

References

Abola, M. V., & Prasad, V. (2016). Industry funding of cancer patient advocacy organizations. *Mayo Clinic Proceedings*, 91(11), 1668-1670.

Ahmad, Z. S., Andersen, R. L., Andersen, L. H., O'Brien, E. C., Kindt, I., Shrader, P., et al. (2016). US physician practices for diagnosing familial hypercholesterolemia: Data from the CASCADE-FH registry. *Journal of Clinical Lipidology*,

Background: In the US familial hypercholesterolemia (FH), patients are underidentified, despite an estimated prevalence of 1:200 to 1:500. Criteria to identify FH patients include Simon Broome, Dutch Lipid Clinic Network (DLCN), or Make Early Diagnosis to Prevent Early Deaths (MEDPED). The use of these criteria in US clinical practices remains unclear. Objective: To characterize the FH diagnostic criteria applied by US lipid specialists participating in the FH Foundation's CASCADE FH (CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia) patient registry. Methods: We performed an observational, cross-sectional analysis of diagnostic criteria chosen for each adult patient, both overall and by baseline patient characteristics, at 15 clinical sites that had contributed data to the registry as of September 8, 2015. A sample of 1867 FH adults was analyzed. The median age at FH diagnosis was 50 years, and the median pretreatment low-density lipoprotein cholesterol (LDL-C) value was 238 mg/dL. The main outcome was the diagnostic criteria chosen. Diagnostic criteria were divided into five nonexclusive categories: "clinical diagnosis," MEDPED, Simon Broome, DLCN, and other. Results: Most adults enrolled in CASCADE FH (55.0%) received a "clinical diagnosis." The most commonly used formal criteria was Simon-Broome only (21%), followed by multiple diagnostic criteria (16%), MEDPED only (7%), DLCN only (1%), and other (0.5%), . P < .0001. Of the patients with only a "clinical diagnosis," 93% would have met criteria for Simon Broome, DLCN, or MEDPED based on the data available in the registry. Conclusions: Our findings demonstrate heterogeneity in the application of FH diagnostic criteria in the United States. A nationwide consensus definition may lead to better identification, earlier treatment, and ultimately CHD prevention. © 2016 National Lipid Association.

Alabi, O., Roos, M., Landry, G., & Moneta, G. (2016). Quality of life assessment as an outcomes measure in critical limb ischemia. *Journal of Vascular Surgery*,

Critical limb ischemia (CLI) is a diagnosis plagued by significant comorbidity and high mortality rates. Overall survival remains poor in this population regardless of the procedure-related success as demonstrated by freedom from amputation, intervention, and patency. The literature has traditionally focused on physician-centered and lesion-centered outcomes with regards to limb salvage procedures, but there remains a relative paucity of studies of CLI patients describing patient-centered outcomes such as quality of life (QoL), independent living, and ambulation status. Review of the available literature indicates patients do not always experience significant gains in their QoL after limb salvage interventions, despite reasonable graft patency, amputation-free survival, and limb salvage rates. Further research is required using QoL tools in a measurable and clinically relevant fashion to guide optimal quality care that maximizes patient-centered outcomes.

Alarcon, G., Cservenka, A., & Nagel, B. J. (2016). Adolescent neural response to reward is related to participant sex and task motivation. *Brain and Cognition*, *111*, 51-62.

Risky decision making is prominent during adolescence, perhaps contributed to by heightened sensation seeking and ongoing maturation of reward and dopamine systems in the brain, which are, in part, modulated by sex hormones. In this study, we examined sex differences in the neural substrates of reward sensitivity during a risky decision-making task and hypothesized that compared with girls, boys would show heightened brain activation in reward-relevant regions, particularly the nucleus accumbens, during reward receipt. Further, we hypothesized that testosterone and estradiol levels would mediate this sex difference. Moreover, we predicted boys would make more risky choices on the task. While boys showed increased nucleus accumbens blood oxygen level-dependent (BOLD) response relative to girls, sex hormones did not mediate this effect. As predicted, boys made a higher percentage of risky decisions during the task. Interestingly, boys also self-reported more motivation to perform well and earn money on the task, while girls self-reported higher state anxiety prior to the scan session. Motivation to earn money partially mediated the effect of sex on nucleus accumbens activity during reward. Previous research shows that increased motivation and salience of reinforcers is linked with more robust

striatal BOLD response, therefore psychosocial factors, in addition to sex, may play an important role in reward sensitivity. Elucidating neurobiological mechanisms that support adolescent sex differences in risky decision making has important implications for understanding individual differences that lead to advantageous and adverse behaviors that affect health outcomes.

Alarcón, G., Cservenka, A., & Nagel, B. J. (2017). Adolescent neural response to reward is related to participant sex and task motivation. *Brain and Cognition, 111*, 51-62.

Risky decision making is prominent during adolescence, perhaps contributed to by heightened sensation seeking and ongoing maturation of reward and dopamine systems in the brain, which are, in part, modulated by sex hormones. In this study, we examined sex differences in the neural substrates of reward sensitivity during a risky decision-making task and hypothesized that compared with girls, boys would show heightened brain activation in reward-relevant regions, particularly the nucleus accumbens, during reward receipt. Further, we hypothesized that testosterone and estradiol levels would mediate this sex difference. Moreover, we predicted boys would make more risky choices on the task. While boys showed increased nucleus accumbens blood oxygen level-dependent (BOLD) response relative to girls, sex hormones did not mediate this effect. As predicted, boys made a higher percentage of risky decisions during the task. Interestingly, boys also self-reported more motivation to perform well and earn money on the task, while girls self-reported higher state anxiety prior to the scan session. Motivation to earn money partially mediated the effect of sex on nucleus accumbens activity during reward. Previous research shows that increased motivation and salience of reinforcers is linked with more robust striatal BOLD response, therefore psychosocial factors, in addition to sex, may play an important role in reward sensitivity. Elucidating neurobiological mechanisms that support adolescent sex differences in risky decision making has important implications for understanding individual differences that lead to advantageous and adverse behaviors that affect health outcomes. © 2016 Elsevier Inc.

Amrock, S. M., Lee, L., & Weitzman, M. (2016). Perceptions of e-cigarettes and noncigarette tobacco products among US youth. *Pediatrics, 138*(5)

BACKGROUND: Electronic cigarettes (e-cigarettes) are now the most commonly used tobacco

product among US youth. The extent to which perceptions of e-cigarettes' harm and addictiveness differ from those of other products remains unknown, as does whether these perceptions have changed over time. METHODS: Data from the 2012 and 2014 National Youth Tobacco Survey, a repeated cross-sectional survey of grade 6 to 12 students, were used. Cross-tabulations and logistic regression models were used to describe correlates of perceptions of harm and addictiveness of e-cigarettes, cigars, and smokeless tobacco compared with cigarettes. Trends in perceptions of e-cigarettes' harm among different demographic groups were also assessed. RESULTS: In 2014, 73.0% believed that e-cigarettes were less harmful than cigarettes, compared with 20.2% for smokeless tobacco and 25.8% for cigars. By comparison, 47.1% believed that e-cigarettes were less addictive than cigarettes, compared with only 14.0% for smokeless tobacco and 31.5% for cigars. Use of each product was associated with a perception of decreased harm and addictiveness in adjusted analyses, as was being male, being a non-Hispanic white, and residing with a household member who used that product. Between 2012 and 2014, increasing numbers of US youth thought they were able to assess the relative harm of e-cigarettes and increasingly believed that e-cigarettes are less harmful than cigarettes. CONCLUSIONS: Most US youth view e-cigarettes as less harmful and addictive than cigarettes. Far fewer think similarly about cigars and smokeless tobacco. Increases in e-cigarettes' perceived safety mirrors rapid increases observed in their use. Perceived safety correlates with use of each tobacco product. Copyright © 2016 by the American Academy of Pediatrics.

Angier, H., O'Malley, J. P., Marino, M., McConnell, K. J., Cottrell, E., Jacob, R. L., et al. (2017).

Evaluating community health centers' adoption of a new global capitation payment (eCHANGE) study protocol. *Contemporary Clinical Trials*, 52, 35-38.

Primary care patient-centered medical homes (PCMHs) are an effective healthcare delivery model. Evidence regarding the most effective payment models for increased coordination efforts is sparse. This protocol paper describes the evaluation of an Alternative Payment Methodology (APM) implemented in a subset of Oregon community health centers (CHCs), using a prospective matched observational design. The APM is a primary care payment reform intervention that changed Oregon's Medicaid payment for several CHCs from fee-for-service reimbursement to a per-member-per-month capitated payment. We will implement a difference-in-difference analytic

approach to evaluate pre-post APM changes between intervention and control groups, including: 1) clinic-level outcomes, 2) patient-level clinical outcomes, and 3) patient-level econometric outcomes. Findings from the project will be of national significance, as there is a need for evidence regarding how novel payment methods might enhance PCMH capabilities and support their capacity to produce better quality and outcomes. If this capitated payment method is proven effective, study findings will inform dissemination of similar APMs nationwide. © 2016 Elsevier Inc.

