

References

- Advani, R. H., Lebovic, D., Chen, A., Brunvand, M., Goy, A., Chang, J. E., et al. (2016). Phase I study of the anti-CD22 antibody-drug conjugate pinatuzumab vedotin with/without rituximab in patients with relapsed/refractory B-cell non-hodgkin's lymphoma. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,
- PURPOSE: Pinatuzumab vedotin is an antibody-drug conjugate with the potent antimicrotubule agent monomethyl auristatin E (MMAE) conjugated to an anti-CD22 antibody via a protease-cleavable linker. This Phase I study determined its recommended Phase II dose (RP2D) and evaluated its safety, tolerability, and anti-tumor activity alone and with rituximab in relapsed/refractory (r/r) non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). EXPERIMENTAL DESIGN: Patients received escalating doses of pinatuzumab vedotin every 21 days. Clinical activity at the RP2D alone or with rituximab was evaluated in r/r diffuse large B-cell lymphoma (DLBCL) and r/r indolent NHL (iNHL) patients. RESULTS: Seventy-five patients received single-agent pinatuzumab vedotin. The RP2D was 2.4 mg/kg, based on dose-limiting toxicities (DLT) of Grade 4 neutropenia >7 days in 1/3 patients and Grade 4 neutropenia <7 days in 2/3 patients treated at 3.2 mg/kg (maximum assessed dose). No DLTs occurred at 2.4 mg/kg. At the RP2D, neutropenia was the most common Grade {greater than or equal to}3 adverse event. Peripheral neuropathy-related Grade {greater than or equal to}2 adverse events most frequently resulted in treatment discontinuation. Rituximab co-treatment did not impact safety, tolerability, or pharmacokinetics of pinatuzumab vedotin. Unconjugated MMAE exposure was much lower than antibody-conjugated MMAE exposure without accumulation with repeat dosing. At the RP2D, objective responses were observed in DLBCL (9/25) and iNHL (7/14) patients; 2/8 patients treated with pinatuzumab vedotin (RP2D) and rituximab had complete responses. CLL patients showed no objective responses. CONCLUSIONS: The RP2D of pinatuzumab vedotin alone and with rituximab was 2.4 mg/kg, which was well tolerated, with encouraging clinical activity in r/r NHL.
- Agarwal, A., & Tyner, J. W. (2016). RNAi screening of leukemia cells using electroporation. *Methods in Molecular Biology (Clifton, N.J.)*, 1470, 85-94.
- RNAi-mediated screening has been an integral tool for biological discovery for the past 15 years.

A variety of approaches have been employed for implementation of this technique, including pooled, depletion/enrichment screening with lentiviral shRNAs, and segregated screening of panels of individual siRNAs. The latter approach of siRNA panel screening requires efficient methods for transfection of siRNAs into the target cells. In the case of suspension leukemia cell lines and primary cells, many of the conventional transfection techniques using liposomal or calcium phosphate-mediated transfection provide very low efficiency. In this case, electroporation is the only transfection technique offering high efficiency transfection of siRNAs into the target leukemia cells. Here, we describe methods for optimization and implementation of siRNA electroporation into leukemia cell lines and primary patient specimens, and we further offer suggested electroporation settings for some commonly used leukemia cell lines.

Aghi, M. K., Chen, C. C., Fleseriu, M., Newman, S. A., Lucas, J. W., Kuo, J. S., et al. (2016). Congress of neurological surgeons systematic review and evidence-based guidelines on the management of patients with nonfunctioning pituitary adenomas: Executive summary. *Neurosurgery*, 79(4), 521-523.

BACKGROUND: Nonfunctioning pituitary adenomas (NFPAs) are the most frequent pituitary tumors. **OBJECTIVE:** To create evidence-based guidelines for the initial management of NFPAs. **METHODS:** A multidisciplinary task force composed of physician volunteers and evidence-based medicine-trained methodologists conducted a systematic review of the literature relevant to the management of NFPAs. To ascertain the class of evidence for the posttreatment follow-ups, the task force used the Clinical Assessment evidence-based classification. **RESULTS:** Seven topics of importance were chosen for detailed evaluation. The topics addressed include preoperative evaluation, primary treatment, treatment options for residual tumors after surgery, and postoperative patient management. For preoperative patient evaluation, the guideline task force focused on preoperative imaging, preoperative laboratory evaluation, and preoperative ophthalmologic evaluation. For primary treatment, this guideline addresses surgical resection, medical therapy, radiation therapy, the natural history of untreated tumors, surgical methodologies, such as endoscopy, microscopy, or craniotomy, and intraoperative adjuncts like neuronavigation, cerebrospinal fluid diversion, or intraoperative imaging. For residual tumor treatment, the guideline task force evaluated radiation vs observation. Additional topics

addressed in this guideline regarding postoperative patient management include the frequency of postoperative imaging, postoperative endocrine evaluation, and postoperative ophthalmologic evaluation. CONCLUSION: Although there is clearly a need for more randomized trials generating higher levels of evidence to help guide physicians managing NFPAs, the existing evidence provided valuable data upon which the guidelines described in the 7 articles generated from this effort are based. The full guidelines document can be located at

[https://www.cns.org/guidelines/guidelines-management-patients-non-functioning-pituitary-](https://www.cns.org/guidelines/guidelines-management-patients-non-functioning-pituitary-adenomas)

adenomas. ABBREVIATION: NFPA, nonfunctioning pituitary adenoma.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2016). RIFM fragrance ingredient safety assessment, 2-ethyl-1-hexanol, CAS registry number 104-76-7. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog 2-butyloctan-1-ol (CAS # 3913-02-8) show that this material does not have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 and 1.4 mg/day, respectively). The developmental and repeat dose toxicity endpoints were completed data on the target material which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Arias, J. F., Colomer-Lluch, M., von Bredow, B., Greene, J. M., MacDonald, J., O'Connor, D. H., et al.

(2016). Tetherin antagonism by HIV-1 group M nef proteins. *Journal of Virology*,

Although Nef is the viral gene product used by most simian immunodeficiency viruses to overcome restriction by tetherin, this activity was acquired by the Vpu protein of HIV-1 group M viruses due to the absence of sequences in human tetherin that confer susceptibility to Nef. Thus,

it is widely accepted that HIV-1 group M uses Vpu instead of Nef to counteract tetherin. Challenging this paradigm, we identified Nef alleles of HIV-1 group M isolates with significant activity against human tetherin. These Nef proteins promoted virus release and tetherin downmodulation from the cell surface, and in the context of vpu-deleted HIV-1 recombinants, enhanced virus replication and resistance to antibody-dependent cell-mediated cytotoxicity (ADCC). Further analysis revealed that the Vpu proteins from several of these viruses lack anti-tetherin activity, suggesting that under certain circumstances, HIV-1 group M Nef may acquire the ability to counteract tetherin to compensate for the loss of this function by Vpu. These observations illustrate the remarkable plasticity of HIV-1 in overcoming restriction by tetherin and challenge the prevailing view that all HIV-1 group M isolates use Vpu to counteract tetherin. **IMPORTANCE:** Most HIV-1 group M viruses, the main group of HIV-1 responsible for the global AIDS pandemic, use their Vpu proteins to overcome restriction by tetherin (BST-2 or CD317), which is a transmembrane protein that inhibits virus release from infected cells. Here we show that the Nef proteins of certain HIV-1 group M isolates can acquire the ability to counteract tetherin. These results challenge the current paradigm that HIV-1 group M exclusively uses Vpu to counteract tetherin and underscore the importance of tetherin antagonism for efficient viral replication.

Artis, K. A., Dyer, E., Mohan, V., & Gold, J. A. (2016). Accuracy of laboratory data communication on ICU daily rounds using an electronic health record. *Critical Care Medicine*,

OBJECTIVES: Accurately communicating patient data during daily ICU rounds is critically important since data provide the basis for clinical decision making. Despite its importance, high fidelity data communication during interprofessional ICU rounds is assumed, yet unproven. We created a robust but simple methodology to measure the prevalence of inaccurately communicated (misrepresented) data and to characterize data communication failures by type. We also assessed how commonly the rounding team detected data misrepresentation and whether data communication was impacted by environmental, human, and workflow factors.

DESIGN: Direct observation of verbalized laboratory data during daily ICU rounds compared with data within the electronic health record and on presenters' paper prerounding notes. **SETTING:** Twenty-six-bed academic medical ICU with a well-established electronic health record.

SUBJECTS: ICU rounds presenter (medical student or resident physician), interprofessional rounding team. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: During 301 observed patient presentations including 4,945 audited laboratory results, presenters used a paper prerounding tool for 94.3% of presentations but tools contained only 78% of available electronic health record laboratory data. Ninety-six percent of patient presentations included at least one laboratory misrepresentation (mean, 6.3 per patient) and 38.9% of all audited laboratory data were inaccurately communicated. Most misrepresentation events were omissions. Only 7.8% of all laboratory misrepresentations were detected. CONCLUSION: Despite a structured interprofessional rounding script and a well-established electronic health record, clinician laboratory data retrieval and communication during ICU rounds at our institution was poor, prone to omissions and inaccuracies, yet largely unrecognized by the rounding team. This highlights an important patient safety issue that is likely widely prevalent, yet underrecognized. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Atherton, I. M., Lasater, K., Richards, E. A., Mathews, L. R., Simpson, V., & Kyle, R. G. (2016).

Population health and nurse education - time to step-up. *Nurse Education Today*,

Bak, G., Shaffer, B., Madriago, E., Allen, A., Kelly, B., Caughey, A., et al. (2016). EP06.10: Detection of fetal cardiac anomalies: What is the most cost-effective strategy? *Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 48 Suppl 1, 290.

Bak, G., Shaffer, B., Madriago, E., Allen, A., Kelly, B., Caughey, A., et al. (2016). EP07.06: Impact of maternal obesity on fetal cardiac screening. *Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 48 Suppl 1, 292-293.

Barneck, M. D., Rhodes, N. L. R., de la Presa, M., Allen, J. P., Poursaid, A. E., Nourian, M. M., et al.

(2016). Violet 405-nm light: A novel therapeutic agent against common pathogenic bacteria.

Journal of Surgical Research, 206(2), 316-324.

Background The increasing incidence of healthcare-associated infections (HAIs) and multidrug-resistant organisms demonstrate the need for innovative technological solutions. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* in particular are common pathogens responsible for a large percentage of indwelling medical device-associated clinical infections. The bactericidal effects of visible light sterilization (VLS) using 405-nm is one potential therapeutic under investigation. **Materials and methods** Light-emitting diodes of 405-nm were used to treat varying concentrations of *S. aureus*, *S. pneumoniae*, *E. coli*, and *P. aeruginosa*. Irradiance levels between 2.71 ± 0.20 to 9.27 ± 0.36 mW/cm² and radiant exposure levels up to 132.98 ± 6.68 J/cm² were assessed. **Results** Dose-dependent effects were observed in all species. Statistically significant reductions were seen in both Gram-positive and Gram-negative bacteria. At the highest radiant exposure levels, bacterial log₁₀ reductions were *E. coli*— 6.27 ± 0.54 , *S. aureus*— 6.10 ± 0.60 , *P. aeruginosa*— 5.20 ± 0.84 , and *S. pneumoniae*— 6.01 ± 0.59 . Statistically significant results (<0.001*) were found at each time point. **Conclusions** We have successfully demonstrated high-efficacy bacterial reduction using 405-nm light sterilization. The VLS showed statistical significance against both Gram-positive and Gram-negative species with the given treatment times. The β -lactam antibiotic-resistant *E. coli* was the most sensitive to VLS, suggesting light therapy could be a suitable option for sterilization in drug-resistant bacterial species. This research illustrates the potential of using VLS in treating clinically relevant bacterial infections. © 2016 Elsevier Inc.

Barton, C. A. (2016). Treatment of coagulopathy related to hepatic insufficiency. *Critical Care Medicine*, 44(10), 1927-1933.

OBJECTIVES: To provide a concise review of the medical management of coagulopathy related to hepatic insufficiency. This review will focus on prevention and management of bleeding episodes in patients with hepatic insufficiency. The treatment and prevention of thromboembolic complications will also be addressed. **DATA SOURCES:** Electronic search of PubMed database using relevant search terms, including hepatic coagulopathy, hemorrhage, liver diseases, blood

coagulation disorders, blood transfusion, disseminated intravascular coagulation, and liver failure. Subsequent searches were done on specific issues. **STUDY SELECTION:** Articles considered include original articles, review articles, guidelines, consensus statements, and conference proceedings. **DATA EXTRACTION:** A detailed review of scientific, peer-reviewed data was performed. Relevant publications were included and summarized. **DATA SYNTHESIS:** Available evidence is used to describe and summarize currently available tests of hemostasis, utilization of prohemostatic agents, transfusion strategies, use of prophylactic anticoagulation and treatment of thromboembolic events in patients with hepatic insufficiency. **CONCLUSIONS:** Dynamic changes to hemostasis occur in patients with hepatic insufficiency. Routine laboratory tests of hemostasis are unable to reflect these changes and should not be used exclusively to evaluate coagulopathy. Newer testing methods are available to provide data on the entire spectrum of clotting but are not validated in acute bleeding. Prohemostatic agents utilized to prevent bleeding should only be considered when the risk of bleeding outweighs the risk of thrombotic complications. Restrictive transfusion strategies may avoid exacerbation of acute bleeding. Prophylaxis against and treatment of thromboembolic events are necessary and should consider patient specific factors.

Beaupin, L. K., Bostrom, B., Barth, M. J., Franklin, I., Jaeger, R., Kamath, P., et al. (2016).

Pegaspargase hypersensitivity reactions: Intravenous infusion versus intramuscular injection - a review. *Leukemia & Lymphoma*, , 1-7.

Pegaspargase is a mainstay in the treatment of acute lymphoblastic leukemia. When intravenous (IV) infusion replaced intramuscular (IM) injection as the standard route of administration, there were early reports suggested an increased hypersensitivity reactions (HSRs) rate with IV administration. There have since been eight published reports comparing the incidence of HSRs occurring with IV versus IM pegaspargase. This review analyzes the reports and summarizes their consistent findings where feasible. For grade 3-4 HSRs, the rates are comparable with IV and IM administration. Grade 2 HSRs appear to be more likely with IV than IM administration but the validity of the difference is uncertain. Multiple factors confound the analyses, including the historically controlled nature of the comparisons and the increased likelihood of reporting adverse

reactions with IV administration. In summary, the reports do not support the conclusion that pegaspargase-induced HSR rate is more frequent with IV administration.

Bennett, R. (2016). Fibromyalgia: Shining a light on fibromyalgia treatment. *Nature Reviews Rheumatology*, 12(10), 568-569.

Bertassoni, L. E., & Swain, M. V. (2016). Removal of dentin non-collagenous structures results in the unraveling of microfibril bundles in collagen type I. *Connective Tissue Research*, AIMS: The structural organization of collagen from mineralized tissues, such as dentin and bone, has been a topic of debate in the recent literature. Recent reports have presented novel interpretations of the complexity of collagen type I at different hierarchical levels and in different tissues. Here we investigate the nanostructural organization of demineralized dentin collagen following the digestion of non-collagenous components with a trypsin enzyme. MATERIALS AND METHODS: Dentin specimens were obtained from healthy third-molars, cut into small cubes and polished down to 1 microm roughness. Samples were then demineralized with 10% citric acid for 2 min. Selected specimens were further treated with a solution containing 1 mg/ml trypsin for 48 hours at 37 masculineC (pH 7.9 - 9.0). Both untreated and trypsin digested samples were analyzed using SDS-PAGE, Field Emission Scanning Electron Microscopy (FE-SEM), and nanoindentation, where surface hardness and creep properties where compared before and after treatments. RESULTS: FE-SEM images of demineralized dentin showed the banded morphology of D-periodical collagen type I, which upon enzymatic digestion with trypsin appeared to dissociate longitudinally, consistently unraveling ~20 nm structures (microfibril bundles). Such nanoscale structures, which we call microfibril bundles, to the best of our knowledge, have not been characterized in dentin previously. Mechanical characterization via nanoindentation showed that the unraveling of such microfibril bundles affected the creep displacement and creep rate of demineralized dentin. CONCLUSION: In summary, our results provide novel evidence of the organization of collagen type I from dentin, which may have important implications for the interaction of dental materials with the organic dentin matrix and the mechanical properties of mineralized tissues.

Bidwell, J. T., Lyons, K. S., & Lee, C. S. (2016). Caregiver well-being and patient outcomes in heart failure: A meta-analysis. *Journal of Cardiovascular Nursing*,

BACKGROUND:: Despite evidence from the broader caregiving literature about the interdependent nature of the caregiving dyad, few studies in heart failure (HF) have examined associations between caregiver and patient characteristics. OBJECTIVE:: The aim of this study is to quantitatively synthesize the relationships between caregiver well-being and patient outcomes. METHODS:: The MEDLINE, PsycINFO, and CINAHL databases were searched for studies of adult HF patients and informal caregivers that tested the relationship between caregiver well-being (perceived strain and psychological distress) and patient outcomes of interest. Summary effects across studies were estimated using random effects meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. RESULTS:: A total of 15 articles meeting inclusion criteria were included in the meta-analysis. Taking into account differences across studies, higher caregiver strain was associated significantly with greater patient symptoms (Fisher $z = 0.22$, $P < .001$) and higher caregiver strain was associated significantly with lower patient quality of life (Fisher $z = -0.36$, $P < .001$). Relationships between caregiver psychological distress and both patient symptoms and quality of life were not significant. Although individual studies largely found significant relationships between worse caregiver well-being and higher patient clinical event-risk, these studies were not amenable to meta-analysis because of substantial variation in event-risk measures. CONCLUSIONS:: Clinical management and research approaches that acknowledge the interdependent nature of the caregiving dyad hold great potential to benefit both patients and caregivers. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved

Billings, C. J., & Grush, L. D. (2016). Signal type and signal-to-noise ratio interact to affect cortical auditory evoked potentials. *Journal of the Acoustical Society of America*, *140*(2), EL221-EL226. Use of speech signals and background noise is emerging in cortical auditory evoked potential (CAEP) studies; however, the interaction between signal type and noise level remains unclear. Two experiments determined the interaction between signal type and signal-to-noise ratio (SNR) on CAEPs. Three signals (syllable /ba/, 1000-Hz tone, and the /ba/ envelope with 1000-Hz fine structure) with varying SNRs were used in two experiments, demonstrating signal-by-SNR

interactions due to both envelope and spectral characteristics. When using real-world stimuli such as speech to evoke CAEPs, temporal and spectral complexity leads to differences with traditional tonal stimuli, especially when presented in background noise. © 2016 U.S. Government.

Bohan, P. K., Yonge, J., Connelly, C., Watson, J. J., Friedman, E., & Fielding, G. (2016). Wernicke encephalopathy after restrictive bariatric surgery. *The American Surgeon*, 82(4), E73-5.

Bourdette, D., & Whitham, R. (2016). Neurologists and the economics of MS treatment: Lighting candles, not cursing the darkness. *Neurology*,

Bradbury, H. (2016). Enough with lewin already! *Action Research*, 14(3), 237-239.

Brown, A., Patel, S., Ward, C., Lorenz, A., Ortiz, M., DuRoss, A., et al. (2016). PEG-lipid micelles enable cholesterol efflux in niemann-pick type C1 disease-based lysosomal storage disorder. *Scientific Reports*, 6, 31750.

2-Hydroxy-propyl-beta-cyclodextrin (HPbetaCD), a cholesterol scavenger, is currently undergoing Phase 2b/3 clinical trial for treatment of Niemann Pick Type C-1 (NPC1), a fatal neurodegenerative disorder that stems from abnormal cholesterol accumulation in the endo/lysosomes. Unfortunately, the extremely high doses of HPbetaCD required to prevent progressive neurodegeneration exacerbates ototoxicity, pulmonary toxicity and autophagy-based cellular defects. We present unexpected evidence that a poly (ethylene glycol) (PEG)-lipid conjugate enables cholesterol clearance from endo/lysosomes of Npc1 mutant (Npc1(-/-)) cells. Herein, we show that distearyl-phosphatidylethanolamine-PEG (DSPE-PEG), which forms 12-nm micelles above the critical micelle concentration, accumulates heavily inside cholesterol-rich late endosomes in Npc1(-/-) cells. This potentially results in cholesterol solubilization and leakage from lysosomes. High-throughput screening revealed that DSPE-PEG, in combination with HPbetaCD, acts synergistically to efflux cholesterol without significantly aggravating autophagy defects. These well-known excipients can be used as admixtures to treat NPC1 disorder. Increasing PEG chain lengths from 350 Da-30 kDa in DSPE-PEG micelles, or increasing DSPE-PEG content in an array of liposomes packaged with HPbetaCD, improved cholesterol egress, while Pluronic block copolymers capable of micelle formation showed slight effects at high

concentrations. We postulate that PEG-lipid based nanocarriers can serve as bioactive drug delivery systems for effective treatment of lysosomal storage disorders.

Brown, C. L., Mulcaster, H. L., Triffitt, K. L., Sittig, D. F., Ash, J. S., Reygate, K., et al. (2016). A systematic review of the types and causes of prescribing errors generated from using computerized provider order entry systems in primary and secondary care. *Journal of the American Medical Informatics Association : JAMIA*,

OBJECTIVE: To understand the different types and causes of prescribing errors associated with computerized provider order entry (CPOE) systems, and recommend improvements in these systems. MATERIALS AND METHODS: We conducted a systematic review of the literature published between January 2004 and June 2015 using three large databases: the Cumulative Index to Nursing and Allied Health Literature, Embase, and Medline. Studies that reported qualitative data about the types and causes of these errors were included. A narrative synthesis of all eligible studies was undertaken. RESULTS: A total of 1185 publications were identified, of which 34 were included in the review. We identified 8 key themes associated with CPOE-related prescribing errors: computer screen display, drop-down menus and auto-population, wording, default settings, nonintuitive or inflexible ordering, repeat prescriptions and automated processes, users' work processes, and clinical decision support systems. Displaying an incomplete list of a patient's medications on the computer screen often contributed to prescribing errors. Lack of system flexibility resulted in users employing error-prone workarounds, such as the addition of contradictory free-text comments. Users' misinterpretations of how text was presented in CPOE systems were also linked with the occurrence of prescribing errors.

DISCUSSION AND CONCLUSIONS: Human factors design is important to reduce error rates. Drop-down menus should be designed with safeguards to decrease the likelihood of selection errors. Development of more sophisticated clinical decision support, which can perform checks on free-text, may also prevent errors. Further research is needed to ensure that systems minimize error likelihood and meet users' workflow expectations.

Brown, R. S., Patibandla, B. K., & Goldfarb-Rumyantzev, A. S. (2016). The survival benefit of "fistula first, catheter last" in hemodialysis is primarily due to patient factors. *Journal of the American*

Society of Nephrology : JASN,

Patients needing hemodialysis are advised to have arteriovenous fistulas rather than catheters because of significantly lower mortality rates. However, disparities in fistula placement raise the possibility that patient factors have a role in this apparent mortality benefit. We derived a cohort of 115,425 patients on incident hemodialysis ≥ 67 years old from the US Renal Data System with linked Medicare claims to identify the first predialysis vascular access placed. We compared mortality outcomes in patients initiating hemodialysis with a fistula placed first, a catheter after a fistula placed first failed, or a catheter placed first ($n=90,517$; reference group). Of 21,436 patients with a fistula placed first, 9794 initiated hemodialysis with that fistula, and 8230 initiated dialysis with a catheter after failed fistula placement. The fistula group had the lowest mortality over 58 months (hazard ratio, 0.50; 95% confidence interval, 0.48 to 0.52; $P<0.001$), with mortality rates at 6, 12, and 24 months after initiation of 9%, 17%, and 31%, respectively, compared with 32%, 46%, and 62%, respectively, in the catheter group. However, the group initiating hemodialysis with a catheter after failed fistula placement also had significantly lower mortality rates than the catheter group had over 58 months (hazard ratio, 0.66; 95% confidence interval, 0.64 to 0.68; $P<0.001$), with mortality rates of 15%, 25%, and 42% at 6, 12, and 24 months, respectively. Thus, patient factors affecting fistula placement, even when patients are hemodialyzed with a catheter instead, may explain at least two thirds of the mortality benefit observed in patients with a fistula.

Bruna, A., Rueda, O. M., Greenwood, W., Batra, A. S., Callari, M., Batra, R. N., et al. (2016). A biobank of breast cancer explants with preserved intra-tumor heterogeneity to screen anticancer compounds. *Cell*, 167(1), 260-274.e22.

The inter- and intra-tumor heterogeneity of breast cancer needs to be adequately captured in pre-clinical models. We have created a large collection of breast cancer patient-derived tumor xenografts (PDXs), in which the morphological and molecular characteristics of the originating tumor are preserved through passaging in the mouse. An integrated platform combining in vivo maintenance of these PDXs along with short-term cultures of PDX-derived tumor cells (PDXCs) was optimized. Remarkably, the intra-tumor genomic clonal architecture present in the originating breast cancers was mostly preserved upon serial passaging in xenografts and in short-

term cultured PDCs. We assessed drug responses in PDCs on a high-throughput platform and validated several ex vivo responses in vivo. The biobank represents a powerful resource for pre-clinical breast cancer pharmacogenomic studies (<http://caldaslab.cruk.cam.ac.uk/bcape>), including identification of biomarkers of response or resistance.

Burton, G. J., Fowden, A. L., & Thornburg, K. L. (2016). Placental origins of chronic disease.

Physiological Reviews, 96(4), 1509-1565.

Epidemiological evidence links an individual's susceptibility to chronic disease in adult life to events during their intrauterine phase of development. Biologically this should not be unexpected, for organ systems are at their most plastic when progenitor cells are proliferating and differentiating. Influences operating at this time can permanently affect their structure and functional capacity, and the activity of enzyme systems and endocrine axes. It is now appreciated that such effects lay the foundations for a diverse array of diseases that become manifest many years later, often in response to secondary environmental stressors. Fetal development is underpinned by the placenta, the organ that forms the interface between the fetus and its mother. All nutrients and oxygen reaching the fetus must pass through this organ. The placenta also has major endocrine functions, orchestrating maternal adaptations to pregnancy and mobilizing resources for fetal use. In addition, it acts as a selective barrier, creating a protective milieu by minimizing exposure of the fetus to maternal hormones, such as glucocorticoids, xenobiotics, pathogens, and parasites. The placenta shows a remarkable capacity to adapt to adverse environmental cues and lessen their impact on the fetus. However, if placental function is impaired, or its capacity to adapt is exceeded, then fetal development may be compromised. Here, we explore the complex relationships between the placental phenotype and developmental programming of chronic disease in the offspring. Ensuring optimal placentation offers a new approach to the prevention of disorders such as cardiovascular disease, diabetes, and obesity, which are reaching epidemic proportions.

Calabrese, L. H., Xie, F., Yun, H., Winthrop, K., Baddley, J. W., Calabrese, C., et al. (2016). Herpes zoster and the risk for stroke in patients with autoimmune diseases. *Arthritis & Rheumatology (Hoboken, N.J.)*,

BACKGROUND: Herpes zoster (HZ) is an opportunistic infection caused by varicella zoster virus (VZV), and observed with increasing frequency in patients on immunosuppressive therapies. Prior literature has suggested that the risk of stroke may increase shortly after herpes zoster, but little is known about this association for patients with autoimmune (AI) diseases, who are at increased risk both for zoster and stroke. **METHODS:** Medicare data (2006-2013) was used to identify patients with autoimmune diseases. The outcome of interest was hospitalized stroke. The hypothesis tested was that the incidence of stroke immediately following HZ was increased compared to the incidence of stroke at later time points. Secondary analysis included assessment of the impact of antiviral therapy on subsequent stroke as well as the influence of VZV-related complications on stroke incidence. **RESULTS:** The crude incidence of stroke ranged from a high of 2.30 (0.96-5.52) per 100 patient years within 90 days of HZ in patients who had HZ-related cranial nerve complications and did not receive treatment to a low of 0.87 (0.75-1.02) per 100py (>1 year after uncomplicated HZ). After multivariable adjustment for multiple stroke-related factors, the incidence rate ratio (IRR) for stroke in the first 90 days after HZ was 1.36 (1.10-1.68) compared to stroke >1 year after HZ. The risk was greater for patients with zoster with cranial nerve complications (IRR 2.08, 95%CI 0.99-4.36). Prompt antiviral therapy was associated with lower incidence of subsequent stroke (IRR 0.83, 95% CI 0.70- 0.98). **CONCLUSION:** In patients with autoimmune diseases, incident HZ was associated with up to a two-fold increased risk for stroke in the subsequent few months. These data provide urgency for developing strategies to reduce the risk of VZV. This article is protected by copyright. All rights reserved.

Cambareri, G. M., Giel, D. W., Bayne, A. P., Corbett, S., Schurtz, E., Kovacevic, L., et al. (2016). Do overweight and obese pediatric stone formers have differences in metabolic abnormalities compared with normal weight stone formers? *Urology*,

OBJECTIVE: To determine if 24-hour urinary parameters in children with nephrolithiasis across four institutions were influenced by body mass index (BMI). **MATERIALS AND METHODS:** The 24-hour urinary parameters obtained from children with nephrolithiasis between 2000-2013 were stratified by BMI percentile ≥ 85 th and < 85 th percentile hyperoxaluria (37.0%). Univariable and multivariable analysis revealed that overweight and obese children were more likely to have

low urinary volume and elevated uric acid compared to normal weight children. CONCLUSION: Although there is a link between stone formation and BMI in adults, no definitive conclusions have been proven in the pediatric literature. Our study indicates that stone forming children who are overweight or obese have low urinary volume and elevated uric acid compared to normal weight stone forming children.

Campbell, J. P., Kalpathy-Cramer, J., Erdogmus, D., Tian, P., Kedarisetti, D., Moleta, C., et al. (2016).

Plus disease in retinopathy of prematurity: A continuous spectrum of vascular abnormality as a basis of diagnostic variability. *Ophthalmology*,

PURPOSE: To identify patterns of interexpert discrepancy in plus disease diagnosis in retinopathy of prematurity (ROP). DESIGN: We developed 2 datasets of clinical images as part of the Imaging and Informatics in ROP study and determined a consensus reference standard diagnosis (RSD) for each image based on 3 independent image graders and the clinical examination results. We recruited 8 expert ROP clinicians to classify these images and compared the distribution of classifications between experts and the RSD. PARTICIPANTS: Eight participating experts with more than 10 years of clinical ROP experience and more than 5 peer-reviewed ROP publications who analyzed images obtained during routine ROP screening in neonatal intensive care units.

METHODS: Expert classification of images of plus disease in ROP. MAIN OUTCOME MEASURES: Interexpert agreement (weighted kappa statistic) and agreement and bias on ordinal classification between experts (analysis of variance [ANOVA]) and the RSD (percent agreement).

RESULTS: There was variable interexpert agreement on diagnostic classifications between the 8 experts and the RSD (weighted kappa, 0-0.75; mean, 0.30). The RSD agreement ranged from 80% to 94% for the dataset of 100 images and from 29% to 79% for the dataset of 34 images.

However, when images were ranked in order of disease severity (by average expert classification), the pattern of expert classification revealed a consistent systematic bias for each expert consistent with unique cut points for the diagnosis of plus disease and preplus disease.

The 2-way ANOVA model suggested a highly significant effect of both image and user on the average score (dataset A: $P < 0.05$ and adjusted $R^2 = 0.82$; and dataset B: $P < 0.05$ and adjusted $R^2 = 0.6615$).

CONCLUSIONS: There is wide variability in the classification of plus disease by ROP experts, which occurs because experts have different cut points for the amounts

of vascular abnormality required for presence of plus and preplus disease. This has important implications for research, teaching, and patient care for ROP and suggests that a continuous ROP plus disease severity score may reflect more accurately the behavior of expert ROP clinicians and may better standardize classification in the future.

Carney, N., Totten, A. M., O'Reilly, C., Ullman, J. S., Hawryluk, G. W., Bell, M. J., et al. (2016).

Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*,

The scope and purpose of this work is 2-fold: to synthesize the available evidence and to translate it into recommendations. This document provides recommendations only when there is evidence to support them. As such, they do not constitute a complete protocol for clinical use.

Our intention is that these recommendations be used by others to develop treatment protocols, which necessarily need to incorporate consensus and clinical judgment in areas where current evidence is lacking or insufficient. We think it is important to have evidence-based

recommendations to clarify what aspects of practice currently can and cannot be supported by evidence, to encourage use of evidence-based treatments that exist, and to encourage creativity in treatment and research in areas where evidence does not exist. The communities of

neurosurgery and neuro-intensive care have been early pioneers and supporters of evidence-based medicine and plan to continue in this endeavor. The complete guideline document, which summarizes and evaluates the literature for each topic, and supplemental appendices (A-I) are

available online at <https://www.braintrauma.org/coma/guidelines>. ABBREVIATIONS: TBI, traumatic brain injury; RESCUEicp, Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP.

Carney, P. A., Crites, G. E., Miller, K. H., Haight, M., Stefanidis, D., Cichoskikelly, E., et al. (2016).

Building and executing a research agenda toward conducting implementation science in medical education. *Medical Education Online*, 21, 32405.

BACKGROUND: Implementation science (IS) is the study of methods that successfully integrate best evidence into practice. Although typically applied in healthcare settings to improve patient care and subsequent outcomes, IS also has immediate and practical applications to medical education toward improving physician training and educational outcomes. The objective of this

article is to illustrate how to build a research agenda that focuses on applying IS principles in medical education. APPROACH: We examined the literature to construct a rationale for using IS to improve medical education. We then used a generalizable scenario to step through a process for applying IS to improve team-based care. PERSPECTIVES: IS provides a valuable approach to medical educators and researchers for making improvements in medical education and overcoming institution-based challenges. It encourages medical educators to systematically build upon the research outcomes of others to guide decision-making while evaluating the successes of best practices in individual environments and generate additional research questions and findings. CONCLUSIONS: IS can act as both a driver and a model for educational research to ensure that best educational practices are easier and faster to implement widely.

Carson, J. W., Carson, K. M., Jones, K. D., Lancaster, L., & Mist, S. D. (2016). Mindful yoga pilot study shows modulation of abnormal pain processing in fibromyalgia patients. *International Journal of Yoga Therapy,*

Published findings from a randomized controlled trial have shown that Mindful Yoga training improves symptoms, functional deficits, and coping abilities in individuals with fibromyalgia and that these benefits are replicable and can be maintained 3 months post-treatment. The aim of this study was to collect pilot data in female fibromyalgia patients (n = 7) to determine if initial evidence indicates that Mindful Yoga also modulates the abnormal pain processing that characterizes fibromyalgia. Pre- and post-treatment data were obtained on quantitative sensory tests and measures of symptoms, functional deficits, and coping abilities. Separation test analyses indicated significant improvements in heat pain tolerance, pressure pain threshold, and heat pain after-sensations at post-treatment. Fibromyalgia symptoms and functional deficits also improved significantly, including physical tests of strength and balance, and pain coping strategies. These findings indicate that further investigation is warranted into the effect of Mindful Yoga on neurobiological pain processing.

Casanueva, F., & Gerecci, D. (2016). Objective comparison of nasal tip contours in the basal view between dome binding and hemitransdomal tip suture techniques in rhinoplasty. *JAMA Facial Plastic Surgery,*

Importance: The dome binding suture (DBS) used for nasal tip refinement creates the unwanted effects of nasal tip pinching owing to shadowing and loss of alar support. The hemitransdomal suture (HTS), however, refines the nasal tip while maintaining a natural contour between the nasal tip and the alar lobule. To our knowledge, no objective comparison between the DBS and HTS techniques has been described in the literature to date. Objective: To determine whether the DBS or HTS technique results in an objectively satisfactory outcome in nasal tip contouring when assessed from the perspective of the basal view. Design, Setting, and Participants: Postoperative basal view photographs of cosmetic rhinoplasty procedures performed on 112 Hispanic/Mestizo patients (85 [76%] women, and 27 [24%] men) in a facial plastic surgery practice in Chile, from May 2013 to May 2015 were reviewed. Only patients who underwent either DBS or HTS were included. Follow-up ranged from 6-24 months. Comparison of the nasal contour to the ideal tip-lobule line was performed and classified as satisfactory or unsatisfactory. Main Outcomes and Measures: Satisfactory or unsatisfactory nasal tip contour in the basal view as analyzed by comparison with the ideal tip-lobule line. Results: A total of 143 rhinoplasty procedures were performed over a 2-year period (May 2013-May 2015). A total of 112 patients met inclusion criteria. Of the 112 participants, mean (SD) age was 30 (9) years; 22 patients underwent DBS and 90 underwent HTS. Of the patients who underwent DBS, 5 of 22 (22.7%) had satisfactory contours. Of the patients who underwent HTS, 84 of 90 (93.3%) had satisfactory contours. Conclusions and Relevance: Comparison of nasal contour in the basal view with the ideal tip-lobule line demonstrates a statistically significant improvement in the rate of satisfactory outcomes using the HTS compared with the DBS technique. This study is the first, to our knowledge, to provide objective data to support the use of this technique when performing tip contouring in rhinoplasty. Level of Evidence: 4.

Champieux, R. (2015). Plumx. *Journal of the Medical Library Association*, 103(1), 63-64.

Chan, T. M., Gottlieb, M., Fant, A. L., Messman, A., Robinson, D. W., Cooney, R. R., et al. (2016). Academic primer series: Five key papers fostering educational scholarship in junior academic faculty. *Western Journal of Emergency Medicine*, 17(5), 519-526.

Introduction: Scholarship is an essential part of academic success. Junior faculty members are

often unfamiliar with the grounding literature that defines educational scholarship. In this article, the authors aim to summarize five key papers which outline education scholarship in the setting of academic contributions for emerging clinician educators. Methods: The authors conducted a consensus-building process to generate a list of key papers that describe the importance and significance of academic scholarship, informed by social media sources. They then used a three-round voting methodology, akin to a Delphi study, to determine the most useful papers. Results: A summary of the five most important papers on the topic of academic scholarship, as determined by this mixed group of junior faculty members and faculty developers, is presented in this paper. These authors subsequently wrote a summary of these five papers and discussed their relevance to both junior faculty members and faculty developers. Conclusion: Five papers on education scholarship, deemed essential by the authors' consensus process, are presented in this paper. These papers may help provide the foundational background to help junior faculty members gain a grasp of the academic scholarly environment. This list may also inform senior faculty and faculty developers on the needs of junior educators in the nascent stages of their careers. © 2016 Chan et al.

