-pituitary-adrenal axis dysfunction in prolactinoma patients before and after dopamine agonist therapy with nonfunctioning pituitary adenoma patients pre-transsphenoidal and post-transsphenoidal surgery. We retrospectively compared hypothalamic-pituitary-adrenal axis function in patients with prolactinomas naive to dopamine agonist therapy with a cohort of nonfunctioning pituitary adenoma patients matched for gender and tumor size by classification (n = 57; 30 male/27 female; 27 microadenoma/30 macroadenoma). Patients with <52 weeks follow up, previous medical therapy, surgery, or radiation therapy were excluded. At baseline, there was no difference between groups for age, mean tumor size, or prevalence of adrenal insufficiency. Recovery from baseline adrenal insufficiency was demonstrated in patients with microprolactinomas and macroprolactinomas at a 52 week follow up ($p = 0.003$ and $p = 0.004$).

These rates were similar to nonfunctioning pituitary adenoma patients after surgery. We show, in a large uniform study, that adrenal insufficiency significantly recovered after dopamine agonist treatment, independent of tumor size and gender in patients with prolactinomas naive to therapy.

Yu, J., Gu, R., Zong, Y., Xu, H., Wang, X., Sun, X., et al. (2016). Relationship between retinal perfusion and retinal thickness in healthy subjects: An optical coherence tomography angiography study. *Investigative Ophthalmology & Visual Science*, *57*(9), OCT204-10.

PURPOSE: To investigate the relationship between retinal perfusion and retinal thickness in the peripapillary and macular areas of healthy subjects. METHODS: Using spectral-domain optic coherence tomography and split-spectrum amplitude decorrelation angiography (SSADA) algorithm, retinal perfusion and retinal thicknesses in the macular and peripapillary areas were measured in healthy volunteers, and correlations among these variables were analyzed. RESULTS: Overall, 64 subjects (121 eyes) including 28 males and 36 females with a mean +/- SD age of 38 +/- 13 years participated. Linear mixed-models showed that vessel area density was significantly correlated with the inner retinal thickness (from the inner limiting membrane to the outer border of the inner nucleus layer; P 0.05) in the parafoveal area. The area of the foveal capillary-free zone was negatively correlated with the inner and full foveal thicknesses (all $P < 0.001$). In the peripapillary area, the vessel area density was positively correlated with the thickness of the retinal nerve fiber layer ($P < 0.001$). CONCLUSIONS: In healthy subjects, retinal perfusion in small vessels was closely correlated with the thickness of the inner retinal layers in both the macular and peripapillary areas.

Zang, P., Liu, G., Zhang, M., Dongye, C., Wang, J., Pechauer, A. D., et al. (2016). Automated motion correction using parallel-strip registration for wide-field en face OCT angiogram. *Biomedical Optics Express*, *7*(7), 2823-2836.

We propose an innovative registration method to correct motion artifacts for wide-field optical coherence tomography angiography (OCTA) acquired by ultrahigh-speed swept-source OCT (>200 kHz A-scan rate). Considering that the number of A-scans along the fast axis is much higher than the number of positions along slow axis in the wide-field OCTA scan, a non-orthogonal scheme is introduced. Two en face angiograms in the vertical priority (2 y-fast) are

divided into microsaccade-free parallel strips. A gross registration based on large vessels and a fine registration based on small vessels are sequentially applied to register parallel strips into a composite image. This technique is extended to automatically montage individual registered, motion-free angiograms into an ultrawide-field view.

Zhang, L., Yang, M., Mayer, T., Johnstone, B., Les, C., Frisch, N., et al. (2016). Use of MicroRNA biomarkers to distinguish enchondroma from low-grade chondrosarcoma. *Connective Tissue Research*, , 1-7.

Establishing a definitive diagnosis between benign enchondroma versus low-grade chondrosarcoma presents a potential challenge to both clinicians and pathologists. microRNAs (small non-coding RNAs) have proven to be effective biomarkers for the identification of tumors and tumor progression. We present analysis, both array and quantitative PCR, that shows consistently and substantially increased expression of two microRNAs, miRs-181a and -138, in low-grade chondrosarcomas compared with enchondromas. The data suggest these microRNAs would provide an analytical distinction between the chondrosarcoma and benign neoplasms that can be performed in formalin-fixed paraffin-embedded specimens. Together with recent publications, these data indicate that miRs-181a and -138 also play a role in tumor development and homeostasis and may provide new targets for the development of much needed therapeutic intervention.

Zhao, Y., Chen, S., Yoshioka, C., Baconguis, I., & Gouaux, E. (2016). Architecture of fully occupied GluA2 AMPA receptor-TARP complex elucidated by cryo-EM. *Nature*, *536*(7614), 108-111.

Fast excitatory neurotransmission in the mammalian central nervous system is largely carried out by AMPA-sensitive ionotropic glutamate receptors. Localized within the postsynaptic density of glutamatergic spines, AMPA receptors are composed of heterotetrameric receptor assemblies associated with auxiliary subunits, the most common of which are transmembrane AMPA receptor regulatory proteins (TARPs). The association of TARPs with AMPA receptors modulates receptor trafficking and the kinetics of receptor gating and pharmacology. Here we report the cryo-electron microscopy (cryo-EM) structure of the homomeric rat GluA2 AMPA receptor saturated with TARP gamma2 subunits, which shows how the TARPs are arranged with four-fold symmetry

around the ion channel domain and make extensive interactions with the M1, M2 and M4 transmembrane helices. Poised like partially opened 'hands' underneath the two-fold symmetric ligand-binding domain (LBD) 'clamshells', one pair of TARPs is juxtaposed near the LBD dimer interface, whereas the other pair is near the LBD dimer-dimer interface. The extracellular 'domains' of TARP are positioned to not only modulate LBD clamshell closure, but also affect conformational rearrangements of the LBD layer associated with receptor activation and desensitization, while the TARP transmembrane domains buttress the ion channel pore.