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-butanol, CAS registry number 97-95-0. *Food and Chemical Toxicology*, 97, S157-S167.

The use of this material under current conditions is supported by existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog 2-ethylhexanol (CAS # 104-76-7) show that this material is not genotoxic. Data from the suitable read across analog isopropyl alcohol (CAS # 67-63-0) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using 2-ethylhexanol (CAS # 104-76-7) and 1-heptanol, 2-propyl (CAS # 10042-59-8) as suitable read across analogs, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using 2-ethyl-hexanol (CAS # 104-76-7) and isobutyl alcohol (CAS # 78-83-1) as suitable read across analogs, 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. © 2016 Elsevier Ltd

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2016). RIFM fragrance ingredient safety assessment, isopropylphenylbutanal, CAS registry number 125109-85-5. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*, 97S, S230-S236.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2016). RIFM fragrance ingredient safety assessment, isobornyl isovalerate, CAS registry number 7779-73-9. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization potential, as well as, environmental safety. Data from the suitable read across analog isobornyl acetate (CAS # 125-12-2) show that this material is not genotoxic, provided a MOE > 100 for the repeated dose, developmental and reproductive endpoints, and does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (threshold of Toxicological Concern) for a Cramer Class II material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Arora, R., & Press, R. D. (2017). Measurement of BCR-ABL1 transcripts on the international scale in the united states: Current status and best practices. *Leukemia and Lymphoma*, 58(1), 8-16. Chronic myeloid leukemia (CML) results from the Philadelphia chromosome (Ph) translocation and expression of its fusion oncoprotein BCR-ABL1. BCR-ABL1 tyrosine kinase inhibitors (TKIs) are the standard therapy for Ph-positive CML. Achievement of deep molecular responses (typically defined as ≥ 4 -log reduction in BCR-ABL1 RNA levels) is an emerging treatment goal becoming attainable for more patients due to the availability of second-generation TKIs. Deep molecular responses are associated with improved long-term outcomes and are required prior to attempting cessation of treatment in treatment-free remission clinical trials. The National Comprehensive Cancer Network and European LeukemiaNet recommend regular monitoring of BCR-ABL1 RNA levels using real-time quantitative polymerase chain reaction (RQ-PCR). However, BCR-ABL1 RQ-PCR is a complex laboratory-developed test; routine quantitative results from clinical diagnostic laboratories may differ from those used to establish the recommendations. Although an International Scale (IS) was developed for standardized reporting of BCR-ABL1 RNA levels, IS adoption has been slow in the United States, but is now used by the vast majority of laboratories. Here, we discuss the importance of molecular monitoring in CML, gaps between current and best

molecular monitoring practices in the United States, and challenges and potential solutions for universal IS adoption in the United States. © 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Artz, A. S., Logan, B., Zhu, X., Akpek, G., Bufarull, R. M., Gupta, V., et al. (2016). The prognostic value of serum C-reactive protein, ferritin, and albumin prior to allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndromes. *Haematologica*, *101*(11), 1426-1433. We sought to confirm the prognostic importance of simple clinically available biomarkers of C-reactive protein, serum albumin, and ferritin prior to allogeneic hematopoietic cell transplantation. The study population consisted of 784 adults with acute myeloid leukemia in remission or myelodysplastic syndromes undergoing unrelated donor transplant reported to the Center for International Blood and Marrow Transplant Research. C-reactive protein and ferritin were centrally quantified by ELISA from cryopreserved plasma whereas each center provided pre-transplant albumin. In multivariate analysis, transplant-related mortality was associated with the pre-specified thresholds of C-reactive protein more than 10 mg/L (P=0.008) and albumin less than 3.5 g/dL (P=0.01) but not ferritin more than 2500 ng/mL. Only low albumin independently influenced overall mortality. Optimal thresholds affecting transplant-related mortality were defined as: C-reactive protein more than 3.67 mg/L, log(ferritin), and albumin less than 3.4 g/dL. A 3-level biomarker risk group based on these values separated risks of transplant-related mortality: low risk (reference), intermediate (HR=1.66, P=0.015), and high risk (HR=2.7, P<0.001). One-year survival was 74%, 67% and 56% for low-, intermediate- and high-risk groups. Routinely available pre-transplant biomarkers independently risk-stratify for transplant-related mortality and survival.

Badawy, S. M., Black, V., Meier, E. R., Myers, K. C., Pinkney, K., Hastings, C., et al. (2016). Early career mentoring through the American Society of Pediatric Hematology/Oncology: Lessons learned from a pilot program. *Pediatric Blood and Cancer*,
Background: Effective networking and mentorship are critical determinants of career satisfaction and success in academic medicine. The American Society of Pediatric Hematology/Oncology (ASPHO) mentoring program was developed to support Early Career (EC) members. Herein, the

authors report on the initial 2-year outcomes of this novel program. Procedure: Mentees selected mentors with expertise in different subspecialties within the field from mentor profiles at the ASPHO Web site. Of 23 enrolled pairs, 19 mentors and 16 mentees completed electronic program feedback evaluations. The authors analyzed data collected between February 2013 and December 2014. The authors used descriptive statistics for categorical data and thematic analysis for qualitative data. Results: The overall response rate was 76% (35/46). At the initiation of the relationship, career development and research planning were the most commonly identified goals for both mentors and mentees. Participants communicated by phone, e-mail, or met in-person at ASPHO annual meetings. Most mentor-mentee pairs were satisfied with the mentoring relationship, considered it a rewarding experience that justified their time and effort, achieved their goals in a timely manner with objective work products, and planned to continue the relationship. However, time constraints and infrequent communications remained a challenge. Conclusions: Participation in the ASPHO mentoring program suggests a clear benefit to a broad spectrum of ASPHO EC members with diverse personal and professional development needs. Efforts to expand the mentoring program are ongoing and focused on increasing enrollment of mentors to cover a wider diversity of career tracks/subspecialties and evaluating career and academic outcomes more objectively. © 2016 Wiley Periodicals, Inc.

Bakhsheshian, J., Scheer, J. K., Gum, J. L., Horner, L., Hostin, R., Lafage, V., et al. (2016).

Comparison of structural disease burden to health-related quality of life scores in 264 adult spinal deformity patients with 2-year follow-up: Novel insights into drivers of disability. *Clinical Spine Surgery*,

STUDY DESIGN: This is a review of a prospective multicenter database. OBJECTIVE: To investigate the relationship between preoperative disability and sagittal deformity in patients with high Oswestry Disability Index (ODI) and no sagittal malalignment, or low ODI and high sagittal malalignment. SUMMARY OF BACKGROUND DATA: The relationship between ODI and sagittal malalignment varies between each adult spinal deformity (ASD) patient. METHODS: A prospective multicenter database of 365 patients with ASD undergoing surgical reconstruction was analyzed. Inclusion criteria entailed: age 18 years or above and the presence of spinal deformity as defined by a coronal Cobb angle ≥ 20 degrees, sagittal vertical axis (SVA) ≥ 5

Bennett, T. A., Katz, V. L., & Zelop, C. M. (2016). Cardiac arrest and resuscitation unique to pregnancy. *Obstetrics and Gynecology Clinics of North America*, 43(4), 809-819.

Maternal cardiopulmonary arrest (MCPA) is a catastrophic event that can cause significant morbidity and mortality. A prepared, multidisciplinary team is necessary to perform basic and advanced cardiac life support specific to the anatomic and physiologic changes of pregnancy. MCPA is a challenging clinical scenario for any provider. Overall, it is an infrequent occurrence that involves 2 patients. However, key clinical intervention performed concurrently can save the life of both mother and baby.

Ben-Shlomo, A., & Flaseriu, M. (2016). Diabetes mellitus. *Endocrinology and Metabolism Clinics of North America*, 45(4), xiii-xiv.

Bergeson, S. E., Nipper, M. A., Jensen, J., Helms, M. L., & Finn, D. A. (2016). Tigecycline reduces ethanol intake in dependent and nondependent male and female C57BL/6J mice. *Alcoholism, Clinical and Experimental Research*, 40(12), 2491-2498.