Chang, A. M., Lin, A., Fu, R., McConnell, K. J., & Sun, B. (2016). Associations of emergency department length-of-stay with publicly reported quality-of-care measures. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*,

OBJECTIVE: The Institute of Medicine identified emergency department (ED) crowding as a critical threat to patient safety. We assess the association between changes in publicly reported ED length-of-stay (LOS) and changes in quality-of-care measures in a national cohort of hospitals. METHODS: Longitudinal analysis of 2012 and 2013 data from the American Hospital Association (AHA) Survey, Center for Medicare and Medicaid Services (CMS) Cost Reports, and CMS Hospital Compare. We included hospitals reporting Hospital Compare timeliness measure of LOS for admitted patients. We used AHA and CMS data to incorporate hospital predictors of interest. We used the method of first differences to test for relationships in the change over time between timeliness measures and six hospital-level measures. RESULTS: The cohort consisted of 2,619 hospitals. Each additional hour of ED LOS was associated with a 0.7% decrease in proportion of patients giving a top satisfaction rating, a 0.7% decrease in proportion of patients

who would "definitely recommend" the hospital, and a 6 minute increase in time to pain management for long bone fracture ($p < 0.01$ for all). A one hour increase in ED LOS is associated with a 44% increase in the odds of having an increase in left without being seen (LWBS) (95% CI 25-68%). ED LOS was not associated with hospital readmissions ($p = 0.14$) or time to percutaneous coronary intervention ($p = 0.14$). CONCLUSION: In this longitudinal study of hospitals across the US, improvements in ED timeliness measures are associated with improvements in the patient experience. This article is protected by copyright. All rights reserved.

Chou, R. (2016). Long-acting opioids for chronic noncancer pain were linked to mortality. *Annals of Internal Medicine*, 165(6), JC34-2016-165-6-034.

Chu, C. Q. (2016). Molecular probing of TNF: From identification of therapeutic target to guidance of therapy in inflammatory diseases. *Cytokine*,
Therapy by blocking tumor necrosis factor (TNF) activity is highly efficacious and profoundly changed the paradigm of several inflammatory diseases. However, a significant proportion of patients with inflammatory diseases do not respond to TNF inhibitors (TNFi). Prediction of therapeutic response is required for TNFi therapy. Isotope labeled anti-TNF antibodies or TNF receptor have been investigated to localize TNF production at inflammatory tissue in animal models and in patients with inflammatory diseases. The in vivo detection of TNF has been associated with treatment response. Recently, fluorophore labeled anti-TNF antibody in combination with confocal laser endomicroscopy in patients with Crohn's disease yielded more accurate and quantitative in vivo detection of TNF in the diseased mucosa. More importantly, this method demonstrated high therapeutic predication value. Fluorophore labeled TNF binding aptamers in combination with modern imaging technology offers additional tools for in vivo TNF probing.

Connelly, C., Martin, K., Elterman, J., Orman, J. A., & Zonies, D. (2016). Early traumatic brain injury screen in 6594 inpatient combat casualties. *Injury*,
INTRODUCTION: The purpose of this study was to review the inpatient traumatic brain injury (TBI) screening program at a Role IV regional resource trauma center. TBI has been coined the "signature wound" during current U.S. combat operations. All patients injured in Iraq or

Afghanistan who transit through Landstuhl Regional Medical Center (LRMC) undergo an initial TBI screen regardless of anatomic injury. The incidence and factors associated with positive screening for concussion (physical event+alteration of consciousness (AOC)) and TBI diagnoses were examined. METHODS: A retrospective review of consecutively admitted patients to LRMC who underwent a TBI screen from 5/06 to 7/11 was performed. Patient characteristics, self-reported symptoms, and TBI diagnoses were analyzed. FINDINGS: Among 43,852 patients screened during the 5-year period, 6594 were admitted, of whom, 6590 received a complete TBI screen. Predominantly male (97.1%), the mean age was 26.7+/-7.4 yrs. The average GCS and ISS at admission were 13.9+/-2.8 and 10.1+/-8.6, respectively. Positively screened patients averaged 1.8 deployments, 69.5% experienced one or more blasts, 16.1% experienced one or more vehicular crashes, with 18.0% reporting a prior head injury. Of the 2805 (42.6%) who screened positive for possible concussion, 2393 (85.3%) were diagnosed with a concussion/TBI during their inpatient stay; the remaining 412 (14.7%) were identified by screening only. Of the screened positive patients, 1953 (69.6%) reported 1 or more current concussion/TBI-related symptoms; of those with symptom(s), 532 (27.2%) reported 5 or more. CONCLUSIONS: Early screening based on self-report identified a large number of patients admitted directly from the combat zone with possible deployment-related concussion and TBI symptoms. Such screening provides valuable information to guide decisions about early management and return to duty. LEVEL OF EVIDENCE: Level III, Therapeutic.

Consani, R. L., Marinho, T., Bacchi, A., Caldas, R. A., Feitosa, V. P., & Pfeifer, C. S. (2016). Repair strength in simulated restorations of methacrylate- or silorane-based composite resins. *Brazilian Dental Journal*, 27(4), 463-467.

The study verified the bond strength in simulated dental restorations of silorane- or methacrylate-based composites repaired with methacrylate-based composite. Methacrylate- (P60) or silorane-based (P90) composites were used associated with adhesive (Adper Single Bond 2). Twenty-four hemi-hourglass-shaped samples were repaired with each composite (n=12). Samples were divided according to groups: G1= P60 + Adper Single Bond 2+ P60; G2= P60 + Adper Single Bond 2 + P60 + thermocycling; G3= P90 + Adper Single Bond 2 + P60; and G4= P90 + Adper Single Bond 2 + P60 + thermocycling. G1 and G3 were submitted to tensile test 24

h after repair procedure, and G2 and G4 after submitted to 5,000 thermocycles at 5 and 55 °C for 30 s in each bath. Tensile bond strength test was accomplished in an universal testing machine at crosshead speed of 0.5 mm/min. Data (MPa) were analyzed by two-way ANOVA and Tukey's test (5%). Sample failure pattern (adhesive, cohesive in resin or mixed) was evaluated by stereomicroscope at 30×; and images were obtained in SEM. Bond strength values of methacrylate-based composite samples repaired with methacrylate-based composite (G1 and G2) were greater than for silorane-based samples (G3 and G4). Thermocycling decreased the bond strength values for both composites. All groups showed predominance of adhesive failures and no cohesive failure in composite resin was observed. In conclusion, higher bond strength values were observed in methacrylate-based resin samples and greater percentage of adhesive failures in silorane-based resin samples, both composites repaired with methacrylate-based resin.

Copenhaver, P. F., & Ramaker, J. M. (2016). Neuronal migration during development and the amyloid precursor protein. *Current Opinion in Insect Science*, 18, 1-10.

The Amyloid Precursor Protein (APP) is the source of amyloid peptides that accumulate in Alzheimer's disease. However, members of the APP family are strongly expressed in the developing nervous systems of invertebrates and vertebrates, where they regulate neuronal guidance, synaptic remodeling, and injury responses. In contrast to mammals, insects express only one APP ortholog (APPL), simplifying investigations into its normal functions. Recent studies have shown that APPL regulates neuronal migration in the developing insect nervous system, analogous to the roles ascribed to APP family proteins in the mammalian cortex. The comparative simplicity of insect systems offers new opportunities for deciphering the signaling mechanisms by which this enigmatic class of proteins contributes to the formation and function of the nervous system. © 2016 Elsevier Inc.

Crabbe, J. C. (2016). Progress with nonhuman animal models of addiction. *Journal of Studies on Alcohol and Drugs*, 77(5), 696-699.

Nonhuman animals have been major contributors to the science of the genetics of addiction. Given the explosion of interest in genetics, it is fair to ask, are we making reasonable progress

toward our goals with animal models? I will argue that our goals are changing and that overall progress has been steady and seems likely to continue apace. Genetics tools have developed almost incredibly rapidly, enabling both more reductionist and more synthetic or integrative approaches. I believe that these approaches to making progress have been unbalanced in biomedical science, favoring reductionism, particularly in animal genetics. I argue that substantial, novel progress is also likely to come in the other direction, toward synthesis and abstraction. Another area in which future progress with genetic animal models seems poised to contribute more is the reconciliation of human and animal phenotypes, or consilience. The inherent power of the genetic animal models could be more profitably exploited. In the end, animal research has continued to provide novel insights about how genes influence individual differences in addiction risk and consequences. The rules of the genetics game are changing so fast that it is hard to remember how comparatively little we knew even a generation ago. Rather than worry about whether we have been wasting time and resources asking the questions we have been, we should look to the future and see if we can come up with some new ones. The valuable findings from the past will endure, and the sidetracks will be forgotten.

Crothers, K., Kross, E., Reisch, L. M., Shahrir, S. F., Slatore, C., Zeliadt, S. B., et al. (2016). Patients' attitudes regarding lung cancer screening and decision aids: A survey and focus group study. *Annals of the American Thoracic Society*,

RATIONALE: Little is known about vulnerable patients' perceptions and understanding of, and preferences for lung cancer screening decision aids. OBJECTIVES: To determine, in a low-income, racially diverse population, participants' experience, preferences and reactions to web-based and paper decision aids, and 2) understanding of harms and benefits of lung cancer screening.

METHODS: We enrolled outpatients at an urban county hospital in 6 focus group discussions that included review of a web-based and a paper-based lung-cancer screening decision aid.

Participants completed surveys before and after the focus groups. MEASUREMENTS AND MAIN

RESULTS: 45 patients participated (mean age 61; 76% current smokers, 24% former smokers); 27% had not completed high school; 50% had an annual income \leq 3 healthcare visits yearly.

Comparing the proportion with correct answers on pre- and postsurveys, participants' understanding of lung cancer screening increased, particularly of the harms of screening including

the potential for false-positives, extra testing, and complications. However, after conclusion of the focus groups, over 50% believed that screening lowered the chance of getting lung cancer. Five major themes emerged from qualitative analyses. PARTICIPANTS: 1) were not aware of the purpose of lung cancer screening; 2) want to know about the benefits and harms; 3) felt physicians need to communicate more effectively; 4) found decision aids helpful and influential for decision-making about screening; and 5) wanted the discussion to be personalized and tailored. Participants expressed surprise that the magnitude of their lung cancer risk and benefits of screening were lower than anticipated. CONCLUSIONS: Vulnerable patients find lung cancer screening decision aids helpful and generally show increased knowledge after reviewing decision aids, particularly of harms. Our results can inform future implementation efforts.

Cuttino, L. W., & Kubicky, C. D. (2016). Who benefits from a tumor bed boost after whole-breast radiotherapy? *JAMA Oncology*,

Davis, J. D., Olsen, M. A., Bommarito, K., LaRue, S. J., Saeed, M., Rich, M. W., et al. (2016). All-payer analysis of heart failure hospitalization 30-day readmission: Comorbidities matter. *The American Journal of Medicine*,

BACKGROUND: Thirty-day readmission following heart failure hospitalization impacts hospital performance measures and reimbursement. We investigated readmission characteristics and the magnitude of 30-day hospital readmissions after hospital discharge for heart failure using the Healthcare Cost and Utilization Project State Inpatient Databases (SID). METHODS: Adults aged ≥ 40 years hospitalized with a primary discharge diagnosis of heart failure from 2007-2011 were identified in the California, New York, and Florida SIDs. Characteristics of patients with and without 7-, 8-30-, and 30-day readmission, and primary readmission diagnoses and risk factors for readmission were examined. RESULTS: We identified 547,068 patients with mean age 74.7 years; 50.7% were female, 65.4% were white. Of 117,123 patients (21.4%) readmitted within 30 days (median 12 days), 69.7% had a non-heart failure primary readmission diagnosis. Patients with 30-day readmissions more frequently had a history of previous admission with heart failure as a secondary diagnosis, fluid and electrolyte disorders and chronic deficiency anemia. There were no significant clinical differences at baseline between those patients whose first

readmission was in the first 7 days after discharge versus in the next 23 days. The most common primary diagnoses for 30-day non-heart failure readmissions were other cardiovascular conditions (14.9%), pulmonary disease (8.5%), and infections (7.7%). CONCLUSIONS: In this large all-payer cohort, approximately 70% of 30-day readmissions were for non-heart failure causes, and the median time to readmission was 12 days. Future interventions to reduce readmissions should focus on common comorbid conditions that contribute to readmission burden.

Davis, M. Y., Johnson, C. O., Leverenz, J. B., Weintraub, D., Trojanowski, J. Q., Chen-Plotkin, A., et al. (2016). Association of GBA mutations and the E326K polymorphism with motor and cognitive progression in parkinson disease. *JAMA Neurology*,

Importance: Parkinson disease (PD) is heterogeneous in symptom manifestation and rate of progression. Identifying factors that influence disease progression could provide mechanistic insight, improve prognostic accuracy, and elucidate novel therapeutic targets. Objective: To determine whether GBA mutations and the E326K polymorphism modify PD symptom progression. Design, Setting, and Participants: The entire GBA coding region was screened for mutations and E326K in 740 patients with PD enrolled at 7 sites from the PD Cognitive Genetics Consortium. Detailed longitudinal motor and cognitive assessments were performed with patients in the on state. Main Outcomes and Measures: Linear regression was used to test for an association between GBA genotype and motor progression, with the Movement Disorder Society-sponsored version of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) score at the last assessment as the outcome and GBA genotype as the independent variable, with adjustment for levodopa equivalent dose, sex, age, disease duration, MDS-UPDRS III score at the first assessment, duration of follow-up, and site. Similar methods were used to examine the association between genotype and tremor and postural instability and gait difficulty (PIGD) scores. To examine the effect of GBA genotype on cognitive progression, patients were classified into those with conversion to mild cognitive impairment or dementia during the study (progression) and those without progression. The association between GBA genotype and progression status was then tested using logistic regression, adjusting for sex, age, disease duration, duration of follow-up, years of education, and site. Results: Of the total sample of 733 patients who underwent successful genotyping, 226 (30.8%) were women and 507 (69.2%) were

men (mean [SD] age, 68.1 [8.8] years). The mean (SD) duration of follow-up was 3.0 (1.7) years. GBA mutations (beta = 4.65; 95% CI, 1.72-7.58; P = .002), E326K (beta = 3.42; 95% CI, 0.66-6.17; P = .02), and GBA variants combined as a single group (beta = 4.01; 95% CI, 1.95-6.07; P = 1.5×10^{-4}) were associated with a more rapid decline in MDS-UPDRS III score. Combined GBA variants (beta = 0.38; 95% CI, 0.23-0.53; P = .01) and E326K (beta = 0.64; 95% CI, 0.43-0.86; P = .002) were associated with faster progression in PIGD scores, but not in tremor scores. A significantly higher proportion of E326K carriers (10 of 21 [47.6%]; P = .01) and GBA variant carriers (15 of 39 [38.5%]; P = .04) progressed to mild cognitive impairment or dementia. Conclusions and Relevance: GBA variants predict a more rapid progression of cognitive dysfunction and motor symptoms in patients with PD, with a greater effect on PIGD than tremor. Thus, GBA variants influence the heterogeneity in symptom progression observed in PD.

De Boer, E., Chen, F., Zha, D., & Nuttall, A. L. (2015). Optical coherence tomography (OCT) leading to more insight into cochlear mechanics. *12th International Workshop on the Mechanics of Hearing: Protein to Perception*, , 1703.

Optical Coherence Tomography (OCT) was used to measure vibrations of the basilar membrane (BM) and the Reticular Lamina (RL) in the cochlea of the Guinea pig, at frequencies up to 25...kHz. Because of the difficulty of the experiments the data have limited sets of parameters and are subject to high noise levels. In a viable Guinea-pig cochlea, the RL moves in the region of maximum response with a larger amplitude than the BM. We cannot rule out that some of that difference is due to a geometrical factor. We also found a consistent increase of this amplitude difference with frequency, which points to a low-pass filtering process. That process might be linked to the mass of the fluid contained in the Organ of Corti channel (OoC channel). © 2015 AIP Publishing LLC.

DeRyckere, D., Lee Sherick, A. B., Huey, M. G., Hill, A. A., Tyner, J. W., Jacobsen, K. M., et al. (2016). UNC2025, a MerTK small molecule inhibitor, is therapeutically effective alone and in combination with methotrexate in leukemia models. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,
PURPOSE: MerTK tyrosine kinase is ectopically expressed in 30-50% of acute lymphoblastic

leukemias (ALL) and over 80% of acute myeloid leukemias (AML) and is a potential therapeutic target. Here, we evaluated the utility of UNC2025, a MerTK tyrosine kinase inhibitor, for treatment of acute leukemia. EXPERIMENTAL DESIGN: Pre-clinical in vitro and in vivo assays using cell lines and primary leukemia patient samples were utilized to evaluate anti-leukemic effect of UNC2025. RESULTS: UNC2025 potently inhibited pro-survival signaling, induced apoptosis and reduced proliferation and colony formation in MerTK-expressing ALL and AML cell lines and patient samples. Approximately 30% of primary leukemia patient samples (78 of 261 total) were sensitive to UNC2025. Sensitive samples were most prevalent in the AML, T-ALL, and minimally differentiated (M0) AML subsets. UNC2025 inhibited MerTK in bone marrow leukemia cells and had significant therapeutic effects in xenograft models, with dose-dependent decreases in tumor burden and consistent two-fold increases in median survival, irrespective of starting disease burden. In a patient-derived AML xenograft model, treatment with UNC2025 induced disease regression. Additionally, UNC2025 increased sensitivity to methotrexate in vivo, suggesting that addition of MerTK-targeted therapy to current cytotoxic regimens may be particularly effective and/or allow for chemotherapy dose reduction. CONCLUSIONS: The broad spectrum activity mediated by UNC2025 in leukemia patient samples and xenograft models, alone or in combination with cytotoxic chemotherapy, support continued development of MerTK inhibitors for treatment of leukemia.

DeVoe, J. E., Likumahuwa-Ackman, S., Shannon, J., & Steiner Hayward, E. (2016). Creating 21st-century laboratories and classrooms for improving population health: A call to action for academic medical centers. *Academic Medicine : Journal of the Association of American Medical Colleges*, Academic medical centers (AMCs) in the United States built world-class infrastructure to successfully combat disease in the 20th century, which is inadequate for the complexity of sustaining and improving population health. AMCs must now build first-rate 21st-century infrastructure to connect combating disease and promoting health. This infrastructure must acknowledge the bio-psycho-social-environmental factors impacting health and will need to reach far beyond the AMC walls to foster community "laboratories" that support the "science of health," complementary to those supporting the "science of medicine"; cultivate community "classrooms" to stimulate learning and discovery in the places where people live, work, and play; and

strengthen bridges between academic centers and these community laboratories and classrooms to facilitate bidirectional teaching, learning, innovation, and discovery. Private and public entities made deep financial investments that contributed to the AMC disease-centered approach to clinical care, education, and research in the 20th century. Many of these same funders now recognize the need to transform U.S. health care into a system that is accountable for population health and the need for a medical workforce equipped with the skills to measure and improve health. Innovative ideas about communities as centers of learning, the importance of social factors as major determinants of health, and the need for multidisciplinary perspectives to solve complex problems are not new; many are 20th-century ideas still waiting to be fully implemented. The window of opportunity is now. The authors articulate how AMCs must take bigger and bolder steps to become leaders in population health.

Devore, E. E., Harrison, S. L., Stone, K. L., Holton, K. F., Barrett-Connor, E., Ancoli-Israel, S., et al. (2016). Association of urinary melatonin levels and aging-related outcomes in older men. *Sleep Medicine, 23*, 73-80.

Background Circadian disruptions can contribute to accelerated aging, and the circadian system regulates cognitive and physical functions; therefore, circadian markers (eg, melatonin) may be associated with key aspects of healthy aging and longevity. Objective To evaluate urinary melatonin levels in relation to cognitive function, physical function, and mortality among 2,821 older men in the Osteoporotic Fractures in Men Study Design Cohort study. Measurements In 2003–2005, participants provided first-morning spot urine samples, which were assayed for 6-sulfatoxymelatonin (the primary melatonin metabolite in urine); cognitive and physical function assessments were completed twice, at baseline and an average of 6.5 years later. Participant deaths were confirmed by central review of death certificates over a mean of 9.2 years of follow up. Results In multivariable-adjusted regression models, we observed a significant trend of better Digit Vigilance Test scores (ie, decreased time to completion) at baseline across increasing melatonin quartiles (p -trend = 0.01); however, mean time-to-completion scores did not significantly differ comparing extreme quartiles (group means: 547.1 seconds (95% CI: 533.6, 560.6) versus 561.3 seconds (95% CI: 547.8, 574.9)), and there were no associations of urinary melatonin levels with other cognitive test scores, or any cognitive change scores over time.

Furthermore, melatonin levels were not related to physical function scores (p-trends = 0.4 for walking speed, 0.7 for chair stands, and 0.6 for grip strength in fully-adjusted models) or mortality risk (p-trend = 0.3 in the fully-adjusted model). Conclusion We found little evidence of associations between urinary melatonin levels and key measures of healthy aging and mortality in this cohort of older men. Further research should explore the relation of melatonin, particularly if assessed earlier in life, and other circadian markers with healthy aging outcomes. © 2016 Elsevier B.V.

Dexter, E. N., Fields, S., Rdesinski, R. E., Sachdeva, B., Yamashita, D., & Marino, M. (2016). Patient-provider communication: Does electronic messaging reduce incoming telephone calls? *Journal of the American Board of Family Medicine*, 29(5), 613-619.

Purpose: Internet-based patient portals are increasingly being implemented throughout health care organizations to enhance health and optimize communication between patients and health professionals. The decision to adopt a patient portal requires careful examination of the advantages and disadvantages of implementation. This study aims to investigate 1 proposed advantage of implementation: Alleviating some of the clinical workload faced by employees. Methods: A retrospective time-series analysis of the correlation between the rate of electronic patient- to-provider messages-a common attribute of Internet-based patient portals-and incoming telephone calls. The rate of electronic messages and incoming telephone calls were monitored from February 2009 to June 2014 at 4 economically diverse clinics (a federally qualified health center, a rural health clinic, a community-based clinic, and a university-based clinic) related to 1 university hospital. Results: All 4 clinics showed an increase in the rate of portal use as measured by electronic patientto- provider messaging during the study period. Electronic patient-to-provider messaging was significantly positively correlated with incoming telephone calls at 2 of the clinics ($r = 0.546$, $P < .001$ and $r = 0.543$, $P < .001$). The remaining clinics were not significantly correlated but demonstrated a weak positive correlation ($r = 0.098$, $P = .560$ and $r = 0.069$, $P = .671$). Conclusions: Implementation and increased use of electronic patient-to-provider messaging was associated with increased use of telephone calls in 2 of the study clinics. While practices are increasingly making the decision of whether to implement a

patient portal as part of their system of care, it is important that the motivation behind such a change not be based on the idea that it will alleviate clinical workload.

Dickson, V. V., Lee, C., Yehle, K. S., Abel, W. M., & Riegel, B. (2016). Psychometric testing of the self-care of hypertension inventory. *Journal of Cardiovascular Nursing,*

BACKGROUND:: Hypertension (HTN) is a global public health issue. Self-care is an essential component of HTN treatment, but no instruments are available with which to measure self-care of HTN. OBJECTIVES:: The purpose of this study is to test the psychometric properties of the Self-care of Hypertension Inventory (SC-HI). METHODS:: Using the Self-care of Chronic Illness theory, we developed a 24-item measure of maintenance, monitoring, and management appropriate for persons with chronic HTN, tested it for content validity, and then tested it in a convenience sample of 193 adults. Exploratory factor analysis was used to identify measure structure. Cronbach's α and factor determinacy scores and were used to assess reliability. Validity was tested with the Medical Outcomes Study General Adherence Scale and the Decision Making Competency Inventory. RESULTS:: Seventy percent of the sample was female; mean age was 56.4 ± 13 years; mean duration of HTN was 11 ± 9 years. Removal of 1 item on alcohol consumption resulted in a unidimensional self-care maintenance factor with acceptable structure and internal consistency ($\alpha = .83$). A multidimensional self-care management factor included "consultative" and "autonomous" factors (factor determinacy score = 0.75). A unidimensional confidence factor captured confidence in and persistence with each aspect of self-care ($\alpha = .83$). All the self-care dimensions in the final 23-item instrument were associated with treatment adherence and several with decision making. CONCLUSION: These findings support the conceptual basis of self-care in patients with HTN as a process of maintenance, monitoring, and management. The SC-HI confidence scale is promising as a measure of self-efficacy in self-care. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved

Dumontier, M., Gray, A. J., Marshall, M. S., Alexiev, V., Ansell, P., Bader, G., et al. (2016). The health care and life sciences community profile for dataset descriptions. *Peerj, 4*, e2331.

Access to consistent, high-quality metadata is critical to finding, understanding, and reusing scientific data. However, while there are many relevant vocabularies for the annotation of a

dataset, none sufficiently captures all the necessary metadata. This prevents uniform indexing and querying of dataset repositories. Towards providing a practical guide for producing a high quality description of biomedical datasets, the W3C Semantic Web for Health Care and the Life Sciences Interest Group (HCLSIG) identified Resource Description Framework (RDF) vocabularies that could be used to specify common metadata elements and their value sets. The resulting guideline covers elements of description, identification, attribution, versioning, provenance, and content summarization. This guideline reuses existing vocabularies, and is intended to meet key functional requirements including indexing, discovery, exchange, query, and retrieval of datasets, thereby enabling the publication of FAIR data. The resulting metadata profile is generic and could be used by other domains with an interest in providing machine readable descriptions of versioned datasets.

Dworkin, A., Lee, D. S., An, A. R., & Goodlin, S. J. (2016). A simple tool to predict development of

delirium after elective surgery. *Journal of the American Geriatrics Society*,

OBJECTIVES: To identify a quick clinical tool to assess the risk of delirium after elective surgery.

DESIGN: Prospective observational study. SETTING: Preoperative assessment clinic at the

Veterans Affairs Portland Health Care System. PARTICIPANTS: Community-living veterans aged 65 and older scheduled for elective surgery requiring general or major anesthesia.

MEASUREMENTS: Confusion Assessment Method (CAM) or Family Confusion Assessment Method (FAM-CAM). Data on education, medications, substance use, Patient Health Questionnaire (PHQ-

9), Study of Osteoporotic Fractures Frailty, Mini-Cog, and Charlson-Deyo score were collected preoperatively. RESULTS: Of 114 veterans who agreed to participate, 76 completed the final

delirium assessment. Ten of the 76 (13%) developed delirium in the 72 hours after surgery as

assessed using the CAM or FAM-CAM. In bivariate analysis, factors that increased the odds of

delirium at least three times were low education; poor PHQ-9, clock draw, word recall, Mini-Cog, and poor preoperative orientation scores; alcohol use; and higher comorbidities as measured

using Charlson-Deyo index. Scoring the Mini-Cog from 0 to 5 had a higher predictive power (area under the receiving operating characteristic curve = 0.77) than other approaches to scoring the

Mini-Cog. Other models did not significantly improve prediction of postoperative delirium risk and

would be complicated to use in a clinical setting. CONCLUSION: In this sample of veterans who

had elective surgery with major anesthesia, Mini-Cog score predicted likelihood of postoperative delirium.

El Youssef, J. (2016). IN CONTROL of type 1 diabetes, despite hypoglycaemia unawareness. *The Lancet.Diabetes & Endocrinology*,

Espay, A. J., Bonato, P., Nahab, F. B., Maetzler, W., Dean, J. M., Klucken, J., et al. (2016). Technology in parkinson's disease: Challenges and opportunities. *Movement Disorders*, 31(9), 1272-1282.

The miniaturization, sophistication, proliferation, and accessibility of technologies are enabling the capture of more and previously inaccessible phenomena in Parkinson's disease (PD).

However, more information has not translated into a greater understanding of disease complexity to satisfy diagnostic and therapeutic needs. Challenges include noncompatible technology platforms, the need for wide-scale and long-term deployment of sensor technology (among vulnerable elderly patients in particular), and the gap between the "big data" acquired with sensitive measurement technologies and their limited clinical application. Major opportunities could be realized if new technologies are developed as part of open-source and/or open-hardware platforms that enable multichannel data capture sensitive to the broad range of motor and nonmotor problems that characterize PD and are adaptable into self-adjusting, individualized treatment delivery systems. The International Parkinson and Movement Disorders Society Task Force on Technology is entrusted to convene engineers, clinicians, researchers, and patients to promote the development of integrated measurement and closed-loop therapeutic systems with high patient adherence that also serve to (1) encourage the adoption of clinico-pathophysiologic phenotyping and early detection of critical disease milestones, (2) enhance the tailoring of symptomatic therapy, (3) improve subgroup targeting of patients for future testing of disease-modifying treatments, and (4) identify objective biomarkers to improve the longitudinal tracking of impairments in clinical care and research. This article summarizes the work carried out by the task force toward identifying challenges and opportunities in the development of technologies with potential for improving the clinical management and the quality of life of individuals with PD.

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Fan, D., O'Brien Johnson, G., Tratnyek, P. G., & Johnson, R. L. (2016). Sulfidation of nano zerovalent iron (nZVI) for improved selectivity during in-situ chemical reduction (ISCR). *Environmental Science and Technology*, 50(17), 9558-9565.

The high reactivity of nano zerovalent iron (nZVI) leads to inefficient treatment due to competition with various natural reductant demand (NRD) processes, especially the reduction of water to hydrogen. Here we show that this limitation can be alleviated by sulfidation (i.e., modification by reducing sulfur compounds). nZVI synthesized on carboxymethylcellulose (CMC-nZVI) was sulfidated with either sulfide or dithionite. The reactivity of the resulting materials was examined with three complementary assays: (i) direct measurement of hydrogen production, (ii) reduction of a colorimetric redox probe (indigo disulfonate, I2S), and (iii) dechlorination of trichloroethylene (TCE). The results indicate that sulfidation at S/Fe molar ratios of ≥ 0.3 , effectively eliminates reaction with water, but retains significant reactivity with TCE. However, sulfidation with sulfide leaves most of the nZVI as Fe(0), whereas dithionite converts a majority of the nZVI to FeS (thus consuming much of the reducing capacity originally provided by the Fe(0)). Simplified numerical models show that the reduction kinetics of I2S and TCE are mainly dependent on the initial reducing equivalents and that the TCE reduction rate is affected by the aging of FeS. Overall, the results suggest that pretreatment of nZVI with reducing sulfur compounds could result in substantial improvement in nZVI selectivity. © 2016 American Chemical Society.

Fan, D., O'Carroll, D. M., Elliott, D. W., Xiong, Z., Tratnyek, P. G., Johnson, R. L., et al. (2016). Selectivity of nano zerovalent iron in in situ chemical reduction: Challenges and improvements. *Remediation*, 26(4), 27-40.

Nano zerovalent iron (nZVI) is a promising remediation technology utilizing in situ chemical reduction (ISCR) to clean up contaminated groundwater at hazardous waste sites. The small particle size and large surface area of nZVI result in high reactivity and rapid destruction of contaminants. Over the past 20 years, a great deal of research has advanced the nZVI technology from bench-scale tests to field-scale applications. However, to date, the overall number of well-characterized nZVI field deployments is still small compared to other alternative remedies that are more widely applied. Apart from the relatively high material cost of nZVI and

questions regarding possible nanotoxicological side effects, one of the major obstacles to the widespread utilization of nZVI in the field is its short persistence in the environment due to natural reductant demand (NRD). The NRD for nZVI is predominantly due to reduction of water, but other reactions with naturally present oxidants (e.g., oxygen) occur, resulting in situ conditions that are reducing (high in ferrous iron phases and H₂) but with little or no Fe(0). This article reviews the main biogeochemical processes that determine the selectivity and longevity of nZVI, summarizes data from prior (laboratory and field) studies on the longevity of various common types of nZVI, and describes modifications of nZVI that could improve its selectivity and longevity for full-scale applications of ISCR. © 2016 Wiley Periodicals, Inc. ©2016 Wiley Periodicals, Inc.

Fazio, S., & Pamir, N. (2016). HDL particle size and functional heterogeneity. *Circulation Research*, *119*(6), 704-707.

Fink, E. L., Prince, D. K., Kaltman, J. R., Atkins, D. L., Austin, M., Warden, C., et al. (2016).

Unchanged pediatric out-of-hospital cardiac arrest incidence and survival rates with regional variation in north america. *Resuscitation*, *107*, 121-128.

AIM: Outcomes for pediatric out-of-hospital cardiac arrest (OHCA) are poor. Our objective was to determine temporal trends in incidence and mortality for pediatric OHCA. METHODS: Adjusted incidence and hospital mortality rates of pediatric non-traumatic OHCA patients from 2007-2012 were analyzed using the 9 region Resuscitation Outcomes Consortium-Epidemiological Registry (ROC-Epistry) database. Children were divided into 4 age groups: perinatal (0.05) but there was a non-significant linear trend (1.3% increase) in infants. In the multivariable logistic regression analysis, infants, unwitnessed event, initial rhythm of asystole, and region were associated with worse survival, all $p < 0.001$. Survival by region ranged from 2.6-14.7%. Regions with the highest survival had more cases of EMS-witnessed OHCA, bystander CPR, and increased EMS-defibrillation (all $p < 0.05$). CONCLUSIONS: Overall incidence and survival of children with OHCA in ROC regions did not significantly change over a recent 5year period. Regional variation represents an opportunity for further study to improve outcomes.

Fino, P. C., Nussbaum, M. A., & Brolinson, P. G. (2016). Decreased high-frequency center-of-pressure complexity in recently concussed asymptomatic athletes. *Gait & Posture, 50*, 69-74.

Two experiments compared multiple methods of estimating postural stability entropy to address: 1) if postural complexity differences exist between concussed and healthy athletes immediately following return-to-play; 2) which methods best detect such differences; and 3) what is an appropriate interpretation of such differences. First, center of pressure (COP) data were collected from six concussed athletes over the six weeks immediately following their concussion and from 24 healthy athletes. Second, 25 healthy non-athletes performed four quiet standing tasks: normal, co-contracting their lower extremity muscles, performing a cognitive arithmetic task, and voluntarily manipulating their sway. Postural complexity was calculated using approximate, sample, multi-variate sample, and multi-variate composite multi-scale (MV-CompMSE) entropy methods for both high-pass filtered and low-pass filtered COP data. MV-CompMSE of the high-pass filtered COP signal identified the most consistent differences between groups, with concussed athletes exhibiting less complexity over the high frequency COP time-series. Among healthy non-athletes, high-pass filtered MV-CompMSE increased only in the co-contraction condition, suggesting the decrease in high frequency MV-CompMSE found in concussed athletes may be due to more relaxed muscles or less complex muscle contractions. This decrease in entropy may associate with reported increases in intra-cortical inhibition. Furthermore, a single-case study suggested high frequency MV-CompMSE may be a useful clinical tool for concussion management.

Fleseriu, M., Bodach, M. E., Tumialan, L. M., Bonert, V., Oyesiku, N. M., Patil, C. G., et al. (2016).

Congress of neurological surgeons systematic review and evidence-based guideline for pretreatment endocrine evaluation of patients with nonfunctioning pituitary adenomas. *Neurosurgery, 79*(4), E527-9.

BACKGROUND: Nonfunctioning pituitary adenomas (NFPAs) are among the most common pituitary lesions and may present with hypopituitarism and/or hyperprolactinemia. OBJECTIVE: To review the existing literature as it pertains to preoperative endocrine assessment in the workup for NFPAs. METHODS: A systematic review methodology was utilized to identify and screen articles assessing the role and results of preoperative laboratory assessment in patients

with NFPAs. The prevalence of individual pituitary hormonal axis deficiencies was reviewed.

RESULTS: Twenty-nine studies met inclusion criteria for analysis. No class I evidence was available, and all studies met criteria for class II evidence. Baseline serum laboratory assessment showed a prevalence of overall hypopituitarism in 37% to 85% of patients. The most common hormonal axis deficiency was growth hormone deficiency, prevalent in 61% to 100% of patients. The next most common deficit was hypogonadism, seen in 36% to 95% of patients. Adrenal insufficiency was diagnosed in 17% to 62% of patients. Finally, hypothyroidism was seen in 8% to 81% of patients. Hyperprolactinemia was seen in 25% to 65% of patients, with a mean level of 39 ng/mL and with a minority of patients exceeding a serum prolactin level of 200 ng/mL. No evidence supporting routine biomarker testing (eg, alpha-subunit or chromogranin A) or genetic testing in patients with sporadic NFPAs was available. **CONCLUSION:** Despite a paucity of class I evidence, multiple retrospective studies have demonstrated a high prevalence of hypopituitarism in patients with NFPAs. Routine endocrine analysis of all anterior pituitary axes to assess for hypopituitarism is recommended, with prolactin and insulin-like growth factor 1 evaluation also valuable to assess for hypersecretion states that might not be clinically suspected. The full guidelines document for this chapter can be located at https://www.cns.org/guidelines/guidelines-management-pituitary-adenomas/Chapter_3. **ABBREVIATIONS:** GH, growth hormone; IGF-1, insulin-like growth factor 1; NFPA, nonfunctioning pituitary adenoma.

Fleseriu, M., & Castinetti, F. (2016). Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: A focus on novel therapies. *Pituitary*,

PURPOSE: Endogenous Cushing's syndrome (CS) is a rare disease that results from exposure to high levels of cortisol; Cushing's disease (CD) is the most frequent form of CS. Patients with CS suffer from a variety of comorbidities that increase the risk of mortality. Surgical resection of the disease-causing lesion is generally the first-line treatment of CS. However, some patients may not be eligible for surgery due to comorbidities, and approximately 25 % of patients, especially those with CD, have recurrent disease. For these patients, adrenal steroidogenesis inhibitors may control cortisol elevation and subsequent symptomatology. CS is rare overall, and clinical studies of adrenal steroidogenesis inhibitors are often small and, in many cases, data are limited

regarding the efficacy and safety of these treatments. Our aim was to better characterize the profiles of efficacy and safety of currently available adrenal steroidogenesis inhibitors, including drugs currently in development. METHODS: We performed a systematic review of the literature regarding adrenal steroidogenesis inhibitors, focusing on novel drugs. RESULTS: Currently available adrenal steroidogenesis inhibitors, including ketoconazole, metyrapone, etomidate, and mitotane, have variable efficacy and significant side effects, and none are approved by the US Food and Drug Administration for CS. Therefore, there is a clear need for novel, prospectively studied agents that have greater efficacy and a low rate of adverse side effects. Efficacy and safety data of current and emerging adrenal steroidogenesis inhibitors, including osilodrostat (LCI699) and levoketoconazole (COR-003), show promising results that will have to be confirmed in larger-scale phase 3 studies (currently ongoing). CONCLUSIONS: The management of CS, and particularly CD, remains challenging. Adrenal steroidogenesis inhibitors can be of major interest to control the hypercortisolism at any time point, either before or after surgery, as discussed in this review.