Zhu, L., Giunzioni, I., Tavori, H., Covarrubias, R., Ding, L., Zhang, Y., et al. (2016). Loss of macrophage low-density lipoprotein receptor-related protein 1 confers resistance to the antiatherogenic effects of tumor necrosis factor-alpha inhibition. *Arteriosclerosis, Thrombosis, and Vascular Biology, 36*(8), 1483-1495.

OBJECTIVE: Antiatherosclerotic effects of tumor necrosis factor-alpha (TNF-alpha) blockade in patients with systemic inflammatory states are not conclusively demonstrated, which suggests that effects depend on the cause of inflammation. Macrophage LRP1 (low-density lipoprotein receptor-related protein 1) and apoE contribute to inflammation through different pathways. We studied the antiatherosclerosis effects of TNF-alpha blockade in hyperlipidemic mice lacking either LRP1 (MPhiLRP1(-/-)) or apoE from macrophages. APPROACH AND RESULTS: Lethally irradiated low-density lipoprotein receptor (LDLR)(-/-) mice were reconstituted with bone marrow from either wild-type, MPhiLRP1(-/-), apoE(-/-) or apoE(-/-)/MPhiLRP1(-/-)(DKO) mice, and then treated with the TNF-alpha inhibitor adalimumab while fed a Western-type diet. Adalimumab reduced plasma TNF-alpha concentration, suppressed blood ly6C(hi) monocyte levels and their migration into the lesion, and reduced lesion cellularity and inflammation in both wild-type-->LDLR(-/-) and apoE(-/-)-->LDLR(-/-) mice. Overall, adalimumab reduced lesion burden by 52% to 57% in these mice. Adalimumab reduced TNF-alpha and blood ly6C(hi) monocyte levels in MPhiLRP1(-/-)-->LDLR(-/-) and DKO-->LDLR(-/-) mice, but it did not suppress ly6C(hi) monocyte migration into the lesion or atherosclerosis progression. CONCLUSIONS: Our results show that TNF-alpha blockade exerts antiatherosclerotic effects that are dependent on the presence of macrophage LRP1.

Zhu, X., Levasseur, P. R., Michaelis, K. A., Burfeind, K. G., & Marks, D. L. (2016). A distinct brain pathway links viral RNA exposure to sickness behavior. *Scientific Reports, 6*, 29885.
Sickness behaviors and metabolic responses to invading pathogens are common to nearly all types of infection. These responses evolved to provide short-term benefit to the host to ward off infection, but impact on quality of life, and when prolonged lead to neurodegeneration, depression, and cachexia. Among the major infectious agents, viruses most frequently enter the brain, resulting in profound neuroinflammation. We sought to define the unique features of the inflammatory response in the brain to these infections. We demonstrate that the molecular pathway defining the central response to dsRNA is distinct from that found in the periphery. The behavioral and physical response to the dsRNA mimetic poly I:C is dependent on signaling via MyD88 when it is delivered centrally, whereas this response is mediated via the TRIF pathway when delivered peripherally. We also define the likely cellular candidates for this MyD88-dependent step. These findings suggest that symptom management is possible without ameliorating protective antiviral immune responses.

Zuloaga, K. L., Johnson, L. A., Roese, N. E., Marzulla, T., Zhang, W., Nie, X., et al. (2016). High fat diet-induced diabetes in mice exacerbates cognitive deficit due to chronic hypoperfusion. *Journal of Cerebral Blood Flow and Metabolism, 36*(7), 1257-1270.
Diabetes causes endothelial dysfunction and increases the risk of vascular cognitive impairment. However, it is unknown whether diabetes causes cognitive impairment due to reductions in cerebral blood flow or through independent effects on neuronal function and cognition. We addressed this using right unilateral common carotid artery occlusion to model vascular cognitive impairment and long-term high-fat diet to model type 2 diabetes in mice. Cognition was assessed using novel object recognition task, Morris water maze, and contextual and cued fear conditioning. Cerebral blood flow was assessed using arterial spin labeling magnetic resonance imaging. Vascular cognitive impairment mice showed cognitive deficit in the novel object recognition task, decreased cerebral blood flow in the right hemisphere, and increased glial activation in white matter and hippocampus. Mice fed a high-fat diet displayed deficits in the novel object recognition task, Morris water maze and fear conditioning tasks and neuronal loss, but no impairments in cerebral blood flow. Compared to vascular cognitive impairment mice fed a

low fat diet, vascular cognitive impairment mice fed a high-fat diet exhibited reduced cued fear memory, increased deficit in the Morris water maze, neuronal loss, glial activation, and global decrease in cerebral blood flow. We conclude that high-fat diet and chronic hypoperfusion impair cognitive function by different mechanisms, although they share commons features, and that high-fat diet exacerbates vascular cognitive impairment pathology.