BACKGROUND: The chronic intermittent ethanol (CIE) paradigm is valuable for screening compounds for efficacy to reduce drinking traits related to alcohol use disorder (AUD), as it measures alcohol consumption and preference under physical dependence conditions. Air control-treated animals allow simultaneous testing of similarly treated, nondependent animals. As a consequence, we used CIE to test the hypothesis that tigecycline, a semisynthetic tetracycline similar to minocycline and doxycycline, would reduce alcohol consumption regardless of dependence status. METHODS: Adult C57BL/6J female and male mice were tested for tigecycline efficacy to reduce ethanol (EtOH) consumption using a standard CIE paradigm. The ability of tigecycline to decrease 2-bottle choice of 15% EtOH (15E) versus water intake in dependent (CIE vapor) and nondependent (air-treated) male and female mice was tested after 4 cycles of CIE vapor or air exposure using a within-subjects design and a dose-response. Drug doses of 0, 40, 60, 80, and 100 mg/kg in saline were administered intraperitoneally (0.01 ml/g body weight) and in random order, with a 1-hour pretreatment time. Baseline 15E intake was re-established prior to administration of subsequent injections, with a maximum of 2 drug injections tested per week. RESULTS: Tigecycline was found to effectively reduce high alcohol consumption in both

dependent and nondependent female and male mice. CONCLUSIONS: Our data suggest that tigecycline may be a promising drug with novel pharmacotherapeutic characteristics for the treatment of mild-to-severe AUD in both sexes.

Bidwell, J. T., Lyons, K. S., Mudd, J. O., Gelow, J. M., Chien, C. V., Hiatt, S. O., et al. (2016). Quality of life, depression, and anxiety in ventricular assist device therapy: Longitudinal outcomes for patients and family caregivers. *The Journal of Cardiovascular Nursing*,

BACKGROUND: Patients who receive ventricular assist device (VAD) therapy typically rely on informal caregivers (family members or friends) to assist them in managing their device.

OBJECTIVE: The purpose of this study is to characterize changes in person-oriented outcomes (quality of life [QOL], depression, and anxiety) for VAD patients and their caregivers together

from pre-implantation to 3 months post-implantation. METHODS: This was a formal interim analysis from an ongoing prospective study of VAD patients and caregivers (n = 41 dyads). Data

on person-oriented outcomes (QOL: EuroQol 5 Dimensions Visual Analog Scale; depression:

Patient Health Questionnaire-8; anxiety: Brief Symptom Inventory) were collected at 3 time

points (just prior to implantation and at 1 and 3 months post-implantation). Trajectories of

change for patients and caregivers on each measure were estimated using latent growth

modeling with parallel processes. RESULTS: Patients' QOL improved significantly over time,

whereas caregiver QOL worsened. Depression and anxiety also improved significantly among

patients but did not change among caregivers. There was substantial variability in change on all

outcomes for both patients and their caregivers. CONCLUSIONS: This is the first quantitative

study of VAD patient-caregiver dyads in modern devices that describes change in person-oriented

outcomes from pre-implantation to post-implantation. This work supports the need for future

studies that account for the inherent relationships between patient and caregiver outcomes and

examine variability in patient and caregiver responses to VAD therapy.

Bishal Gyawali, & Prasad, V. (2016). Same data; different interpretations. *Journal of Clinical Oncology*, 34(31), 3729-3732.

Bohnen, J. D., Mavros, M. N., Ramly, E. P., Chang, Y., Yeh, D. D., Lee, J., et al. (2016). Intraoperative adverse events in abdominal surgery: What happens in the operating room does not stay in the

operating room. *Annals of Surgery*,

OBJECTIVE: We sought to assess the impact of intraoperative adverse events (iAEs) on 30-day postoperative mortality, 30-day postoperative morbidity, and postoperative length of stay (LOS) among patients undergoing abdominal surgery. We hypothesized that iAEs would be associated with significant increases in each outcome. **SUMMARY OF BACKGROUND DATA:** The relationship between iAEs and postoperative clinical outcomes remains largely unknown. **METHODS:** The 2007 to 2012 institutional ACS-NSQIP and administrative databases for abdominal surgeries were matched then screened for iAEs using the Agency for Healthcare Research and Quality's 15 Patient Safety Indicator, "Accidental Puncture/Laceration". Each chart flagged during the initial screen was then manually reviewed to confirm whether an iAE occurred. Univariate then multivariable logistic regression models were constructed to assess the independent impact of iAEs on 30-day mortality, 30-day morbidity, and prolonged (≥ 7 days) postoperative LOS, controlling for preoperative/intraoperative variables (eg, age, comorbidities, ASA, wound classification), procedure type (eg, laparoscopic vs open, intestinal, foregut, hepatopancreaticobiliary vs abdominal wall procedure), and complexity (eg, adhesions; relative value units). Propensity score analyses were conducted with each iAE patient matched with 5 non-iAE patients. Sensitivity analyses were performed. **RESULTS:** A total of 9288 cases were included; 183 had iAEs. Most iAEs consisted of bowel (44%) or vessel (29%) injuries and were addressed intraoperatively (92%). In multivariable analyses, iAEs were independently associated with increased 30-day mortality [OR = 3.19, 95% confidence interval (CI) 1.52-6.71, $P = 0.002$], 30-day morbidity (OR = 2.68, 95% CI 1.89-3.81, $P < 0.001$), and prolonged postoperative LOS (OR = 1.85, 95% CI 1.27-2.70, $P = 0.001$). Postoperative complications associated with iAEs included deep/organ-space surgical site infection (OR = 1.94, 95% CI 1.20-3.14), $P = 0.007$), sepsis (OR = 2.14, 95% CI 1.32-3.47, $P = 0.002$), pneumonia (OR = 2.18, 95% CI 1.11-4.26, $P = 0.023$), and failure to wean ventilator (OR = 3.88, 95% CI 2.17-6.95, $P < 0.001$). Propensity score matching confirmed these findings, as did multiple sensitivity analyses. **CONCLUSIONS:** iAEs are independently associated with substantial increases in postoperative mortality, morbidity, and prolonged LOS. Quality improvement efforts should focus on iAE prevention, mitigation of harm after iAEs occur, and risk/severity-adjusted iAE tracking and benchmarking.

Boitz, J. M., Gilroy, C. A., Olenyik, T. D., Paradis, D., Perdeh, J., Dearman, K., et al. (2016). Arginase is essential for survival of leishmania donovani promastigotes but not intracellular amastigotes. *Infection and Immunity*,

Studies in Leishmania donovani have shown that both ornithine decarboxylase and spermidine synthase, two enzymes of the polyamine biosynthetic pathway, are critical for promastigote proliferation and required for maximum infection in mice. However, the importance of arginase (ARG), the first enzyme of the polyamine pathway in Leishmania, has not been analyzed in L. donovani To test ARG function in intact parasites, we generated Deltaarg null mutants in L. donovani and evaluated their ability to proliferate in vitro and trigger infections in mice. The Deltaarg knockout was incapable of growth in the absence of polyamine supplementation, but the auxotrophic phenotype could be bypassed by addition of either millimolar concentrations of ornithine or micromolar concentrations of putrescine or by complementation with either glycosomal or cytosolic versions of ARG. Spermidine supplementation of the medium did not circumvent the polyamine auxotrophy of the Deltaarg line. Although ARG was found to be essential for ornithine and polyamine synthesis, ornithine decarboxylase appeared to be the rate-limiting enzyme for polyamine production. Mouse infectivity studies revealed that the Deltaarg lesion reduced parasite burdens in livers by an order of magnitude but had little impact on the numbers of parasites recovered from spleens. Thus, ARG is essential for proliferation of promastigotes but not intracellular amastigotes. Coupled with previous studies, these data support a model in which L. donovani amastigotes readily salvage ornithine and have some access to host spermidine pools, while host putrescine appears to be unavailable for salvage by the parasite.

Bonora, G., Mancini, M., Carpinella, I., Chiari, L., Horak, F. B., & Ferrarin, M. (2016). Gait initiation is impaired in subjects with parkinson's disease in the OFF state: Evidence from the analysis of the anticipatory postural adjustments through wearable inertial sensors. *Gait & Posture*, 51, 218-221.