Fleseriu, M., Hamrahian, A. H., Hoffman, A. R., Kelly, D. F., Katznelson, L., & AACE Neuroendocrine and Pituitary Scientific Committee *. (2016). Diagnosis of recurrence in Cushing's disease: American association of clinical endocrinologists and American college of endocrinology disease state clinical review. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*,
Recurrence of hypercortisolemia after initial treatment of Cushing's disease (CD) is more common than previously thought, with a third of patients suffering a recurrence over their lifetime. Awareness of this high rate and delayed timeline (sometimes decades) of potential recurrence is critical and patients with CD should be monitored at regular intervals throughout their lives. In this manuscript, we review the complex evaluation needed for defining CD remission versus persistent disease after surgery, and focus on challenges in diagnosing early recurrent hypercortisolemia. Late night salivary cortisol appears to be an earlier predictor of recurrence when compared with urinary free cortisol excretion. We also review the criteria suggested to define recurrence of hypercortisolemia in patients treated with medical therapy. Further research

is needed to determine the optimal way to evaluate a patient with Cushing's disease recurrence as well as the risk-benefit ratio of treatment in early, mild recurrent disease.

Ford, G. A., Denniston, S., Sesser, D., Skeels, M. R., & LaFranchi, S. H. (2016). Transient versus permanent congenital hypothyroidism after the age of 3 years in infants detected on the first versus second newborn screening test in Oregon, USA. *Hormone Research in Paediatrics*, , 169-177.

Background/Aims: The newborn screening (NBS) program in Oregon, USA, collects two routine specimens in all infants. The aim of our study was to determine the incidence of permanent versus transient congenital hypothyroidism (CH) in infants detected on the first versus second screening test. Methods: Thyroid function was determined in infants after the age of 3 years diagnosed with CH and born in Oregon between 2005 and 2011. Permanent hypothyroidism was defined as a TSH rise >10 mIU/ml after the first year on treatment or a TSH rise >6 mIU/ml with temporary discontinuation of l-thyroxine after the age of 3 years. Results: Of the cases detected on the first test, 72 of 87 (83%) were permanent and 15 of 87 (17%) were transient, while of the cases detected on the second test, 5 of 22 (23%) were permanent and 17 of 22 (77%) were transient (OR 16.3, $p < 0.001$). There was a female preponderance detected on the first screen versus a male preponderance on the second screen. Blood spot and serum thyroid function tests at diagnosis, before treatment, were not meaningfully different between the two groups. The mean l-thyroxine dose at the age of 3 years was greater on the first screen: 61.2 versus 36.6 $\mu\text{g}/\text{day}$. Conclusions: Infants detected on the second NBS specimen have a higher incidence of transient CH. © 2016 S. Karger AG, Basel

Fridberger, A., & Guinan, J. J., Jr. (2015). What shapes the stimulus to the inner hair cell?: A moderated discussion. *12th International Workshop on the Mechanics of Hearing: Protein to Perception*, , 1703.

The following is an edited transcript of a recorded discussion session on the topic of "What Shapes the Stimulus to the Inner Hair Cell?". The discussion, moderated by the authors, took place at the 12th International Workshop on the Mechanics of Hearing held at Cape Sounio, Greece, in June 2014. All participants knew that the session was being recorded. In view of both

the spontaneous nature of the discussion and the editing, however, this transcript may not represent the considered or final views of the participants, and may not represent a consensus of experts in the field. The reader is advised to consult additional independent publications. © 2015 AIP Publishing LLC.

Fujiwara, K., Irei, M., Kiyota, N., Yaguchi, C., & Maeda, K. (2016). Event-related brain potential and postural muscle activity during standing on an oscillating table while the knee, hip, and trunk are fixed. *Journal of Physiological Anthropology*, 35, 6-016-0088-4.

BACKGROUND: In this study, a cast brace was used to immobilize the knee, hip, and trunk, and relations between the event-related brain potential (ERP) and postural muscle activity were investigated while standing on an oscillating table. **METHODS:** Twelve healthy young adults maintained a standing posture for 1 min per trial while oscillating in the anteroposterior direction at 0.5 Hz with a 2.5-cm amplitude. Trials were performed without and with the cast brace (no-fixation and fixation condition, respectively) until the subject had adapted to the floor oscillation. The ERP from the Cz electrode, postural muscle activity, and joint movement range were analyzed for the first and last two trials (before and after adaptation, respectively). **RESULTS:** Movement range of the hip and knee was lower in the fixation condition than in the no-fixation condition, and postural control was achieved by pivoting at the ankle. Peak muscle activity was largest in the gastrocnemius (GcM) in both conditions. GcM activity significantly increased after fixation and then decreased with adaptation. The time of peak erector spinae (ES) activity in the fixation condition was significantly earlier than in the no-fixation condition and was not significantly different from the time of the anterior reversal and peak of triceps surae activity. The negative ERP peaked approximately 80 ms after the anterior reversal. Significant correlations between the time of the peak negative ERP and the peak GcM, soleus, and ES activity were observed only after the adaptation, and were greater in the fixation condition ($r = 0.83, 0.84,$ and $0.83,$ respectively) than in the no-fixation condition ($r = 0.62, 0.73,$ and $0.51,$ respectively). **CONCLUSION:** All joints of the leg and trunk except for the ankle were rigidly fixed by the cast brace, and the phase differences between body segments were very small in the fixation condition. High correlations between the time of the peak negative ERP and the peak GcM, soleus, and ES activity after adaptation in the fixation condition suggest that attention would be

more focused on anticipatory processing of muscle sensory information from the triceps surae and/or ES, particularly GcM, which had the greatest activation.

Gaglioti, A. H., Werner, J. J., Rust, G., Fagnan, L. J., & Neale, A. V. (2016). Practice-based research networks (PBRNs) bridging the gaps between communities, funders, and policymakers. *Journal of the American Board of Family Medicine*, 29(5), 630-635.

In this commentary, we propose that practice-based research networks (PBRNs) engage with funders and policymakers by applying the same engagement strategies they have successfully used to build relationships with community stakeholders. A community engagement approach to achieve new funding streams for PBRNs should include a strategy to engage key stakeholders from the communities of funders, thought leaders, and policymakers using collaborative principles and methods. PBRNs that implement this strategy would build a robust network of engaged partners at the community level, across networks, and would reach state and federal policymakers, academic family medicine departments, funding bodies, and national thought leaders in the redesign of health care delivery.

Gajendrareddy, P. K., Junges, R., Cygan, G., Zhao, Y., Marucha, P. T., & Engeland, C. G. (2016).

Increased oxygen exposure alters collagen expression and tissue architecture during ligature-induced periodontitis. *Journal of Periodontal Research*,

BACKGROUND AND OBJECTIVE: The aim of this study was to evaluate the effects of increased oxygen availability on gene expression and on collagen deposition/maturation in the periodontium following disease. MATERIAL AND METHODS: Male Wistar rats had ligatures placed around their molars to induce periodontal disease, and a subset of animals underwent hyperbaric oxygen (HBO) treatment for 2 h twice per day. At 15 and 28 d, tissue gene expression of COL1A1, transforming growth factor-beta1 and alkaline phosphatase was determined; other histological samples were stained with Picrosirius red to evaluate levels of collagen deposition, maturation and thickness. RESULTS: In animals that underwent HBO treatment, type I collagen expression was higher and collagen deposition, maturation and thickness were more robust. Reduced mRNA levels of transforming growth factor-beta1 and alkaline phosphatase in HBO-treated rats on day 28 suggested that a quicker resolution in both soft tissue and bone

remodeling occurred following oxygen treatment. No differences in inflammation were observed between groups. CONCLUSIONS: The extracellular matrix regenerated more quickly in the HBO-treated group as evidenced by higher collagen expression, deposition and maturation.

Galon, J., Fox, B. A., Bifulco, C. B., Masucci, G., Rau, T., Botti, G., et al. (2016). Immunoscore and immunoprofiling in cancer: An update from the melanoma and immunotherapy bridge 2015. *Journal of Translational Medicine*, 14, 273-016-1029-z.

The fifth "Melanoma Bridge Meeting" took place in Naples, December 1-5th, 2015. The main topics discussed at this meeting were: Molecular and Immuno advances, Immunotherapies and Combination Therapies, Tumor Microenvironment and Biomarkers and Immunoscore. The natural history of cancer involves interactions between the tumor and the immune system of the host. The immune infiltration at the tumor site may be indicative of host response. Significant correlations were shown between the levels of immune cell infiltration in tumors and patient's clinical outcome. Moreover, incredible progress comes from the discovery of mutation-encoded tumor neoantigens. In fact, as tumors grow, they acquire mutations that are able to influence the response of patients to immune checkpoint inhibitors. It has been demonstrated that sensitivity to PD-1 and CTLA-4 blockade in patients with advanced NSCLC and melanoma was enhanced in tumors enriched for clonal neoantigens. The road ahead is still very long, but the knowledge of the mechanisms of immune escape, the study of tumor neo-antigens as well as of tumor microenvironment and the development of new immunotherapy strategies, will make cancer a more and more treatable disease.

Gao, S. S., Jia, Y., Liu, L., Zhang, M., Takusagawa, H. L., Morrison, J. C., et al. (2016). Compensation for reflectance variation in vessel density quantification by optical coherence tomography angiography. *Investigative Ophthalmology and Visual Science*, 57(10), 4485-4492.

PURPOSE. To compensate for reflectance variation when quantifying vessel density by optical coherence tomography angiography (OCTA). METHODS. Healthy participants received 636-mm macular and 4.534.5-mm optic nerve head (ONH) angiography scans on a 70-kHz spectral-domain optical coherence tomography system. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to compute the OCTA signal. Mean reflectance

projection and maximum decorrelation projection were used to create en face OCT and OCTA images. Background OCTA noise in static tissue was evaluated in the foveal avascular zone (FAZ). Vessel density was calculated from en face retinal OCTA that was binarized according to a decorrelation threshold. RESULTS. The average retinal decorrelation noise in the FAZ was linearly related to the average logarithmic-scale OCT reflectance signal. Based on this relationship, a reflectance-adjusted decorrelation threshold equation was developed to filter out 97.5% of background OCTA noise. A fixed threshold was also used for comparison. The superficial vascular complex vessel density in the macula and ONH were significantly correlated with reflectance signal strength index (SSI) using the fixed threshold. This correlation was removed by using the reflectance-adjusted threshold. Reflectance compensation reduced population variation in 25 healthy eyes from 8.5% to 4.8% (coefficient of variation) in the macula and from 6.7% to 5.4% in the peripapillary region. Within-visit repeatability also improved from 4.4% to 1.8% in the macula and from 3% to 1.7% in the peripapillary region. CONCLUSIONS. Compensating for reflectance variation resulted in more reliable vessel density quantification in OCTA. © 2016, Association for Research in Vision and Ophthalmology Inc. All rights reserved.

Ghaehri, B. A., Cole, M., Fausel, S. C., Chuop, M., & Mace, J. C. (2016). Breastfeeding improvement following tongue-tie and lip-tie release: A prospective cohort study. *The Laryngoscope*,
OBJECTIVES/HYPOTHESIS: Numerous symptoms may arise that prevent mother-infant dyads from maintaining desired breastfeeding intervals. Investigations into treatments that positively influence breastfeeding outcomes allow for improved patient counseling for treatment decisions to optimize breastfeeding quality. This investigation aimed to determine the impact of surgical tongue-tie/lip-tie release on breastfeeding impairment. STUDY DESIGN: Prospective, cohort study from June 2014 to April 2015 in a private practice setting. METHODS: Study participants consisted of breastfeeding mother-infant (0-12 weeks of age) dyads with untreated ankyloglossia and/or tethered maxillary labial frenula who completed preoperative, 1 week, and 1 month postoperative surveys consisting of the Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF), visual analog scale (VAS) for nipple pain severity, and the revised Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R). Breastmilk intake was measured preoperatively and 1 week postoperatively. RESULTS: A total of 237 dyads were enrolled after self-electing laser lingual

frenotomy and/or maxillary labial frenectomy. Isolated posterior tongue-tie was identified in 78% of infants. Significant postoperative improvements were reported between mean preoperative scores compared to 1 week and 1 month scores of the BSES-SF ($F(2) = 212.3$; $P < .001$), the I-GERQ-R ($F(2) = 85.3$; $P < .001$), and VAS pain scale ($F(2) = 259.8$; $P < .001$). Average breastmilk intake improved 155% from 3.0 (2.9) to 4.9 (4.5) mL/min ($P < .001$).

CONCLUSIONS: Surgical release of tongue-tie/lip-tie results in significant improvement in breastfeeding outcomes. Improvements occur early (1 week postoperatively) and continue to improve through 1 month postoperatively. Improvements were demonstrated in both infants with classic anterior tongue-tie and less obvious posterior tongue-tie. This study identifies a previously under-recognized patient population that may benefit from surgical intervention if abnormal breastfeeding symptoms exist. LEVEL OF EVIDENCE: 2c Laryngoscope, 2016.

Godsey, M. H., Davulcu, O., Nix, J. C., Skalicky, J. J., Bruschiweiler, R. P., & Chapman, M. S. (2016).

The sampling of conformational dynamics in ambient-temperature crystal structures of arginine kinase. *Structure (London, England : 1993)*,

Arginine kinase provides a model for functional dynamics, studied through crystallography, enzymology, and nuclear magnetic resonance. Structures are now solved, at ambient temperature, for the transition state analog (TSA) complex. Analysis of quasi-rigid sub-domain displacements show that differences between the two TSA structures average about 5% of changes between substrate-free and TSA forms, and they are nearly co-linear. Small backbone hinge rotations map to sites that also flex on substrate binding. Anisotropic atomic displacement parameters (ADPs) are refined using rigid-body TLS constraints. Consistency between crystal forms shows that they reflect intrinsic molecular properties more than crystal lattice effects. In many regions, the favored directions of thermal/static displacement are appreciably correlated with movements on substrate binding. Correlation between ADPs and larger substrate-associated movements implies that the latter approximately follow paths of low-energy intrinsic motions.

Green, Y. S., Kwon, S., Mimoto, M. S., Xie, Y., & Christian, J. L. (2016). Tril targets Smad7 for degradation to allow for hematopoietic specification in xenopus embryos. *Development (Cambridge, England)*,

In *Xenopus laevis*, Bone morphogenetic proteins induce expression of the transcription factor Gata2 during gastrulation, and Gata2 is required in both ectodermal and mesodermal cells to enable mesoderm to commit to a hematopoietic fate. In the current studies, we identify tril as a Gata2 target gene that is required in both ectoderm and mesoderm for primitive hematopoiesis to occur. Tril is a transmembrane protein that functions as a co-receptor for Toll like receptors to mediate innate immune responses in the adult brain, but developmental roles for this molecule have not been identified. We show that Tril function is required both upstream and downstream of Bmp receptor mediated Smad1 phosphorylation for induction of Bmp target genes. Mechanistically, Tril triggers degradation of the Bmp inhibitor, Smad7. Tril-dependent down regulation of Smad7 relieves repression of endogenous Bmp signaling during gastrulation and this enables mesodermal progenitors to commit to a blood fate. Thus, Tril is a novel component of a Bmp-Gata2 positive feedback loop that plays an essential role in hematopoietic specification.

Grosh, K., Ren, T., He, W., Fridberger, A., Li, Y., & Nankali, A. (2015). Light-induced basilar membrane vibrations in the sensitive cochlea. *12th International Workshop on the Mechanics of Hearing: Protein to Perception*, , 1703.

The exceptional sensitivity of mammalian hearing organ is attributed to an outer hair cell-mediated active process, where forces produced by sensory cells boost sound-induced vibrations, making soft sounds audible. This process is thought to be local, with each section of the hearing organ capable of amplifying sound-evoked movement, and nearly instantaneous, since amplification can work for sounds at frequencies up to 100 kHz in some species. To test these precepts, we developed a method for focally stimulating the living hearing organ with light. Light pulses caused intense and highly damped mechanical responses followed by traveling waves that developed with considerable delay. The delayed response was identical to movements evoked by click-like sounds. A physiologically based mathematical model shows that such waves engage the active process, enhancing hearing sensitivity. The experiments and the theoretical analysis show that the active process is neither local nor instantaneous, but requires mechanical waves traveling from the cochlear base toward its apex. © 2015 AIP Publishing LLC.

Gundle, K. R., Punt, S. E., Mattioli-Lewis, T., & Conrad, E. U., 3rd. (2016). Can a made-for-consumer activity monitor assess physical activity in adolescents and young adults after lower extremity limb salvage for osseous tumors? *Journal of Pediatric Orthopedics*,

BACKGROUND: The purpose of this study was to test the validity of a consumer-oriented activity monitor in adolescents and young adults undergoing limb salvage for primary bone malignancies.

METHODS: A cross-sectional population of participants with an average age of 16 (range 12 to 22) years produced 472 days of activity monitoring during 25 evaluation periods alongside

patient-reported outcome measures. RESULTS: Average daily steps ranged from 557 to 12,756 (mean=4711) and was moderately associated with the short-form (SF) 36 physical component subscale ($r=0.46$, $P=0.04$) as well as the SF6D health state utility measure ($r=0.48$, $P=0.04$), but not the SF36 mental component subscale ($P=0.66$) or Toronto extremity salvage score ($P=0.07$).

Time from surgery was strongly correlated with average daily steps ($r=0.7$, $P<0.001$).

CONCLUSIONS: A made-for-consumer activity monitor provided real-world data regarding the outcome of adolescent and young adult limb salvage, and evidence of validity in this population.

Such lower cost, user-friendly devices may facilitate assessment of free-living activity and allow novel comparisons of treatment strategies. LEVEL OF EVIDENCE: Level II-diagnostic.

Gyawali, B., & Prasad, V. (2016). Negative trials in ovarian cancer: Is there such a thing as too much optimism? *Ecancermedicalscience*, 10, ed58.

Recently, two clinical trials of novel agents in metastatic ovarian cancer were published: a phase 3 study of nintedanib and a phase 2 study of volasertib. There seemed to be discordance between the results and conclusions in the publication of both these trials. Despite not very optimistic results, the studies concluded optimistically in favor of the new agents under study. Using these examples, we point out the discrepancies and the risks of concluding optimistically based on statistical significance when the actual benefit is minimal. We also appeal against conducting large phase 3 trials that require significant resources without good phase 2 evidence for doing so.

Gyawali, B., & Prasad, V. (2016). Same data; different interpretations. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

Haisley, K. R., Dolan, J. P., Olson, S. B., Toledo-Valdovinos, S. A., Hart, K. D., Bakis, G., et al. (2016).

Sponge sampling with fluorescent in situ hybridization as a screening tool for the early detection of esophageal cancer. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*,

INTRODUCTION: Sponge cytology is a novel screening tool for esophageal cancer but has been unable to be validated for widespread use. Our aim was to apply fluorescent in situ hybridization to sponge cytology samples in order to evaluate the safety and efficacy of this modality in screening for esophageal cancer. MATERIALS AND METHODS: At a single, multidisciplinary, NCI-designated cancer center, patients completed sponge cytology sampling prior to upper endoscopy. Samples were analyzed by p53 fluorescent in situ hybridization, and results were compared to the endoscopic diagnosis. RESULTS: Fifty patients were enrolled (96 % Caucasian, 68 % male, median age of 67). All patients successfully swallowed the capsule. No complications (string breakage, bleeding, mucosal injury) occurred. Endoscopy revealed that 38 % had normal esophageal mucosa and 62 % had an esophageal mucosal abnormality. In total, six samples demonstrated p53 loss (94 % specificity for any abnormality). The sensitivity of the p53 fluorescent in situ hybridization probe was 13.3 % for any abnormality, 10 % for intestinal metaplasia, and 0 % for dysplasia or esophageal cancer. DISCUSSION: Esophageal sponge cytology is a promising, safe, and tolerable method for collecting esophageal cell samples. However, our data suggest that p53 fluorescent in situ hybridization does not improve the sensitivity for detecting cancer in these samples.

Hansen, M., Loker, W., & Warden, C. (2016). Geospatial analysis of pediatric EMS run density and endotracheal intubation. *Western Journal of Emergency Medicine*, 17(5), 656-661.

Introduction: The association between geographic factors, including transport distance, and pediatric emergency medical services (EMS) run clustering on out-of-hospital pediatric endotracheal intubation is unclear. The objective of this study was to determine if endotracheal intubation procedures are more likely to occur at greater distances from the hospital and near clusters of pediatric calls. Methods: This was a retrospective observational study including all EMS runs for patients less than 18 years of age from 2008 to 2014 in a geographically large and diverse Oregon county that includes densely populated urban areas near Portland and remote

rural areas. We geocoded scene addresses using the automated address locator created in the cloud-based mapping platform ArcGIS, supplemented with manual address geocoding for remaining cases. We then use the Getis-Ord Gi spatial statistic feature in ArcGIS to map statistically significant spatial clusters (hot spots) of pediatric EMS runs throughout the county. We then superimposed all intubation procedures performed during the study period on maps of pediatric EMS-run hot spots, pediatric population density, fire stations, and hospitals. We also performed multivariable logistic regression to determine if distance traveled to the hospital was associated with intubation after controlling for several confounding variables. Results: We identified a total of 7,797 pediatric EMS runs during the study period and 38 endotracheal intubations. In univariate analysis we found that patients who were intubated were similar to those who were not in gender and whether or not they were transported to a children's hospital. Intubated patients tended to be transported shorter distances and were older than non-intubated patients. Increased distance from the hospital was associated with reduced odds of intubation after controlling for age, sex, scene location, and trauma system entry status in a multivariate logistic regression. The locations of intubations were superimposed on hot spots of all pediatric EMS runs. This map demonstrates that most of the intubations occurred within areas where pediatric EMS calls were highly clustered. By mapping the intubation procedures and pediatric population density, we found that intubation procedures were not clustered in a similar distribution to the pediatric population in the county. Conclusion: In this geographically diverse county the location of intubation procedures was similar to the clustering of pediatric EMS calls, and increased distance from the hospital was associated with reduced odds of intubation after controlling for several potential confounding variables. Copyright: © 2016 Hansen et al.

Hebson, C., Book, W., Elder, R. W., Ford, R., Jokhadar, M., Kanter, K., et al. (2016). "Frontiers in fontan failure: A summary of conference proceedings". *Congenital Heart Disease*, "Frontiers in Fontan Failure" was the title of a 2015 conference sponsored by Children's Healthcare of Atlanta and Emory University School of Medicine. In what is hoped to be the first of many such gatherings, speakers and attendees gathered to discuss the problem of long-term clinical deterioration in these patients. Specific focuses included properly defining the problem and then discussing different treatment strategies, both medical and surgical. The health of the

liver after Fontan palliation was a particular point of emphasis, as were quality of life and future directions.

Heeman, P. A., & Lunsford, R. (2015). Can overhearers predict who will speak next? *2015 AAAI Spring Symposium, , SS-15-07*. pp. 30-35.

One theory of turn-taking in dialogue is that the current speaker controls when the other conversant can speak, which is also the basis of most spoken dialogue systems. A second theory is that the two conversants negotiate who will speak next. In this paper, we test these theories by examining how well an overhearer can predict this, based only on the current speaker's utterance, which is what the other conversant would have access to. We had overhearers listen to the current speaker and indicate whether they felt the current speaker will continue or not. Our results support the negotiative model. Copyright © 2015, Association for the Advancement of Artificial Intelligence (www.aaai.org). All rights reserved.

Hershman, D. L., Unger, J. M., Wright, J. D., Ramsey, S., Till, C., Tangen, C. M., et al. (2016).

Adverse health events following intermittent and continuous androgen deprivation in patients with metastatic prostate cancer. *JAMA Oncology, 2*(4), 453-461.

IMPORTANCE: Although intermittent androgen-deprivation therapy (ADT) has not been associated with better overall survival in prostate cancer (PC), it has the potential for lower adverse effects. To our knowledge, the incidence of long-term adverse health events has not been reported. **OBJECTIVE:** To examine long-term late events in elderly patients randomized to intermittent or continuous ADT to determine whether late cardiovascular and endocrine events would be lower in patients treated with intermittent ADT. **DESIGN, SETTING, AND PARTICIPANTS:** This was a secondary analysis of a multicenter clinical trial using linkage between patient data from S9346, a randomized SWOG trial of intermittent vs continuous ADT in men with metastatic PC, and corresponding Medicare claims. **EXPOSURE:** Intermittent or continuous ADT. **MAIN OUTCOMES AND MEASURES:** The main outcome was to identify long-term adverse health events by treatment arm. Patients were classified as having an adverse health event if they had any hospital claim--or at least 2 physician or outpatient claims at least 30 days apart--for any of the following diagnoses: ischemic and thrombotic events, endocrine events, sexual dysfunction,

dementia, and depression. To incorporate time from beginning of observation through evidence of an event, we determined the cumulative incidence of each event. Competing risks Cox regression was used, adjusting for covariates. RESULTS: In total, 1134 eligible US-based male patients with metastatic PC were randomized to continuous vs intermittent ADT in the S9346 trial. A total of 636 of trial participants (56%) had at least 1 year of continuous Medicare parts A and B coverage and no health maintenance organization participation. The median age was 71.3 years. The most common long-term events were hypercholesterolemia (31%) and osteoporosis (19%). The 10-year cumulative incidence of ischemic and thrombotic events differed by arm; 24% for continuous and 33% for intermittent ADT (hazard ratio, 0.69; P = .02). There were no statistically significant differences by arm in any other adverse health events. CONCLUSIONS AND RELEVANCE: Contrary to our hypothesis that intermittent ADT would reduce long-term health-related events compared with continuous ADT, we found that older men assigned to intermittent ADT had no apparent reduction in bone, endocrine, or cognitive events and an increased incidence of ischemic and thrombotic events. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00002651.

Higgins, M. C., Hwang, W. T., Richard, C., Chapman, C. H., Laporte, A., Both, S., et al. (2016).

Underrepresentation of women and minorities in the United States IR academic physician workforce. *Journal of Vascular and Interventional Radiology : JVIR*,

PURPOSE: To assess the United States interventional radiology (IR) academic physician workforce diversity and comparative specialties. METHODS: Public registries were used to assess demographic differences among 2012 IR faculty and fellows, diagnostic radiology (DR) faculty and residents, DR subspecialty fellows (pediatric, abdominal, neuroradiology, and musculoskeletal), vascular surgery and interventional cardiology trainees, and 2010 US medical school graduates and US Census using binomial tests with .001 significance level (Bonferroni adjustment for multiple comparisons). Significant trends in IR physician representation were evaluated from 1992 to 2012. RESULTS: Women (15.4%), blacks (2.0%), and Hispanics (6.2%) were significantly underrepresented as IR fellows compared with the US population. Women were underrepresented as IR (7.3%) versus DR (27.8%) faculty and IR fellows (15.4%) versus medical school graduates (48.3%), DR residents (27.8%), pediatric radiology fellows (49.4%),

and vascular surgery trainees (27.7%) (all $P < .001$). IR ranked last in female representation among radiologic subspecialty fellows. Blacks (1.8%, 2.1%, respectively, for IR faculty and fellows); Hispanics (1.8%, 6.2%); and combined American Indians, Alaska Natives, Native Hawaiians, and Pacific Islanders (1.8%, 0) showed no significant differences in representation as IR fellows compared with IR faculty, DR residents, other DR fellows, or interventional cardiology or vascular surgery trainees. Over 20 years, there was no significant increase in female or black representation as IR fellows or faculty. CONCLUSIONS: Women, blacks, and Hispanics are underrepresented in the IR academic physician workforce relative to the US population. Given prevalent health care disparities and an increasingly diverse society, research and training efforts should address IR physician workforce diversity.

Holihan, J. L., Li, L. T., Askenasy, E. P., Greenberg, J. A., Keith, J. N., Martindale, R. G., et al. (2016). Analysis of model development strategies: Predicting ventral hernia recurrence. *Journal of Surgical Research*, 206(1), 159-167.

Background There have been many attempts to identify variables associated with ventral hernia recurrence; however, it is unclear which statistical modeling approach results in models with greatest internal and external validity. We aim to assess the predictive accuracy of models developed using five common variable selection strategies to determine variables associated with hernia recurrence. Methods Two multicenter ventral hernia databases were used. Database 1 was randomly split into "development" and "internal validation" cohorts. Database 2 was designated "external validation". The dependent variable for model development was hernia recurrence. Five variable selection strategies were used: (1) "clinical"—variables considered clinically relevant, (2) "selective stepwise"—all variables with a P value ≤ 0.10 was considered "reasonable". Results The recurrence rate was 32.9% ($n = 173/526$; median/range follow-up, 20/1-58 mo) for the development cohort, 36.0% ($n = 95/264$, median/range follow-up 20/1-61 mo) for the internal validation cohort, and 12.7% ($n = 155/1224$, median/range follow-up 9/1-50 mo) for the external validation cohort. Internal validation demonstrated reasonable predictive accuracy (C-statistics = 0.772, 0.760, 0.767, 0.757, 0.763), while on external validation, predictive accuracy dipped precipitously (C-statistic = 0.561, 0.557, 0.562, 0.553, 0.560). Conclusions Predictive accuracy was equally adequate on internal validation among models; however, on external

validation, all five models failed to demonstrate utility. Future studies should report multiple variable selection techniques and demonstrate predictive accuracy on external data sets for model validation. © 2016 Elsevier Inc.

Holliday, E., Fuller, C. D., Kalpathy-Cramer, J., Gomez, D., Rimner, A., Li, Y., et al. (2016).

Quantitative assessment of target delineation variability for thymic cancers: Agreement evaluation of a prospective segmentation challenge. *Journal of Radiation Oncology*, 5(1), 55-61.

OBJECTIVES: We sought to quantitatively determine the inter-observer variability of expert radiotherapy target-volume delineation for thymic cancers, as part of a larger effort to develop an expert-consensus contouring atlas. METHODS: A pilot dataset was created consisting of a standardized case presentation with pre- and post-operative DICOM CT image sets from a single patient with Masaoka-Koga Stage III thymoma. Expert thoracic radiation oncologists delineated tumor targets on the pre- and post-operative scans as they would for a definitive and adjuvant case, respectively. Respondents completed a survey including recommended dose prescription and target volume margins for definitive and post-operative scenarios. Inter-observer variability was analyzed quantitatively with Warfield's simultaneous truth, performance level estimation (STAPLE) algorithm and Dice similarity coefficient (DSC). RESULTS: Seven users completed contouring for definitive and adjuvant cases; of these, 5 completed online surveys. Segmentation performance was assessed, with high mean \pm SD STAPLE-estimated segmentation sensitivity for definitive case GTV and CTV at 0.77 and 0.80, respectively, and post-operative CTV sensitivity of 0.55; all volumes had specificity of \geq 0.99. Inter-observer agreement was markedly higher for the definitive target volumes, with mean \pm SD DSC of 0.88 \pm 0.03 and 0.89 \pm 0.04 for GTV and CTV respectively, compared to post-op CTV DSC of 0.69 \pm 0.06 (Kruskal-Wallis $p < 0.01$). CONCLUSION: Expert agreement for definitive case volumes was exceptionally high, though significantly lower agreement was noted post-operatively. Technique and dose prescription between experts was substantively consistent, and these preliminary results will be utilized to create an expert-consensus contouring atlas to aid the non-expert radiation oncologist in the planning of these challenging, rare tumors.

Hollis, K. F. (2016). To share or not to share: Ethical acquisition and use of medical data. *AMIA Joint Summits on Translational Science Proceedings*. *AMIA Joint Summits on Translational Science, 2016*, 420-427.

The Health Information Technology for Economic and Clinical Health (HITECH) Act proposes the meaningful use of interoperable electronic health records throughout the United States health care delivery system as a critical national goal. As we have moved from medical records on paper to interoperable electronic health records, the rapid and easy sharing of medical data through the Internet makes medical data insecure. Electronic data is easy to share but many steps to ensure security of the data need to be taken. Beyond medical data security, we need to ethically acquire, use and manage data so that all people involved with the data from producer to data manager are recognized and respected. This paper advocates that sharing medical data can be ethically the right choice for everyone in health care if data sharing guidelines are available for people to use, modify and strengthen for specific purposes.

Hornick, N. I., Doron, B., Abdelhamed, S., Huan, J., Harrington, C. A., Shen, R., et al. (2016). AML suppresses hematopoiesis by releasing exosomes that contain microRNAs targeting c-MYB. *Science Signaling*, *9*(444), ra88.

Exosomes are paracrine regulators of the tumor microenvironment and contain complex cargo. We previously reported that exosomes released from acute myeloid leukemia (AML) cells can suppress residual hematopoietic stem and progenitor cell (HSPC) function indirectly through stromal reprogramming of niche retention factors. We found that the systemic loss of hematopoietic function is also in part a consequence of AML exosome-directed microRNA (miRNA) trafficking to HSPCs. Exosomes isolated from cultured AML or the plasma from mice bearing AML xenografts exhibited enrichment of miR-150 and miR-155. HSPCs cocultured with either of these exosomes exhibited impaired clonogenicity, through the miR-150- and miR-155-mediated suppression of the translation of transcripts encoding c-MYB, a transcription factor involved in HSPC differentiation and proliferation. To discover additional miRNA targets, we captured miR-155 and its target transcripts by coimmunoprecipitation with an attenuated RNA-induced silencing complex (RISC)-trap, followed by high-throughput sequencing. This approach identified known and previously unknown miR-155 target transcripts. Integration of the miR-155 targets

with information from the protein interaction database STRING revealed proteins indirectly affected by AML exosome-derived miRNA. Our findings indicate a direct effect of AML exosomes on HSPCs that, through a stroma-independent mechanism, compromises hematopoiesis. Furthermore, combining miRNA target data with protein-protein interaction data may be a broadly applicable strategy to define the effects of exosome-mediated trafficking of regulatory molecules within the tumor microenvironment.

Hurtado, D. A., Hessel, P., & Avendano, M. (2016). The hidden costs of informal work: Lack of social protection and subjective well-being in Colombia. *International Journal of Public Health*,
OBJECTIVES: To examine the association between informal work and subjective well-being in Colombia. METHODS: Repeated cross-sectional study based on data from three nationally representative surveys of 1997, 2005 and 2011 (n = 4485). Life satisfaction was measured with a Likert scale ranging from 1 to 10 points. Informal work was defined as paid work without pension/unemployment contributions. Individual-level pooled Generalized Estimating Equation (GEE) models were used to assess the association between informal work and life satisfaction. Propensity Score Matching (PSM) was applied to address potential selection into informal work. RESULTS: Informal work increased from 52 % in 1997 to 68 % in 2011. Informal workers averaged significantly lower life satisfaction than formal (GEE: b = -0.14, 95 % CI -0.26, -0.01, p < 0.05). These results were confirmed in PSM models that controlled for selection by measured confounders (PSM: b = -0.15, 95 % CI -0.23, -0.03, p < 0.05). CONCLUSIONS: Informal workers who are not covered by social security systems had lower subjective well-being than workers in the formal economy. Results suggest that recent increases in informal work may also translate into reduced subjective well-being.

Ibrahim, S. A., Kim, H., & McConnell, K. J. (2016). The CMS comprehensive care model and racial disparity in joint replacement. *Jama*, 316(12), 1258-1259.

Jacob, T., Gray, J. W., Troxell, M., & Vu, T. Q. (2016). Multiplexed imaging reveals heterogeneity of PI3K/MAPK network signaling in breast lesions of known PIK3CA genotype. *Breast Cancer Research and Treatment*, 159(3), 575-583.

PURPOSE: Activating genetic changes in the phosphatidylinositol-3-kinase (PI3K) signaling

pathway are found in over half of invasive breast cancers (IBCs). Previously, we discovered numerous hotspot PIK3CA mutations in proliferative breast lesions. Here, we investigate the spatial nature of PI3K pathway signaling and its relationship with PI3K genotype in breast lesions. METHODS: We identified PI3K phosphosignaling network signatures in columnar cell change (CCL), usual ductal hyperplasia (UDH), ductal carcinoma in situ (DCIS), and IBC in 26 lesions of known PIK3CA genotype from 10 human breast specimens using a hyperspectral-based multiplexed tissue imaging platform (MTIP) to simultaneously quantitate PI3K/MAPK pathway targets (pAKT473, pAKT308, pPRAS40, pS6, and pERK) in FFPE tissue, with single-cell resolution. RESULTS: We found that breast lesional epithelia contained spatially heterogeneous patterns of PI3K pathway phosphoprotein signatures, even within microscopic areas of CCL, UDH, DCIS, and IBC. Most lesions contained 3-12 unique phosphoprotein signatures within the same microscopic field. The dominant phosphoprotein signature for each lesion was not well correlated with lesion genotype or lesion histology, yet samples from the same patient tended to group together. Further, 5 UDH/CCL lesions across different patients had a common phosphosignature at the epithelial-stromal interface (possible myoepithelial cells) that was distinct from both the adjacent lesional epithelium and distinct from adjacent stroma. CONCLUSION: We present the first spatial mapping of PI3K phosphoprotein networks in proliferative breast lesions and demonstrate complex PI3K signaling heterogeneity that defies simple correlation between PIK3CA genotype and phosphosignal pattern.

Jaffe, G. J., Dick, A. D., Brezin, A. P., Nguyen, Q. D., Thorne, J. E., Kestelyn, P., et al. (2016).

Adalimumab in patients with active noninfectious uveitis. *The New England Journal of Medicine*, 375(10), 932-943.

Background Patients with noninfectious uveitis are at risk for long-term complications of uncontrolled inflammation, as well as for the adverse effects of long-term glucocorticoid therapy. We conducted a trial to assess the efficacy and safety of adalimumab as a glucocorticoid-sparing agent for the treatment of noninfectious uveitis. Methods This multinational phase 3 trial involved adults who had active noninfectious intermediate uveitis, posterior uveitis, or panuveitis despite having received prednisone treatment for 2 or more weeks. Investigators and patients were unaware of the study-group assignments. Patients were randomly assigned in a 1:1 ratio to

receive adalimumab (a loading dose of 80 mg followed by a dose of 40 mg every 2 weeks) or matched placebo. All patients received a mandatory prednisone burst followed by tapering of prednisone over the course of 15 weeks. The primary efficacy end point was the time to treatment failure occurring at or after week 6. Treatment failure was a multicomponent outcome that was based on assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade. Nine ranked secondary efficacy end points were assessed, and adverse events were reported. Results The median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Among the 217 patients in the intention-to-treat population, those receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% confidence interval, 0.36 to 0.70; $P < 0.001$). Outcomes with regard to three secondary end points (change in anterior chamber cell grade, change in vitreous haze grade, and change in best corrected visual acuity) were significantly better in the adalimumab group than in the placebo group. Adverse events and serious adverse events were reported more frequently among patients who received adalimumab (1052.4 vs. 971.7 adverse events and 28.8 vs. 13.6 serious adverse events per 100 person-years). Conclusions In our trial, adalimumab was found to be associated with a lower risk of uveitic flare or visual impairment and with more adverse events and serious adverse events than was placebo. (Funded by AbbVie; VISUAL I ClinicalTrials.gov number, NCT01138657).

Jessee, M. A., & Tanner, C. A. (2016). Pursuing improvement in clinical reasoning: Development of the clinical coaching interactions inventory. *Journal of Nursing Education, 55*(9), 495-504.