People with Parkinson's disease (PD) typically demonstrate impaired anticipatory postural adjustments (APAs) that shift the body center of mass forward (imbalance) and over the stance leg (unloading) prior to gait initiation. APAs are known to be smallest when people with PD are in their OFF-medication state compared to ON-medication or healthy controls. The aim of this pilot

study is to validate a previously developed method for the assessment of gait initiation on PD patients in OFF state with body-worn, inertial sensors. Ten subjects with mild-to-moderate idiopathic PD and twelve healthy controls of similar age performed three gait initiation trials. The spatio-temporal parameters of APAs were extracted from three wearable sensors, placed on the shins and on the lower back, and validated with two force plates. Temporal parameters extracted from sensors and force plates, as well as the trunk medio-lateral acceleration and the correspondent displacement of the center of pressure, were significantly correlated. Subjects with PD showed hypometric adjustments in the medio-lateral direction ($p\text{-value}<0.003$) and increased duration of the unloading phase ($p\text{-value}=0.04$). The unloading phase was significantly longer than the imbalance ($p\text{-value}=0.003$) only in subjects with PD. The validity of the method of quantifying APAs from inertial sensors was confirmed in PD subjects by comparison with force plates. Sensitivity in discriminating PD patients from healthy controls was proven by both spatial and temporal parameters. Objective measures of gait initiation deficits with wearable technology provides valuable instrument for the assessment of gait initiation in clinical environments.

Bonora, G., Mancini, M., Carpinella, I., Chiari, L., Horak, F. B., & Ferrarin, M. (2017). Gait initiation is impaired in subjects with parkinson's disease in the OFF state: Evidence from the analysis of the anticipatory postural adjustments through wearable inertial sensors. *Gait and Posture*, *51*, 218-221.

People with Parkinson's disease (PD) typically demonstrate impaired anticipatory postural adjustments (APAs) that shift the body center of mass forward (imbalance) and over the stance leg (unloading) prior to gait initiation. APAs are known to be smallest when people with PD are in their OFF-medication state compared to ON-medication or healthy controls. The aim of this pilot study is to validate a previously developed method for the assessment of gait initiation on PD patients in OFF state with body-worn, inertial sensors. Ten subjects with mild-to-moderate idiopathic PD and twelve healthy controls of similar age performed three gait initiation trials. The spatio-temporal parameters of APAs were extracted from three wearable sensors, placed on the shins and on the lower back, and validated with two force plates. Temporal parameters extracted from sensors and force plates, as well as the trunk medio-lateral acceleration and the correspondent displacement of the center of pressure, were significantly correlated. Subjects with

PD showed hypometric adjustments in the medio-lateral direction (p-value < 0.003) and increased duration of the unloading phase (p-value = 0.04). The unloading phase was significantly longer than the imbalance (p-value = 0.003) only in subjects with PD. The validity of the method of quantifying APAs from inertial sensors was confirmed in PD subjects by comparison with force plates. Sensitivity in discriminating PD patients from healthy controls was proven by both spatial and temporal parameters. Objective measures of gait initiation deficits with wearable technology provides valuable instrument for the assessment of gait initiation in clinical environments. © 2016

Bonura, E. M., Ramsey, K., & Armstrong, W. S. (2016). Reply to Sullivan. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*,

Brenowitz, W. D., Hubbard, R. A., Keene, C. D., Hawes, S. E., Longstreth, W. T., Jr, Woltjer, R. L., et al. (2016). Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*,
INTRODUCTION: Whether co-occurring neuropathologies interact or independently affect clinical disease progression is uncertain. We estimated rates of clinical progression and tested whether associations between clinical progression and Alzheimer's disease neuropathology (ADNP) were modified by co-occurring Lewy body disease (LBD) or vascular brain injury (VBI). METHODS: Linear mixed effects models evaluated longitudinal trends in the Clinical Dementia Rating Sum of Boxes on 2046 autopsied participants seen at a U.S. Alzheimer's Disease Center. RESULTS: Annual clinical progression was slightly faster for ADNP + LBD compared with ADNP only (P = .06) and slightly slower for ADNP + VBI (P = .003). Differences in progression were less than expected if each neuropathology independently contributed to progression; ADNP interacted with LBD (P = .002) and VBI (P = .003). In secondary models, the effect of additional pathologies on clinical progression was greater in those with intermediate compared with high levels of ADNP. DISCUSSION: The impact of co-occurring pathologies on progression may depend on severity of ADNP.

Bronchain, O. J., Chesneau, A., Monsoro-Burq, A. -, Jolivet, P., Paillard, E., Scanlan, T. S., et al. (2017). Implication of thyroid hormone signaling in neural crest cells migration: Evidence from

thyroid hormone receptor beta knockdown and NH3 antagonist studies. *Molecular and Cellular Endocrinology*, 439, 233-246.

Thyroid hormones (TH) have been mainly associated with post-embryonic development and adult homeostasis but few studies report direct experimental evidence for TH function at very early phases of embryogenesis. We assessed the outcome of altered TH signaling on early embryogenesis using the amphibian *Xenopus* as a model system. Precocious exposure to the TH antagonist NH-3 or impaired thyroid receptor beta function led to severe malformations related to neurocristopathies. These include pathologies with a broad spectrum of organ dysplasias arising from defects in embryonic neural crest cell (NCC) development. We identified a specific temporal window of sensitivity that encompasses the emergence of NCCs. Although the initial steps in NCC ontogenesis appeared unaffected, their migration properties were severely compromised both in vivo and in vitro. Our data describe a role for TH signaling in NCCs migration ability and suggest severe consequences of altered TH signaling during early phases of embryonic development. © 2016 Elsevier Ireland Ltd

Brown, T., Kelly, D. D., Vercauteren, S., Wilson, W. H., & Werner, A. (2016). How biobanks are assessing and measuring their financial sustainability. *Biopreservation and Biobanking*, As guest editors of this sustainability issue of *Biopreservation and Biobanking* focused on business planning, utilization, and marketing, we invited a number of experts from different sectors of the biobanking arena to provide their views on business planning issues. Each expert was asked to provide a brief background statement on their biobanks, to build a context to understand their answers to the sustainability questions. We hope that these insights and experiences can provide valuable considerations and ideas for other biobanks who wish to develop or refine their own business plans, measure their utilization rates, and work toward financial sustainability. In addition, after the expert input was gathered, the guest editors invited an additional expert to provide summary comments and observations on cost and operational optimization strategies. The broad experiences from all of the experts included and scope of the biobanks they represent should provide a level of relevant representation for all interested parties.

Burchill, L. J. (2016). Heart transplantation in adult congenital heart disease. *Heart*,

Heart failure (HF) in adult congenital heart disease (ACHD) is vastly different to that observed in acquired heart disease. Unlike acquired HF in which pharmacological strategies are the cornerstone for protecting and improving ventricular function, ACHD-related HF relies heavily upon structural and other interventions to achieve these aims. Patients with ACHD constitute a small percentage of the total adult heart transplant population (~3%), although the number of ACHD heart transplant recipients is growing rapidly with a 40% increase over the last two decades. The worldwide experience to date has confirmed heart transplantation as an effective life-extending treatment option in carefully selected patients with ACHD with end-stage cardiac disease. Opportunities for improving outcomes in patients with ACHD-related HF include (i) earlier recognition and referral to centres with combined expertise in ACHD and HF, (ii) increased awareness of arrhythmia and sudden cardiac death risk in this population, (iii) greater collaboration between HF and ACHD specialists at the time of heart transplant assessment, (iv) expert surgical planning to reduce ischaemic time and bleeding risk at the time of transplant, (v) tailored immunosuppression in the posttransplant period and (vi) development and validation of ACHD-specific risk scores to predict mortality and guide patient selection. The purpose of this article is to review current approaches to diagnosing and treating advanced HF in patients with ACHD including indications, contraindications and clinical outcomes after heart transplantation. © 2016 BMJ Publishing Group Ltd & British Cardiovascular Society.

Burgess, D. J., Beach, M. C., & Saha, S. (2016). Mindfulness practice: A promising approach to reducing the effects of clinician implicit bias on patients. *Patient Education and Counseling*,

Like the population at large, health care providers hold implicit racial and ethnic biases that may contribute to health care disparities. Little progress has been made in identifying and implementing effective strategies to address these normal but potentially harmful unconscious cognitive processes. We propose that meditation training designed to increase healthcare providers' mindfulness skills is a promising and potentially sustainable way to address this problem. Emerging evidence suggests that mindfulness practice can reduce the provider contribution to healthcare disparities through several mechanisms including: reducing the likelihood that implicit biases will be activated in the mind, increasing providers' awareness of and

ability to control responses to implicit biases once activated, increasing self-compassion and compassion toward patients, and reducing internal sources of cognitive load (e.g., stress, burnout, and compassion fatigue). Mindfulness training may also have advantages over current approaches to addressing implicit bias because it focuses on the development of skills through practice, promotes a nonjudgmental approach, can circumvent resistance some providers feel when directly confronted with evidence of racism, and constitutes a holistic approach to promoting providers' well-being. We close with suggestions for how a mindfulness approach can be practically implemented and identify potential challenges and research gaps to be addressed.

© 2016.

Burns, E. C., Burns, B., Newgard, C. D., Laurie, A., Fu, R., Graif, T., et al. (2016). Pediatric minor traumatic brain injury with intracranial hemorrhage: Identifying low-risk patients who may not benefit from ICU admission. *Pediatric Emergency Care*,

BACKGROUND: Pediatric patients with any severity of traumatic intracranial hemorrhage (tICH) are often admitted to intensive care units (ICUs) for early detection of secondary injury. We hypothesize that there is a subset of these patients with mild injury and tICH for whom ICU care is unnecessary. OBJECTIVES: To quantify tICH frequency and describe disposition and to identify patients at low risk of inpatient critical care intervention (CCI). METHODS: We retrospectively reviewed patients aged 0 to 17 years with tICH at a single level I trauma center from 2008 to 2013. The CCI included mechanical ventilation, invasive monitoring, blood product transfusion, hyperosmolar therapy, and neurosurgery. Binary recursive partitioning analysis led to a clinical decision instrument classifying patients as low risk for CCI. RESULTS: Of 296 tICH admissions without prior CCI in the field or emergency department, 29 had an inpatient CCI. The decision instrument classified patients as low risk for CCI when patients had absence of the following: midline shift, depressed skull fracture, unwitnessed/unknown mechanism, and other nonextremity injuries. This clinical decision instrument produced a high likelihood of excluding patients with CCI (sensitivity, 96.6%; 95% confidence interval, 82.2%-99.9%) from the low-risk group, with a negative likelihood ratio of 0.056 (95% confidence interval, -0.053-0.166). The decision instrument misclassified 1 patient with CCI into the low-risk group, but would have impacted disposition of 164 pediatric ICU admissions through 5 years (55% of the sample).

CONCLUSIONS: A subset of low-risk patients may not require ICU admission. The proposed decision rule identified low-risk children with tICH who may be observable outside an ICU, although this rule requires external validation before implementation.

Burwitz, B. J., Malouli, D., Bimber, B. N., Reed, J. S., Ventura, A. B., Hancock, M. H., et al. (2016). Cross-species rhesus cytomegalovirus infection of cynomolgus macaques. *PLoS Pathogens*, *12*(11), e1006014.

Cytomegaloviruses (CMV) are highly species-specific due to millennia of co-evolution and adaptation to their host, with no successful experimental cross-species infection in primates reported to date. Accordingly, full genome phylogenetic analysis of multiple new CMV field isolates derived from two closely related nonhuman primate species, Indian-origin rhesus macaques (RM) and Mauritian-origin cynomolgus macaques (MCM), revealed distinct and tight lineage clustering according to the species of origin, with MCM CMV isolates mirroring the limited genetic diversity of their primate host that underwent a population bottleneck 400 years ago. Despite the ability of Rhesus CMV (RhCMV) laboratory strain 68-1 to replicate efficiently in MCM fibroblasts and potentially inhibit antigen presentation to MCM T cells in vitro, RhCMV 68-1 failed to productively infect MCM in vivo, even in the absence of host CD8+ T and NK cells. In contrast, RhCMV clone 68-1.2, genetically repaired to express the homologues of the HCMV anti-apoptosis gene UL36 and epithelial cell tropism genes UL128 and UL130 absent in 68-1, efficiently infected MCM as evidenced by the induction of transgene-specific T cells and virus shedding. Recombinant variants of RhCMV 68-1 and 68-1.2 revealed that expression of either UL36 or UL128 together with UL130 enabled productive MCM infection, indicating that multiple layers of cross-species restriction operate even between closely related hosts. Cumulatively, these results implicate cell tropism and evasion of apoptosis as critical determinants of CMV transmission across primate species barriers, and extend the macaque model of human CMV infection and immunology to MCM, a nonhuman primate species with uniquely simplified host immunogenetics.

Buxton, O. M., Lee, S., Beverly, C., Berkman, L. F., Moen, P., Kelly, E. L., et al. (2016). Work-family conflict and employee sleep: Evidence from IT workers in the work, family and health study. *Sleep*, *39*(10), 1871-1882.

Study Objectives: Work-family conflict is a threat to healthy sleep behaviors among employees. This study aimed to examine how Work-to-Family Conflict (demands from work that interfere with one's family/personal life; WTFC) and Family-to-Work Conflict (demands from family/personal life that interfere with work; FTWC) are associated with several dimensions of sleep among information technology workers. Methods: Employees at a U.S. IT firm (n = 799) provided self-reports of sleep sufficiency (feeling rested upon waking), sleep quality, and sleep maintenance insomnia symptoms (waking up in the middle of the night or early morning) in the last month. They also provided a week of actigraphy for nighttime sleep duration, napping, sleep timing, and a novel sleep inconsistency measure. Analyses adjusted for work conditions (job demands, decision authority, schedule control, and family-supportive supervisor behavior), and household and sociodemographic characteristics. Results: Employees who experienced higher WTFC reported less sleep sufficiency, poorer sleep quality, and more insomnia symptoms. Higher WTFC also predicted shorter nighttime sleep duration, greater likelihood of napping, and longer nap duration. Furthermore, higher WTFC was linked to greater inconsistency of nighttime sleep duration and sleep clock times, whereas higher FTWC was associated with more rigidity of sleep timing mostly driven by wake time. Conclusions: Results highlight the unique associations of WTFC/FTWC with employee sleep independent of other work conditions and household and sociodemographic characteristics. Our novel methodological approach demonstrates differential associations of WTFC and FTWC with inconsistency of sleep timing. Given the strong associations between WTFC and poor sleep, future research should focus on reducing WTFC.

Calkins, M. J., Vartanian, V., Owen, N., Kirkali, G., Jaruga, P., Dizdaroglu, M., et al. (2016). Enhanced sensitivity of *Neil1*^{-/-} mice to chronic UVB exposure. *DNA Repair*, 48, 43-50.

Oxidative stress and reactive oxygen species (ROS)-induced DNA base damage are thought to be central mediators of UV-induced carcinogenesis and skin aging. However, increased steady-state levels of ROS-induced DNA base damage have not been reported after chronic UV exposure.

Accumulation of ROS-induced DNA base damage is governed by rates of lesion formation and repair. Repair is generally performed by Base Excision Repair (BER), which is initiated by DNA glycosylases, such as 8-oxoguanine glycosylase and Nei-Endonuclease VIII-Like 1 (NEIL1). In the current study, UV light (UVB) was used to elicit protracted low-level ROS challenge in wild-type

(WT) and Neil1^{-/-} mouse skin. Relative to WT controls, Neil1^{-/-} mice showed an increased sensitivity to tissue destruction from the chronic UVB exposure, and corresponding enhanced chronic inflammatory responses as measured by cytokine message levels and profiling, as well as neutrophil infiltration. Additionally, levels of several ROS-induced DNA lesions were measured including 4,6-diamino-5-formamidopyrimidine (FapyGua), 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyAde), 8-hydroxyguanine (8-OH-Gua), 5,6-dihydroxyuracil (5,6-diOH-Ura) and thymine glycol (ThyGly). In WT mice, chronic UVB exposure led to increased steady-state levels of FapyGua, FapyAde, and ThyGly with no significant increases in 8-OH-Gua or 5,6-diOH-Ura. Interestingly, the lesions that accumulated were all substrates of NEIL1. Collectively, these data suggest that NEIL1-initiated repair of a subset of ROS-induced DNA base lesions may be insufficient to prevent the initiation of inflammatory pathways during chronic UV exposure in mouse skin.

Carney, P. A., Waller, E., Dexter, E., Marino, M., Rosener, S. E., Green, L. A., et al. (2016).

Association between patient-centered medical home features and satisfaction with family medicine residency training in the US. *Family Medicine*, 48(10), 784-794.