Background: Clinical coaching has been identified as a signature pedagogy in nursing education. Recent findings indicate that clinical coaching interactions in the clinical learning environment fail to engage students in the higher order thinking skills believed to promote clinical reasoning. Method: The Clinical Coaching Interactions Inventory (CCII) was based on evidence of supervisor questioning techniques, the Tanner clinical judgment model, Bloom's Taxonomy, and simulation evaluation tools. Content validity was established with expert assessment, student testing for clarity, and calculation of scale-content validity index/ average (S-CVI/Ave). Reliability was established with KuderRichardson Formula 20 (KR-20). Results: CVI (S-CVI/Ave) was .91, and KR-20 was .70. The CCII identified differences in clinical coaching behaviors in university faculty

supervisors and staff nurse preceptor supervisors. Conclusion: The CCII advances the measurement of clinical coaching interactions from qualitative to quantitative. Ultimately, results from use of this inventory may facilitate the design of prelicensure clinical coaching strategies that promote the improvement of students' clinical reasoning skill. © SLACK Incorporated.

Kalpathy-Cramer, J., Campbell, J. P., Erdogmus, D., Tian, P., Kedariseti, D., Moleta, C., et al. (2016).

Plus disease in retinopathy of prematurity: Improving diagnosis by ranking disease severity and using quantitative image analysis. *Ophthalmology*,

PURPOSE: To determine expert agreement on relative retinopathy of prematurity (ROP) disease severity and whether computer-based image analysis can model relative disease severity, and to propose consideration of a more continuous severity score for ROP. DESIGN: We developed 2 databases of clinical images of varying disease severity (100 images and 34 images) as part of the Imaging and Informatics in ROP (i-ROP) cohort study and recruited expert physician, nonexpert physician, and nonphysician graders to classify and perform pairwise comparisons on both databases. PARTICIPANTS: Six participating expert ROP clinician-scientists, each with a minimum of 10 years of clinical ROP experience and 5 ROP publications, and 5 image graders (3 physicians and 2 nonphysician graders) who analyzed images that were obtained during routine ROP screening in neonatal intensive care units. METHODS: Images in both databases were ranked by average disease classification (classification ranking), by pairwise comparison using the Elo rating method (comparison ranking), and by correlation with the i-ROP computer-based image analysis system. MAIN OUTCOME MEASURES: Interexpert agreement (weighted kappa statistic) compared with the correlation coefficient (CC) between experts on pairwise comparisons and correlation between expert rankings and computer-based image analysis modeling.

RESULTS: There was variable interexpert agreement on diagnostic classification of disease (plus, preplus, or normal) among the 6 experts (mean weighted kappa, 0.27; range, 0.06-0.63), but good correlation between experts on comparison ranking of disease severity (mean CC, 0.84; range, 0.74-0.93) on the set of 34 images. Comparison ranking provided a severity ranking that was in good agreement with ranking obtained by classification ranking (CC, 0.92). Comparison ranking on the larger dataset by both expert and nonexpert graders demonstrated good correlation (mean CC, 0.97; range, 0.95-0.98). The i-ROP system was able to model this

continuous severity with good correlation (CC, 0.86). CONCLUSIONS: Experts diagnose plus disease on a continuum, with poor absolute agreement on classification but good relative agreement on disease severity. These results suggest that the use of pairwise rankings and a continuous severity score, such as that provided by the i-ROP system, may improve agreement on disease severity in the future.

Kaplan, J. S., Nipper, M. A., Richardson, B. D., Jensen, J., Helms, M., Finn, D. A., et al. (2016).

Pharmacologically counteracting a phenotypic difference in cerebellar GABAA receptor response to alcohol prevents excessive alcohol consumption in a high alcohol-consuming rodent genotype. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 36(35), 9019-9025.

Cerebellar granule cell GABAA receptor responses to alcohol vary as a function of alcohol consumption phenotype, representing a potential neural mechanism for genetic predilection for alcohol abuse (Kaplan et al., 2013; Mohr et al., 2013). However, there are numerous molecular targets of alcohol in the cerebellum, and it is not known how they interact to affect cerebellar processing during consumption of socially relevant amounts of alcohol. Importantly, direct evidence for a causative role of the cerebellum in alcohol consumption phenotype is lacking. Here we determined that concentrations of alcohol that would be achieved in the blood after consumption of 1-2 standard units (9 mm) suppresses transmission through the cerebellar cortex in low, but not high, alcohol consuming rodent genotypes (DBA/2J and C57BL/6J mice, respectively). This genotype-selective suppression is mediated exclusively by enhancement of granule cell GABAA receptor currents, which only occurs in DBA/2J mice. Simulating the DBA/2J cellular phenotype in C57BL/6J mice by infusing the GABAA receptor agonist, 4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridine-3-ol hydrochloride, into cerebellar lobules IV-VI, in vivo, significantly reduced their alcohol consumption and blood alcohol concentrations achieved. 4,5,6,7-Tetrahydroisoxazolo-[5,4-c]pyridine-3-ol hydrochloride infusions also significantly decreased sucrose consumption, but they did not affect consumption of water or general locomotion. Thus, genetic differences in cerebellar response to alcohol contributes to alcohol consumption phenotype, and targeting the cerebellar GABAA receptor system may be a clinically viable therapeutic strategy for reducing excessive alcohol consumption. SIGNIFICANCE

STATEMENT: Alcohol abuse is a leading cause of preventable death and illness; and although alcohol use disorders are 50%-60% genetically determined, the cellular and molecular mechanisms of such genetic influences are largely unknown. Here we demonstrate that genetic differences in cerebellar granule cell GABAA receptor responses to recreational concentrations of alcohol are the primary determinant of alcohol's impact on cerebellar processing and that pharmacologically modifying such responses alters alcohol consumption. These data highlight the cerebellum as an important neuroanatomical region in alcohol consumption phenotype and as a target for pharmacological treatment of alcohol use disorders. The results also add to the growing list of cognitive/emotional roles of the cerebellum in psychiatric disease and drug abuse.

Khairy, P., Aboulhosn, J., Broberg, C. S., Cohen, S., Cook, S., Dore, A., et al. (2016).

Thromboprophylaxis for atrial arrhythmias in congenital heart disease: A multicenter study. *International Journal of Cardiology*, 223, 729-735.

BACKGROUND: There is a paucity of data to guide decisions regarding thromboprophylaxis for atrial arrhythmias in congenital heart disease. METHODS: A retrospective multicenter cohort study enrolled patients with documented sustained atrial arrhythmias and congenital heart disease from 12 North American centers to quantify thromboembolic and bleeding rates associated with antiplatelet and anticoagulation therapy, and explore associated factors. A blinded committee adjudicated all qualifying arrhythmias and outcomes. RESULTS: A total of 482 patients, 45.2% female, age 32.0+/-18.0years, were followed for 11.3+/-9.4years since the qualifying arrhythmia. Antiplatelet therapy was administered to 37.8%, anticoagulation to 54.4%, and neither to 7.9%. Congenital heart disease complexity was simple, moderate, and severe in 18.5%, 34.4%, and 47.1%, respectively. Freedom from thromboembolic events was 84.7+/-2.7% at 15years, with no difference between anticoagulation versus antiplatelet therapy (P=0.97). Congenital heart disease complexity was independently associated with thromboembolic events, with rates of 0.00%, 0.93%, and 1.95%/year in those with simple, moderate, and severe forms (P<0.001). CHADS2 and CHA2DS2-VASc scores were not predictive of thromboembolic risk. Annualized bleeding rates with antiplatelet and anticoagulation therapy were 0.66% and 1.82% (P=0.039). In multivariable analyses, anticoagulation [hazard ratio (HR) 4.76, 95% CI (1.05-21.58), P=0.043] and HAS-BLED score [HR 3.15, 95% CI (1.02, 9.78),

P=0.047] were independently associated with major bleeds. CONCLUSION: Current management of atrial arrhythmias in congenital heart disease is associated with a modest rate of thromboembolic events, which is predicted by disease complexity but not CHADS2/CHA2DS2-VASc scores. HAS-BLED score is applicable to the congenital population in predicting major bleeds.

Knupp, K. G., Leister, E., Coryell, J., Nickels, K. C., Ryan, N., Juarez-Colunga, E., et al. (2016).

Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort. *Epilepsia*,

Objective: Infantile spasms (IS) represent a severe epileptic encephalopathy presenting in the first 2 years of life. Recommended first-line therapies (hormonal therapy or vigabatrin) often fail. We evaluated response to second treatment for IS in children in whom the initial therapy failed to produce both clinical remission and electrographic resolution of hypsarhythmia and whether time to treatment was related to outcome. Methods: The National Infantile Spasms Consortium established a multicenter, prospective database enrolling infants with new diagnosis of IS. Children were considered nonresponders to first treatment if there was no clinical remission or persistence of hypsarhythmia. Treatment was evaluated as hormonal therapy (adrenocorticotrophic hormone [ACTH] or oral corticosteroids), vigabatrin, or "other." Standard treatments (hormonal and vigabatrin) were compared to all other nonstandard treatments. We compared response rates using chi-square tests and multivariable logistic regression models. Results: One hundred eighteen infants were included from 19 centers. Overall response rate to a second treatment was 37% (n = 44). Children who received standard medications with differing mechanisms for first and second treatment had higher response rates than other sequences (27/49 [55%] vs. 17/69 [25%], $p < 0.001$). Children receiving first treatment within 4 weeks of IS onset had a higher response rate to second treatment than those initially treated later (36/82 [44%] vs. 8/34 [24%], $p = 0.040$). Significance: Greater than one third of children with IS will respond to a second medication. Choosing a standard medication (ACTH, oral corticosteroids, or vigabatrin) that has a different mechanism of action appears to be more effective. Rapid initial treatment increases the likelihood of response to the second treatment. © 2016 International League Against Epilepsy.

Kratochvil, H. T., Carr, J. K., Matulef, K., Annen, A. W., Li, H., Maj, M., et al. (2016). Instantaneous ion configurations in the K⁺ ion channel selectivity filter revealed by 2D IR spectroscopy. *Science*, 353(6303), 1040-1044.

Potassium channels are responsible for the selective permeation of K ions across cell membranes. K⁺ ions permeate in single file through the selectivity filter, a narrow pore lined by backbone carbonyls that compose four K⁺ binding sites. Here we report on the two-dimensional infrared (2D IR) spectra of a semisynthetic KcsA channel with sitespecific heavy (¹³C¹⁸O) isotope labels in the selectivity filter. The ultrafast time resolution of 2D IR spectroscopy provides an instantaneous snapshot of the multi-ion configurations and structural distributions that occur spontaneously in the filter. Two elongated features are resolved revealing the statistical weighting of two structural conformations. The spectra are reproduced by molecular dynamics simulations of structures with water separating two K⁺ ions in the binding sites, ruling out configurations with ions occupying adjacent sites.

Kudenchuk, P. J., Daya, M., & Dorian, P. (2016). The authors reply. *New England Journal of Medicine*, 375(8), 802-803.

Labberton, L., Kenne, E., Long, A. T., Nickel, K. F., Di Gennaro, A., Rigg, R. A., et al. (2016).

Neutralizing blood-borne polyphosphate in vivo provides safe thromboprotection. *Nature Communications*, 7, 12616.

Polyphosphate is an inorganic procoagulant polymer. Here we develop specific inhibitors of polyphosphate and show that this strategy confers thromboprotection in a factor XII-dependent manner. Recombinant *Escherichia coli* exopolyphosphatase (PPX) specifically degrades polyphosphate, while a PPX variant lacking domains 1 and 2 (PPX_Delta12) binds to the polymer without degrading it. Both PPX and PPX_Delta12 interfere with polyphosphate- but not tissue factor- or nucleic acid-driven thrombin formation. Targeting polyphosphate abolishes procoagulant platelet activity in a factor XII-dependent manner, reduces fibrin accumulation and impedes thrombus formation in blood under flow. PPX and PPX_Delta12 infusions in wild-type mice interfere with arterial thrombosis and protect animals from activated platelet-induced venous thromboembolism without increasing bleeding from injury sites. In contrast, targeting

polyphosphate does not provide additional protection from thrombosis in factor XII-deficient animals. Our data provide a proof-of-concept approach for combating thrombotic diseases without increased bleeding risk, indicating that polyphosphate drives thrombosis via factor XII.

Lahvis, G. P. (2016). Social reward and empathy as proximal contributions to altruism: The camaraderie effect. *Current Topics in Behavioral Neurosciences*,
Natural selection favors individuals to act in their own interests, implying that wild animals experience a competitive psychology. Animals in the wild also express helping behaviors, presumably at their own expense and suggestive of a more compassionate psychology. This apparent paradox can be partially explained by ultimate mechanisms that include kin selection, reciprocity, and multilevel selection, yet some theorists argue such ultimate explanations may not be sufficient and that an additional "stake in others" is necessary for altruism's evolution. We suggest this stake is the "camaraderie effect," a by-product of two highly adaptive psychological experiences: social motivation and empathy. Rodents can derive pleasure from access to others and this appetite for social rewards motivates individuals to live together, a valuable psychology when group living is adaptive. Rodents can also experience empathy, the generation of an affective state more appropriate to the situation of another compared to one's own. Empathy is not a compassionate feeling but it has useful predictive value. For instance, empathy allows an individual to feel an unperceived danger from social cues. Empathy of another's stance toward one's self would predict either social acceptance or ostracism and amplify one's physiological sensitivity to social isolation, including impaired immune responses and delayed wound healing. By contrast, altruistic behaviors would promote well-being in others and feelings of camaraderie from others, thereby improving one's own physiological well-being. Together, these affective states engender a stake in others necessary for the expression of altruistic behavior.

Lawrenson, K., Kar, S., McCue, K., Kuchenbaecker, K., Michailidou, K., Tyrer, J., et al. (2016). Functional mechanisms underlying pleiotropic risk alleles at the 19p13.1 breast-ovarian cancer susceptibility locus. *Nature Communications*, 7, 12675.
A locus at 19p13 is associated with breast cancer (BC) and ovarian cancer (OC) risk. Here we analyse 438 SNPs in this region in 46,451 BC and 15,438 OC cases, 15,252 BRCA1 mutation

carriers and 73,444 controls and identify 13 candidate causal SNPs associated with serous OC ($P=9.2 \times 10^{-20}$), ER-negative BC ($P=1.1 \times 10^{-13}$), BRCA1-associated BC ($P=7.7 \times 10^{-16}$) and triple negative BC ($P\text{-diff}=2 \times 10^{-5}$). Genotype-gene expression associations are identified for candidate target genes ANKLE1 ($P=2 \times 10^{-3}$) and ABHD8 ($P<2 \times 10^{-3}$). Chromosome conformation capture identifies interactions between four candidate SNPs and ABHD8, and luciferase assays indicate six risk alleles increased transactivation of the ABHD8 promoter. Targeted deletion of a region containing risk SNP rs56069439 in a putative enhancer induces ANKLE1 downregulation; and mRNA stability assays indicate functional effects for an ANKLE1 3'-UTR SNP. Altogether, these data suggest that multiple SNPs at 19p13 regulate ABHD8 and perhaps ANKLE1 expression, and indicate common mechanisms underlying breast and ovarian cancer risk.

Lee, B., Lee, S., Lee, S. K., & Lee, J. W. (2016). The LIM-homeobox transcription factor Isl1 plays critical roles in development of multiple arcuate nucleus neurons. *Development (Cambridge, England)*,

Neurons in the hypothalamic arcuate nucleus relay and translate important cues from the periphery into the central nervous system. However, the gene regulatory program directing their development remains poorly understood. Here we report that the LIM-homeodomain transcription factor Isl1 is expressed in several subpopulations of developing arcuate neurons and plays crucial roles in their fate specification. Mice with conditional deletion of the Isl1 gene in developing hypothalamus display severe deficits in both feeding and linear growth. Consistent with these results, their arcuate nucleus fails to express key fate markers of Isl1-expressing neurons that regulate feeding and growth. These include the orexigenic neuropeptides AgRP and NPY for specifying AgRP-neurons, the anorexigenic neuropeptide alphaMSH for POMC-neurons, and the two growth-stimulatory peptides, growth hormone-releasing hormone (GHRH) for GHRH-neurons and somatostatin (Sst) for Sst-neurons. Finally, we show that Isl1 directly enhances the expression of AgRP by cooperating with the key orexigenic transcription factors glucocorticoid receptor and brain-specific homeobox factor. Our results identify Isl1 as a critical transcription factor that plays critical roles in the gene regulatory program directing development of multiple arcuate neuronal subpopulations.

Leonard, J. T., Rowley, J. S., Eide, C. A., Traer, E., Hayes-Lattin, B., Loriaux, M., et al. (2016).

Targeting BCL-2 and ABL/LYN in Philadelphia chromosome-positive acute lymphoblastic leukemia. *Science Translational Medicine*, 8(354), 354ra114.

Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph(+))ALL remains a challenge. Although the addition of targeted tyrosine kinase inhibitors (TKIs) to standard cytotoxic therapy has greatly improved upfront treatment, treatment-related morbidity and mortality remain high. TKI monotherapy provides only temporary responses and renders patients susceptible to the development of TKI resistance. Thus, identifying agents that could enhance the activity of TKIs is urgently needed. Recently, a selective inhibitor of B cell lymphoma 2 (BCL-2), ABT-199 (venetoclax), has shown impressive activity against hematologic malignancies. We demonstrate that the combination of TKIs with venetoclax is highly synergistic in vitro, decreasing cell viability and inducing apoptosis in Ph(+))ALL. Furthermore, the multikinase inhibitors dasatinib and ponatinib appear to have the added advantage of inducing Lck/Yes novel tyrosine kinase (LYN)-mediated proapoptotic BCL-2-like protein 11 (BIM) expression and inhibiting up-regulation of antiapoptotic myeloid cell leukemia 1 (MCL-1), thereby potentially overcoming the development of venetoclax resistance. Evaluation of the dasatinib-venetoclax combination for the treatment of primary Ph(+))ALL patient samples in xenografted immunodeficient mice confirmed the tolerability of this drug combination and demonstrated its superior antileukemic efficacy compared to either agent alone. These data suggest that the combination of dasatinib and venetoclax has the potential to improve the treatment of Ph(+))ALL and should be further evaluated for patient care.

Leonard, J. T., & Stock, W. (2016). The persistence of minimal residual disease in Philadelphia chromosome-positive acute lymphoblastic leukemia: We know it's bad, now what? *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

Levine, R. A., & McAllister, B. S. (2016). Implant site development using ti-mesh and cellular allograft in the esthetic zone for restorative-driven implant placement: A case report. *International Journal of Periodontics and Restorative Dentistry*, 36(3), 372-381.

This article presents a case report of implant site development in a healthy, nonsmoking 62-year-old man using titanium mesh (Ti-mesh) in conjunction with human cellular allograft for ridge augmentation of a type 4 alveolar ridge defect. The patient presented initially with a severely periodontally abscessed maxillary right central incisor probing to the apex. The tooth was extracted, and after 8 weeks a bone reconstructive procedure was completed using a well-stabilized Ti-mesh and cellular allograft that was covered with a quickly resorbing collagen matrix. After 7 months of undisturbed healing, cone beam computed tomographic evaluation demonstrated a horizontal bone increase of 7 mm and a vertical bone increase of 2.3 mm. This case report demonstrates the benefits of predictable regenerative space maintenance using Ti-mesh in conjunction with a cellular allograft to allow for prosthetically driven implant placement in the esthetic zone. © 2016 by Quintessence Publishing Co Inc.

Lichtenheld, A., Nomura, M., Chapin, N., Burgess, T., & Kornegay, J. (2015). Development and implementation of an emergency medicine podcast for medical students: EMIGcast. *The Western Journal of Emergency Medicine*, 16(6), 877-878.

Lindauer, A., Harvath, T. A., Berry, P. H., & Wros, P. (2016). The meanings african american caregivers ascribe to dementia-related changes: The paradox of hanging on to loss. *Gerontologist*, 56(4), 733-742.

Purpose of the Study: Using an interpretive phenomenological approach, this study explored the meaning African American (AA) caregivers ascribed to the dementia-related changes in their care-recipients. Design and Methods: Data were gathered in this qualitative study with 22 in-depth interviews. Eleven AA caregivers for persons with dementia, living in the Pacific Northwestern United States, were interviewed twice. Four caregivers participated in an optional observation session. Results: Analysis based on the hermeneutic circle revealed that, for these caregivers, the dementia-related changes meant that they had to hang on to the care-recipients for as long as possible. Caregivers recognized that the valued care-recipients were changed, but still here and worthy of respect and compassion. Ancestral family values, shaped by historical oppression, appeared to influence these meanings. Implications: The results from this study suggest that AA caregivers tend to focus on the aspects of the care-recipients' personalities that

remain, rather than grieve the dementia-related losses. These findings have the potential to deepen gerontologists' understanding of the AA caregiver experience. This, in turn, can facilitate effective caregiver decision making and coping. © The Author 2015. Published by Oxford University Press on behalf of The Gerontological Society of America. All rights reserved.

Liu, X., Qian, Z. Y., Xie, F., Fan, W., Nelson, J. W., Xiao, X., et al. (2016). Functional screening for G protein-coupled receptor targets of 14,15-epoxyeicosatrienoic acid. *Prostaglandins & Other Lipid Mediators*,

Epoxyeicosatrienoic acids (EETs) are potent vasodilators that play important roles in cardiovascular physiology and disease, yet the molecular mechanisms underlying the biological actions of EETs are not fully understood. Multiple lines of evidence suggest that the actions of EETs are in part mediated via G protein-coupled receptor (GPCR) signaling, but the identity of such a receptor has remained elusive. We sought to identify 14,15-EET-responsive GPCRs. A set of 105 clones were expressed in *Xenopus* oocyte and screened for their ability to activate cAMP-dependent chloride current. Several receptors responded to micromolar concentrations of 14,15-EET, with the top five being prostaglandin receptor subtypes (PTGER2, PTGER4, PTGFR, PTGDR, PTGER3IV). Overall, our results indicate that multiple low-affinity 14,15-EET GPCRs are capable of increasing cAMP levels following 14,15-EET stimulation, highlighting the potential for cross-talk between prostanoid and other eicosanoid GPCRs. Our data also indicate that none of the 105 GPCRs screened met our criteria for a high-affinity receptor for 14,15-EET.

Lopez, L. M., Ramesh, S., Chen, M., Edelman, A., Otterness, C., Trussell, J., et al. (2016). Progestin-only contraceptives: Effects on weight. *Cochrane Database of Systematic Reviews*, 2016(8)
Background: Progestin-only contraceptives (POCs) are appropriate for many women who cannot or should not take estrogen. POCs include injectables, intrauterine contraception, implants, and oral contraceptives. Many POCs are long-acting, cost-effective methods of preventing pregnancy. However, concern about weight gain can deter the initiation of contraceptives and cause early discontinuation among users. Objectives: The primary objective was to evaluate the association between progestin-only contraceptive use and changes in body weight. Search methods: Until 4 August 2016, we searched MEDLINE, CENTRAL, POPLINE, LILACS, ClinicalTrials.gov, and ICTRP.

For the initial review, we contacted investigators to identify other trials. Selection criteria: We considered comparative studies that examined a POC versus another contraceptive method or no contraceptive. The primary outcome was mean change in body weight or mean change in body composition. We also considered the dichotomous outcome of loss or gain of a specified amount of weight. Data collection and analysis: Two authors extracted the data. Non-randomized studies (NRS) need to control for confounding factors. We used adjusted measures for the primary effects in NRS or the results of matched analysis from paired samples. If the report did not provide adjusted measures for the primary analysis, we used unadjusted outcomes. For RCTs and NRS without adjusted measures, we computed the mean difference (MD) with 95% confidence interval (CI) for continuous variables. For dichotomous outcomes, we calculated the Mantel-Haenszel odds ratio (OR) with 95% CI. Main results: We found 22 eligible studies that included a total of 11,450 women. With 6 NRS added to this update, the review includes 17 NRS and 5 RCTs. By contraceptive method, the review has 16 studies of depot medroxyprogesterone acetate (DMPA), 4 of levonorgestrel-releasing intrauterine contraception (LNG-IUC), 5 for implants, and 2 for progestin-only pills. Comparison groups did not differ significantly for weight change or other body composition measure in 15 studies. Five studies with moderate or low quality evidence showed differences between study arms. Two studies of a six-rod implant also indicated some differences, but the evidence was low quality. Three studies showed differences for DMPA users compared with women not using a hormonal method. In a retrospective study, weight gain (kg) was greater for DMPA versus copper (Cu) IUC in years one (MD 2.28, 95% CI 1.79 to 2.77), two (MD 2.71, 95% CI 2.12 to 3.30), and three (MD 3.17, 95% CI 2.51 to 3.83). A prospective study showed adolescents using DMPA had a greater increase in body fat (%) compared with a group not using a hormonal method (MD 11.00, 95% CI 2.64 to 19.36). The DMPA group also had a greater decrease in lean body mass (%) (MD -4.00, 95% CI -6.93 to -1.07). A more recent retrospective study reported greater mean increases with use of DMPA versus Cu IUC for weight (kg) at years 1 (1.3 vs 0.2), 4 (3.5 vs 1.9), and 10 (6.6 vs 4.9). Two studies reported a greater mean increase in body fat mass (%) for POC users versus women not using a hormonal method. The method was LNG-IUC in two studies (reported means 2.5 versus -1.3; $P = 0.029$); (MD 1.60, 95% CI 0.45 to 2.75). One also studied a desogestrel-containing pill (MD 3.30, 95% CI 2.08 to 4.52). Both studies showed a greater decrease in lean body mass among POC users. Authors'

conclusions: We considered the overall quality of evidence to be low; more than half of the studies had low quality evidence. The main reasons for downgrading were lack of randomizations (NRS) and high loss to follow-up or early discontinuation. These 22 studies showed limited evidence of change in weight or body composition with use of POCs. Mean weight gain at 6 or 12 months was less than 2 kg (4.4 lb) for most studies. Those with multiyear data showed mean weight change was approximately twice as much at two to four years than at one year, but generally the study groups did not differ significantly. Appropriate counseling about typical weight gain may help reduce discontinuation of contraceptives due to perceptions of weight gain. © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Los, E. A., Ramsey, K. L., Guttmann-Bauman, I., & Ahmann, A. J. (2016). Reliability of trained dogs to alert to hypoglycemia in patients with type 1 diabetes. *Journal of Diabetes Science and Technology*,

BACKGROUND: We examined the reliability of trained dogs to alert to hypoglycemia in individuals with type 1 diabetes. METHODS: Patients with type 1 diabetes who currently used diabetes alert dogs participated in this exploratory study. Subjects reported satisfaction, perceived dog glucose sensing ability and reasons for obtaining a trained dog. Reliability of dog alerts was assessed using capillary blood glucose (CBG) and blinded continuous glucose monitoring (CGM) as comparators in 8 subjects (age 4-48). Hypoglycemia was defined as CBG or CGM <70 mg/dL. RESULTS: Dog users were very satisfied (8.9/10 on a Likert-type scale) and largely confident (7.9/10) in their dog's ability to detect hypoglycemia. Detection of hypoglycemia was the primary reason for obtaining a trained dog. During hypoglycemia, spontaneous dog alerts occurred at a rate 3.2 (2.0-5.2, 95% CI) times higher than during euglycemia (70-179 mg/dL). Dogs provided timely alerts in 36% (sensitivity) of all hypoglycemia events (n = 45). Due to inappropriate alerts, the PPV of a dog alert for hypoglycemia was 12%. When there was concurrence of a hypoglycemic event between the dog alert and CGM (n = 30), CGM would have alerted prior to the dog in 73% of events (median 22-minute difference). CONCLUSIONS: This is the first study evaluating reliability of trained dogs to alert to hypoglycemia under real-life conditions. Trained dogs often alert a human companion to otherwise unknown hypoglycemia; however due to high false-positive rate, a dog alert alone is unlikely to be helpful in differentiating hypo-/hyper-

/euglycemia. CGM often detects hypoglycemia before a trained dog by a clinically significant margin.

Loudin, M., Deloughery, T., & Shatzel, J. (2016). Mononucleosis induced pseudo neutropenia. *American Journal of Hematology,*

Luk, L. J., Mosen, D., MacArthur, C. J., & Grosz, A. H. (2016). Implementation of a pediatric posttonsillectomy pain protocol in a large group practice. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery, 154(4), 720-724.*

OBJECTIVE: In response to the increased risk of respiratory failure and death after tonsillectomy related to codeine use, Kaiser Permanente Northwest restricted use of opioids in patients <7 years old via electronic health record (EHR). However, opioids could be prescribed at physician discretion by overriding the EHR. This study aims to examine protocol compliance in a large group practice using EHR order sets and complication rates as compared with historical data.

STUDY DESIGN: Case series with chart review. SETTING: Ambulatory care within a health maintenance organization. SUBJECTS AND METHODS: Procedural codes were used to identify children <7 years old who underwent tonsillectomy or adenotonsillectomy approximately 1.5 years before and after implementation of EHR protocol (n = 437). Primary outcome was opioid pain prescriptions received by patients. Secondary outcomes were emergency or urgent care utilization, postoperative bleeding, nausea, vomiting, dehydration, death, and reasons for prescribing opioid pain medication after EHR protocol implementation. Chi-square analysis and Fischer's exact testing were used to compare differences in event rates. RESULTS:

Implementation of an age-based narcotic protocol significantly decreased physician narcotic prescribing from 82.2% to 15.4% (P < .0001). The most common reason for narcotic prescription after the intervention was the report of inadequate pain control by phone call (35%). There was no significant difference in rate of emergency or urgent care utilization between pre- and postimplementation groups (4% vs 6%, P = .29). CONCLUSIONS: Implementation of an age-based narcotic restriction for posttonsillectomy patients using an EHR order set is an effective and safe way to influence physician prescription practices.

Lund, A. W. (2016). Re-energizing exhausted T cells? *Science Translational Medicine*, 8(353)

Lund, A. W., Wagner, M., Fankhauser, M., Steinskog, E. S., Broggi, M. A., Spranger, S., et al. (2016). Lymphatic vessels regulate immune microenvironments in human and murine melanoma. *Journal of Clinical Investigation*, 126(9), 3389-3402.

Lymphatic remodeling in tumor microenvironments correlates with progression and metastasis, and local lymphatic vessels play complex and poorly understood roles in tumor immunity. Tumor lymphangiogenesis is associated with increased immune suppression, yet lymphatic vessels are required for fluid drainage and immune cell trafficking to lymph nodes, where adaptive immune responses are mounted. Here, we examined the contribution of lymphatic drainage to tumor inflammation and immunity using a mouse model that lacks dermal lymphatic vessels (K14-VEGFR3-Ig mice). Melanomas implanted in these mice grew robustly, but exhibited drastically reduced cytokine expression and leukocyte infiltration compared with those implanted in control animals. In the absence of local immune suppression, transferred cytotoxic T cells more effectively controlled tumors in K14-VEGFR3-Ig mice than in control mice. Furthermore, gene expression analysis of human melanoma samples revealed that patient immune parameters are markedly stratified by levels of lymphatic markers. This work suggests that the establishment of tumor-associated inflammation and immunity critically depends on lymphatic vessel remodeling and drainage. Moreover, these results have implications for immunotherapies, the efficacies of which are regulated by the tumor immune microenvironment.

Mager, R., Daneshmand, S., Evans, C. P., Palou, J., Martinez-Salamanca, J. I., Master, V. A., et al.

(2016). Renal cell carcinoma with inferior vena cava involvement: Prognostic effect of tumor thrombus consistency on cancer specific survival. *Journal of Surgical Oncology*,
BACKGROUND: Renal cell carcinoma forming a venous tumor thrombus (VTT) in the inferior vena cava (IVC) has a poor prognosis. Recent investigations have been focused on prognostic markers of survival. Thrombus consistency (TC) has been proposed to be of significant value but yet there are conflicting data. The aim of this study is to test the effect of IVC VTT consistency on cancer specific survival (CSS) in a multi-institutional cohort. METHODS: The records of 413 patients collected by the International Renal Cell Carcinoma-Venous Thrombus Consortium were

retrospectively analyzed. All patients underwent radical nephrectomy and tumor thrombectomy. Kaplan-Meier estimate and Cox regression analyses investigated the impact of TC on CSS in addition to established clinicopathological predictors. RESULTS: VTT was solid in 225 patients and friable in 188 patients. Median CSS was 50 months in solid and 45 months in friable VTT. TC showed no significant association with metastatic spread, pT stage, perinephric fat invasion, and higher Fuhrman grade. Survival analysis and Cox regression rejected TC as prognostic marker for CSS. CONCLUSIONS: In the largest cohort published so far, TC seems not to be independently associated with survival in RCC patients and should therefore not be included in risk stratification models. J. Surg. Oncol. (c) 2016 Wiley Periodicals, Inc.

Mair, C. A., Quiñones, A. R., & Pasha, M. A. (2016). Care preferences among middle-aged and older adults with chronic disease in Europe: Individual health care needs and national health care infrastructure. *Gerontologist, 56*(4), 687-701.

Purpose of the Study: The purpose of this study is to expand knowledge of care options for aging populations cross-nationally by examining key individual-level and nation-level predictors of European middle-aged and older adults' preferences for care. Design and Methods: Drawing on data from the Survey of Health, Ageing and Retirement in Europe and the Organisation for Economic Co-operation and Development, we analyze old age care preferences of a sample of 6,469 adults aged 50 and older with chronic disease in 14 nations. Using multilevel modeling, we analyze associations between individual-level health care needs and nation-level health care infrastructure and preference for family-based (vs. state-based) personal care. Results: We find that middle-aged and older adults with chronic disease whose health limits their ability to perform paid work, who did not receive personal care from informal sources, and who live in nations with generous long-term care funding are less likely to prefer family-based care and more likely to prefer state-based care. Implications: We discuss these findings in light of financial risks in later life and the future role of specialized health support programs, such as long-term care. © The Author 2015. Published by Oxford University Press on behalf of The Gerontological Society of America.

Maragakis, A., Siddharthan, R., Rachbeisel, J., & Snipes, C. (2016). Creating a 'reverse' integrated primary and mental healthcare clinic for those with serious mental illness. *Primary Health Care Research and Development*, 17(5), 421-427.

Individuals with serious mental illness (SMI) are more likely to experience preventable medical health issues, such as diabetes, hyperlipidemia, obesity, and cardiovascular disease, than the general population. To further compound this issue, these individuals are less likely to seek preventative medical care. These factors result in higher usage of expensive emergency care, lower quality of care, and lower life expectancy. This manuscript presents literature that examines the health disparities this population experiences, and barriers to accessing primary care. Through the identification of these barriers, we recommend that the field of family medicine work in collaboration with the field of mental health to implement 'reverse' integrated care (RIC) systems, and provide primary care services in the mental health settings. By embedding primary care practitioners in mental health settings, where individuals with SMI are more likely to present for treatment, this population may receive treatment for somatic care by experts. This not only would improve the quality of care received by patients, but would also remove the burden of managing complex somatic care from providers trained in mental health. The rationale for this RIC system, as well as training and policy reforms, are discussed. © Cambridge University Press 2015.

Martin, G. M., Rex, E. A., Devaraneni, P., Denton, J. S., Boodhansingh, K. E., DeLeon, D. D., et al. (2016). Pharmacological correction of trafficking defects in ATP-sensitive potassium channels caused by sulfonylurea receptor 1 mutations. *The Journal of Biological Chemistry*, ATP-sensitive potassium (KATP) channels play a key role in mediating glucose-stimulated insulin secretion by coupling metabolic signals to beta-cell membrane potential. Loss of KATP channel function due to mutations in ABCC8 or KCNJ11, genes encoding the sulfonylurea receptor 1 (SUR1) or the inwardly rectifying potassium channel Kir6.2, respectively, results in congenital hyperinsulinism. Many SUR1 mutations prevent trafficking of channel proteins from the endoplasmic reticulum to the cell surface. Channel inhibitors including sulfonylureas and carbamazepine have been shown to correct channel trafficking defects. In the present study, we identified 13 novel SUR1 mutations that cause channel trafficking defects, the majority of which

are amenable to pharmacological rescue by glibenclamide and carbamazepine. By contrast, none of the mutant channels were rescued by KATP channel openers. Crosslinking experiments showed that KATP channel inhibitors promoted interactions between the N-terminus of Kir6.2 and SUR1, whereas channel openers did not, suggesting the inhibitors enhance inter-subunit interactions to overcome channel biogenesis and trafficking defects. Functional studies of rescued mutant channels indicate that most mutants rescued to the cell surface exhibited wild-type like sensitivity to ATP, MgADP, and diazoxide. In intact cells, recovery of channel function upon trafficking rescue by reversible sulfonylureas or carbamazepine was facilitated by the KATP channel opener diazoxide. Our study expands the KATP channel trafficking mutations whose function can be recovered by pharmacological ligands and provides further insight into the structural mechanism by which channel inhibitors correct channel biogenesis and trafficking defects.

Martin, I. (2016). A glucocerebrosidase chaperone to ward off parkinson's disease. *Science Translational Medicine*, 8(351)

May, L. M., Reinka, M. A., Tipsord, J. M., Felver, J. C., & Berkman, E. T. (2016). Parenting an early adolescent: A pilot study examining neural and relationship quality changes of a mindfulness intervention. *Mindfulness*, 7(5), 1203-1213.

Relating to adolescent children can be challenging for parents, and yet children's perceptions of positive parent-child relationships are protective against deleterious outcomes. Therefore, it is valuable to understand and explore strategies that can support positive parent-adolescent relationships during adolescence. The present study investigates the effects of mindfulness training on parents' neural activity, children's perceptions of the parent-child relationship, and the relationship between the two. As such, this design allowed us to investigate intervention-induced changes in the parent-child relationship. One parent per family (N = 18) completed a task measuring mindful awareness of breathing during functional magnetic resonance imaging before and after attending an 8-week Mindful Families Stress Reduction (MFSR) course with their early-adolescent children. Across the sample, parent neural activation from pre- to post-intervention increased in areas related to self-awareness and evaluation (precuneus, ventromedial prefrontal cortex), emotional awareness and interoception (mid-insula), and

emotion regulation (lateral prefrontal cortex). Changes in parents' activation in the left anterior insula/inferior frontal gyrus, an area often related to empathy and emotional processing/regulation, were specifically related to changes in children's reports of the parent-child relationship. The neural regions showing an intervention effect overlapped to a significantly greater degree with emotion regulation-related than attention-related regions. These findings implicate parental empathy and emotion/regulation in children's perceptions of the family relationship and suggest that parent emotion and/or emotion regulation is a potential mechanism by which mindful parenting interventions affect change. © 2016, Springer Science+Business Media New York.

McCaul, C., Caulfield, K., Sinha, R., & Ellison, D. (2016). Anaesthesia recommendations for patients suffering from liddle's syndrome. *Anesthesiologie Und Intensivmedizin*, 57(9), S500-S505.

The clinical phenotype resembles primary hyperaldosteronism, and the presenting feature is typically hypertension in teenage years. Patients are often asymptomatic. Renal impairment may occur due to hypertension. Muscle weakness in combination with severe hypertension has been reported in elderly population with the syndrome [2]. The defining factor in the diagnosis is evidence of suppressed aldosterone levels, and the lack of response to treatment with the mineralocorticoid receptor blocker spironolactone [6;7]. Metabolic abnormalities can be corrected by dietary salt restriction, and administration of antagonists of the epithelial sodium channel such as amiloride or triamterene [8]. Renal transplantation has been used as treatment.

McClintick, M. N., & Grant, K. A. (2016). Aggressive temperament predicts ethanol self-administration in late adolescent male and female rhesus macaques. *Psychopharmacology*, , 1-12.

Rationale: Anxiety and aggression are associated with ethanol self-administration, but these behaviors can serve as either risk factors for or consequences of heavy drinking in rodents and humans. Baseline levels of aggressive-like and anxious-like behavior in non-human primates have not yet been characterized in relation to future or prior ethanol intake. Objective: The objective of the study was to test the association between temperament at baseline with future ethanol self-administration in late adolescent male (n = 21) and female (n = 11) rhesus monkeys. Methods: Shortly after entering the laboratory and before exposure to ethanol, the

Human Intruder Test (HIT) and the Novel Object Test (NOT) were used to determine baseline anxious-like and aggressive-like behavior in age-matched male and female rhesus monkeys (*Macaca mulatta*). The monkeys were induced to drink ethanol 4 % (w/v) using a schedule-induced polydipsia procedure, followed by "open-access" ethanol self-administration in which the monkeys were allowed a choice of water or 4 % ethanol (w/v) for 22 h/day for 52 weeks. Results: Aggressive monkeys self-administered more ethanol and attained higher blood ethanol concentrations (BECs). No significant differences in ethanol intakes or BECs were found between anxious and non-anxious monkeys or between behaviorally inhibited and non-inhibited monkeys. Baseline aggressive behavior positively correlated with ethanol intake and intoxication. Conclusions: Baseline reactive aggression was associated with higher future ethanol intake and intoxication. While significant sex differences in HIT reactivity were observed, the relationship between aggression and ethanol drinking was observed across sex and is not sex-specific. © 2016 Springer-Verlag Berlin Heidelberg

McEvoy, C. T., & Spindel, E. R. (2016). Pulmonary effects of maternal smoking on the fetus and child: Effects on lung development, respiratory morbidities, and life long lung health. *Paediatric Respiratory Reviews*,
Maternal smoking during pregnancy is the largest preventable cause of abnormal in-utero lung development. Despite well known risks, rates of smoking during pregnancy have only slightly decreased over the last ten years, with rates varying from 5-40% worldwide resulting in tens of millions of fetal exposures. Despite multiple approaches to smoking cessation about 50% of smokers will continue to smoke during pregnancy. Maternal genotype plays an important role in the likelihood of continued smoking during pregnancy and the degree to which maternal smoking will affect the fetus. The primary effects of maternal smoking on offspring lung function and health are decreases in forced expiratory flows, decreased passive respiratory compliance, increased hospitalization for respiratory infections, and an increased prevalence of childhood wheeze and asthma. Nicotine appears to be the responsible component of tobacco smoke that affects lung development, and some of the effects of maternal smoking on lung development can be prevented by supplemental vitamin C. Because nicotine is the key agent for affecting lung

development, e-cigarette usage during pregnancy is likely to be as dangerous to fetal lung development as is maternal smoking.

McKenzie, G., Lasater, K., Delander, G. E., Neal, M. B., Morgove, M., & Eckstrom, E. (2016). Falls prevention education: Interprofessional training to enhance collaborative practice. *Gerontology and Geriatrics Education*, , 1-12.

The gap between the complex health care needs of older adults and the availability of geriatrics-trained health care professionals is widening. Interprofessional education offers an opportunity to engage multiple professions in interactive learning and clinically relevant problem solving to achieve high-quality patient-centered care. This article describes a project that engaged an interprofessional teaching team to support interprofessional practice teams to reduce falls in older adults via implementation of evidence-based practice guidelines. Ninety-five participants from 25 teams were trained on multiple strategies to decrease the risk of falls in older adults. The intervention facilitated increases in knowledge, confidence in skill performance, and team commitment to change practice patterns to support the health and safety of older adults. Findings suggest that community-based practices can successfully support the training of interprofessional teams and that training may lead to improved care processes and outcomes for older adults. © 2016 Taylor & Francis

McNeal, D. W., Brandner, D. D., Gong, X., Postupna, N. O., Montine, T. J., Dirk Keene, C., et al. (2016). Unbiased stereological analysis of reactive astrogliosis to estimate age-associated cerebral white matter injury. *Journal of Neuropathology and Experimental Neurology*, 75(6), 539-554.

Cerebral white matter injury (WMI) contributes to cognitive dysfunction associated with pathological aging. Because reactive astrocyte-related factors contribute to remyelination failure after WMI, we sought accurate, cost-effective, and reproducible histopathological approaches for quantification of morphometric features of reactive astrogliosis in aged human white matter in patients with vascular brain injury (VBI). We compared 7 distinct approaches to quantify the features of glial fibrillary acidic protein (GFAP)-labeled astrocytes in the prefrontal white matter of brains from patients with VBI (n=17, mean age 88.8 years) and controls that did not exhibit VBI

(n=11, mean age 86.6 years). Only modern stereological techniques (ie, optical fractionator and spaceballs) and virtual process thickness measurements demonstrated significant changes in astrocyte number, process length, or proximal process thickness in cases with VBI relative to controls. The widely employed methods of neuropathological scoring, antibody capture assay (histelide), area fraction fractionator, and Cavalieri point counting failed to detect significant differences in GFAP expression between the groups. Unbiased stereological approaches and virtual thickness measurements provided the only sensitive and accurate means to quantify astrocyte reactivity as a surrogate marker of WMI in human brains with VBI. © 2016 American Association of Neuropathologists, Inc. All rights reserved.

Mejía-Pérez, D., Angel-Muller, E., Rodríguez-Hernández, A. E., Ruiz-Parra, A. I., Tolosa-Ardila, J. E., & Gaitán-Duarte, H. (2016). Answering to comments on "operational characteristics of the clinical diagnosis in the office, with and without tests (pH and amine test), for diagnosing bacterial vaginosis in symptomatic patients in bogotá, colombia". [Respuesta a: Comentarios sobre el artículo "características operativas del diagnóstico clínico con y sin pruebas de consultorio (ph y prueba de aminas) para el diagnóstico de vaginosis bacteriana, en pacientes sintomáticas en Bogotá, Colombia"] *Revista Colombiana De Obstetricia y Ginecologia*, 67(2), 164-165.

Meyer, T. J., Held, U., Nevenon, K. A., Klawitter, S., Pirzer, T., Carbone, L., et al. (2016). The flow of the gibbon LAVA element is facilitated by the LINE-1 retrotransposition machinery. *Genome Biology and Evolution*,
LAVA (L: INE- A: lu- V: NTR- A: lu-like) elements comprise a family of non-autonomous, composite, non-LTR retrotransposons specific to gibbons and may have played a role in the evolution of this lineage. A full-length LAVA element consists of portions of repeats found in most primate genomes: CT-rich, Alu-like, and VNTR regions from the SVA retrotransposon, and portions of the AluSz and L1ME5 elements. To evaluate whether the gibbon genome currently harbors functional LAVA elements capable of mobilization by the endogenous LINE-1 (L1) protein machinery and which LAVA components are important for retrotransposition, we established a trans-mobilization assay in HeLa cells. Specifically, we tested if a full-length member of the older LAVA subfamily C that was isolated from the gibbon genome and named LAVAC, or its

components, can be mobilized in the presence of the human L1 protein machinery. We show that L1 proteins mobilize the LAVAC element at frequencies exceeding processed pseudogene formation and human SVAE retrotransposition by >100-fold and ≥ 3 -fold, respectively. We find that only the SVA-derived portions confer activity, and truncation of the 3' L1ME5 portion increases retrotransposition rates by at least 100%. Tagged de novo insertions integrated into intronic regions in cell culture, recapitulating findings in the gibbon genome. Finally, we present alternative models for the rise of the LAVA retrotransposon in the gibbon lineage.

Meyers, D. E., & Goodlin, S. J. (2016). End-of-life decisions and palliative care in advanced heart failure. *The Canadian Journal of Cardiology*, 32(9), 1148-1156.

Advanced heart failure (HF) therapies are focused on extending life and improving function. In contrast, palliative care is a holistic approach that focuses on symptom alleviation and patients' physical, psychosocial, and spiritual needs. HF clinicians can integrate palliative care strategies by incorporating several important components of planning and decision-making for HF patients. Future care planning (FCP) for HF patients should incorporate the basic tenets of shared decision-making (SDM). These include understanding the patient's perspective and care preferences, articulating what is medically feasible, and integrating these considerations into the overall care plan. Use of defined triggers for FCP can stimulate important patient-caregiver conversations. Guidelines advocate an annual review of HF status and future care preferences. Advance directives are important for any individual with a chronic, life-limiting illness and should be integrated into FCP. Nevertheless, use of advance directives by HF patients is extremely low. Consideration of illness trajectories and risk-scoring tools might facilitate prognostication and delivery of appropriate HF care. Decisions about heart transplantation or left ventricular assist device implantation should include planning for potential complications associated with these therapies. Such decisions also should include a discussion of palliative management, as an alternative to intervention and also as an option for managing symptoms or adverse events after intervention. Palliative care, including FCP and SDM, should be integrated into the course of all patients with advanced HF. Clinicians who provide HF care should acquire the skills necessary for conducting FCP and SDM discussions.

Meza-Romero, R., Benedek, G., Jordan, K., Leng, L., Pantouris, G., Lolis, E., et al. (2016). Modeling of both shared and distinct interactions between MIF and its homologue D-DT with their common receptor CD74. *Cytokine*, 88, 62-70.

D-dopachrome tautomerase (D-DT) shares amino acid sequence similarity, structural architecture and biological activity with the cytokine MIF. Recent studies show that the two protein homologs also bind to the same cell surface receptor, CD74, to activate the ERK1/2 pathway that ultimately leads to pro-inflammatory and pro-survival gene expression. We recently showed that RTL1000 and DRa1-MOG-35-55, two biological drugs with potent anti-inflammatory properties that treat experimental autoimmune encephalomyelitis (EAE) in mice, bind to the cell surface receptor CD74 with high affinity and compete with MIF for binding to the same regions of CD74.

Computational modeling of MIF and RTL1000 binding interactions with CD74 predicted the presence of three CD74 binding regions for each MIF homotrimer. Through a similar approach we have now expanded our work to study the D-DT (MIF-2) interaction with CD74 that is mainly defined by three elements scattered throughout the disordered regions of the interacting molecules. The model predicted: (a) a hydrophobic cradle between CD74 and D-DT consisting of N-terminal tyrosine residues of three CD74 monomers arranged in a planar alignment interacts with aromatic amino acid residues located in the disordered D-DT C-terminus; (b) a triad consisting of the E103 residue on one D-DT monomer in close contact with R179 and S181 on one chain of the CD74 trimer forms an intermolecular salt bridge; and (c) amino acid residues on the C-terminus random coil of CD74 chain C form a long interacting area of approximately 500Å² with a disordered region of D-DT chain B. These three binding elements were also present in MIF/CD74 binding interactions, with involvement of identical or highly similar amino acid residues in each MIF homotrimer that partner with the exact same residues in CD74. Topologically, however, the location of the three CD74 binding regions of the D-DT homotrimer differs substantially from that of the three MIF binding regions. This key difference in orientation appears to derive from a sequence insertion in D-DT that topologically limits binding to only one CD74 molecule per D-DT homotrimer, in contrast to predicted binding of up to three CD74 molecules per MIF homotrimer. These results have implications for the manner in which D-DT and MIF compete with each other for binding to the CD74 receptor and for the relative potency of

DRa1-MOG-35-55 and RTL1000 for competitive inhibition of D-DT and MIF binding and activation through CD74.

Miller, L. M., Whitlatch, C. J., & Lyons, K. S. (2016). Shared decision-making in dementia: A review of patient and family carer involvement. *Dementia, 15*(5), 1141-1157.

This paper reviews empirical findings concerning the decision-making process of persons with dementia and their family carers, with a particular focus on the extent and determinants of involvement of persons with dementia in the decision-making process. To be included in this review, studies needed to be published in peer-reviewed journals between 1999 and 2014, report empirical data from participants with dementia and/or their family carers, and pertain to the involvement of persons with dementia and their family carers in decisions about everyday care, medical care and treatment, or long-term care. A total of 36 studies were included. Results indicated that not all persons with dementia are excluded from participating in the decision-making process, but there is a broad spectrum of what constitutes shared decision-making in dementia. Studies concerning the determinants of shared decision-making mostly focused on non-modifiable factors. Future research is needed to better promote shared decision-making among persons with dementia and their family carers. © 2014, © The Author(s) 2014.

Moghanaki, D., Timmerman, R. D., Slatore, C. G., Niewoehner, D. E., & Karas, T. Z. (2016). In regard to valle et al. *International Journal of Radiation Oncology, Biology, Physics, 96*(2), 482-483.

Moses, Z. B., Ozpinar, A., Abd-El-Barr, M. M., Quinonez, L. G., Emani, S. M., & Goumnerova, L. C. (2016). Direct heart shunt placement for CSF diversion: Technical note. *Journal of Neurosurgery.Pediatrics, , 1-4*.

The authors report a complex case of an 18-year-old male with a history of hydrocephalus secondary to intraventricular hemorrhage of prematurity, with more than 30 previous shunt revisions, who presented to the authors' institution with shunt malfunction. After exhausting his peritoneal cavity and pleural space as possible distal sites of shunt placement, he underwent a direct heart shunt placement when it was discovered he had thrombosis of his subclavian vein precluding a standard wire-guided atrial cannulation. His course was complicated by postoperative distal catheter migration and repeat surgery for reimplantation of the shunt directly

into the atrium. At the 16-month follow-up visit, the patient showed no symptoms of shunt malfunction or pericardial effusion. Imaging studies demonstrated a functioning shunt system. This is the second reported successful ventricle to direct heart shunt placement in an adult. The authors report on the technical aspects of the case and review the relevant literature.

Motika, P. V., & Spencer, D. C. (2016). Treatment of epilepsy in the elderly. *Current Neurology and Neuroscience Reports*, 16(11)

The treatment of epilepsy in older individuals is an increasingly important topic in neurology and an area that all treating neurologists should have familiarity with. As the population ages, the number of patients over 65 who present with new-onset epilepsy will increase, as will the complexity of their comorbid medical and neurological disorders. In older patients, seizures are often unwitnessed, or present with atypical symptoms, making the diagnosis more challenging. Additionally, there are relatively limited data to guide the use of anti-epileptic medications and other treatments in this patient population. Elderly patients may experience increased side effects from anti-epileptic drugs compared with younger patients and in general, are likely to have a narrower therapeutic window and greater degree of individual variation with respect to side effects. Familiarity with anti-epileptic medication dosing and titration schedules, possible adverse effects, and potential pharmacokinetic and drug interactions can be helpful when considering treatment options and may increase the likelihood of success. © 2016, Springer Science+Business Media New York.

Mu, E. W., Lewin, J. M., Stevenson, M. L., Meehan, S. A., Carucci, J. A., & Gareau, D. S. (2016). Use of digitally stained multimodal confocal mosaic images to screen for nonmelanoma skin cancer. *JAMA Dermatology*,

Importance: Confocal microscopy has the potential to provide rapid bedside pathologic analysis, but clinical adoption has been limited in part by the need for physician retraining to interpret grayscale images. Digitally stained confocal mosaics (DSCMs) mimic the colors of routine histologic specimens and may increase adaptability of this technology. Objective: To evaluate the accuracy and precision of 3 physicians using DSCMs before and after training to detect basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in Mohs micrographic surgery fresh-tissue

specimens. Design: This retrospective study used 133 DSCMs from 64 Mohs tissue excisions, which included clear margins, residual BCC, or residual SCC. Discarded tissue from Mohs surgical excisions from the dermatologic surgery units at Memorial Sloan Kettering Cancer Center and Oregon Health & Science University were collected for confocal imaging from 2006 to 2011. Final data analysis and interpretation took place between 2014 and 2016. Two Mohs surgeons and a Mohs fellow, who were blinded to the correlating gold standard frozen section diagnoses, independently reviewed the DSCMs for residual nonmelanoma skin cancer (NMSC) before and after a brief training session (about 5 minutes). The 2 assessments were separated by a 6-month washout period. Main Outcomes and Measures: Diagnostic accuracy was characterized by sensitivity and specificity of detecting NMSC using DSCMs vs standard frozen histopathologic specimens. The diagnostic precision was calculated based on interobserver agreement and kappa scores. Paired 2-sample t tests were used for comparative means analyses before and after training. Results: The average respective sensitivities and specificities of detecting NMSC were 90% (95% CI, 89%-91%) and 79% (95% CI, 52%-100%) before training and 99% (95% CI, 99%-99%) (P = .001) and 93% (95% CI, 90%-96%) (P = .18) after training; for BCC, they were 83% (95% CI, 59%-100%) and 92% (95% CI, 81%-100%) before training and 98% (95% CI, 98%-98%) (P = .18) and 97% (95% CI, 95%-100%) (P = .15) after training; for SCC, they were 73% (95% CI, 65%-81%) and 89% (95% CI, 72%-100%) before training and 100% (P = .004) and 98% (95% CI, 95%-100%) (P = .21) after training. The pretraining interobserver agreement was 72% (kappa = 0.58), and the posttraining interobserver agreement was 98% (kappa = 0.97) (P = .04). Conclusions and Relevance: Diagnostic use of DSCMs shows promising correlation to frozen histologic analysis, but image quality was affected by variations in image contrast and mosaic-stitching artifact. With training, physicians were able to read DSCMs with significantly improved accuracy and precision to detect NMSC.

Muoto, I., Luck, J., Yoon, J., Bernell, S., & Snowden, J. M. (2016). Oregon's coordinated care organizations increased timely prenatal care initiation and decreased disparities. *Health Affairs (Project Hope)*, 35(9), 1625-1632.

Policies at the state and federal levels affect access to health services, including prenatal care. In 2012 the State of Oregon implemented a major reform of its Medicaid program. The new model,

called a coordinated care organization (CCO), is designed to improve the coordination of care for Medicaid beneficiaries. This reform effort provides an ideal opportunity to evaluate the impact of broad financing and delivery reforms on prenatal care use. Using birth certificate data from Oregon and Washington State, we evaluated the effect of CCO implementation on the probability of early prenatal care initiation, prenatal care adequacy, and disparities in prenatal care use by type of insurance. Following CCO implementation, we found significant increases in early prenatal care initiation and a reduction in disparities across insurance types but no difference in overall prenatal care adequacy. Oregon's reforms could serve as a model for other Medicaid and commercial health plans seeking to improve prenatal care quality and reduce disparities.

Nabavizadeh, N., Shukla, R., Elliott, D. A., Mitin, T., Vaccaro, G. M., Dolan, J. P., et al. (2016).

Preoperative carboplatin and paclitaxel-based chemoradiotherapy for esophageal carcinoma: Results of a modified CROSS regimen utilizing radiation doses greater than 41.4 Gy. *Diseases of the Esophagus*, 29(6), 614-620.

Summary: Trimodality therapy for resectable esophageal and gastroesophageal junction cancers utilizing preoperative radiotherapy with concurrent carboplatin and paclitaxel-based chemotherapy is being increasingly utilized secondary to the results of the phase III CROSS trial. However, there is a paucity of reports of this regimen as a component of chemoradiotherapy in North America. We aim to report on our clinical experience using a modified CROSS regimen with higher radiotherapy doses. Patients with advanced (cT2–cT4 or node positive) esophageal or gastroesophageal junction carcinoma who received preoperative carboplatin/paclitaxel-based chemoradiotherapy with radiation doses of greater than 41.4 Gray (Gy) followed by esophagectomy were identified from an institutional database. Patient, imaging, treatment, and tumor response characteristics were analyzed. Twenty-four patients were analyzed. All but one tumor had adenocarcinoma histology. The median radiation dose was 50.4 Gy. Pathologic complete response was achieved in 29% of patients, with all receiving 50.4 Gy. Three early postoperative deaths were seen, due in part to acute respiratory distress syndrome and all three patients received 50–50.4 Gy. With a median follow-up of 9.4 months (23 days–2 years), median survival was 24 months. Trimodality therapy utilizing concurrent carboplatin/paclitaxel with North American radiotherapy doses appeared to have similar pathologic complete response rates

compared with the CROSS trial, but may be associated with higher toxicity. Although the sample size is small and further follow-up is necessary, radiation doses greater than 41.4 Gy may not be warranted secondary to a potentially increased risk of severe radiation-induced acute lung injury.

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Nagel, C. L., Kirby, M. A., Zambrano, L. D., Rosa, G., Barstow, C. K., Thomas, E. A., et al. (2016).

Study design of a cluster-randomized controlled trial to evaluate a large-scale distribution of cook stoves and water filters in western province, Rwanda. *Contemporary Clinical Trials Communications*, 4, 124-135.

Background In Rwanda, pneumonia and diarrhea are the first and second leading causes of death, respectively, among children under five. Household air pollution (HAP) resultant from cooking indoors with biomass fuels on traditional stoves is a significant risk factor for pneumonia, while consumption of contaminated drinking water is a primary cause of diarrheal disease. To date, there have been no large-scale effectiveness trials of programmatic efforts to provide either improved cookstoves or household water filters at scale in a low-income country. In this paper we describe the design of a cluster-randomized trial to evaluate the impact of a national-level program to distribute and promote the use of improved cookstoves and advanced water filters to the poorest quarter of households in Rwanda. **Methods/Design** We randomly allocated 72 sectors (administratively defined units) in Western Province to the intervention, with the remaining 24 sectors in the province serving as controls. In the intervention sectors, roughly 100,000 households received improved cookstoves and household water filters through a government-sponsored program targeting the poorest quarter of households nationally. The primary outcome measures are the incidence of acute respiratory infection (ARI) and diarrhea among children under five years of age. Over a one-year surveillance period, all cases of acute respiratory infection (ARI) and diarrhea identified by health workers in the study area will be extracted from records maintained at health facilities and by community health workers (CHW). In addition, we are conducting intensive, longitudinal data collection among a random sample of households in the study area for in-depth assessment of coverage, use, environmental exposures, and additional health measures. **Discussion** Although previous research has examined the impact of providing household water treatment and improved cookstoves on child health, there have been

no studies of national-level programs to deliver these interventions at scale in a developing country. The results of this study, the first RCT of a large-scale programmatic cookstove or household water filter intervention, will inform global efforts to reduce childhood morbidity and mortality from diarrheal disease and pneumonia. Trial registration This trial is registered at Clinicaltrials.gov (NCT02239250). © 2016 The Authors

Newman, L., Duffus, A. L. J., & Lee, C. (2016). Using the free program MEGA to build phylogenetic trees from molecular data. *American Biology Teacher*, 78(7), 608-612.

Building evolutionary trees can be an excellent way for students to see how different gene sequences or organisms are related to one another. Molecular Evolutionary Genetics Analysis (MEGA) software is a free package that lets anyone build evolutionary trees in a user-friendly setup. There are several options to choose from when building trees from molecular data in MEGA, but the most commonly used are neighbor joining and maximum likelihood, both of which give good estimates on the relationship between different molecular sequences. In this article, we describe how to collect data from GenBank, insert the data into a text editor, import the data into MEGA, and use the dataset to create phylogenetic trees. © 2016 National Association of Biology Teachers.

Nicoara, D., Zhang, Y., Nelson, J. T., Brewer, A. L., Maharaj, P., DeWald, S. N., et al. (2016).

Hyperbaric oxygen treatment suppresses withdrawal signs in morphine-dependent mice. *Brain Research*, 1648, 434-437.

Hyperbaric oxygen (HBO₂) therapy reportedly reduces opiate withdrawal in human subjects. The purpose of this research was to determine whether HBO₂ treatment could suppress physical signs of withdrawal in opiate-dependent mice. Male NIH Swiss mice were injected s.c. with morphine sulfate twice a day for 4 days, the daily dose gradually increasing from 50 mg/kg on day 1 to 125 mg/kg on day 4. On day 5, withdrawal was precipitated by i.p. injection of 5.0 mg/kg naloxone. Mice were observed for physical withdrawal signs, including jumping, forepaw tremor, wet-dog shakes, rearing and defecation for 30 min. Sixty min prior to the naloxone injection, different groups of mice received either a 30-min or 60-min HBO₂ treatment at 3.5 atm absolute. HBO₂ treatment significantly reduced naloxone-precipitated jumping, forepaw tremor, wet-dog

shakes, rearing and defecation. Based on these experimental findings, we concluded that treatment with HBO2 can suppress physical signs of withdrawal syndrome in morphine-dependent mice. © 2016 Elsevier B.V.

Nicolaidis, C., Raymaker, D., McDonald, K., Kapp, S., Weiner, M., Ashkenazy, E., et al. (2016). The development and evaluation of an online healthcare toolkit for autistic adults and their primary care providers. *Journal of General Internal Medicine*, 31(10), 1180-1189.

Background: The healthcare system is ill-equipped to meet the needs of adults on the autism spectrum. Objective: Our goal was to use a community-based participatory research (CBPR) approach to develop and evaluate tools to facilitate the primary healthcare of autistic adults.

Design: Toolkit development included cognitive interviewing and test-retest reliability studies.

Evaluation consisted of a mixed-methods, single-arm pre/post-intervention comparison.

Participants: A total of 259 autistic adults and 51 primary care providers (PCPs) residing in the

United States. Interventions: The AASPIRE Healthcare toolkit includes the Autism Healthcare Accommodations Tool (AHAT)—a tool that allows patients to create a personalized

accommodations report for their PCP—and general healthcare- and autism-related information, worksheets, checklists, and resources for patients and healthcare providers. Main Measures:

Satisfaction with patient-provider communication, healthcare self-efficacy, barriers to healthcare, and satisfaction with the toolkit's usability and utility; responses to open-ended questions. Key

Results: Preliminary testing of the AHAT demonstrated strong content validity and adequate test-retest stability. Almost all patient participants (>94 %) felt that the AHAT and the toolkit were

easy to use, important, and useful. In pre/post-intervention comparisons, the mean number of

barriers decreased (from 4.07 to 2.82, $p < 0.0001$), healthcare self-efficacy increased (from 37.9

to 39.4, $p = 0.02$), and satisfaction with PCP communication improved (from 30.9 to 32.6, $p =$

0.03). Patients stated that the toolkit helped clarify their needs, enabled them to self-advocate

and prepare for visits more effectively, and positively influenced provider behavior. Most of the

PCPs surveyed read the AHAT (97 %), rated it as moderately or very useful (82 %), and would

recommend it to other patients (87 %). Conclusions: The CBPR process resulted in a reliable

healthcare accommodation tool and a highly accessible healthcare toolkit. Patients and providers

indicated that the tools positively impacted healthcare interactions. The toolkit has the potential

to reduce barriers to healthcare and improve healthcare self-efficacy and patient-provider communication. © 2016, Society of General Internal Medicine.

Nilsson, O., Isoherranen, N., Guo, M. H., Lui, J. C., Jee, Y. H., Guttman-Bauman, I., et al. (2016).

Accelerated skeletal maturation in disorders of retinoic acid metabolism: A case report and focused review of the literature. *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme*,

Nutritional excess of vitamin A, a precursor for retinoic acid (RA), causes premature epiphyseal fusion, craniosynostosis, and light-dependent retinopathy. Similarly, homozygous loss-of-function mutations in CYP26B1, one of the major RA-metabolizing enzymes, cause advanced bone age, premature epiphyseal fusion, and craniosynostosis. In this paper, a patient with markedly accelerated skeletal and dental development, retinal scarring, and autism-spectrum disease is presented and the role of retinoic acid in longitudinal bone growth and skeletal maturation is reviewed. Genetic studies were carried out using SNP array and exome sequencing. RA isomers were measured in the patient, family members, and in 18 age-matched healthy children using high-performance liquid chromatography coupled to tandem mass spectrometry. A genomic SNP array identified a novel 8.3 megabase microdeletion on chromosome 10q23.2-23.33. The 79 deleted genes included CYP26A1 and C1, both major RA-metabolizing enzymes. Exome sequencing did not detect any variants that were predicted to be deleterious in the remaining alleles of these genes or other known retinoic acid-metabolizing enzymes. The patient exhibited elevated plasma total RA (16.5 vs. 12.6 \pm 1.5 nM, mean \pm SD, subject vs. controls) and 13-cisRA (10.7 nM vs. 6.1 \pm 1.1). The findings support the hypothesis that elevated RA concentrations accelerate bone and dental maturation in humans. CYP26A1 and C1 haploinsufficiency may contribute to the elevated retinoic acid concentrations and clinical findings of the patient, although this phenotype has not been reported in other patients with similar deletions, suggesting that other unknown genetic or environmental factors may also contribute.

Nishijima, D. K., Laurie, A. L., Weiss, R. E., Yagapen, A. N., Malveau, S. E., Adler, D. H., et al. (2016).

Reliability of clinical assessments in older adults with syncope or near syncope. *Academic Emergency Medicine*, 23(9), 1014-1021.

Objectives: Clinical prediction models for risk stratification of older adults with syncope or near syncope may improve resource utilization and management. Predictors considered for inclusion into such models must be reliable. Our primary objective was to evaluate the inter-rater agreement of historical, physical examination, and electrocardiogram (ECG) findings in older adults undergoing emergency department (ED) evaluation for syncope or near syncope. Our secondary objective was to assess the level of agreement between clinicians on the patient's overall risk for death or serious cardiac outcomes. Methods: We conducted a cross-sectional study at 11 EDs in adults 60 years of age or older who presented with unexplained syncope or near syncope. We excluded patients with a presumptive cause of syncope (e.g., seizure) or if they were unable or unwilling to follow-up. Evaluations of the patient's past medical history and current medication use were completed by treating provider and trained research associate pairs. Evaluations of the patient's physical examination and ECG interpretation were completed by attending/resident, attending/advanced practice provider, or attending/attending pairs. All evaluations were blinded to the responses from the other rater. We calculated the percent agreement and kappa statistic for binary variables. Inter-rater agreement was considered acceptable if the kappa statistic was 0.6 or higher. Results: We obtained paired observations from 255 patients; mean (\pm SD) age was 73 (\pm 9) years, 137 (54%) were male, and 204 (80%) were admitted to the hospital. Acceptable agreement was achieved in 18 of the 21 (86%) past medical history and current medication findings, none of the 10 physical examination variables, and three of the 13 (23%) ECG interpretation variables. There was moderate agreement (Spearman correlation coefficient, $r = 0.40$) between clinicians on the patient's probability of 30-day death or serious cardiac outcome, although as the probability increased, there was less agreement. Conclusions: Acceptable agreement between raters was more commonly achieved with historical rather than physical examination or ECG interpretation variables. Clinicians had moderate agreement in assessing the patient's overall risk for a serious outcome at 30 days. Future development of clinical prediction models in older adults with syncope should account for variability of assessments between raters and consider the use of objective clinical variables. © 2016 by the Society for Academic Emergency Medicine

Nowotny, M., Hummel, J., Kössl, M., Udayashankar, A. P., & Wolf, K. (2015). Mechanical investigations of sound-induced responses in a simple ear. *12th International Workshop on the Mechanics of Hearing: Protein to Perception*, , 1703.

Previous in-vivo studies have shown that the tonotopically-organized hearing organ, the crista acustica, of the bushcricket *Mecopoda elongata* is a promising model for investigations of basic hearing mechanics. This linearly arranged organ with a length of <1 mm consists of about 45 receptor units and processes frequencies from about 4 up to at least 80 kHz. Pure-tone stimulation of the crista acustica leads to travelling waves along the longitudinal axis of the hearing organ. We found that the amplitude maximum of the sound-induced travelling waves is shifted in the radial direction during the propagation of the travelling wave. The overall amplitude maximum was found to be located always on one side (anterior) in respect to the transduction place. This mechanical biasing presumably optimizes the signal transduction. Additionally, the amplitude response maximum of the travelling wave during one cycle of motion exhibits different degrees in the radial shift. During broad-band noise stimulation, the mechanical response of the crista acustica exhibits a low-frequency dominance. When using the conspecific chirp of *M. elongata* (2-90 kHz), as stimulus frequencies above 30 kHz do not lead to large responses even though the hearing organ is able to detect frequencies up to at least 80 kHz, covering the frequency range of the chirp with its amplitude maximum at about 70 kHz. © 2015 AIP Publishing LLC.

Olufs, E. L., Valleley, R. J., Hembree, K. C., & Evans, J. H. (2016). Brief educational "curbside consultation": Impact on attention-deficit/hyperactivity disorder referrals in an integrated healthcare setting. *Families, Systems and Health*, 34(3), 221-228.

Introduction: As behavioral health providers integrate into primary health care clinics, it is important to examine methods used to increase primary care providers' (PCPs) knowledge of behavioral health providers' areas of expertise and service provision. Attention-deficit/hyperactivity disorder (ADHD) has been identified as one of the most common behavioral health disorders PCPs diagnose and treat in children. Method: This study examined whether 2 brief educational "curbside consults," during which a psychologist provided information regarding the assessment and treatment of ADHD, had an impact on PCPs' referral practices. Information was

collected via medical records review for the same 6-month period prior to and following provider education. Results: The results indicated that there was an increase in ADHD referrals to the behavioral health clinic (BHC) following educational consultation. In addition, there was some evidence to suggest that following PCP education, fewer children were diagnosed by the PCP with ADHD and fewer children were previously prescribed a psychotropic medication upon referral to the BHC. Treatment (e.g., behavioral therapy, pharmacotherapy, combined approach) also differed between families previously diagnosed and prescribed psychotropic medication. Discussion: The current study provides some preliminary evidence that brief educational consultation with PCPs may increase both referrals for ADHD concerns and may influence the way PCPs diagnose and address behavioral health concerns. Implications of these findings and suggestions for future research are discussed. © 2016 American Psychological Association.

O'Neal, W. T., Wang, Y. G., Wu, H. T., Zhang, Z. M., Li, Y., Tereshchenko, L. G., et al. (2016).

Electrocardiographic J wave and cardiovascular outcomes in the general population (from the atherosclerosis risk in communities study). *The American Journal of Cardiology*, 118(6), 811-815.

The association between the J wave, a key component of the early repolarization pattern, and adverse cardiovascular outcomes remains unclear. Inconsistencies have stemmed from the different methods used to measure the J wave. We examined the association between the J wave, detected by an automated method, and adverse cardiovascular outcomes in 14,592 (mean age = 54 +/- 5.8 years; 56% women; 26% black) participants from the Atherosclerosis Risk In Communities (ARIC) study. The J wave was detected at baseline (1987 to 1989) and during follow-up study visits (1990 to 1992, 1993 to 1995, and 1996 to 1998) using a fully automated method. Sudden cardiac death, coronary heart disease death, and cardiovascular mortality were ascertained from hospital discharge records, death certificates, and autopsy data through December 31, 2010. A total of 278 participants (1.9%) had evidence of a J wave. Over a median follow-up of 22 years, 4,376 of the participants (30%) died. In a multivariable Cox regression analysis adjusted for demographics, cardiovascular risk factors, and potential confounders, the J wave was not associated with an increased risk of sudden cardiac death (hazard ratio [HR] 0.74, 95% CI 0.36 to 1.50), coronary heart disease death (HR 0.72, 95% CI 0.40 to 1.32), or cardiovascular mortality (HR 1.16, 95% CI 0.87 to 1.56). An interaction was detected for

cardiovascular mortality by gender with men (HR 1.54, 95% CI 1.09 to 2.19) having a stronger association than women (HR 0.74, 95% CI 0.43 to 1.25; P-interaction = 0.030). In conclusion, our findings suggest that the J wave is a benign entity that is not associated with an increased risk for sudden cardiac arrest in middle-aged adults in the United States.

Ong, J. S., Cuellar-Partida, G., Lu, Y., Ovarian Cancer Study, A., Fasching, P. A., Hein, A., et al.

(2016). Association of vitamin D levels and risk of ovarian cancer: A mendelian randomization study. *International Journal of Epidemiology*,

BACKGROUND: In vitro and observational epidemiological studies suggest that vitamin D may play a role in cancer prevention. However, the relationship between vitamin D and ovarian cancer is uncertain, with observational studies generating conflicting findings. A potential limitation of observational studies is inadequate control of confounding. To overcome this problem, we used Mendelian randomization (MR) to evaluate the association between single nucleotide polymorphisms (SNPs) associated with circulating 25-hydroxyvitamin D [25(OH)D] concentration and risk of ovarian cancer. METHODS: We employed SNPs with well-established associations with 25(OH)D concentration as instrumental variables for MR: rs7944926 (DHCR7), rs12794714 (CYP2R1) and rs2282679 (GC). We included 31 719 women of European ancestry (10 065 cases, 21 654 controls) from the Ovarian Cancer Association Consortium, who were genotyped using customized Illumina Infinium iSelect (iCOGS) arrays. A two-sample (summary data) MR approach was used and analyses were performed separately for all ovarian cancer (10 065 cases) and for high-grade serous ovarian cancer (4121 cases). RESULTS: The odds ratio for epithelial ovarian cancer risk (10 065 cases) estimated by combining the individual SNP associations using inverse variance weighting was 1.27 (95% confidence interval: 1.06 to 1.51) per 20 nmol/L decrease in 25(OH)D concentration. The estimated odds ratio for high-grade serous epithelial ovarian cancer (4121 cases) was 1.54 (1.19, 2.01). CONCLUSIONS: Genetically lowered 25-hydroxyvitamin D concentrations were associated with higher ovarian cancer susceptibility in Europeans. These findings suggest that increasing plasma vitamin D levels may reduce risk of ovarian cancer.

Ormseth, M. J., Yancey, P. G., Yamamoto, S., Oeser, A. M., Gebretsadik, T., Shintani, A., et al.

(2016). Net cholesterol efflux capacity of HDL enriched serum and coronary atherosclerosis in

rheumatoid arthritis. *IJC Metabolic and Endocrine*, 13, 6-11.