BACKGROUND AND OBJECTIVES: Primary care residencies are undergoing dramatic changes because of changing health care systems and evolving demands for updated training models. We examined the relationships between residents' exposures to patient-centered medical home (PCMH) features in their assigned continuity clinics and their satisfaction with training. METHODS: Longitudinal surveys were collected annually from residents evaluating satisfaction with training using a 5-point Likert-type scale (1=very unsatisfied to 5=very satisfied) from 2007 through 2011, and the presence or absence of PCMH features were collected from 24 continuity clinics during the same time period. Odds ratios on residents' overall satisfaction were compared according to whether they had no exposure to PCMH features, some exposure (1-2 years), or full exposure (all 3 or more years). RESULTS: Fourteen programs and 690 unique residents provided data to this study. Resident satisfaction with training was highest with full exposure for integrated case management compared to no exposure, which occurred in 2010 (OR=2.85, 95% CI=1.40, 5.80). Resident satisfaction was consistently statistically lower with any or full exposure (versus none) to expanded clinic hours in 2007 and 2009 (eg, OR for some exposure in 2009 was 0.31

95% CI=0.19, 0.51, and OR for full exposure 0.28 95% CI=0.16, 0.49). Resident satisfaction for many electronic health record (EHR)-based features tended to be significantly lower with any exposure (some or full) versus no exposure over the study period. For example, the odds ratio for resident satisfaction was significantly lower with any exposure to electronic health records in continuity practice in 2008, 2009, and 2010 (OR for some exposure in 2008 was 0.36; 95% CI=0.19, 0.70, with comparable results in 2009, 2010). CONCLUSIONS: Resident satisfaction with training was inconsistently correlated with exposure to features of PCMH. No correlation between PCMH exposure and resident satisfaction was sustained over time.

Cervera-Juanes, R., Wilhelm, L. J., Park, B., Grant, K. A., & Ferguson, B. (2016). Genome-wide analysis of the nucleus accumbens identifies DNA methylation signals differentiating low/binge from heavy alcohol drinking. *Alcohol (Fayetteville, N.Y.)*,

Alcohol use disorders encompass a range of drinking levels and behaviors, including low, binge and heavy drinking. In this regard, investigating the neural state of individuals who chronically self-administer lower doses of alcohol may provide insight into mechanisms that prevent the escalation of alcohol use. DNA methylation is one of the epigenetic mechanisms that stabilizes adaptations in gene expression and has been associated with alcohol use. Thus, we investigated DNA methylation, gene expression and the predicted neural effects in the nucleus accumbens core (NAcc) of male rhesus macaques categorized as "low" or "binge" drinkers, compared to "alcohol-naïve" and "heavy" drinkers based on drinking patterns during a 12 month alcohol self-administration protocol. Using genome-wide CpG-rich region enrichment and bisulfite sequencing, the methylation levels of 2.6 million CpGs were compared between alcohol naïve (AN), low/binge (L/BD) and heavy/very heavy (H/VHD) drinking subjects (n = 24). Through regional clustering analysis, we identified nine significant differential methylation regions (DMRs) that specifically distinguished ANs and L/BDs, and then compared those DMRs among H/VHDs. The DMRs mapped to genes encoding ion channels, receptors, cell adhesion molecules and cAMP, NF-kappaB and Wnt signaling pathway proteins. Two of the DMRs, linked to PDE10A and PKD2L2, were also differentially methylated in H/VHDs, suggesting an alcohol-dose independent effect. However two other DMRs, linked to the CCBE1 and FZD5 genes, had L/BD methylation levels that significantly differed from both ANs and H/VHDs. The remaining 5 DMRs also differentiated L/BDs and ANs,

however H/VHDs methylation levels were not distinguishable from either of the two groups. Functional validation of two DMRs, linked to FZD5 and PDE10A, support their role in regulating gene expression and exon usage, respectively. In summary, the findings demonstrate that L/BD is associated with unique DNA methylation signatures in the primate NAcc, and identifies synaptic genes that may play a role in preventing the escalation of alcohol use.

Chahrour, M., O'Roak, B. J., Santini, E., Samaco, R. C., Kleiman, R. J., & Manzini, M. C. (2016).

Current perspectives in autism spectrum disorder: From genes to therapy. *Journal of Neuroscience*, 36(45), 11402-11410.

Autism spectrum disorder (ASD) is a constellation of neurodevelopmental presentations with high heritability and both phenotypic and genetic heterogeneity. To date, mutations in hundreds of genes have been associated to varying degrees with increased ASD risk. A better understanding of the functions of these genes and whether they fit together in functional groups or impact similar neuronal circuits is needed to develop rational treatment strategies. We will review current areas of emphasis in ASD research, starting from human genetics and exploring how mouse models of human mutations have helped identify specific molecular pathways (protein synthesis and degradation, chromatin remodeling, intracellular signaling), which are linked to alterations in circuit function and cognitive/social behavior. We will conclude by discussing how we can leverage the findings on molecular and cellular alterations found in ASD to develop therapies for neurodevelopmental disorders. © 2016 the authors.

Chakkaramakkil Verghese, S., Goloviznina, N. A., & Kurre, P. (2016). Phenotypic correction of fanconi

anemia cells in the murine bone marrow after carrier cell mediated delivery of lentiviral vector. *Stem Cell Research & Therapy*, 7(1), 170.

Fanconi anemia (FA) is an autosomal-recessive disorder associated with hematopoietic failure and it is a candidate for hematopoietic stem cell (HSC)-directed gene therapy. However, the characteristically reduced HSC numbers found in FA patients, their ineffective mobilization from the marrow, and re-oxygenation damage during ex vivo manipulation have precluded clinical success using conventional in vitro approaches. We previously demonstrated that lentiviral vector (LV) particles reversibly attach to the cell surface where they gain protection from serum

complement neutralization. We reasoned that cellular delivery of LV to the bone marrow niche could avoid detrimental losses during FA HSC mobilization and in vitro modification. Here, we demonstrate that a VSV-G pseudotyped lentivector, carrying the FANCC transgene, can be transmitted from carrier to bystander cells. In cell culture and transplantation models of FA, we further demonstrate that LV carrier cells migrate along SDF-1alpha gradients and transfer vector particles that stably integrate and phenotypically correct the characteristic DNA alkylator sensitivity in murine and human FA-deficient target bystander cells. Altogether, we demonstrate that cellular homing mechanisms can be harnessed for the functional phenotype correction in murine FA hematopoietic cells.

Chang, H. C., Tzou, D. T., Usawachintachit, M., Duty, B. D., Hsi, R. S., Harper, J. D., et al. (2016).

Rationale and design of the registry for stones of the kidney and ureter (ReSKU): A prospective observational registry to study the natural history of urolithiasis patients. *Journal of Endourology*, 30(12), 1332-1338.

OBJECTIVES: Registry-based clinical research in nephrolithiasis is critical to advancing quality in urinary stone disease management and ultimately reducing stone recurrence. A need exists to develop Health Insurance Portability and Accountability Act (HIPAA)-compliant registries that comprise integrated electronic health record (EHR) data using prospectively defined variables. An EHR-based standardized patient database-the Registry for Stones of the Kidney and Ureter (ReSKU)-was developed, and herein we describe our implementation outcomes. **MATERIALS AND METHODS:** Interviews with academic and community endourologists in the United States, Canada, China, and Japan identified demographic, intraoperative, and perioperative variables to populate our registry. Variables were incorporated into a HIPAA-compliant Research Electronic Data Capture database linked to text prompts and registration data within the Epic EHR platform. Specific data collection instruments supporting New patient, Surgery, Postoperative, and Follow-up clinical encounters were created within Epic to facilitate automated data extraction into ReSKU. **RESULTS:** The number of variables within each instrument includes the following: New patient-60, Surgery-80, Postoperative-64, and Follow-up-64. With manual data entry, the mean times to complete each of the clinic-based instruments were (minutes) as follows: New patient-12.06 +/- 2.30, Postoperative-7.18 +/- 1.02, and Follow-up-8.10 +/- 0.58. These times were

significantly reduced with the use of ReSKU structured clinic note templates to the following: New patient-4.09 +/- 1.73, Postoperative-1.41 +/- 0.41, and Follow-up-0.79 +/- 0.38. With automated data extraction from Epic, manual entry is obviated. CONCLUSIONS: ReSKU is a longitudinal prospective nephrolithiasis registry that integrates EHR data, lowering the barriers to performing high quality clinical research and quality outcome assessments in urinary stone disease.

Chang, Y. H., Foley, P., Azimi, V., Borkar, R., & Lefman, J. (2016). Primer for image informatics in personalized medicine. *Humanitarian Technology: Science, Systems and Global Impact 2016, HumTech2016*, , 159. pp. 58-65.