Background/objectives Cardiovascular (CV) risk is increased in patients with rheumatoid arthritis (RA), but not fully explained by traditional risk factors such as LDL and HDL cholesterol concentrations. The cholesterol efflux capacity of HDL may be a better CV risk predictor than HDL concentrations. We hypothesized that HDL's cholesterol efflux capacity is impaired and inversely associated with coronary atherosclerosis in patients with RA. Methods We measured the net cholesterol efflux capacity of apolipoprotein B depleted serum and coronary artery calcium score in 134 patients with RA and 76 control subjects, frequency-matched for age, race and sex. The relationship between net cholesterol efflux capacity and coronary artery calcium score and other clinical variables of interest was assessed in patients with RA. Results Net cholesterol efflux capacity was similar among RA (median [IQR]: 34% removal [28, 41%]) and control subjects (35% removal [27%, 39%]) (P = 0.73). In RA, increasing net cholesterol efflux capacity was not significantly associated with decreased coronary calcium score (OR = 0.78 (95% CI 0.51-1.19), P = 0.24, adjusted for age, race and sex, Framingham risk score and presence of diabetes). Net cholesterol efflux capacity was not significantly associated with RA disease activity score, C-reactive protein, urinary F2-isoprostanes, or degree of insulin resistance in RA. Conclusions Net cholesterol efflux capacity is not significantly altered in patients with relatively well-controlled RA nor is it significantly associated with coronary artery calcium score. © 2016

Penna, M., Whiteford, M., Hompes, R., & Sylla, P. (2016). Developing and assessing a cadaveric training model for transanal total mesorectal excision: Initial experience in the UK and USA. *Colorectal Disease : The Official Journal of the Association of Coloproctology of Great Britain and Ireland*,
AIM: Transanal Total Mesorectal Excision (taTME) has become one of the most promising technical advancement in the surgical treatment of rectal cancer, with rising numbers of surgeons seeking training. We describe our experience with human cadaveric courses for taTME delivered in two countries. METHOD: Four fresh human cadaveric workshops conducted in Oxford, UK in 2015 and two in Chicago, USA in 2013-2014, trained a total of 52 surgeons. Parameters of operative performance for each delegate were recorded. Previous surgical experience and uptake of taTME in the surgeons' clinical setting were surveyed. RESULTS: 47 taTME cases were

performed on cadaveric models. Participating surgeons had previous experience in laparoscopic TME surgery and transanal approaches but limited taTME exposure. The purse-string remained occluded throughout in 93% of UK and 60% of USA cases. Operative timings for key procedural steps were similar between the two countries with mean time from start of circumferential dissection to peritoneal entry of 79.5 minutes (range=25-155). 96% of surgeons dissected transanally to a level S2 or above. The TME specimen quality was complete or near complete in 81%, with improvements noted between the first and second procedure performed. 81% of surgeons surveyed are currently performing taTME in their local hospitals. CONCLUSION: Fresh frozen cadavers provide excellent teaching models for complex pelvic surgery. A structured training curriculum including reading material, dry-lab purse-string practice and post-course mentorship will provide surgeons a more complete training package and ongoing support, to ultimately ensure the safe introduction of taTME in the clinical setting. This article is protected by copyright. All rights reserved.

Peters, A. L., Ahmann, A. J., Battelino, T., Evert, A., Hirsch, I. B., Murad, M. H., et al. (2016).

Diabetes technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, , jc20162534.

OBJECTIVE: To formulate clinical practice guidelines for the use of continuous glucose monitoring and continuous subcutaneous insulin infusion in adults with diabetes. PARTICIPANTS: The participants include an Endocrine Society-appointed Task Force of seven experts, a methodologist, and a medical writer. The American Association for Clinical Chemistry, the American Association of Diabetes Educators, and the European Society of Endocrinology co-sponsored this guideline. EVIDENCE: The Task Force developed this evidence-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned one systematic review and used the best available evidence from other published systematic reviews and individual studies. CONSENSUS PROCESS: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the American Association for Clinical Chemistry, the American Association

of Diabetes Educators, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. CONCLUSIONS: Continuous subcutaneous insulin infusion and continuous glucose monitoring have an important role in the treatment of diabetes. Data from randomized controlled trials are limited on the use of medical devices, but existing studies support the use of diabetes technology for a wide variety of indications. This guideline presents a review of the literature and practice recommendations for appropriate device use.

Pham, A. N., Bubalo, J. S., & Lewis, J. S., 2nd. (2016). Experience utilizing 400 mg daily of posaconazole tablet formulation in order to achieve desired minimum serum concentrations in adult patients with a hematologic malignancy or stem cell transplant. *Antimicrobial Agents and Chemotherapy*,

We describe our experience using the posaconazole delayed-release tablet formulation 400 mg once daily dosing in 20 hematologic malignancy or hematopoietic stem cell transplant patients who were unable to attain pre-specified target minimum serum (trough) concentrations for invasive fungal infection treatment or prophylaxis. The higher dose allowed the majority of patients to achieve pre-specified target trough concentrations without incurring additional toxicities.

Pierce, M., & Madison, L. (2016). Evaluation and initial management of hypopituitarism. *Pediatrics in Review*, 37(9), 370-376.

Polen, L. A., Rossi, J. K., Berg, C. K., Balise, R. R., Herfkens, R. J., & Auerbach, P. S. (2016). Failure of real-time passive notification about radiation exposure to influence physician ordering behavior. *Cureus*, 8(7), e695.

Objectives To determine whether real-time passive notification of patient radiation exposure via a computerized physician order entry system would alter the number of computed tomography scans ordered by physicians in the Emergency Department (ED) setting. Methods When a practitioner ordered a computed tomography scan, a passive notification was immediately and prominently displayed via the computerized physician order entry system. The notification stated the following: the amount of estimated radiation in millisieverts (mSv), the equivalent number of single-view chest radiographs, and equivalent days of average environmental background

radiation to which a patient during a specific computed tomography scan would be exposed. The primary outcome was changed in the number of computed tomography scans ordered when comparing data collected before and after the addition of the notification. Results Before the dosimetry notification ("intervention") was instituted, 1,747 computed tomography scans were performed on patients during 11,709 Emergency Department visits (14.9% computed tomography scan rate). After the intervention had been instituted, 1,827 computed tomography scans were performed on patients during 11,582 Emergency Department patient visits (15.8% computed tomography scan rate). No statistically significant difference was found for all chief complaints combined ($p = 0.17$), or for any individual chief complaint, between the number of computed tomography scans performed on Emergency Department patients before versus after the intervention. Conclusions Passive real-time notification of patient radiation exposure displayed in a computerized physician order entry system at the time of computed tomography scan ordering in the Emergency Department did not significantly change the number of ordered scans.

Potter, G. B., & Petryniak, M. A. (2016). Neuroimmune mechanisms in krabbe's disease. *Journal of Neuroscience Research*, 94(11), 1341-1348.

Neuroinflammation, activation of innate immune components of the nervous system followed by an adaptive immune response, is observed in most leukodystrophies and coincides with white matter pathology, disease progression, and morbidity. Despite this, there is a major gap in our knowledge of the contribution of the immune system to disease phenotype. Inflammation in Krabbe's disease has been considered a secondary effect, resulting from cell-autonomous oligodendroglial cell death or myelin loss resulting from psychosine accumulation. However, recent studies have shown immune activation preceding clinical symptoms and white matter pathology. Moreover, the therapeutic effect underlying hematopoietic stem cell transplantation, the only treatment for Krabbe's disease, has been demonstrated to occur via immunomodulation. This Review highlights recent advances in elaboration of the immune cascade involved in Krabbe's disease. Mechanistic insight into the inflammatory pathways participating in myelin and axon loss or preservation may lead to novel therapeutic approaches for this disorder. (c) 2016 The Authors. *Journal of Neuroscience Research* Published by Wiley Periodicals, Inc.

Prabhu, A., Obi, K., Lieberman, D., & Rubenstein, J. H. (2016). The race-specific incidence of esophageal squamous cell carcinoma in individuals with exposure to tobacco and alcohol. *The American Journal of Gastroenterology*,

OBJECTIVES: The relative impact of esophageal squamous cell carcinoma (ESCC) in minority populations is incompletely understood. We aimed to estimate the race-specific incidences of ESCC and place these in the context of the incidence of esophageal adenocarcinoma (EAC) in white men with gastroesophageal reflux disease (GERD). METHODS: The race- and sex-specific exposures to tobacco and alcohol in the United States were obtained from the National Health Interview Survey. The standardized incidence ratios of exposure to tobacco smoke and/or alcohol for ESCC were estimated from meta-analyses. Existing incidences of ESCC in the United States were obtained from the Surveillance, Epidemiology, and End Results (SEER) program. We then used this data to inform a Markov computer model estimating the incidence of ESCC. RESULTS: The incidence of ESCC reported in SEER was the greatest among African-Americans compared with white non-Hispanics, Hispanics, or Asians. In our model, the estimated incidence of ESCC in African-American men exposed to tobacco and alcohol approached the risk of EAC in white non-Hispanic men with weekly GERD. For instance, at age 60 years, the incidence of ESCC in African-American men who have used both tobacco and alcohol was 30/100,000 compared with an incidence of EAC in white men with GERD of 40/100,000. In comparison, the risk of EAC in white non-Hispanic women with weekly GERD at this age was 6.2/100,000. CONCLUSIONS: The incidence of ESCC in African-American men who use alcohol and tobacco is the highest and comparable to other screened diseases. Development of screening and prevention programs for ESCC in high-risk populations should be considered. *Am J Gastroenterol* advance online publication, 30 August 2016; doi:10.1038/ajg.2016.346.

Prakash, S. K., Bondy, C. A., Maslen, C. L., Silberbach, M., Lin, A. E., Perrone, L., et al. (2016). Autosomal and X chromosome structural variants are associated with congenital heart defects in turner syndrome: The NHLBI GenTAC registry. *American Journal of Medical Genetics. Part A*,

Turner Syndrome (TS) is a developmental disorder caused by partial or complete loss of one sex chromosome. Bicuspid aortic valve and other left-sided congenital heart lesions (LSL), including thoracic aortic aneurysms and acute aortic dissections, are 30-50 times more frequent in TS than

in the general population. In 454 TS subjects, we found that LSL are significantly associated with reduced dosage of Xp genes and increased dosage of Xq genes. We also showed that genome-wide copy number variation is increased in TS and identify a common copy number variant (CNV) in chromosome 12p13.31 that is associated with LSL with an odds ratio of 3.7. This CNV contains three protein-coding genes (SLC2A3, SLC2A14, and NANOGP1) and was previously implicated in congenital heart defects in the 22q11 deletion syndrome. In addition, we identified a subset of rare and recurrent CNVs that are also enriched in non-syndromic BAV cases. These observations support our hypothesis that X chromosome and autosomal variants affecting cardiac developmental genes may interact to cause the increased prevalence of LSL in TS. (c) 2016 Wiley Periodicals, Inc.

Prasad, V. (2016). Perspective: The precision-oncology illusion. *Nature*, 537(7619), S63.

Promjunyakul, N. -, Lahna, D. L., Kaye, J. A., Dodge, H. H., Erten-Lyons, D., Rooney, W. D., et al.

(2016). Comparison of cerebral blood flow and structural penumbras in relation to white matter hyperintensities: A multi-modal magnetic resonance imaging study. *Journal of Cerebral Blood Flow and Metabolism*, 36(9), 1528-1536.

Normal-appearing white matter (NAWM) surrounding WMHs is associated with decreased structural integrity and perfusion, increased risk of WMH growth, and is referred to as the WMH penumbra. Studies comparing structural and cerebral blood flow (CBF) penumbras within the same individuals are lacking, however, and would facilitate our understanding of mechanisms resulting in WM damage. This study aimed to compare both CBF and structural WMH penumbras in non-demented aging. Eighty-two elderly volunteers underwent 3T-MRI including fluid attenuated inversion recovery (FLAIR), pulsed arterial spin labeling and diffusion tensor imaging (DTI). A NAWM layer mask was generated for periventricular and deep WMHs. Mean CBF, DTI-fractional anisotropy (DTI-FA), DTI-mean diffusivity (DTI-MD) and FLAIR intensity for WMHs and its corresponding NAWM layer masks were computed and compared against its mean within total brain NAWM using mixed effects models. For both periventricular and deep WMHs, DTI-FA, DTI-MD and FLAIR intensity changes extended 2-9 mm surrounding WMHs ($p \leq 0.05$), while CBF changes extended 13-14 mm ($p \leq 0.05$). The CBF penumbra is more extensive than structural

penumbras in relation to WMHs and includes WM tissue both with and without microstructural changes. Findings implicate CBF as a potential target for the prevention of both micro and macro structural WM damage. © The Author(s) 2016.

Purice, M. D., Speese, S. D., & Logan, M. A. (2016). Delayed glial clearance of degenerating axons in aged drosophila is due to reduced PI3K/Draper activity. *Nature Communications*, 7, 12871.

Advanced age is the greatest risk factor for neurodegenerative disorders, but the mechanisms that render the senescent brain vulnerable to disease are unclear. Glial immune responses provide neuroprotection in a variety of contexts. Thus, we explored how glial responses to neurodegeneration are altered with age. Here we show that glia-axon phagocytic interactions change dramatically in the aged *Drosophila* brain. Aged glia clear degenerating axons slowly due to low phosphoinositide-3-kinase (PI3K) signalling and, subsequently, reduced expression of the conserved phagocytic receptor Draper/MEGF10. Importantly, boosting PI3K/Draper activity in aged glia significantly reverses slow phagocytic responses. Moreover, several hours post axotomy, early hallmarks of Wallerian degeneration (WD) are delayed in aged flies. We propose that slow clearance of degenerating axons is mechanistically twofold, resulting from deferred initiation of axonal WD and reduced PI3K/Draper-dependent glial phagocytic function. Interventions that boost glial engulfment activity, however, can substantially reverse delayed clearance of damaged neuronal debris.

Ramamoorthy, S., Chen, F., Zha, D., Jacques, S. L., Wang, R., Choudhury, N., et al. (2015). The second filter's second coming. *12th International Workshop on the Mechanics of Hearing: Protein to Perception*, , 1703.

We measured sound-evoked vibrations at the stereociliary side of inner and outer hair cells and their surrounding supporting cells, using optical coherence tomography interferometry in living anesthetized Guinea pigs. Our measurements demonstrate a gradient in frequency tuning among different cell types, going from a high best frequency at the inner hair cells to a lower one at the Hensen cells. This causes the locus of maximum inner hair cell activation to be shifted toward the apex of the cochlea as compared to the outer hair cells. These observations show that additional processing and filtering of acoustic signals occurs within the organ of Corti prior to inner hair cell

excitation, thus reinstating a transformed second filter as a mechanism contributing to cochlear frequency tuning. © 2015 AIP Publishing LLC.

Ramsey, S. D., Nademanee, A., Masszi, T., Holowiecki, J., Abidi, M., Chen, A., et al. (2016). Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with hodgkin lymphoma. *British Journal of Haematology*,

Brentuximab vedotin (BV) significantly improved progression-free survival in a phase 3 study in patients with relapsed or refractory Hodgkin lymphoma (RR-HL) post-autologous-haematopoietic stem cell transplant (auto-HSCT); we report the impact of BV on quality of life (QOL) from this trial. The European Quality of Life five dimensions questionnaire was administered at the beginning of each cycle, end of treatment, and every 3 months during follow-up; index value scores were calculated using the time trade-off (TTO) method for UK-weighted value sets. Questionnaire adherence during the trial was 87.5% (N = 329). In an intent-to-treat analysis, compared with placebo, TTO scores in the BV arm did not exceed the minimally important difference (MID) of 0.08 except at month 15 (-0.084; 95% confidence interval, -0.143 to -0.025). On-treatment index scores were similar between arms and did not reach the MID at any time point; mixed-effect modelling showed that BV treatment effect was not significant (P = 0.2127). BV-associated peripheral neuropathy did not meaningfully impact QOL. Utility scores for patients who progressed declined compared with those who did not; TTO scores between these patients exceeded the MID beginning at month 15. In conclusion, QOL decreased modestly with BV consolidation treatment in patients with RR-HL at high risk of relapse after auto-HSCT.

Recht, M., Konkle, B. A., Jackson, S., Neufeld, E. J., Rockwood, K., & Pipe, S. (2016). Recognizing the need for personalization of haemophilia patient-reported outcomes in the prophylaxis era.

Haemophilia : The Official Journal of the World Federation of Hemophilia,

The safety and efficacy of treatment options for patients with haemophilia have significantly improved over the last two decades, particularly with greater utilization of prophylactic approaches. Consequently, it is becoming increasingly difficult to differentiate the treatment benefits of available choices based on standard endpoints such as annualized bleeding rates and

joint health scores. Patient-reported outcomes (PROs) have shown limited ability to discriminate between treatment outcomes, in part because of their comprehensive nature; i.e. differences in specific outcomes meaningful to individual patients are masked by a global scoring system based on a fixed set of items, many of which may be unimportant for any given patient. There is a clear need for new outcome measures. Initiatives to develop patient-centric outcomes that capture clinically meaningful change are ongoing. One such approach, goal attainment scaling (GAS), allows patients, in collaboration with a trained clinician, to select goals from a medical condition-specific menu of options and subsequently facilitates quantitative assessment of goal realization. Thus, it is fully personalized and sensitive to small, often idiosyncratic, treatment benefits, such as improvements in functional capacity. In this paper, we present the underlying rationale for GAS and one other novel approach to PRO personalization, and discuss their potential to augment current outcome measures by reliably detecting and quantifying treatment effects in individuals with haemophilia on prophylaxis.

Reddington, J. A., Mendez, G. A., Ching, A., Kubicky, C. D., Klimo, P., Jr., & Ragel, B. T. (2016).

Imaging characteristic analysis of metastatic spine lesions from breast, prostate, lung, and renal cell carcinomas for surgical planning: Osteolytic versus osteoblastic. *Surgical Neurology International*, 7(14), S361-S365.

Background: Surgeons treating metastatic spine disease can use computed tomography (CT) imaging to determine whether lesions are osteolytic, osteoblastic, or mixed. This enables treatment that considers the structural integrity of the vertebral body (VB), which is impaired with lytic lesions but not blastic lesions. The authors analyzed CT imaging characteristics of spine metastasis from breast, lung, prostate, and renal cell carcinomas (RCCs) to determine the metastasis patterns of each of these common tumors. Methods: The authors identified patients with metastatic spine disease treated during a 3-year period. Variables studied included age, sex, and cancer type. Lesions from breast, lung, prostate, and RCC primary lesions were selected for imaging analysis. Results: Sixty-six patients were identified: 17 had breast metastasis, 14 prostate, 18 lung, and 17 RCC. Breast cancer metastasis involved 33% of VBs with 56%, 20%, and 24% osteolytic, osteoblastic, and mixed, respectively. Prostate cancer metastasis involved 35% of VBs with 14%, 62%, and 24% osteolytic, osteoblastic, and mixed, respectively. Lung

cancer metastasis involved 13% of VBs with 64%, 33%, and 3% osteolytic, osteoblastic, and mixed, respectively. RCC metastasis involved 11% of VBs with 91%, 7%, and 2% osteolytic, osteoblastic, and mixed lesions, respectively. Conclusions: To improve surgical planning, we advocate the use of CT prior to surgery to evaluate whether spine metastases are osteolytic or osteoblastic. In cases of osteolytic lesions, the concern is of segmental instability requiring reconstruction and the risk for screw pull out should instrumentation be considered. In cases of osteoblastic lesions, surgeons should consider debulking dense bone. © 2016 Surgical Neurology International | Published by Wolters Kluwer - Medknow.

Reiner, A. (2015). The power of story in delivering cancer care. *Clinical Journal of Oncology Nursing*, 19(1), 10-11.

Ren, T., & He, W. (2015). Electrically evoked reticular lamina and basilar membrane vibrations in mice with alpha tectorin C1509G mutation. *12th International Workshop on the Mechanics of Hearing: Protein to Perception*, , 1703.

Mechanical coupling between the tectorial membrane and the hair bundles of outer hair cells is crucial for stimulating mechano-electrical transduction channels, which convert sound-induced vibrations into electrical signal, and for transmitting outer hair cell-generated force back to the basilar membrane to boost hearing sensitivity. It has been demonstrated that the detached tectorial membrane in mice with C1509G alpha tectorin mutation caused hearing loss, but enhanced electrically evoked otoacoustic emissions. To understand how the mutated cochlea emits sounds, the reticular lamina and basilar membrane vibrations were measured in the electrically stimulated cochlea in this study. The results showed that the electrically evoked basilar membrane vibration decreased dramatically while the reticular lamina vibration and otoacoustic emissions exhibited no significant change in C1509G mutation mice. This result indicates that a functional cochlear amplifier and a normal basilar membrane vibration are not required for the outer hair cell-generated sound to exit the cochlea. © 2015 AIP Publishing LLC.

Roeder, Z., Chen, Q., Davis, S., Carlson, J. D., Tupone, D., & Heinricher, M. M. (2016). Parabrachial complex links pain transmission to descending pain modulation. *Pain*,

The rostral ventromedial medulla (RVM) has a well-documented role in pain modulation and

exerts antinociceptive and pronociceptive influences mediated by 2 distinct classes of neurons, OFF-cells and ON-cells. OFF-cells are defined by a sudden pause in firing in response to nociceptive inputs, whereas ON-cells are characterized by a "burst" of activity. Although these reflex-related changes in ON- and OFF-cell firing are critical to their pain-modulating function, the pathways mediating these responses have not been identified. The present experiments were designed to test the hypothesis that nociceptive input to the RVM is relayed through the parabrachial complex (PB). In electrophysiological studies, ON- and OFF-cells were recorded in the RVM of lightly anesthetized male rats before and after an infusion of lidocaine or muscimol into PB. The ON-cell burst and OFF-cell pause evoked by noxious heat or mechanical probing were substantially attenuated by inactivation of the lateral, but not medial, parabrachial area. Retrograde tracing studies showed that neurons projecting to the RVM were scattered throughout PB. Few of these neurons expressed calcitonin gene-related peptide, suggesting that the RVM projection from PB is distinct from that to the amygdala. These data show that a substantial component of "bottom-up" nociceptive drive to RVM pain-modulating neurons is relayed through the PB. While the PB is well known as an important relay for ascending nociceptive information, its functional connection with the RVM allows the spinoparabrachial pathway to access descending control systems as part of a recurrent circuit.

Rosenbaum, J. T., & Asquith, M. J. (2016). The microbiome: A revolution in treatment for rheumatic diseases? *Current Rheumatology Reports*, 18(10), 62-016-0614-8.

PURPOSE OF REVIEW: The microbiome is the term that describes the microbial ecosystem that cohabits an organism such as humans. The microbiome has been implicated in a long list of immune-mediated diseases which include rheumatoid arthritis, ankylosing spondylitis, and even gout. The mechanisms to account for this effect are multiple. The clinical implications from observations on the microbiome and disease are broad. **RECENT FINDINGS:** A growing number of microbiota constituents such as *Prevotella copri*, *Porphyromonas gingivalis*, and *Collinsella* have been correlated or causally related to rheumatic disease. The microbiome has a marked effect on the immune system. Our understanding of immune pathways modulated by the microbiota such as the induction of T helper 17 (Th17) cells and secretory immunoglobulin A (IgA) responses to segmented filamentous bacteria continues to expand. In addition to the gut microbiome, bacterial

communities of other sites such as the mouth, lung, and skin have also been associated with the pathogenesis of rheumatic diseases. Strategies to alter the microbiome or to alter the immune activation from the microbiome might play a role in the future therapy for rheumatic diseases.

Rosenkrantz, J. L., & Carbone, L. (2016). Investigating somatic aneuploidy in the brain: Why we need a new model. *Chromosoma*,

The steady occurrence of DNA mutations is a key source for evolution, generating the genomic variation in the population upon which natural selection acts. Mutations driving evolution have to occur in the oocytes and sperm in order to be transmitted to the next generation. Through similar mechanisms, mutations also accumulate in somatic cells (e.g., skin cells, neurons, lymphocytes) during development and adult life. The concept that somatic cells can collect new mutations with time suggests that we are a mosaic of cells with different genomic compositions. Particular attention has been recently paid to somatic mutations in the brain, with a focus on the relationship between this phenomenon and the origin of human diseases. Given this progressive accumulation of mutations, it is likely that an increased load of somatic mutations is present later in life and that this could be associated with late-life diseases and aging. In this review, we focus on a particular type of mutation: the loss and/or gain of whole chromosomes (i.e., aneuploidy) caused by errors in chromosomes segregation in neurons and glia. Currently, it is hard to grasp the functional impact of somatic mutation in the brain because we lack reliable estimates of the proportion of aneuploid cells in the normal brain across different ages. Here, we revisit the key studies that attempted to quantify the proportion of aneuploid cells in both normal and diseased brains and highlight the deep inconsistencies among the different studies done in the last 15 years. Finally, our review highlights several limitations of studies performed in human and rodent models and explores a possible translational role for non-human primates.

Saitz, T. R., & Serefoglu, E. C. (2016). The epidemiology of premature ejaculation. *Translational Andrology and Urology*, 5(4), 409-415.

Vast advances have occurred over the past decade with regards to understanding the epidemiology, pathophysiology and management of premature ejaculation (PE); however, we still have much to learn about this common sexual problem. As a standardized evidence-based

definition of PE has only recently been established, the reported prevalence rates of PE prior to this definition have been difficult to interpret. As a result, a large range of conflicting prevalence rates have been reported. In addition to the lack of a standardized definition and operational criteria, the method of recruitment for study participation and method of data collection have obviously contributed to the broad range of reported prevalence rates. The new criteria and classification of PE will allow for continued research into the diverse phenomenology, etiology and pathogenesis of the disease to be conducted. While the absolute pathophysiology and true prevalence of PE remains unclear, developing a better understanding of the true prevalence of the disease will allow for the completion of more accurate analysis and treatment of the disease.

Saleh, M. G., Parikh, M., & Lin, P. (2016). Treatment of epithelial downgrowth masquerading as unilateral hypopyon uveitis in a HLA-B27+ individual. *Ocular Immunology and Inflammation*, , 1-3.

We report a case of an elderly woman with congenital rubella who presented with epithelial downgrowth (EDG) masquerading as hypopyon uveitis. We highlight the importance of endoscopy to completely identify all ingrowing epithelium with combined use of 5-fluorouracil to completely eradicate invading tissue.

Salvador, J., Goodkind, J., & Ewing, S. F. (2016). Perceptions and use of community- and school-based behavioral health services among urban American Indian/Alaska Native youth and families. *American Indian and Alaska Native Mental Health Research*, 23(3), 221-247.

Understanding youths' awareness and use of behavioral health services is important for improving services and engagement. Interviews and focus groups were conducted with students, parents, and teachers/staff in an urban area to understand awareness and use of a school's Native-tailored and -staffed school-based behavioral health center (NT-BHC) and community-based services. Results showed overwhelmingly positive responses regarding NT-BHC staff and services, with concerns focused on too few staff and services, and on privacy and confidentiality, as well as important differences in awareness and use of behavioral health services among youth, parents, and teachers/staff, valuable for improving engagement with and services for AI/AN youth. © Centers for American Indian and Alaska Native Health.

Savalia, N. K., Agres, P. F., Chan, M. Y., Feczko, E. J., Kennedy, K. M., & Wig, G. S. (2016). Motion-related artifacts in structural brain images revealed with independent estimates of in-scanner head motion. *Human Brain Mapping*,

Motion-contaminated T1-weighted (T1w) magnetic resonance imaging (MRI) results in misestimates of brain structure. Because conventional T1w scans are not collected with direct measures of head motion, a practical alternative is needed to identify potential motion-induced bias in measures of brain anatomy. Head movements during functional MRI (fMRI) scanning of 266 healthy adults (20-89 years) were analyzed to reveal stable features of in-scanner head motion. The magnitude of head motion increased with age and exhibited within-participant stability across different fMRI scans. fMRI head motion was then related to measurements of both quality control (QC) and brain anatomy derived from a T1w structural image from the same scan session. A procedure was adopted to "flag" individuals exhibiting excessive head movement during fMRI or poor T1w quality rating. The flagging procedure reliably reduced the influence of head motion on estimates of gray matter thickness across the cortical surface. Moreover, T1w images from flagged participants exhibited reduced estimates of gray matter thickness and volume in comparison to age- and gender-matched samples, resulting in inflated effect sizes in the relationships between regional anatomical measures and age. Gray matter thickness differences were noted in numerous regions previously reported to undergo prominent atrophy with age. Recommendations are provided for mitigating this potential confound, and highlight how the procedure may lead to more accurate measurement and comparison of anatomical features. *Hum Brain Mapp*, 2016. (c) 2016 The Authors Human Brain Mapping Published by Wiley Periodicals, Inc.

Schenning, K. J., Casson, H., Click, S. V., Brambrink, L., Chatkupt, T. T., Alkayed, N. J., et al. (2016). Vapor pressures of anesthetic agents at temperatures below 0°C and a novel anesthetic delivery device. *Anesthesia and Analgesia*,

At room temperature, the vapor pressures of desflurane, isoflurane, and sevoflurane are well above the clinically useful range. We hypothesized that therapeutic concentrations of these agents could be achieved at temperatures below 0°C, but the vapor pressure-temperature relationship is unknown below 0. Second, we hypothesized that this relationship could be

exploited to deliver therapeutic-range concentrations of anesthetic vapor. We therefore set out to determine the low temperature–vapor pressure relationships of each anesthetic agent, thereby identifying the saturated vapor concentration of each agent at any temperature below 0°C. To test our hypothesis, we measured the saturated vapor concentration at 1 atm of pressure for temperatures between –60 and 0°C, thus developing an empiric relationship for each agent. There was consistency in repeated experiments for all 3 agents. To test the empiric data, we constructed a digitally controlled thermoelectric anesthetic vaporizer, characterized the device, and used it to deliver anesthetic vapor to laboratory mice. We report, for the first time, the temperature–vapor pressure relationship at temperatures below 0°C for desflurane, isoflurane, and sevoflurane as well as the TMAC of these agents: the temperature at which the vapor pressure is equal to the minimum alveolar concentration. We describe the construction and limited validation of an anesthetic vaporizer prototype on the basis of this principle. We conclude that clinically relevant concentrations of volatile anesthetics may be achieved at low temperatures. © 2016 International Anesthesia Research Society

Schlansky, B., Naugler, W. E., Orloff, S. L., & Enestvedt, C. K. (2016). Higher mortality and survival benefit in obese patients awaiting liver transplantation. *Transplantation*,
BACKGROUND: Over 85% of U.S. centers adhere to practice guidelines that consider morbid obesity to be a contraindication to liver transplantation (LT). The relationship of morbid obesity with LT outcomes and survival benefit in the current era is unknown. METHODS: We investigated the association of BMI with waitlist and post-LT outcomes, and survival benefit, using the United Network for Organ Sharing registry. We categorized BMI 18.5-29.9 kg/m as normal/overweight, 30-34.9 obese, 35-39.9 severely obese, and ≥ 40 morbidly obese, and evaluated waitlist outcomes using competing risk regression and post-LT outcomes and survival benefit using Cox regression. RESULTS: 3.9% of 80,221 waitlisted and 3.5% of 38,177 transplanted patients were morbidly obese. Waitlist mortality was higher for morbidly obese than normal/overweight patients (subdistribution hazard ratio 1.16, 95% confidence interval [CI]:1.08-1.26), but post-LT mortality and graft failure were comparable (hazard ratio [HR] 1.01, 95% CI:0.86-1.19; and HR 1.15, 95% CI:0.95-1.40). Morbidly obese patients also benefited more from LT (88% mortality reduction versus 80% for normal/overweight). Morbid obesity predicted higher post-LT mortality

before 2007 (HR 1.18, 95% CI:1.04-1.34), but not afterward (HR 0.98, 95% CI:0.81-1.18).

CONCLUSIONS: Morbid obesity is associated with higher mortality on the LT waitlist, but no longer predicts inferior outcomes after LT. Morbidly obese patients should be considered potential candidates for LT.

Schlosser, R. J., Smith, T. L., Mace, J., & Soler, Z. M. (2016). Asthma quality of life and control after sinus surgery in patients with chronic rhinosinusitis. *Allergy,*

BACKGROUND: Patients with chronic rhinosinusitis (CRS) often have comorbid asthma. Prior studies have not examined the impact of CRS or endoscopic sinus surgery (ESS) upon asthma quality of life (QOL) and asthma control using validated outcome metrics. METHODS: Patients with CRS, both with and without polyps, and comorbid asthma completed the Mini Asthma QOL Questionnaire (miniAQLQ) and Asthma Control Test (ACT) at baseline and 6 months postoperatively as part of a multi-institutional, prospective study. RESULTS: Baseline metrics were available on 86 patients. Patients undergoing ESS reported improved miniAQLQ [0.5 (SD +/-1.1), 95% CI: 0.2-0.7; P = 0.002] and ACT scores [1.3 (+/-4.1), 95% CI: 0.2-2.4; P = 0.025]. Uncontrolled baseline asthma (ACT \leq 0.5 points) and 50% of the time for ACT scores (\geq 3.0 points). After adjustment with linear regression, baseline miniAQLQ scores were worse in patients with comorbid allergy (P = 0.045) and chronic obstructive pulmonary disease (COPD; P = 0.015). Adjusted baseline ACT scores were worse in patients with COPD (P = 0.004). Covariates associated with changes in miniAQLQ scores after ESS were pre-operative corticosteroid dependency (P = 0.011) and change in total SNOT-22 score (P = 0.010). Covariate associated with significantly less improvement in ACT scores was obstructive sleep apnea (P = 0.016). CONCLUSIONS: Patients with CRS often present with uncontrolled asthma, and ESS improves both miniAQLQ and ACT. Approximately half of patients with uncontrolled asthma improve after ESS, yet there are few CRS-specific factors associated with asthma QOL or control or ESS outcomes.

Schwarzmaier, S. M., De Chaumont, C., Balbi, M., Terpolilli, N. A., Kleinschnitz, C., Gruber, A., et al. (2016). The formation of microthrombi in parenchymal microvessels after traumatic brain injury is independent of coagulation factor XI. *Journal of Neurotrauma, 33*(17), 1634-1644.

Microthrombus formation and bleeding worsen the outcome after traumatic brain injury (TBI). The aim of the current study was to characterize these processes in the brain parenchyma after experimental TBI and to determine the involvement of coagulation factor XI (FXI). C57BL/6 mice (n = 101) and FXI-deficient mice (n = 15) were subjected to controlled cortical impact (CCI). Wild-type mice received an inhibitory antibody against FXI (14E11) or control immunoglobulin G 24 h before or 30 or 120 min after CCI. Cerebral microcirculation was visualized in vivo by 2-photon microscopy 2-3 h post-trauma and histopathological outcome was assessed after 24 h. TBI induced hemorrhage and microthrombus formation in the brain parenchyma (p < 0.001). Inhibition of FXI activation or FXI deficiency did not reduce cerebral thrombogenesis, lesion volume, or hemispheric swelling. However, it also did not increase intracranial hemorrhage. Formation of microthrombosis in the brain parenchyma after TBI is independent of the intrinsic coagulation cascade since it was not reduced by inhibition of FXI. However, since targeting FXI has well-established antithrombotic effects in humans and experimental animals, inhibition of FXI could represent a reasonable strategy for the prevention of deep venous thrombosis in immobilized patients with TBI. © Copyright 2016, Mary Ann Liebert, Inc. 2016.

Shaw, D., Guise, J. M., Shah, N., Gemzell-Danielsson, K., Joseph, K. S., Levy, B., et al. (2016).

Drivers of maternity care in high-income countries: Can health systems support woman-centred care? *Lancet (London, England)*,

In high-income countries, medical interventions to address the known risks associated with pregnancy and birth have been largely successful and have resulted in very low levels of maternal and neonatal mortality. In this Series paper, we present the main care delivery models, with case studies of the USA and Sweden, and examine the main drivers of these models.

Although nearly all births are attended by a skilled birth attendant and are in an institution, practice, cadre, facility size, and place of birth vary widely; for example, births occur in homes, birth centres, midwifery-led birthing units in hospitals, and in high intervention hospital birthing facilities. Not all care is evidenced-based, and some care provision may be harmful. Fear prevails among subsets of women and providers. In some settings, medical liability costs are enormous, human resource shortages are common, and costs of providing care can be very high. New challenges linked to alteration of epidemiology, such as obesity and older age during pregnancy,

are also present. Data are often not readily available to inform policy and practice in a timely way and surveillance requires greater attention and investment. Outcomes are not equitable, and disadvantaged segments of the population face access issues and substantially elevated risks. At the same time, examples of excellence and progress exist, from clinical interventions to models of care and practice. Labourists (who provide care for all the facility's women for labour and delivery) are discussed as a potential solution. Quality and safety factors are informed by women's experiences, as well as medical evidence. Progress requires the ability to normalise birth for most women, with integrated services available if complications develop. We also discuss mechanisms to improve quality of care and highlight areas where research can address knowledge gaps with potential for impact. Evaluation of models that provide woman-centred care and the best outcomes without high costs is required to provide an impetus for change.

Sheridan, D. C., Laurie, A., Hendrickson, R. G., Fu, R., Kea, B., & Horowitz, B. Z. (2016). Association of overall opioid prescriptions on adolescent opioid abuse. *The Journal of Emergency Medicine*,

BACKGROUND: Opioid abuse is a public health epidemic in the United States. Much literature has focused on the prescribing practices of physicians and opioid misuse by adults. However, there are limited data on the effect of opioid prescriptions on adolescent recreational ingestion of these medications. OBJECTIVES: The objective of this study was to assess for a relationship between opioid prescribing practices across the United States and adolescent opioid ingestion calls to poison centers. METHODS: This was an observational study using the National Poison Data System. The study population consisted of poison center calls regarding adolescents between 2005 and 2010 in the database with a coding of "intentional abuse" and an opioid ingestion. National opioid prescription estimates were generated using nationally representative outpatient and inpatient databases. RESULTS: There were 4186 adolescent opioid ingestion calls during the study period. There was a general increase between 2005 and 2010 in both teen opioid abuse calls (617 in 2005 to 782 in 2010) and national opioid prescriptions (approximately 78 million in 2005 to 108 million in 2010). For each opioid prescription increase per 100 persons per year, the annual teen opioid abuse calls increased by 1.8% (95% confidence interval 0.9-2.8%), equivalent to an absolute increase of about 0.04 to 0.05 calls per 100,000 teens annually. CONCLUSIONS: There appears to be an association between opioid prescriptions nationally and poison center

calls for adolescent opioid ingestions. This is particularly important in this patient population because of impulsivity and early exposure to substance abuse. Providers should be aware of the nonmedical use of opioids by adolescents and educate patients accordingly.

Sheridan, D. C., & Meckler, G. D. (2016). Inpatient pediatric migraine treatment: Does choice of abortive therapy affect length of stay? *The Journal of Pediatrics*,

OBJECTIVE: To describe the inpatient management of pediatric migraine and the association between specific medications and hospital length of stay (LOS). STUDY DESIGN: Historical cohort study review of patients age <19 years of age admitted to a single tertiary care children's hospital between 2010 and 2015 for treatment of migraine headache. RESULTS: The cohort consisted of 58 encounters with an average patient age of 14.3 years (SD 3.2 years) with a female predominance (62%). The mean number of inpatient medications received by patients was 3 (range 1-7), with dopamine antagonists and dihydroergotamine used most commonly (67% and 59% of encounters, respectively). The average LOS was 56 hours (95% CI 48.2-63.2) and did not vary by medication received, although patients who received an opioid had a significantly longer LOS (79.2 vs 47.9 hours respectively; $P < .001$). CONCLUSIONS: Children admitted to the hospital for treatment of migraine headache frequently require a large number of medications over an average hospital LOS of more than 2 days without apparent differences based on medication received other than prolonged stays for subjects who received opioids.

Sheth, K. N., Elm, J. J., Molyneaux, B. J., Hinson, H., Beslow, L. A., Sze, G. K., et al. (2016). Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): A randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet.Neurology*, 15(11), 1160-1169.

BACKGROUND: Preclinical models of stroke have shown that intravenous glyburide reduces brain swelling and improves survival. We assessed whether intravenous glyburide (RP-1127; glibenclamide) would safely reduce brain swelling, decrease the need for decompressive craniectomy, and improve clinical outcomes in patients presenting with a large hemispheric infarction. METHODS: For this double-blind, randomised, placebo-controlled phase 2 trial, we enrolled patients (aged 18-80 years) with a clinical diagnosis of large anterior circulation

hemispheric infarction for less than 10 h and baseline diffusion-weighted MRI image lesion volume of 82-300 cm³ on MRI at 18 hospitals in the USA. We used web-based randomisation (1:1) to allocate patients to the placebo or intravenous glyburide group. Intravenous glyburide was given as a 0.13 mg bolus intravenous injection for the first 2 min, followed by an infusion of 0.16 mg/h for the first 6 h and then 0.11 mg/h for the remaining 66 h. The primary efficacy outcome was the proportion of patients who achieved a modified Rankin Scale (mRS) score of 0-4 at 90 days without undergoing decompressive craniectomy. Analysis was by per protocol. Safety analysis included all randomly assigned patients who received the study drug. This trial is registered with ClinicalTrials.gov, number NCT01794182. FINDINGS: Between May 3, 2013, and April 30, 2015, 86 patients were randomly assigned but enrolment was stopped because of funding reasons. The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment. The per-protocol study population was 41 participants who received intravenous glyburide and 36 participants who received placebo. 17 (41%) patients in the intravenous glyburide group and 14 (39%) in the placebo group had an mRS score of 0-4 at 90 days without decompressive craniectomy (adjusted odds ratio 0.87, 95% CI 0.32-2.32; p=0.77). Ten (23%) of 44 participants in the intravenous glyburide group and ten (26%) of 39 participants in the placebo group had cardiac events (p=0.76), and four of 20 had serious adverse events (two in the intravenous glyburide group and two in the placebo group, p=1.00). One cardiac death occurred in each group (p=1.00). INTERPRETATION: Intravenous glyburide was well tolerated in patients with large hemispheric stroke at risk for cerebral oedema. There was no difference in the composite primary outcome. Further study is warranted to assess the potential clinical benefit of a reduction in swelling by intravenous glyburide. FUNDING: Remedy Pharmaceuticals.

Sieper, J., Deodhar, A., Marzo-Ortega, H., Aelion, J. A., Blanco, R., Jui-Cheng, T., et al. (2016).

Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: Results from the MEASURE 2 study. *Annals of the Rheumatic Diseases*,
BACKGROUND: There is significant unmet need in patients with ankylosing spondylitis (AS) who have inadequate response or intolerance to anti-tumour necrosis factor (TNF) treatment. Secukinumab, an anti-interleukin-17A monoclonal antibody, significantly improved signs and

symptoms of AS in the MEASURE 2 study (NCT01649375). METHODS: Subjects with active AS (N=219) received secukinumab (150 or 75 mg) or placebo at baseline, weeks 1, 2, 3 and 4, and every 4 weeks thereafter. Randomisation was stratified by prior anti-TNF use: anti-TNF-naive or inadequate response/intolerance to one anti-TNF (anti-TNF-IR). The primary endpoint was Assessment of SpondyloArthritis International Society criteria (ASAS) 20 at week 16. RESULTS: At week 16, 68.2% of anti-TNF-naive subjects treated with secukinumab 150 mg achieved ASAS20 compared with 31.1% treated with placebo ($p<0.001$). In the anti-TNF-IR group, 50.0% of subjects treated with secukinumab 150 mg achieved an ASAS20 response compared with 24.1% treated with placebo ($p<0.05$). Numerically greater improvements were observed with secukinumab than with placebo for most secondary endpoints. Clinical responses were sustained through week 52. CONCLUSIONS: Secukinumab 150 mg provided sustained improvements in signs and symptoms of AS in anti-TNF-naive and anti-TNF-IR subjects through 52 weeks of therapy. TRIAL REGISTRATION NUMBER: NCT01649375.

Simmons, K. B., & Edelman, A. B. (2016). Hormonal contraception and obesity. *Fertility and Sterility*, The rising rate of overweight and obesity is a public health crisis in the United States and increasingly around the globe. Rates of contraceptive use are similar among women of all weights, but because contraceptive development studies historically excluded women over 130% of ideal body weight, patients and providers have a gap in understanding of contraceptive efficacy for obese and overweight women. Because of a range of drug metabolism alterations in obesity, there is biologic plausibility for changes in hormonal contraception effectiveness in obese women. However, these pharmacokinetic changes are not linearly related to body mass index or weight, and it is unknown what degree of obesity begins to affect pharmacokinetic or pharmacodynamics processes. Overall, most studies of higher quality do not demonstrate a difference in oral contraceptive pill effectiveness in obese compared with non-obese women. However, data are scant for women in the highest categories of obesity, and differences by progestin type are incompletely understood. Effectiveness of most non-oral contraceptives does not seem to be compromised in obesity. Exceptions to this include the combined hormonal patch and oral levonorgestrel emergency contraception, which may have lower rates of effectiveness in obese women. The purpose of this review is to summarize evidence on contraceptive use in

women with obesity, including differences in steroid hormone metabolism, contraceptive effectiveness, and safety, compared with women of normal weight or body mass index using the same methods.

Singh, B., Hughes, A. J., Mehta, G., Erwin, P. J., & Parsaik, A. K. (2016). Efficacy of prazosin in posttraumatic stress disorder: A systematic review and meta-analysis. *Primary Care Companion to the Journal of Clinical Psychiatry, 18*(4)

Objective: To consolidate the evidence from the literature to evaluate the role of prazosin in the treatment of posttraumatic stress disorder (PTSD). Data Sources: Major databases, including PubMed, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Ovid PsycINFO, and Scopus, were searched through August 2015 for studies reporting the role of prazosin in the treatment of PTSD with no language constraints. Keywords included (PTSD OR posttraumatic stress OR posttraumatic stress OR nightmares) AND prazosin. Study Selection: Of 402 screened articles, 6 studies were included in the systematic review and meta-analysis. Data Extraction: Two reviewers independently extracted relevant data (study characteristics, type of intervention, outcome measures, and follow-up) from the included studies using a standardized data extraction form. Only randomized controlled trials comparing prazosin to a placebo or control group in patients with PTSD were included. Results: The patients with PTSD receiving prazosin showed significant improvement in nightmares (standardized mean difference [SMD] = 1.01; 95% CI, 0.72–1.30), overall PTSD symptoms (SMD = 0.77; 95% CI, 0.48–1.06), and clinical global improvement (SMD = 0.94; 95% CI, 0.6–1.29) compared to the placebo/control group. Prazosin improved sleep quality (SMD = 0.87; 95% CI, 0.55–1.19), hyperarousal symptoms (SMD = 1.04; 95% CI, 0.23–1.84), dream content (SMD = 1.33; 95% CI, 0.69–1.97), and total sleep time (60.98 minutes; 95% CI, 18.69–103.26). Prazosin was fairly well tolerated. Minor side effects were reported, which were similar between the prazosin and placebo groups. Conclusions: This study suggests that prazosin improves nightmares and overall PTSD symptoms including hyperarousal, sleep disturbances, total sleep time, and sleep quality. © 2016 Physicians Postgraduate Press, Inc.

Slatore, C. G., Wiener, R. S., Golden, S. E., Au, D. H., & Ganzini, L. (2016). Longitudinal assessment of distress among veterans with incidental pulmonary nodules. *Annals of the American Thoracic Society*,

RATIONALE: Millions of patients are diagnosed every year with pulmonary nodules. Increased distress may be a common harm but methods to mitigate this distress are unclear. OBJECTIVES: We aimed to determine whether high quality communication regarding the discovery of a pulmonary nodule is associated with a lower level of patient distress. METHODS: We conducted a prospective, repeated-measures cohort study of 121 patients with newly-reported, incidentally-detected pulmonary nodules. The primary exposure was participant-reported quality of communication regarding the nodule. Secondary exposures included communication measures regarding participants' values, preferences and decision making. The main outcome was nodule-related distress measured using the Impact of Event Scale. We utilized adjusted generalized estimating equations to measure the association between nodule communication quality and at least mild distress. MEASUREMENTS AND MAIN RESULTS: Most participants (57%) reported at least mild distress at least once. While average distress scores decreased over time, one quarter still had elevated distress after two years of surveillance for a nodule. The average calculated risk of cancer at baseline was 10 % (SD 13%) but 52.4% believed they had greater than 30% risk of lung cancer at baseline, and this percentage remained fairly constant at all visits. High quality nodule communication was associated with decreased odds of distress (adjOR 0.42, 95% CI 0.24 - 0.73). Lower quality communication processes regarding participants' values and preferences were also associated with increased odds of distress, but concordance between the actual and preferred decision making role was not. CONCLUSIONS: Among patients with incidentally discovered pulmonary nodules, distress is common and persistent for about 25%. Many participants substantially overestimate their risk of lung cancer. Incorporating patients' values and preferences into communication about a pulmonary nodule and its evaluation may mitigate distress.

Smedley, D., Schubach, M., Jacobsen, J. O., Kohler, S., Zemojtel, T., Spielmann, M., et al. (2016). A whole-genome analysis framework for effective identification of pathogenic regulatory variants in mendelian disease. *American Journal of Human Genetics*, 99(3), 595-606.

The interpretation of non-coding variants still constitutes a major challenge in the application of whole-genome sequencing in Mendelian disease, especially for single-nucleotide and other small non-coding variants. Here we present Genomiser, an analysis framework that is able not only to score the relevance of variation in the non-coding genome, but also to associate regulatory variants to specific Mendelian diseases. Genomiser scores variants through either existing methods such as CADD or a bespoke machine learning method and combines these with allele frequency, regulatory sequences, chromosomal topological domains, and phenotypic relevance to discover variants associated to specific Mendelian disorders. Overall, Genomiser is able to identify causal regulatory variants as the top candidate in 77% of simulated whole genomes, allowing effective detection and discovery of regulatory variants in Mendelian disease.

Smith, N. R., Gallagher, A. C., & Wong, M. H. (2016). Defining a stem cell hierarchy in the intestine: Markers, caveats and controversies. *Journal of Physiology*, 594(17), 4781-4790.

The past decade has appreciated rapid advance in identifying the once elusive intestinal stem cell (ISC) populations that fuel the continual renewal of the epithelial layer. This advance was largely driven by identification of novel stem cell marker genes, revealing the existence of quiescent, slowly- and active-cycling ISC populations. However, a critical barrier for translating this knowledge to human health and disease remains elucidating the functional interplay between diverse stem cell populations. Currently, the precise hierarchical and regulatory relationships between these ISC populations are under intense scrutiny. The classical theory of a linear hierarchy, where quiescent and slowly-cycling stem cells self-renew but replenish an active-cycling population, is well established in other rapidly renewing tissues such as the haematopoietic system. Efforts to definitively establish a similar stem cell hierarchy within the intestinal epithelium have yielded conflicting results, been difficult to interpret, and suggest non-conventional alternatives to a linear hierarchy. While these new and potentially paradigm-shifting discoveries are intriguing, the field will require development of a number of critical tools, including highly specific stem cell marker genes along with more rigorous experimental methodologies, to delineate the complex cellular relationships within this dynamic organ system. (Figure presented.). © 2016 The Authors. The Journal of Physiology © 2016 The Physiological Society

Snowden, J. M., Tilden, E. L., & Caughey, A. B. (2016). The increased perinatal mortality rate over weekends is proof that we require a 7-day maternity service: FOR: No baby should die simply because they are born at a weekend. *BJOG: An International Journal of Obstetrics and Gynaecology*, 123(8), 1358.

Solomon, A. J., Bourdette, D. N., Cross, A. H., Applebee, A., Skidd, P. M., Howard, D. B., et al. (2016). The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. *Neurology*, 87(13), 1393-1399.

OBJECTIVE: To characterize patients misdiagnosed with multiple sclerosis (MS). METHODS: Neurologists at 4 academic MS centers submitted data on patients determined to have been misdiagnosed with MS. RESULTS: Of 110 misdiagnosed patients, 51 (46%) were classified as "definite" and 59 (54%) "probable" misdiagnoses according to study definitions. Alternate diagnoses included migraine alone or in combination with other diagnoses 24 (22%), fibromyalgia 16 (15%), nonspecific or nonlocalizing neurologic symptoms with abnormal MRI 13 (12%), conversion or psychogenic disorders 12 (11%), and neuromyelitis optica spectrum disorder 7 (6%). Duration of misdiagnosis was 10 years or longer in 36 (33%) and an earlier opportunity to make a correct diagnosis was identified for 79 patients (72%). Seventy-seven (70%) received disease-modifying therapy and 34 (31%) experienced unnecessary morbidity because of misdiagnosis. Four (4%) participated in a research study of an MS therapy. Leading factors contributing to misdiagnosis were consideration of symptoms atypical for demyelinating disease, lack of corroborative objective evidence of a CNS lesion as satisfying criteria for MS attacks, and overreliance on MRI abnormalities in patients with nonspecific neurologic symptoms.

CONCLUSIONS: Misdiagnosis of MS leads to unnecessary and potentially harmful risks to patients. Misinterpretation and misapplication of MS clinical and radiographic diagnostic criteria are important contemporary contributors to misdiagnosis.

Southey, M. C., Goldgar, D. E., Winqvist, R., Pylkas, K., Couch, F., Tischkowitz, M., et al. (2016). PALB2, CHEK2 and ATM rare variants and cancer risk: Data from COGS. *Journal of Medical Genetics*,

BACKGROUND: The rarity of mutations in PALB2, CHEK2 and ATM make it difficult to estimate

precisely associated cancer risks. Population-based family studies have provided evidence that at least some of these mutations are associated with breast cancer risk as high as those associated with rare BRCA2 mutations. We aimed to estimate the relative risks associated with specific rare variants in PALB2, CHEK2 and ATM via a multicentre case-control study. METHODS: We genotyped 10 rare mutations using the custom iCOGS array: PALB2 c.1592delT, c.2816T>G and c.3113G>A, CHEK2 c.349A>G, c.538C>T, c.715G>A, c.1036C>T, c.1312G>T, and c.1343T>G and ATM c.7271T>G. We assessed associations with breast cancer risk (42 671 cases and 42 164 controls), as well as prostate (22 301 cases and 22 320 controls) and ovarian (14 542 cases and 23 491 controls) cancer risk, for each variant. RESULTS: For European women, strong evidence of association with breast cancer risk was observed for PALB2 c.1592delT OR 3.44 (95% CI 1.39 to 8.52, $p=7.1 \times 10^{-5}$), PALB2 c.3113G>A OR 4.21 (95% CI 1.84 to 9.60, $p=6.9 \times 10^{-8}$) and ATM c.7271T>G OR 11.0 (95% CI 1.42 to 85.7, $p=0.0012$). We also found evidence of association with breast cancer risk for three variants in CHEK2, c.349A>G OR 2.26 (95% CI 1.29 to 3.95), c.1036C>T OR 5.06 (95% CI 1.09 to 23.5) and c.538C>T OR 1.33 (95% CI 1.05 to 1.67) (p OR 3.03 (95% CI 1.53 to 6.03, $p=0.0006$) for African men and CHEK2 c.1312G>T OR 2.21 (95% CI 1.06 to 4.63, $p=0.030$) for European men. No evidence of association with ovarian cancer was found for any of these variants. CONCLUSIONS: This report adds to accumulating evidence that at least some variants in these genes are associated with an increased risk of breast cancer that is clinically important.

Sparks, T. N., Shaffer, B. L., Page, J., & Caughey, A. B. (2016). Gastroschisis: Mortality risks with each additional week of expectant management. *American Journal of Obstetrics and Gynecology*,
BACKGROUND: Prior studies have evaluated the overall risk of stillbirth in pregnancies with fetal gastroschisis. However, the gestational age at which mortality is minimized, balancing the risk of stillbirth against neonatal mortality, remains unclear. OBJECTIVE: We sought to evaluate the gestational age at which prenatal and postnatal mortality risk is minimized for fetuses with gastroschisis. STUDY DESIGN: This was a retrospective cohort study of singleton pregnancies delivered between 24 0/7 and 39 6/7 weeks, using 2005 through 2006 US national linked birth and death certificate data. Among pregnancies with fetal gastroschisis, prospective risk of stillbirth and risk of infant death were determined for each gestational age week. Risk of infant

death with delivery was further compared to composite fetal/infant mortality risk with expectant management for 1 additional week. RESULTS: Among 2,119,049 pregnancies, 860 cases (0.04%) of gastroschisis were identified. The overall stillbirth rate among gastroschisis cases was 4.8%, and infant death occurred in 8.3%. Prospective risk of stillbirth became more consistently elevated beginning at 35 weeks, rising to 13.9 per 1000 pregnancies (95% confidence interval, 10.8-17.1) at 39 weeks. Risk of infant death concurrently nadired in the third trimester, ranging between 62.4-66.8 per 1000 live births between 32-39 weeks. Comparing mortality with expectant management vs delivery, relative risk was significantly greater with expectant management between 37-39 weeks, reaching 1.90 (95% confidence interval, 1.73-2.08) at 39 weeks with a number needed to deliver of 17.49 (95% confidence interval, 15.34-20.32) to avoid 1 excess death. CONCLUSION: Risk of prenatal and postnatal mortality for fetuses with gastroschisis may be minimized with delivery as early as 37 weeks.

Stacey, D., Légaré, F., Col, N. F., Bennett, C. L., Barry, M. J., Eden, K. B., et al. (2014). Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews, 2014*(1)

Background Decision aids are intended to help people participate in decisions that involve weighing the benefits and harms of treatment options often with scientific uncertainty. Objectives To assess the effects of decision aids for people facing treatment or screening decisions. Search methods For this update, we searched from 2009 to June 2012 in MEDLINE; CENTRAL; EMBASE; PsycINFO; and grey literature. Cumulatively, we have searched each database since its start date including CINAHL (to September 2008). Selection criteria We included published randomized controlled trials of decision aids, which are interventions designed to support patients' decision making by making explicit the decision, providing information about treatment or screening options and their associated outcomes, compared to usual care and/or alternative interventions. We excluded studies of participants making hypothetical decisions. Data collection and analysis Two review authors independently screened citations for inclusion, extracted data, and assessed risk of bias. The primary outcomes, based on the International Patient Decision Aid Standards (IPDAS), were: A) 'choice made' attributes; B) 'decision-making process' attributes. Secondary outcomes were behavioral, health, and health-system effects. We pooled results using mean

differences (MD) and relative risks (RR), applying a random-effects model. Main results This update includes 33 new studies for a total of 115 studies involving 34,444 participants. For risk of bias, selective outcome reporting and blinding of participants and personnel were mostly rated as unclear due to inadequate reporting. Based on 7 items, 8 of 115 studies had high risk of bias for 1 or 2 items each. Of 115 included studies, 88 (76.5%) used at least one of the IPDAS effectiveness criteria: A) 'choice made' attributes criteria: knowledge scores (76 studies); accurate risk perceptions (25 studies); and informed value-based choice (20 studies); and B) 'decision-making process' attributes criteria: feeling informed (34 studies) and feeling clear about values (29 studies). A) Criteria involving 'choice made' attributes: Compared to usual care, decision aids increased knowledge (MD 13.34 out of 100; 95% confidence interval (CI) 11.17 to 15.51; n = 42). When more detailed decision aids were compared to simple decision aids, the relative improvement in knowledge was significant (MD 5.52 out of 100; 95% CI 3.90 to 7.15; n = 19). Exposure to a decision aid with expressed probabilities resulted in a higher proportion of people with accurate risk perceptions (RR 1.82; 95% CI 1.52 to 2.16; n = 19). Exposure to a decision aid with explicit values clarification resulted in a higher proportion of patients choosing an option congruent with their values (RR 1.51; 95% CI 1.17 to 1.96; n = 13). B) Criteria involving 'decision-making process' attributes: Decision aids compared to usual care interventions resulted in: a) lower decisional conflict related to feeling uninformed (MD -7.26 of 100; 95% CI -9.73 to -4.78; n = 22) and feeling unclear about personal values (MD -6.09; 95% CI -8.50 to -3.67; n = 18); b) reduced proportions of people who were passive in decision making (RR 0.66; 95% CI 0.53 to 0.81; n = 14); and c) reduced proportions of people who remained undecided post-intervention (RR 0.59; 95% CI 0.47 to 0.72; n = 18). Decision aids appeared to have a positive effect on patient-practitioner communication in all nine studies that measured this outcome. For satisfaction with the decision (n = 20), decision-making process (n = 17), and/or preparation for decision making (n = 3), those exposed to a decision aid were either more satisfied, or there was no difference between the decision aid versus comparison interventions. No studies evaluated decision-making process attributes for helping patients to recognize that a decision needs to be made, or understanding that values affect the choice. C) Secondary outcomes Exposure to decision aids compared to usual care reduced the number of people of choosing major elective invasive surgery in favour of more conservative options (RR 0.79; 95%

CI 0.68 to 0.93; n = 15). Exposure to decision aids compared to usual care reduced the number of people choosing to have prostate-specific antigen screening (RR 0.87; 95% CI 0.77 to 0.98; n = 9). When detailed compared to simple decision aids were used, fewer people chose menopausal hormone therapy (RR 0.73; 95% CI 0.55 to 0.98; n = 3). For other decisions, the effect on choices was variable. The effect of decision aids on length of consultation varied from 8 minutes shorter to 23 minutes longer (median 2.55 minutes longer) with 2 studies indicating statistically-significantly longer, 1 study shorter, and 6 studies reporting no difference in consultation length. Groups of patients receiving decision aids do not appear to differ from comparison groups in terms of anxiety (n = 30), general health outcomes (n = 11), and condition-specific health outcomes (n = 11). The effects of decision aids on other outcomes (adherence to the decision, costs/resource use) were inconclusive. Authors' conclusions There is high-quality evidence that decision aids compared to usual care improve people's knowledge regarding options, and reduce their decisional conflict related to feeling uninformed and unclear about their personal values. There is moderate-quality evidence that decision aids compared to usual care stimulate people to take a more active role in decision making, and improve accurate risk perceptions when probabilities are included in decision aids, compared to not being included. There is low-quality evidence that decision aids improve congruence between the chosen option and the patient's values. New for this updated review is further evidence indicating more informed, values-based choices, and improved patient-practitioner communication. There is a variable effect of decision aids on length of consultation. Consistent with findings from the previous review, decision aids have a variable effect on choices. They reduce the number of people choosing discretionary surgery and have no apparent adverse effects on health outcomes or satisfaction. The effects on adherence with the chosen option, cost-effectiveness, use with lower literacy populations, and level of detail needed in decision aids need further evaluation. Little is known about the degree of detail that decision aids need in order to have a positive effect on attributes of the choice made, or the decision-making process. © 2014 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

Stankoska, K., Sarram, L., Smith, S., Bedran-Russo, A. K., Little, C. B., Swain, M. V., et al. (2016). Immunolocalization and distribution of proteoglycans in carious dentine. *Australian Dental*

Journal, 61(3), 288-297.

Background: Collagen type I, proteoglycans (PG) and non-collagenous proteins represent important building blocks of the dentine matrix. While different PGs have been identified in dentine, changes in the distribution of these macromolecules with the progression of caries have been poorly characterized. The aim of this study was to compare the immunolocalization of three small collagen-binding PGs (biglycan, fibromodulin and lumican) as well as collagen (types I and VI) in healthy versus carious dentine. Methods: Longitudinal demineralized sections of extracted teeth were stained with antibodies recognizing specific PG core proteins and collagens, as well as glycosaminoglycans (GAGs) with toluidine blue. Results: In healthy dentine, PGs appeared to be more abundant near the tubule walls and directly under the cusps. Conversely, in carious dentine, specific locations appeared to be more prone to PG degradation than others. These degradation patterns were well correlated with the progression of caries into the tissue, and also appeared to trigger interesting morphological changes in the tissue structure, such as the deformation of dentine tubules near highly infected areas and the lower concentration of PG in tertiary dentine. Conclusions: This study presents new insights into the involvement of PGs in the progression of caries. © 2015 Australian Dental Association

Steele, T. O., Buniel, M. C., Mace, J. C., Rassi, E. E., & Smith, T. L. (2016). Lymphoma of the nasal cavity and paranasal sinuses: A case series. *American Journal of Rhinology and Allergy*, 30(5), 335-339.

Background: Lymphomas of the sinonasal tract are a rare and heterogeneous subset of solid sinonasal neoplasms. Objective: To characterize, in this case series, presenting symptoms, treatment modalities, and outcomes for patients with sinonasal lymphoma with a single institution. Methods: Retrospective patient data were collected from an academic, oncologic center and entered into a repository designed to capture outcomes for sinonasal malignancies. Patient demographics, presenting symptoms, imaging findings, treatment modalities, and health status were retrospectively extrapolated and evaluated by using Kaplan-Meier estimations for survival probability. Results: Patients with sinonasal lymphoma with a mean follow-up of 50 months were identified (n =). Histologic nosology included the following: diffuse large B-cell lymphoma (n = 9), natural killer/T-cell lymphoma (n = 5), follicular lymphoma (n = 1), T-cell

lymphoma (n = 1), and lymphoma-not otherwise specified (n = 2). The most frequent presenting symptoms were nasal obstruction (78%), facial pain (72%), al swelling (50%), and nasal discharge (44%). Treatment before lymphoma diagnosis included antibiotics (83%), oral steroids (22%), decongestants (22%), and topical steroids (11%). Treatment regimens after diagnosis included both chemotherapy (94%) and chemoradiotherapy (56%). Survival rates by lymphoma subtype were 56% for B-cell lymphoma and 40% for natural killer/T-cell lymphoma. Overall, 2- and 5-year survival rates were 67% and 50%, respectively. The combination of chemotherapy and radiation resulted in significantly higher survival rates ($p \geq 0.001$) than emotherapy ne. Conclusion: Sinonasal lymphomas are characterized by meager survival rates, which differ by histopathologic subtype. The diagnosis of sinonasal lymphoma is challenging because symptoms frequently parallel those of chronic rhinosinusitis. Increased awareness of these rare malignancies may improve detection and more timely treatment. Clinical trial registration NCT01332136. © 2016, OceanSide Publications, Inc., U.S.A.

Sturgill, E. R., Malouli, D., Hansen, S. G., Burwitz, B. J., Seo, S., Schneider, C. L., et al. (2016).

Natural killer cell evasion is essential for infection by rhesus cytomegalovirus. *PLoS Pathogens*, 12(8), e1005868.

The natural killer cell receptor NKG2D activates NK cells by engaging one of several ligands (NKG2DLs) belonging to either the MIC or ULBP families. Human cytomegalovirus (HCMV) UL16 and UL142 counteract this activation by retaining NKG2DLs and US18 and US20 act via lysosomal degradation but the importance of NK cell evasion for infection is unknown. Since NKG2DLs are highly conserved in rhesus macaques, we characterized how NKG2DL interception by rhesus cytomegalovirus (RhCMV) impacts infection in vivo. Interestingly, RhCMV lacks homologs of UL16 and UL142 but instead employs Rh159, the homolog of UL148, to prevent NKG2DL surface expression. Rh159 resides in the endoplasmic reticulum and retains several NKG2DLs whereas UL148 does not interfere with NKG2DL expression. Deletion of Rh159 releases human and rhesus MIC proteins, but not ULBPs, from retention while increasing NK cell stimulation by infected cells. Importantly, RhCMV lacking Rh159 cannot infect CMV-naive animals unless CD8+ cells, including NK cells, are depleted. However, infection can be rescued by replacing Rh159 with HCMV UL16 suggesting that Rh159 and UL16 perform similar functions in vivo. We therefore conclude that

cytomegaloviral interference with NK cell activation is essential to establish but not to maintain chronic infection.

Su, J. P., Chandwani, R., Gao, S. S., Pechauer, A. D., Zhang, M., Wang, J., et al. (2016). Calibration of optical coherence tomography angiography with a microfluidic chip. *Journal of Biomedical Optics*, 21(8)

A microfluidic chip with microchannels ranging from 8 to 96 μm was used to mimic blood vessels down to the capillary level. Blood flow within the microfluidic channels was analyzed with split-spectrum amplitude-decorrelation angiography (SSADA)-based optical coherence tomography (OCT) angiography. It was found that the SSADA decorrelation value was related to both blood flow speed and channel width. SSADA could differentiate nonflowing blood inside the microfluidic channels from static paper. The SSADA decorrelation value was approximately linear with blood flow velocity up to a threshold V_{sat} of 5.83 ± 1.33 mm/s (mean \pm standard deviation over the range of channel widths). Beyond this threshold, it approached a saturation value D_{sat} . D_{sat} was higher for wider channels, and approached a maximum value D_{sm} as the channel width became much larger than the beam focal spot diameter. These results indicate that decorrelation values (flow signal) in capillary networks would be proportional to both flow velocity and vessel caliber but would be capped at a saturation value in larger blood vessels. These findings are useful for interpretation and quantification of clinical OCT angiography results. © 2016 Society of Photo-Optical Instrumentation Engineers (SPIE).

Sullivan, D. R., Forsberg, C. W., Ganzini, L., Au, D. H., Gould, M. K., Provenzale, D., et al. (2016).

Depression symptom trends and health domains among lung cancer patients in the CanCORS study. *Lung Cancer (Amsterdam, Netherlands)*, 100, 102-109.

OBJECTIVES: Among lung cancer patients depression symptoms are common and impact outcomes. The aims of this study were to determine risk factors that contribute to persistent or new onset depression symptoms during lung cancer treatment, and examine interactions between depression symptoms and health domains that influence mortality. MATERIALS AND METHODS: Prospective observational study in five healthcare systems and 15 Veterans Affairs medical centers. Patients in the Cancer Care Outcomes Research and Surveillance (CanCORS)

Consortium with lung cancer were eligible. The 8-item Center for Epidemiologic Studies Depression (CES-D) scale was administered at baseline and follow-up. Scores ≥ 4 indicated elevated depressive symptoms. Health domains were measured using validated instruments. We applied logistic regression and Cox proportional hazards modeling to explore the association between depression symptoms, health domains, and mortality. RESULTS: Of 1790 participants, 38% had depression symptoms at baseline and among those still alive, 31% at follow-up. Risk factors for depression symptoms at follow-up included younger age (OR=2.81), female sex (OR=1.59), low income (OR=1.45), not being married (OR=1.74) and current smoking status (OR=1.80); high school education was associated with reduced odds of depression symptoms at follow-up, compared with lesser educational attainment (OR=0.74) (all p values < 0.05). Patients with depression symptoms had worse health-related quality of life, vitality, cancer-specific symptoms, and social support than patients without depression symptoms (all $p < 0.001$). The association between depression symptoms and increased mortality is greater among patients with more lung cancer symptoms ($p = 0.008$) or less social support ($p = 0.04$). CONCLUSIONS: Patient risk factors for depression symptoms at follow-up were identified and these subgroups should be targeted for enhanced surveillance. Patients with depression symptoms suffer across all health domains; however, only more lung cancer symptoms or less social support are associated with worse mortality among these patients. These potentially modifiable health domains suggest targets for possible intervention in future studies.

Sun, H. -, Alexander, B. D., Huprikar, S., Forrest, G. N., Bruno, D., Lyon, G. M., et al. (2015).

Predictors of immune reconstitution syndrome in organ transplant recipients with cryptococcosis: Implications for the management of immunosuppression. *Clinical Infectious Diseases*, 60(1), 36-44.

Background. Risk factors including how changes in immunosuppression influence the occurrence of immune reconstitution syndrome (IRS) in solid organ transplant (SOT) recipients with cryptococcosis have not been fully defined. Methods. SOT recipients with cryptococcosis were identified and followed for 12 months. IRS was defined based on previously proposed criteria. Results. Of 89 SOT recipients, 13 (14%) developed IRS. Central nervous system (CNS) disease (adjusted odds ratio [AOR], 6.23; $P = .03$) and discontinuation of calcineurin inhibitor (AOR,

5.11; $P = .02$) were independently associated with IRS. Only 2.6% (1/13) of the patients without these risk factors developed IRS compared with 18.8% (6/32) with 1 risk factor, and 50% (6/12) with both risk factors (X^2 for trend, $P = .0001$). Among patients with CNS disease, those with neuroimaging abnormalities ($P = .03$) were more likely to develop IRS, irrespective of serum or CSF cryptococcal antigen titers and fungemia. Graft rejection after cryptococcosis was observed in 15.4% (2/13) of the patients with IRS compared with 2.6% (2/76) of those without IRS ($P = .07$). Conclusions. We determined variables that pose a risk for IRS and have shown that discontinuation of calcineurin inhibitors was independently associated with 5-fold increased risk of IRS in transplant recipients with cryptococcosis. © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved.

Szatmari, P., Zwaigenbaum, L., Georgiades, S., Elsabbagh, M., Waddell, C., Bennett, T., et al. (2016). Resilience and developmental health in autism spectrum disorder. (pp. 91-109) Elsevier Inc. The goal of this chapter is to discuss the concept of "resilience" against the background of the remarkable heterogeneity seen in the natural history of autism spectrum disorder (ASD). Classically, resilience refers to the occurrence of an unexpected "good outcome" in the face of adversity. In this chapter, adversity is the diagnosis of ASD and resilience becomes a marker of heterogeneity in prognosis in the context of that adversity. However, it is important to adopt more current concepts of resilience which emphasize better-than-expected outcomes as a result of the interactions between the characteristics of the child and those of his/her environment. It is also important to think of resilience in a developmental context and to consider the views of parents and individuals with ASD in defining a good outcome. Research in resilience can assist the field in moving toward a "strengths-based" approach in understanding children with ASD and in intervening to improve the lives of all people with ASD, not only those who are "resilient." © 2016 Elsevier Inc. All rights reserved.

Tateno, M., Teo, A. R., Shirasaka, T., Tayama, M., Watabe, M., & Kato, T. A. (2016). Internet addiction and self-evaluated ADHD traits among Japanese college students. *Psychiatry and Clinical Neurosciences*,
AIM: Internet addiction (IA), also referred to as internet use disorder, is a serious problem all

over the world, especially in Asian countries. Severe IA in students may be linked to academic failure, Attention Deficit Hyperactivity Disorder (ADHD), and forms of social withdrawal such as hikikomori. In this study, we performed a survey to investigate the relation between IA and ADHD symptoms among college students. METHODS: Severity of IA and ADHD traits were assessed by self-report scales. Subjects were 403 college students (response rate 78%) who completed a questionnaire including the Young's Internet Addiction Test (IAT) and Adult ADHD Self-Report Scale (ASRS)-V1.1. RESULTS: Out of 403 subjects, 165 were male, mean age was 18.4 +/- 1.2 yrs, and mean total IAT score was 45.2 +/- 12.6. One hundred forty-eight respondents (36.7%) were average internet users (IAT <40), 240 (59.6%) had possible addiction (IAT 40 to 69), and 15 (3.7%) had severe addiction (IAT 70 and higher). Mean length of internet use was 4.1 +/- 2.8 hrs/day on weekdays and 5.9 +/- 3.7 hrs/day on the weekend. Females used the internet mainly for social networking services (SNS) while males preferred online games. Students with a positive ADHD screen scored significantly higher on the IAT than those negative for ADHD screen (50.2 +/- 12.9 vs. 43.3 +/- 12.0). CONCLUSION: Our results suggest that internet misuse may be related to ADHD traits among Japanese youth. Further investigation of the links between IA and ADHD is warranted.

Teresa Munoz-Calvo, M., Barrios, V., Pozo, J., Chowen, J. A., Martos-Moreno, G. A., Hawkins, F., et al. (2016). Treatment with recombinant human insulin-like growth factor-I improves growth in patients with PAPP-A2 deficiency. *The Journal of Clinical Endocrinology and Metabolism*, , jc20162751.

CONTEXT: Pregnancy-associated plasma protein-A2 (PAPP-A2) is a metalloproteinase that specifically cleaves IGFBP-3 and IGFBP-5. Mutations in the PAPP-A2 gene have recently been shown to cause postnatal growth failure in humans, with specific skeletal features, due to the resulting decrease in IGF-I bioavailability. However, a pharmacological treatment of this entity is yet to be established. CASE DESCRIPTION: A 10.5 year old girl and a 6 year old boy, siblings from a Spanish family, with short stature due to a homozygous loss-of-function mutation in the PAPP-A2 gene (p.D643fs25*) and undetectable PAPP-A2 activity, were treated with progressive doses (40, 80, 100 and 120 mug/kg) of recombinant human IGF-I (rhIGF-I) twice daily for one year. There was a clear increase in growth velocity and height in both siblings. Bioactive IGF-I

was increased and spontaneous GH secretion was diminished after acute administration of rhIGF-I, while serum total IGF-I and IGFBP-3 levels remained elevated. No episodes of hypoglycemia or any other secondary effects were observed during treatment. CONCLUSION: Short-term treatment with rhIGF-I improves growth in patients with PAPP-A2 deficiency.

Thomas, A. J., Orlandi, R. R., Ashby, S., Mace, J. C., Smith, T. L., & Alt, J. A. (2016). Nasal

obstruction has a limited impact on sleep quality and quality of life in patients with chronic rhinosinusitis. *Laryngoscope*, 126(9), 1971-1976.

Objectives/Hypothesis: Nasal obstruction is a cardinal symptom in diagnosing chronic rhinosinusitis (CRS), and decreased sleep quality (SQ) and quality of life (QOL) are commonly reported in CRS. It is, however, unclear what role nasal obstruction severity plays in this decreased SQ and QOL. Using validated instruments, we evaluated the relationship between nasal obstruction severity, SQ, and QOL. Study Design: Prospective case series. Methods: Patients with CRS refractory to standard medical therapy (n = 28) were prospectively enrolled and completed the Nasal Obstruction Symptom Evaluation (NOSE), Pittsburg Sleep Quality Index (PSQI), Rhinosinusitis Disability Index, and the 22-item Sinonasal Outcome Test. CRS disease severity was evaluated with computed tomography and endoscopy. NOSE scores were compared to SQ, QOL, and disease severity measures. Spearman correlations were used to identify significant associations between measures. Results: All patients reported symptomatic nasal obstruction (NOSE score ≥ 30), whereas poor sleep (PSQI ≥ 5) was reported by 82%. The NOSE sleeping subdomain correlated strongly with the PSQI total score, whereas other elements of the NOSE instrument correlated weakly or not at all with this measurement of SQ. Nasal obstruction correlated weakly with disease-specific QOL and had no correlation with the PSQI total.

Conclusions: Nasal obstruction appears to have a limited association with CRS-specific QOL and CRS-associated decrease in SQ. Further, the NOSE instrument, because it contains a question about sleep, may have overlap with the PSQI as a measure of SQ. The total NOSE score in CRS patients does not appear to be purely a measure of nasal obstruction. Level of Evidence: 4

Laryngoscope, 126:1971–1976, 2016. © 2016 The American Laryngological, Rhinological and Otological Society, Inc.