Image informatics encompasses the concept of extracting and quantifying information contained in image data. Scenes, what an image contains, come from many imager devices such as consumer electronics, medical imaging systems, 3D laser scanners, microscopes, or satellites. There is a marked increase in image informatics applications as there have been simultaneous advances in imaging platforms, data availability due to social media, and big data analytics. An area ready to take advantage of these developments is personalized medicine, the concept where the goal is tailor healthcare to the individual. Patient health data is computationally profiled against a large of pool of feature-rich data from other patients to ideally optimize how a physician chooses care. One of the daunting challenges is how to effectively utilize medical image data in personalized medicine. Reliable data analytics products require as much automation as possible, which is a difficulty for data like histopathology and radiology images because we require highly trained expert physicians to interpret the information. This review targets biomedical scientists interested in getting started on tackling image analytics. We present high level discussions of sample preparation and image acquisition; data formats; storage and databases; image processing; computer vision and machine learning; and visualization and interactive programming. Examples will be covered using existing open-source software tools such as ImageJ, CellProfiler, and IPython Notebook. We discuss how difficult real-world challenges faced by image informatics and personalized medicine are being tackled with open-source biomedical data and software. © 2016 The Authors.

Chen, Y. -, Chen, H. -, Tseng, W. -, Hsu, J. -, Huang, T. -, Chen, C. -, et al. (2016). A C. elegans thermosensory circuit regulates longevity through crh-1/CREB-dependent flp-6 neuropeptide signaling. *Developmental Cell*, 39(2), 209-223.

Sensory perception, including thermosensation, shapes longevity in diverse organisms, but longevity-modulating signals from the sensory neurons are largely obscure. Here we show that CRH-1/CREB activation by CMK-1/CaMKI in the AFD thermosensory neuron is a key mechanism that maintains lifespan at warm temperatures in C. elegans. In response to temperature rise and crh-1 activation, the AFD neurons produce and secrete the FMRFamide neuropeptide FLP-6. Both CRH-1 and FLP-6 are necessary and sufficient for longevity at warm temperatures. Our data suggest that FLP-6 targets the AIY interneurons and engages DAF-9 sterol hormone signaling. Moreover, we show that FLP-6 signaling downregulates ins-7/insulin-like peptide and several insulin pathway genes, whose activity compromises lifespan. Our work illustrates how temperature experience is integrated by the thermosensory circuit to generate neuropeptide signals that remodel insulin and sterol hormone signaling and reveals a neuronal-endocrine circuit driven by thermosensation to promote temperature-specific longevity. © 2016 Elsevier Inc.

Chiang, M. F. (2016). Imaging in retinopathy of prematurity: Where are we, and where are we going? *Journal of AAPOS : The Official Publication of the American Association for Pediatric Ophthalmology and Strabismus*,

Choo, E. K., Feldstein Ewing, S. W., & Lovejoy, T. I. (2016). Opioids out, cannabis in: Negotiating the unknowns in patient care for chronic pain. *Jama*, 316(17), 1763-1764.

Choo, E. K., Tapé, C., Glerum, K. M., Mello, M. J., Zlotnick, C., & Guthrie, K. M. (2016). "That's where the arguments come in": A qualitative analysis of booster sessions following a brief intervention for drug use and intimate partner violence in the emergency department. *Substance Abuse: Research and Treatment*, 10, 77-87.

Although booster phone calls have been used to enhance the impact of brief interventions in the emergency department, there has been less number of studies describing the content of these boosters. We conducted a qualitative analysis of booster calls occurring two weeks after an initial

Web-based intervention for drug use and intimate partner violence (IPV) among women presenting for emergency care, with the objective of identifying the following: progress toward goals set during the initial emergency department visit, barriers to positive change, and additional resources and services needed in order to inform improvements in future booster sessions. The initial thematic framework was developed by summarizing codes by major themes and subthemes; the study team collaboratively decided on a final thematic framework. Eighteen participants completed the booster call. Most of them described a therapeutic purpose for their drug use. Altering the social milieu was the primary means of drug use change; this seemed to increase isolation of women already in abusive relationships. Women described IPV as interwoven with drug use. Participants identified challenges in attending substance use treatment service and domestic violence agencies. Women with substance use disorders and in abusive relationships face specific barriers to reducing drug use and to seeking help after a brief intervention. © the authors, publisher and licensee Libertas Academica Limited.

Christy, A., Nyhan, W., & Wilson, J. (2016). Severe respiratory acidosis in status epilepticus as a possible etiology of sudden death in lesch-nyhan disease: A case report and review of the literature. *JIMD Reports*,

INTRODUCTION: Lesch-Nyhan disease (LND) is an X-linked disorder of purine metabolism, associated with self-mutilation, dystonia, and chorea. Seizures are uncommon in LND. Patients with LND are at risk for sudden and unexpected death. The etiology of this is unknown, but appears to occur from a respiratory process. We propose that respiratory failure secondary to subclinical seizure may lead to sudden death in these patients. CASE: We report a case of an 11-year-old boy with LND who had two episodes of nocturnal gasping. The second event was immediately followed by a 10 min generalized seizure. Upon arrival at the hospital, an arterial blood gas test revealed a severe respiratory acidosis. Following aggressive treatment of his seizures, this patient did well, and was discharged home on oxcarbazepine with rectal diazepam. No further seizures have been noted in 1 year of follow-up. CONCLUSIONS: In this case report and review, we hypothesize that sudden death from respiratory failure in Lesch-Nyhan disease may in some cases be due to seizure-induced respiratory failure, akin to sudden unexpected death in epilepsy (SUDEP). We suggest screening for paroxysmal respiratory events;

consideration of electroencephalography for patients with LND presenting in respiratory distress or failure; and consideration of more aggressive treatment of seizures in these patients. Brief Summary: We present an 11-year-old boy with Lesch-Nyhan disease (LND) who developed respiratory failure and severe respiratory acidosis from his first known seizure, which evolved to subclinical status epilepticus. We propose that patients with LND have a predisposition to respiratory failure and sudden death, which in some cases may be provoked by seizure (sudden unexpected death in epilepsy, or SUDEP).

Cuevas-Ramos, D., & Fleseriu, M. (2016). Medical treatment of Cushing's disease. *Minerva Endocrinologica*, 41(3), 324-340.

Cushing's Syndrome (CS) is a serious endocrine disease that results from the adverse clinical consequences of chronic exposure to high levels of glucocorticoids. Most patients with endogenous CS have an adrenocorticotropin (ACTH)-secreting pituitary corticotroph adenoma, i.e. Cushing's Disease (CD). The first-line therapy for CD is transsphenoidal pituitary surgery. If tumor removal is incomplete or unsuccessful, persistent hypercortisolism will require further treatment. Repeat surgery, medical therapy, radiation and bilateral adrenalectomy are all second line therapy options; however, medical therapy can be also used as first line therapy in patients who cannot undergo surgery, or to decrease Cortisol values and/or improve co-morbidities. Medications used in the treatment of CD, classified into three groups: pituitary directed drugs, adrenal steroidogenesis inhibitors and glucocorticoid receptor blockers, are reviewed. Future 'on the horizon' treatment options are also discussed. © 2016 EDIZIONI MINERVA MEDICA.

de Vries, Y. A., Roest, A. M., Beijers, L., Turner, E. H., & de Jonge, P. (2016). Bias in the reporting of harms in clinical trials of second-generation antidepressants for depression and anxiety: A meta-analysis. *European Neuropsychopharmacology*, 26(11), 1752-1759.

Previous research has shown that reporting bias has inflated the apparent efficacy of antidepressants. We investigated whether apparent safety was also affected. We included 133 trials, involving 31,296 patients, of second-generation antidepressants for the treatment of major depressive disorder (MDD) or anxiety disorders, obtained from Food and Drug Administration (FDA) reviews. We extracted data on overall discontinuation, discontinuation due to adverse

events, and serious adverse events (SAEs). Meta-analysis was used to compare discontinuation rates between FDA reviews and matching journal articles, while SAEs were compared qualitatively. The odds ratio for overall discontinuation, comparing drug to placebo, was 1.0 for both sources, while that for discontinuation due to adverse events was 2.4 for both sources. Seventy-seven of 97 (79%) journal articles provided incomplete information on SAEs; sixty-one (63%) articles made no mention of SAEs at all. Of 21 articles which could be compared to the FDA, only 6 (29%) had full reporting without discrepancies. Nine (43%) articles reported a discrepant number of SAEs. Descriptions were absent or discrepant in 6 (29%) additional articles, even for important SAEs such as suicide attempts. In conclusion, reporting bias has not affected average discontinuation rates over trials. However, SAE reporting is not only very poor, with over half of articles failing to discuss SAEs altogether, but discrepancies between the FDA and articles were common and often led to a more favorable drug-placebo comparison. These findings suggest that journal articles are an unreliable source of data on SAEs in antidepressant trials. © 2016 Elsevier B.V. and ECNP

DeConde, A. S., Mace, J. C., Levy, J. M., Rudmik, L., Alt, J. A., & Smith, T. L. (2016). Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *The Laryngoscope*,