Thomas, A. S., Branham, K., Van Gelder, R. N., Daiger, S. P., Sullivan, L. S., Bowne, S. J., et al. (2016). Multimodal imaging in wagner syndrome. *Ophthalmic Surgery Lasers and Imaging Retina*, 47(6), 574-579.

Wagner syndrome is a rare vitreoretinopathy described in a limited number of families. Here the authors describe four cases of suspected Wagner syndrome. All four cases had depressed rod and cone function on electroretinography, outer retinal disruption on spectral-domain optical coherence tomography, and constricted central visual fields with smaller isopter testing. Fundus autofluorescence performed in one patient highlighted a perivascular pattern to chorioretinal atrophy. Two patients had a history of uveitis with active cystoid macular edema. The diagnosis of Wagner syndrome was supported in three cases with genetic testing for VCAN mutations, whereas the other case harbored a variation of unknown significance in VCAN that may have been nonpathogenic. © 2016, Slack Incorporated. All rights reserved.

Thomas, A. S., & Lin, P. (2016). Ocular manifestations of inflammatory bowel disease. *Current Opinion in Ophthalmology*,

PURPOSE OF REVIEW: Extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) are numerous and can often involve the eye. This review highlights the ocular complications associated with IBD including the critical role the ophthalmologist can play in the diagnosis of IBD, the pathogenesis of IBD, its ocular complications, and the treatment of ocular inflammation associated with IBD. RECENT FINDINGS: Polygenic and environmental influences, as well as gut microbial dysbiosis, have been implicated in the pathogenesis of IBD. IBD and its EIMs appear to respond well to TNFalpha-targeted biologics. SUMMARY: IBD is thought to be caused by polygenic and environmental influences, including a dysbiotic gut microbiota. It is a systemic immune-mediated disease with varying types of ocular manifestations that can precede, occur simultaneously, or follow intestinal involvement. The diagnosis of IBD can be confused with other seronegative spondyloarthropathies as well as Behcet's disease. Treatment of IBD-associated ocular inflammation can range from corticosteroids to steroid-sparing immunosuppression such as azathioprine or methotrexate. Refractory disease can respond well to TNFalpha inhibitors.

Thorne, J. E., Suhler, E., Skup, M., Tari, S., Macaulay, D., Chao, J., et al. (2016). Prevalence of noninfectious uveitis in the united states: A claims-based analysis. *JAMA Ophthalmology*,

Importance: Noninfectious uveitis (NIU) is a collection of intraocular inflammatory disorders that may be associated with significant visual impairment. To our knowledge, few studies have investigated NIU prevalence overall or stratified by inflammation location, severity, presence of systemic conditions, age, or sex. Objective: To estimate NIU prevalence using a large, retrospective, administrative claims database. Design, Setting, and Participants: This analysis used the OptumHealth Reporting and Insights database to estimate 2012 NIU prevalence. Analysis was conducted in September 2016. The large administrative insurance claims database includes 14 million privately insured individuals in 69 self-insured companies spanning diverse industries. Included in the study were patients with NIU with 2 or more uveitis diagnoses on separate days in 2012 and continuous enrollment in a health plan for all of 2012 and categorized by inflammation site. Main Outcomes and Measures: We estimated overall NIU prevalence by inflammation site, severity, sex, and age. Patients with anterior NIU were categorized by the presence of systemic conditions. Results: Of the approximately 4 million eligible adult patients, approximately 2.1 million were women, and of the 932260 children, 475481 were boys. The adult prevalence of NIU was 121 cases per 100000 persons (95% CI, 117.5-124.3). The pediatric NIU prevalence was 29 cases per 100000 (95% CI, 26.1-33.2). Anterior NIU accounted for 81% (3904 cases) of adult NIU cases (98 per 100000; 95% CI, 94.7-100.9) and 75% (207 cases) of pediatric NIU cases (22 per 100000; 95% CI, 19.3-25.4). The prevalences of noninfectious intermediate, posterior, and panuveitis were, for adults, 1 (95% CI, 0.8-1.5), 10 (95% CI, 9.4-11.5), and 12 (95% CI, 10.6-12.7) per 100000, respectively, and for pediatric patients, 0 (95% CI, 0.1-1.1), 3 (95% CI, 1.8-4.1), and 4 (95% CI, 2.9-5.6) per 100000, respectively. The prevalence of NIU increased with age and was higher among adult females than males. Application of these estimates to the US population suggests that NIU affected approximately 298801 American adults (95% CI, 290512-307324) and 21879 children (95% CI, 19360-24626) in 2015. Conclusions and Relevance: The estimated prevalence of NIU was 121 cases per 100000 for adults (95% CI, 117.5-124.3) and 29 per 100000 for children (95% CI, 26.1-33.2). Prevalence was estimated using administrative claims from a commercially insured population,

which may have a different prevalence than other segments of the US population. A better understanding of the prevalence of NIU will help to determine the number of patients affected.

Tovar, K. R., & Westbrook, G. L. (2016). Modulating synaptic NMDA receptors. *Neuropharmacology*, Recent structural information on ligand-gated glutamate receptors and newly-discovered clinical uses for NMDA receptor antagonists has renewed interest in understanding the mechanisms of drug action at these receptors. Although the voltage-dependence and calcium permeability of NMDA receptors are well-studied, the mechanisms affecting the time course of synaptic NMDA receptor activation may be of more therapeutic value by serving as a rheostat for the total synaptic response. The NMDA receptor-mediated EPSC time course has been thought of as a fixed parameter based simply on receptor subunit composition as variably constrained by anatomical and developmental expression patterns, albeit subject to modification by kinetic behaviors such as modal gating. However, the EPSC time course also can be manipulated by endogenous and exogenous ligands. In this commentary we discuss insights into the in situ composition and kinetic behavior of synaptic NMDA receptors and propose new opportunities to target modulatory sites on NMDA receptors and to develop useful therapeutics. The emerging data on the atomic structure of NMDA receptors and knowledge of the kinetics of native receptors in neurons provide a roadmap in this regard.

Usher, C. (2015). Here/In this issue and There/Abstract thinking: Milestones. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(1), 1-2.

Valderrabano, R. J., Lui, L. Y., Lee, J., Cummings, S. R., Orwoll, E. S., Hoffman, A. R., et al. (2016). Bone density loss is associated with blood cell counts. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, Hematopoiesis depends on a supportive microenvironment. Preclinical studies in mice have demonstrated that osteoblasts influence the development of blood cells, particularly erythrocytes, B lymphocytes, and neutrophils. However, it is unknown whether osteoblast numbers or function impact blood cell counts in humans. We tested the hypothesis that men with low BMD or greater BMD loss have decreased circulating erythrocytes and lymphocytes and increased myeloid cells. We performed a cross-sectional analysis and prospective analysis in the Osteoporotic Fractures in

Men (MrOS), a multi-site longitudinal cohort study. 2571 community-dwelling men (>65 years) who were able to walk without assistance, did not have a hip replacement or fracture and had complete blood counts (CBCs) at the third study visit were analyzed. Multivariable (MV)-adjusted logistic regression estimated odds of white blood cell subtypes (highest and lowest quintile vs middle), and anemia (clinically defined) associated with BMD by DXA scan (at visit 3), annualized percent BMD change (baseline to visit 3), and high BMD loss (>0.5%/year, from baseline to visit 3) at the femoral neck (FN) and total hip (TH). MV adjusted models included age, BMI, cancer history, smoking status, alcohol intake, corticosteroid use, self-reported health, thiazide use and physical activity. At visit 3 greater TH BMD loss (per standard deviation) was associated with increased odds of anemia, high neutrophils, and low lymphocytes. Annualized BMD loss of >0.5% was associated with increased odds of anemia, high neutrophils, and low lymphocytes. Similar results were observed for FN BMD regarding anemia and lymphocytes. We concluded that community-dwelling older men with declining hip BMD over about 7 years had increased risks of anemia, lower lymphocyte count, and higher neutrophil count, consistent with pre-clinical studies. Bone health and hematopoiesis may have greater interdependency than previously recognized. This article is protected by copyright. All rights reserved.

Wagner, J., Fleseriu, C. M., Ibrahim, A., & Cetas, J. S. (2016). Idiopathic intracranial hypertension following surgical treatment of cushing disease: Case report and review of management strategies. *World Neurosurgery*,

BACKGROUND: Idiopathic intracranial hypertension (IIH) in Cushing's disease (CD) patients, following treatment, is rarely described, in adults. Etiology is thought to be multifactorial, potentially related to a relative decrease in cortisol following surgical resection or medical treatment of a corticotroph pituitary adenoma. We investigated our center's CD database (140 surgically and 60 medically (primary or adjunct) treated patients) for cases of IIH, describe our center's experience with symptomatic IIH, and review treatment strategies in adults with CD after transphenoidal resection. CASE DESCRIPTION: We present the case of a 22-year-old female who presented with worsening headache, nausea, vomiting, blurry vision, diplopia, visual loss and facial numbness 14 weeks after surgical resection of adrenocorticotrophic hormone-positive pituitary adenoma. Her CD had been in remission since surgery with subsequent adrenal

insufficiency (AI), which was initially treated with supraphysiologic glucocorticoid (GC) replacement, tapered down to physiologic doses at the time the IIH symptoms developed.

CONCLUSION: Symptomatic IIH is very rare in adult patients, but can be severe and result in permanent vision loss. A high index of suspicion should be maintained and a fundus exam is necessary to exclude papilledema, whenever there are suggestive symptoms that initially may overlap with AI. It is possible that some cases of mild IIH are misdiagnosed as GC withdrawal and/or AI, however further studies are needed. Treatment consists of re-initiation of higher steroid doses together with acetazolamide with or without cerebrospinal fluid diversion and the priority is to preserve vision and reverse any visual loss.

Walcott-Sapp, S., Van Horn, J., Phillips, B., & Gee, A. (2016). Splenic hemorrhage at altitude in a patient with undiagnosed sickle-cell trait. *The American Surgeon*, 82(3), E63-4.

Wallace, L. S., Angier, H., Huguet, N., Gaudino, J. A., Krist, A., Dearing, M., et al. (2016). Patterns of electronic portal use among vulnerable patients in a nationwide practice-based research network: From the OCHIN practice-based research network (PBRN). *Journal of the American Board of Family Medicine*, 29(5), 592-603.

Background: Underserved patient populations experience barriers to accessing and engaging within the complex health care system. Electronic patient portals have been proposed as a potential new way to improve access and engagement. We studied patient portal use for 12 consecutive months (365 days) among a large, nationally distributed, underserved patient population within the OCHIN (originally created as the Oregon Community Health Information Network and renamed OCHIN as other states joined) practice-based research network (PBRN).

Methods: We retrospectively assessed adoption and use of Epic's MyChart patient portal in the first 12 months after MyChart was made available to the OCHIN PBRN. We examined electronic health record data from 36,549 patients aged ≥ 18 years who were offered a MyChart access code between May 1, 2012, and April 30, 2013, across the OCHIN PBRN in 13 states. Results: Overall, 29% of patients offered an access code logged into their MyChart account. Superusers (minimum of 2 logins per month over a 12-month period) accounted for 6% of users overall. Men, nonwhite patients, Hispanic patients, Spanish-speaking patients, and those with the lowest incomes were

significantly less likely to activate. Publicly insured and uninsured patients were also less likely to log in to their MyChart account, but once activated they were more likely than privately insured patients to use MyChart functions. Conclusions: Our findings suggest that, compared with others, certain patient groups may be less interested in using patient portals or may have experienced significant barriers that prevented use. Making portal access available is a first step. Additional studies need to specifically identify health system-, clinic-, and patient-level barriers and facilitators to portal adoption and use.

Wang, Q., S Abdul, S., Almeida, L., Ananiadou, S., Balderas-Martinez, Y. I., Batista-Navarro, R., et al.

(2016). Overview of the interactive task in BioCreative V. *Database : The Journal of Biological Databases and Curation*, 2016, 10.1093/database/baw119. Print 2016.

Fully automated text mining (TM) systems promote efficient literature searching, retrieval, and review but are not sufficient to produce ready-to-consume curated documents. These systems are not meant to replace biocurators, but instead to assist them in one or more literature curation steps. To do so, the user interface is an important aspect that needs to be considered for tool adoption. The BioCreative Interactive task (IAT) is a track designed for exploring user-system interactions, promoting development of useful TM tools, and providing a communication channel between the biocuration and the TM communities. In BioCreative V, the IAT track followed a format similar to previous interactive tracks, where the utility and usability of TM tools, as well as the generation of use cases, have been the focal points. The proposed curation tasks are user-centric and formally evaluated by biocurators. In BioCreative V IAT, seven TM systems and 43 biocurators participated. Two levels of user participation were offered to broaden curator involvement and obtain more feedback on usability aspects. The full level participation involved training on the system, curation of a set of documents with and without TM assistance, tracking of time-on-task, and completion of a user survey. The partial level participation was designed to focus on usability aspects of the interface and not the performance per se. In this case, biocurators navigated the system by performing pre-designed tasks and then were asked whether they were able to achieve the task and the level of difficulty in completing the task. In this manuscript, we describe the development of the interactive task, from planning to execution and discuss major findings for the systems tested. Database URL: <http://www.biocreative.org>.

Wang, Y., Wu, S., Li, D., Mehrabi, S., & Liu, H. (2016). A part-of-speech term weighting scheme for biomedical information retrieval. *Journal of Biomedical Informatics*,

In the era of digitalization, information retrieval (IR), which retrieves and ranks documents from large collections according to users' search queries, has been popularly applied in the biomedical domain. Building patient cohorts using electronic health records (EHRs) or searching literature for topics of interest are some IR use cases. Meanwhile, natural language processing (NLP), such as tokenization or Part-of-Speech (POS) tagging, has been developed for processing clinical documents or biomedical literature. We hypothesize that NLP can be incorporated into IR to strengthen the conventional IR models. In this study, we propose two NLP-empowered IR models, POS-BoW and POS-MRF, which incorporate automatic POS-based term weighting schemes into bag-of-word (BoW) and Markov Random Field (MRF) IR models, respectively. In the proposed models, the POS-based term weights are iteratively calculated by utilizing a cyclic coordinate method where golden section line search algorithm is applied along each coordinate to optimize the objective function defined by mean average precision (MAP). In the empirical experiments, we used the data sets from the Medical Records track in Text REtrieval Conference (TREC) 2011 and 2012 and the Genomics track in TREC 2004. The evaluation on TREC 2011 and 2012 Medical Records tracks shows that, for the POS-BoW models, the mean improvement rates for IR evaluation metrics, MAP, bpref, and P@10, are 10.88%, 4.54%, and 3.82%, compared to the BoW models; and for the POS-MRF models, these rates are 13.59%, 8.20%, and 8.78%, compared to the MRF models. Additionally, we experimentally verify that the proposed weighting approach is superior to the simple heuristic and frequency based weighting approaches, and validate our POS category selection. Using the optimal weights calculated in this experiment, we tested the proposed models on the TREC 2004 Genomics track and obtained average of 8.63% and 10.04% improvement rates for POS-BoW and POS-MRF, respectively. These significant improvements verify the effectiveness of leveraging POS tagging for biomedical IR tasks.

Weinstock, M. A., Lott, J. P., Wang, Q., Titus, L. J., Onega, T., Nelson, H. D., et al. (2016). Skin biopsy utilization and melanoma incidence among medicare beneficiaries. *The British Journal of Dermatology*,

BACKGROUND: Melanoma incidence has increased in recent decades in the United States.

Uncertainty remains regarding how much of this increase is attributable to greater melanoma screening activities, potential detection bias and overdiagnosis. OBJECTIVE: Use a cross-sectional ecological analysis to evaluate the relationship between skin biopsy and melanoma incidence rates over a more recent time period than prior reports. METHODS: Examination of the association of biopsy rates and melanoma incidence (invasive and in situ) in SEER-Medicare data (including 10 states) for 2002-2009. RESULTS: The skin biopsy rate increased approximately 50% (6% per year) throughout this 8-year period, from 7,012 biopsies per 100,000 persons in 2002 to 10,528 biopsies per 100,000 persons in 2009. Overall melanoma incidence rate increased approximately 4% (< 1% per year) over the same time period. Incidence of melanoma in situ increased approximately 10% (1% per year), while incidence of invasive melanoma increased from 2002-5 then decreased from 2006-9. Regression models estimated that, on average, for every 1,000 skin biopsies performed, an additional 5.2 (95% CI: 4.1, 6.3) cases of melanoma in situ were diagnosed and 8.1 (95%CI: 6.7, 9.5) cases of invasive melanoma were diagnosed. When considering individual states, some demonstrated a positive association between biopsy rate and invasive melanoma incidence, others an inverse association, and still others a more complex pattern. CONCLUSIONS AND RELEVANCE: Increased skin biopsies over time are associated with increased diagnosis of in situ melanoma, but the association with invasive melanoma is more complex. This article is protected by copyright. All rights reserved.

Whitehead, K. J., Sautter, N. B., McWilliams, J. P., Chakinala, M. M., Merlo, C. A., Johnson, M. H., et al. (2016). Effect of topical intranasal therapy on epistaxis frequency in patients with hereditary hemorrhagic telangiectasia: A randomized clinical trial. *Jama*, 316(9), 943-951.

IMPORTANCE: Epistaxis is a major factor negatively affecting quality of life in patients with hereditary hemorrhagic telangiectasia (HHT; also known as Osler-Weber-Rendu disease). Optimal treatment for HHT-related epistaxis is uncertain. OBJECTIVE: To determine whether topical therapy with any of 3 drugs with differing mechanisms of action is effective in reducing HHT-related epistaxis. DESIGN, SETTING, AND PARTICIPANTS: The North American Study of Epistaxis in HHT was a double-blind, placebo-controlled randomized clinical trial performed at 6 HHT centers of excellence. From August 2011 through March 2014, there were 121 adult patients who met the clinical criteria for HHT and had experienced HHT-related epistaxis with an Epistaxis

Severity Score of at least 3.0. Follow-up was completed in September 2014. INTERVENTIONS: Patients received twice-daily nose sprays for 12 weeks with either bevacizumab 1% (4 mg/d), estriol 0.1% (0.4 mg/d), tranexamic acid 10% (40 mg/d), or placebo (0.9% saline). MAIN OUTCOMES AND MEASURES: The primary outcome was median weekly epistaxis frequency during weeks 5 through 12. Secondary outcomes included median duration of epistaxis during weeks 5 through 12, Epistaxis Severity Score, level of hemoglobin, level of ferritin, need for transfusion, emergency department visits, and treatment failure. RESULTS: Among the 121 patients who were randomized (mean age, 52.8 years [SD, 12.9 years]; 44% women with a median of 7.0 weekly episodes of epistaxis [interquartile range {IQR}, 3.0-14.0]), 106 patients completed the study duration for the primary outcome measure (43 were women [41%]). Drug therapy did not significantly reduce epistaxis frequency ($P = .97$). After 12 weeks of treatment, the median weekly number of bleeding episodes was 7.0 (IQR, 4.5-10.5) for patients in the bevacizumab group, 8.0 (IQR, 4.0-12.0) for the estriol group, 7.5 (IQR, 3.0-11.0) for the tranexamic acid group, and 8.0 (IQR, 3.0-14.0) for the placebo group. No drug treatment was significantly different from placebo for epistaxis duration. All groups had a significant improvement in Epistaxis Severity Score at weeks 12 and 24. There were no significant differences between groups for hemoglobin level, ferritin level, treatment failure, need for transfusion, or emergency department visits. CONCLUSIONS AND RELEVANCE: Among patients with HHT, there were no significant between-group differences in the use of topical intranasal treatment with bevacizumab vs estriol vs tranexamic acid vs placebo and epistaxis frequency. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01408030.

Winthrop, K. L., Strand, V., van der Heijde, D. M., Mease, P. J., Crow, M. K., Weinblatt, M., et al. (2016). The unmet need in rheumatology: Reports from the targeted therapies meeting 2016. *Clinical and Experimental Rheumatology*, 34(4 Suppl 98), 69-76.

The 18th annual international Targeted Therapies meeting brought together over 100 leading scientists and clinicians from around the world in the field of rheumatology. During the meeting, breakout sessions were held consisting of 5 disease-specific groups each with 20-40 experts assigned to each group based on clinical or scientific expertise. Specific groups included: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis/spondyloarthritis, systemic lupus

erythematous, and other connective tissue diseases (e.g. Sjogren's, Behcet's, others). In each group, experts were asked to identify unmet needs in 3 categorical areas: basic/translational science, clinical science and therapeutic development, and clinical care. Needs were prioritised as primary or secondary. Overall, similar primary unmet needs were identified within each disease foci. Within translational science, these included the need for better understanding the heterogeneity within each disease, such that predictive tools for therapeutic response could be developed. Within clinical science and therapeutic trials, the ability to prevent progression to disease onset in those at risk, and the ability to cure disease were identified. A further unmet need was to develop new and accessible therapeutics, as well as to conduct strategic trials of currently approved therapies. Within the clinical care realm, improved co-morbidity management and patient-centered care were identified as unmet needs. Lastly, it was strongly felt there was a need to develop a scientific infrastructure for well-characterised, longitudinal cohorts married with biobanks and mechanisms to support data-sharing. This infrastructure could facilitate many of the unmet needs identified within each disease area.

Wong, C. K., Young, R. S., Ow-Wing, C., & Karimi, P. (2016). Determining 1-yr prosthetic use for mobility prognoses for community-dwelling adults with lower-limb amputation: Development of a clinical prediction rule. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists*, 95(5), 339-347.

OBJECTIVE: The objective of this study was to develop a prognostic clinical prediction rule to identify people not achieving community walking level prosthetic use after 1 yr. DESIGN: This is a prospective longitudinal cohort study of community-dwelling adults with lower-limb amputations recruited from support groups and prosthetic clinics. Participants completed Activities-specific Balance Confidence and Houghton prosthetic use for mobility self-report scales and the Berg Balance Scale. The clinical prediction rule was developed using multivariate logistic regression, receiver operating curves, and probability statistics to identify people not achieving community walking level prosthetic use (Houghton scores 0.96) using four criteria: initial Houghton, Activities-specific Balance Confidence, and Berg Balance Scale tasks 9 (retrieve object from floor) and 10 (look behind over shoulders). Failure to exceed cutoff scores in two or more criteria yielded posttest probability of not reaching community walking prosthetic use 1 yr later

for 90% of participants or higher. CONCLUSIONS: Accurate 1-yr prosthetic use for mobility prognoses can be obtained by screening prosthetic use, balance confidence, and balance ability to identify community-dwelling people with lower-limb amputations unlikely to achieve community walking prosthetic use.

Woodward, Z., Williams, J. L., & Sonnenberg, A. (2016). Length of endoscopic workup in gastrointestinal bleeding. *European Journal of Gastroenterology & Hepatology*, 28(10), 1166-1171.

BACKGROUND: The number of procedures utilized in the general management of gastrointestinal bleeding (GIB) has not been investigated previously. We used the National Endoscopic Database of the Clinical Outcomes Research Initiative for an observational study to analyze the average length of workup in GIB. METHODS: The electronic database was queried for all patients aged 18 years and older who underwent an endoscopic evaluation for any bleeding indication between 2000 and 2014. Data were stratified by indication, type, and number of endoscopies per patient, and length of workup. RESULTS: A total of 603 807 endoscopic procedures among 451 470 individual patients were used in the workup of GIB, with 152 337 procedures among 113 030 patients (25%) being performed as a secondary procedure. The average length was 2.4+/-0.9 procedures per workup in procedural sequences involving multiple endoscopies. The length of workup was independent of the initial type of GIB. An esophago-gastro-duodenoscopy (EGD), followed by a colonoscopy or a colonoscopy, followed by an EGD were the most frequent combinations. In another substantial fraction of two consecutive procedures, the first and the second procedure were identical. This pattern applied not only to EGD and colonoscopy but also to flexible sigmoidoscopy, enteroscopy, and video capsule endoscopy. CONCLUSION: The majority of patients with GIB require only one type of endoscopy to manage their bleeding. However, in a quarter of patients, on average, 2.4 procedures are needed. Previous trials assessing the outcomes of individual types of endoscopy may have exaggerated their overall success rates in diagnosing and treating GIB.

Yadava, M., & Shapiro, M. D. (2016). Applications of advanced imaging in cardiac electrophysiology. *Current Treatment Options in Cardiovascular Medicine*, 18(11), 66.

OPINION STATEMENT: Imaging modalities such as computed tomography, magnetic resonance, positron emission tomography, and single-photon emission computed tomography are an indispensable component of cardiac arrhythmia management. Over the last two decades, developments in imaging techniques have facilitated safer and more effective cardiac ablation and device implantation procedures. Pre-procedural assessment of arrhythmogenic substrate and integration with electroanatomic data has significantly impacted the management of atrial fibrillation and ventricular tachycardia. Furthermore, cardiovascular imaging enhances patient selection, prognostication, and follow-up of patients undergoing ablation procedures. Imaging also provides valuable anatomic information in patients being considered for cardiac resynchronization therapy (CRT). While the optimal modality for assessing efficacy of resynchronization is currently unclear, further study holds promise in mitigating the substantial burden of CRT non-response. This article aims to highlight the utility and evidence for various advanced imaging modalities in the practice of cardiac electrophysiology with an emphasis on recent developments and future directions.

Yarbrough, K., Danko, C., Krol, A., Zonana, J., & Leitenberger, S. (2016). The importance of chilblains as a diagnostic clue for mild aicardi-goutieres syndrome. *American Journal of Medical Genetics.Part A*,

Aicardi-Goutieres syndrome (AGS) is classically characterized by early-onset encephalopathy. However, in some cases, the presenting symptom of concern may actually be cutaneous rather than neurological, leading to the misdiagnosis of the condition. We report the case of three teenage siblings who presented with a lifetime history of chilblain lesions, only one of whom had notable neurologic deficits. Additional findings included acrocyanosis, Raynaud's phenomenon, low-pitch hoarse voice, headache, and arthritis. They were found to have two pathogenic sequence variants in the SAMHD1 gene: a c.602T>A substitution resulting in p.Ile201Asn protein change, previously reported as a pathogenic mutation, as well as a deletion c.719delT which has not been previously reported but results in a predicted pathogenic frame shift mutation. It is important to consider the diagnosis of AGS in patients and families with chilblain lesions in the presence of unexplained neurologic and rheumatic symptoms. (c) 2016 Wiley Periodicals, Inc.

Yarbrough, K. B., Tollefson, M. M., Krol, A. L., Leitenberger, S. L., Mann, J. A., & MacArthur, C. J.

(2016). Is routine electrocardiography necessary before initiation of propranolol for treatment of infantile hemangiomas? *Pediatric Dermatology*,

BACKGROUND: In recent years propranolol has become the treatment of choice for infantile hemangiomas (IHs). There is broad variation in the approach to propranolol initiation in clinical practice. This retrospective study explored the effectiveness of routine pre-treatment ECG in screening infants being considered for systemic treatment with propranolol. **METHODS:** All patients seen in the outpatient pediatric dermatology clinics at Oregon Health and Sciences University (OHSU) and The Mayo Clinic Rochester (MCR), as well as those seen in multidisciplinary vascular anomalies clinics, who had ECGs obtained prior to planned initiation of propranolol for treatment of IH from 2008 to 2013, were identified. A total of 162 patients were included in the study. **RESULTS:** We found that 43% (69) of routine ECGs were read as abnormal, leading to 28 formal consultation appointments with pediatric cardiologists. After either formal consultation or informal discussion with cardiology, no patients with initially "abnormal" ECGs were ultimately excluded from treatment with propranolol based on routine ECG findings. Additionally no patients in our cohort experienced an adverse effect during treatment that could have been predicted or prevented by ECG prior to initiation of the propranolol. **CONCLUSION:** Our findings suggest that routine ECG may not be necessary or helpful in the vast majority of patients treated with propranolol for IHs.

Zeng, W. Z., Grillet, N., Dewey, J. B., Trouillet, A., Krey, J. F., Barr-Gillespie, P. G., et al. (2016).

Neuroplastin isoform Np55 is expressed in the stereocilia of outer hair cells and required for normal outer hair cell function. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 36(35), 9201-9216.

Neuroplastin (Nptn) is a member of the Ig superfamily and is expressed in two isoforms, Np55 and Np65. Np65 regulates synaptic transmission but the function of Np55 is unknown. In an N-ethyl-N-nitrosourea mutagenesis screen, we have now generated a mouse line with an Nptn mutation that causes deafness. We show that Np55 is expressed in stereocilia of outer hair cells (OHCs) but not inner hair cells and affects interactions of stereocilia with the tectorial membrane. In vivo vibrometry demonstrates that cochlear amplification is absent in Nptn mutant mice, which

is consistent with the failure of OHC stereocilia to maintain stable interactions with the tectorial membrane. Hair bundles show morphological defects as the mutant mice age and while mechanotransduction currents can be evoked in early postnatal hair cells, cochlea microphonics recordings indicate that mechanotransduction is affected as the mutant mice age. We thus conclude that differential splicing leads to functional diversification of *Nptn*, where *Np55* is essential for OHC function, while *Np65* is implicated in the regulation of synaptic function. SIGNIFICANCE STATEMENT: Amplification of input sound signals, which is needed for the auditory sense organ to detect sounds over a wide intensity range, depends on mechanical coupling of outer hair cells to the tectorial membrane. The current study shows that neuroplastin, a member of the Ig superfamily, which has previously been linked to the regulation of synaptic plasticity, is critical to maintain a stable mechanical link of outer hair cells with the tectorial membrane. In vivo recordings demonstrate that neuroplastin is essential for sound amplification and that mutation in neuroplastin leads to auditory impairment in mice.

Zhang, C., Murata, S., Murata, M., Fuller, C. D., Thomas, C. R., Jr, Choi, M., et al. (2016). Factors associated with increased academic productivity among US academic radiation oncology faculty. *Practical Radiation Oncology*,

OBJECTIVES: Publication productivity metrics can help evaluate academic faculty for hiring, promotion, grants, and awards; however, limited benchmarking data exist, which makes intra- and interdepartmental comparisons difficult. Therefore, we sought to evaluate the scholarly activity of physician faculty at academic radiation oncology (RO) departments and establish factors associated with increased academic productivity. METHODS AND MATERIALS: Citation database searches were performed for all physician-faculty in US residency-affiliated academic RO departments. Demographics, National Institutes of Health (NIH) funding, and bibliometrics (number of publications, Hirsch-[h]-index, and m-index [Hirsch index divided by the number of years since first publication]) were collected and stratified by academic rank. Senior academic rank was defined as full professor, professor, and/or chair. Junior academic rank was defined as all others. Logistic regression was performed to determine the association of academic rank and other factors with h- and m-indices. RESULTS: A total of 1191 academic RO physician faculty from 75 institutions were included in the analysis. The mean (standard deviation) number of

publications and h- and m-indices were 48.2 (71.2), 14.5 (15), and 0.86 (0.83), respectively. The median (interquartile range) number of publications and h- and m-indices were 20 (6-61), 9 (4-20), and 0.69 (0.38-1.10), respectively. Recursive partitioning analysis revealed a statistically significant numeric h-index threshold of 21 between junior and senior faculty (LogWorth 114; receiver operating characteristic, 0.828). Senior faculty status, receipt of NIH funding, and a larger department size were associated with increased h- and m-indices. CONCLUSIONS: Current academic RO departments have relatively high objective metrics of scholastic productivity compared with prior benchmarking analyses of RO departments and compared with published metrics from other academic medicine subspecialties. An h-index of 21 or greater was associated with senior faculty status. Additionally, receipt of NIH funding and greater departmental size were associated with a higher h-index. These data may be of interest to faculty preparing for promotion or award applications as well as institutional leadership evaluating their departments.

Zhang, X., Dastiridou, A., Francis, B. A., Tan, O., Varma, R., Greenfield, D. S., et al. (2016). Baseline fourier-domain OCT structural risk factors for visual field progression in the advanced imaging for glaucoma study. *American Journal of Ophthalmology*,

PURPOSE: To identify baseline structural parameters that predict the progression of visual field (VF) loss in patients with open angle glaucoma. DESIGN: Multicenter cohort study. METHODS: Participants from Advanced Imaging for Glaucoma (AIG) study were enrolled and followed-up. VF progression is defined as either a confirmed progression event on Humphrey Progression Analysis or a significant ($p < 0.05$) negative slope for VF index (VFI). Fourier-domain optical coherence tomography (FD-OCT) was used to measure optic disc, peripapillary retinal nerve fiber layer (NFL) and macular ganglion cell complex (GCC) thickness parameters. RESULTS: 277 eyes of 188 participants were followed up for 3.7 +/- 2.1 years. VF progression was observed in 83 eyes (30%). Several baseline NFL and GCC parameters, but not disc parameters, were found to be significant predictors of progression on univariate Cox regression analysis. The most accurate single predictors were the GCC focal loss volume (FLV), followed closely by NFL-GCC. An abnormal GCC-FLV at baseline increased risk of progression by a hazard ratio of 3.1. Multivariate Cox analysis showed that combining age and central corneal thickness with GCC-FLV in a composite index called "Glaucoma Composite Progression Index" (GCPI) further improved the

accuracy of progression prediction. GCC-FLV and GCPI were both found to be significantly correlated with the annual rate of change in VFI. CONCLUSION: Focal GCC and NFL loss as measured by FD-OCT are the strongest predictors for VF progression among the measurements considered. Older age and thinner central corneal thickness can enhance the predictive power using the composite risk model.

Zhang, Z., Garzotto, M., Beer, T. M., Thuillier, P., Lieberman, S., Mori, M., et al. (2016). Effects of omega-3 fatty acids and catechins on fatty acid synthase in the prostate: A randomized controlled trial. *Nutrition and Cancer*, , 1-11.

Animal and human studies suggest fish oil and green tea may have protective effect on prostate cancer. Fatty acid synthase (FAS) has been hypothesized to be linked to chemoprotective effects of both compounds. This study evaluated the independent and joint effects of fish oil (FO) and green tea supplement (epigallocatechin-3-gallate, EGCG) on FAS and Ki-67 levels in prostate tissue. Through a double-blinded, randomized controlled trial with 2 x 2 factorial design, 89 men scheduled for repeat prostate biopsy following an initial negative prostate biopsy were randomized into either FO alone (1.9 g DHA + EPA/day), EGCG alone (600 mg/day), a combination of FO and EGCG, or placebo. We used linear mixed-effects models to test the differences of prostate tissue FAS and Ki-67 by immunohistochemistry between pre- and post-intervention within each group, as well as between treatment groups. Results did not show significant difference among treatment groups in pre-to-post-intervention changes of FAS (P = 0.69) or Ki-67 (P = 0.26). Comparing placebo group with any of the treatment groups, we did not find significant difference in FAS or Ki-67 changes (all P > 0.05). Results indicate FO or EGCG supplementation for a short duration may not be sufficient to produce biologically meaningful changes in FAS or Ki-67 levels in prostate tissue.

Ziu, M., Dunn, I. F., Hess, C., Fleseriu, M., Bodach, M. E., Tumialan, L. M., et al. (2016). Congress of neurological surgeons systematic review and evidence-based guideline on posttreatment follow-up evaluation of patients with nonfunctioning pituitary adenomas. *Neurosurgery*, 79(4), E541-3. BACKGROUND: Nonfunctioning pituitary adenomas (NFPAs) are the most frequent pituitary tumors. Due to the lack of hormonal hypersecretion, posttreatment follow-up evaluation of NFPAs

is challenging. OBJECTIVE: To create evidence-based guidelines in an attempt to formulate guidance for posttreatment follow-up in a consistent, rigorous, and cost-effective way.

METHODS: An extensive literature search was performed. Only clinical articles describing postoperative follow-up of adult patients with NFPA were included. To ascertain the class of evidence for the posttreatment follow-ups, the authors used the Clinical Assessment evidence-based classification. RESULTS: Twenty-three studies met the inclusion criteria with respect to answering the questions on the posttreatment radiologic, endocrinologic, and ophthalmologic follow-up. Through this search, the authors formulated evidence-based guidelines for radiologic, endocrinologic, and ophthalmologic follow-up after surgical and/or radiation treatment.

CONCLUSION: Long-term radiologic, endocrinologic, and ophthalmologic surveillance monitoring after surgical and/or radiation therapy treatment of NFPA to evaluate for tumor recurrence or regrowth, as well as pituitary and visual status, is recommended. There is insufficient evidence to make a recommendation on the duration of time of surveillance and its frequency. It is recommended that the first radiologic study to evaluate the extent of resection of the NFPA be performed ≥ 3 months after surgical intervention. The full guidelines document for this chapter can be located at https://www.cns.org/guidelines/guidelines-management-patients-non-functioning-pituitary-adenomas/Chapter_8. ABBREVIATION: NFPA, nonfunctioning pituitary adenoma.

Zivney, M., Lin, P., Edmunds, B., Parikh, M., Takusagawa, H., & Tehrani, S. (2016). Combined glaucoma tube shunt (ahmed) and fluocinolone acetonide (retisert) implantation compared to ahmed alone in uveitic glaucoma. *Ophthalmology and Therapy*,

INTRODUCTION: Glaucoma is a known complication of uveitis, and may require glaucoma tube shunt implantation for intraocular pressure (IOP) control. The success of glaucoma tube shunt implantation in the setting of a local ocular steroid depot in uveitic glaucoma remains unknown. The purpose of this study was to determine whether patients who underwent combined glaucoma tube shunt (Ahmed) and fluocinolone acetonide (Retisert, Bausch + Lomb, Bridgewater, NJ, USA) implantation have superior outcomes compared to patients with Ahmed implants only in the setting of uveitic glaucoma. METHODS: All participants were studied retrospectively and underwent Ahmed implantation alone or with existing/concurrent Retisert implantation (combined

group) at a single academic institution. The main outcome measures were IOP, visual acuity (VA), number of IOP-lowering medications, and adverse events at 6 months after Ahmed implantation. Secondary outcome measures included adverse events and surgical success at 6 months after Ahmed implantation. RESULTS: Mean IOP at 6 months after Ahmed implantation was 15.3 +/- 4.8 and 15.1 +/- 4.9 mm Hg in the Ahmed only group (n = 17) and the combined group (n = 17), respectively (p = 0.89). The mean number of IOP-lowering medications at 6 months after Ahmed implantation was 1.7 +/- 1.0 and 1.8 +/- 1.0 in the Ahmed only group and the combined group, respectively (p = 0.86). Mean VA at 6 months after Ahmed implantation was 0.35 +/- 0.29 and 0.42 +/- 0.33 log mean angle of resolution in the Ahmed only group and the combined group, respectively (p = 0.50). No significant differences in surgical success or adverse events were noted between the two groups. CONCLUSION: At 6 months, no significant differences in mean IOP, mean number of IOP-lowering medications, VA, surgical success, or adverse events were noted between Ahmed implantation alone or combined Ahmed and Retisert implantation in patients with uveitic glaucoma.