OBJECTIVES/HYPOTHESIS: Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a disease process that is driven, in part, by intrinsic mucosal inflammation. Surgery plus continued medical therapy is commonly elected by medically recalcitrant, symptomatic patients. The objective was to evaluate the prevalence of nasal polyp recurrence up to 18 months after endoscopic sinus surgery (ESS) with congruent continuing medical management. STUDY DESIGN: Prospective, multicenter cohort of adult patients undergoing ESS for medically recalcitrant CRSwNP performed between August 2004 and February 2015. METHODS: All patients received baseline nasal endoscopy quantified using Lund-Kennedy grading. All patients included for final analysis provided at least 6 months of postoperative endoscopy examinations. Multivariate analysis was used to identify risk factors for polyp recurrence. RESULTS: Three hundred sixty-three CRSwNP patients having undergone ESS involving polypectomy were enrolled. A total of 244 (67%) participants had graded postoperative endoscopies with average of follow-up of 14.3 +/- 7.0

months. Surgery plus postoperative medical management significantly improved endoscopy total scores at 6 months ($P < .001$). The recurrence of nasal polyposis 6 months after ESS was 35% (68/197), compared to 38% (48/125) after 12 months, and 40% (52/129) after 18 months. Multivariate analysis identified both prior ESS (odds ratio [OR]: 2.6, 95% confidence interval [CI]: 1.5-4.6; $P = .001$) and worse preoperative polyposis severity (OR: 1.4, 95% CI: 1.1-1.8; $P = .016$) as risk factors for recurrent polyposis. CONCLUSIONS: Polyp recurrence is common after ESS with control of polyps up to 18 months found in approximately 60% to 70% of patients. Investigation into both surgical and medical management strategies is warranted to improve upon the observed prevalence of recurrence. LEVEL OF EVIDENCE: 2c. *Laryngoscope*, 2016.

Denard, P. J., & Lädermann, A. (2016). Immediate versus delayed passive range of motion following total shoulder arthroplasty. *Journal of Shoulder and Elbow Surgery*, 25(12), 1918-1924.

Background The goal of this study was to compare immediate with delayed range of motion (ROM) following total shoulder arthroplasty (TSA). The hypothesis was that ROM gains would occur earlier with immediate motion but that there would be no difference in ultimate ROM or functional outcome. **Methods** Sixty patients were randomized to immediate motion (IM) or delayed motion (DM) following TSA. A lesser tuberosity osteotomy was performed in all cases. ROM and functional outcome were compared at 4 weeks, 8 weeks, 3 months, 6 months, and 1 year postoperatively. **Results** Compared with preoperative values, in the IM group, forward flexion improved from 106° to 141° at 1 year postoperatively, external rotation improved from 21° to 65° , and internal rotation improved by 2 spinal levels ($P < .05$). In the DM group, forward flexion improved from 104° to 144° , external rotation improved from 20° to 53° , and internal rotation improved by 4 spinal levels ($P < .05$). The 2 groups regained motion differently, but there were no significant differences in final ROM or functional outcome scores between the 2 groups. The IM group had higher functional outcome scores initially, but by 3 months postoperatively, there was no difference. The rate of osteotomy healing was 81% in the IM group compared with 96% in the DM group ($P = .101$). **Conclusion** Immediate ROM provides a more rapid return of function compared with a delayed ROM protocol following TSA. However, there are no differences in ultimate ROM or functional outcome between the 2 groups. Moreover, immediate ROM may

lower the healing rate of a lesser tuberosity osteotomy. © 2016 Journal of Shoulder and Elbow Surgery Board of Trustees

Dengina, N., Tsimafeyeu, I., & Mitin, T. (2016). Current role of radiotherapy for renal-cell carcinoma:

Review. *Clinical Genitourinary Cancer*,

Surgery is the standard of care for patients with renal-cell carcinoma (RCC). Radiotherapy (RT) can decrease the risk of local recurrence after surgery and can lead to excellent outcomes in patients unfit for surgery. We reviewed clinical experience with various forms of RT, including conventional fractionated RT and intraoperative radiotherapy (IORT) as adjunct to surgery, hypofractionated high-dose stereotactic body radiotherapy (SBRT), and particle therapy in unresectable RCC. We discuss future directions for using RT in the treatment of RCC. We encourage clinicians to incorporate RT modalities in prospective clinical trials.

Devereaux, J., Ferrara, S. J., Banerji, T., Placzek, A. T., & Scanlan, T. S. (2016). Increasing

thyromimetic potency through halogen substitution. *Chemmedchem*, *11*(21), 2459-2465.

Sobetirome is one of the most studied thyroid hormone receptor β (TR β)-selective thyromimetics in the field due to its excellent selectivity and potency. A small structural change—replacing the 3,5-dimethyl groups of sobetirome with either chlorine or bromine—produces significantly more potent compounds, both in vitro and in vivo. These halogenated compounds induce transactivation of a TR β -mediated cell-based reporter with an EC₅₀ value comparable to that of T₃, access the central nervous system (CNS) at levels similar to their parent, and activate an endogenous TR-regulated gene in the brain with an EC₅₀ value roughly five-fold lower than that of sobetirome. Previous studies suggest that this apparent increase in affinity can be explained by halogen bonding between the ligand and a backbone carbonyl group in the receptor. This makes the new analogues potential candidates for treating CNS disorders that may respond favorably to thyroid-hormone-stimulated pathways. © 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Dieckmann, N. F., Gregory, R., Peters, E., & Hartman, R. (2016). Seeing what you want to see: How imprecise uncertainty ranges enhance motivated reasoning. *Risk Analysis*,

In this article, we consider a novel criterion for evaluating representations of uncertainty ranges, namely, the extent to which a representation enhances motivated reasoning. In two studies, we

show that perceptions of the distribution underlying ambiguous numerical ranges are affected by the motivations and worldviews of end users. This motivated reasoning effect remained after controlling for objective numeracy and fluid intelligence but was attenuated when the correct interpretation was made clear. We suggest that analysts and communicators explicitly consider the potential for motivated evaluation when evaluating uncertainty displays. © 2016 Society for Risk Analysis.

Dissen, G. A., Adachi, K., Lomniczi, A., Chatkupt, T., Davidson, B. L., Nakai, H., et al. (2016).

Engineering a gene silencing viral construct that targets the cat hypothalamus to induce permanent sterility: An update. *Reproduction in Domestic Animals = Zuchthygiene*,

The intent of this contribution is to provide an update of the progress we have made towards developing a method/treatment to permanently sterilize cats. Our approach employs two complementary methodologies: RNA interference (RNAi) to silence genes involved in the central control of reproduction and a virus-based gene therapy system intended to deliver RNAi selectively to the hypothalamus (where these genes are expressed) via the systemic administration of modified viruses. We selected the hypothalamus because it contains neurons expressing Kiss1 and Tac3, two genes essential for reproduction and fertility. We chose the non-pathogenic adeno-associated virus (AAV) as a vector whose tropism could be modified to target the hypothalamus. The issues that must be overcome to utilize this vector as a delivery vehicle to induce sterility include modification of the wild-type AAV to target the hypothalamic region of the brain with a simultaneous reduction in targeting of peripheral tissues and non-hypothalamic brain regions, identification of RNAi targets that will effectively reduce the expression of Kiss1 and Tac3 without off-target effects, and determination if neutralizing antibodies to the AAV serotype of choice are present in cats. Successful resolution of these issues will pave the way for the development of a powerful tool to induce the permanent sterility in cats.

Dixon-Ibarra, A., Driver, S., VanVolkenburg, H., & Humphries, K. (2017). Formative evaluation on a physical activity health promotion program for the group home setting. *Evaluation and Program Planning, 60*, 81-90.

Physical inactivity and high rates of chronic conditions is a public health concern for adults with

intellectual disability. Few health promotion programs target the group home setting which is the pre-dominant form of residential accommodation for persons with intellectual disability. A process evaluation of a physical activity health promotion program, Menu-Choice, was conducted with five group home sites for adults with intellectual and developmental disabilities. Menu-Choice assists group home staff in including physical activity goals within resident schedules. The physical activity program was designed based on theoretical frameworks, community-based participatory approaches, and established health promotion guidelines for adults with disabilities. Fourteen program coordinators (age M 39; 77% females), 22 staff (age M 39; 82% females), and 18 residents (age M 59; 72% females; 56% ambulatory) participated. Results from the fidelity survey and program completion highlight potential challenges with implementation. Findings will assist with the refinement of the program for continued implementation trials in the group home community. © 2016

Donaldson, M., & Goodchild, J. H. (2016). Pharmacological reversal agents in dental practice: Keys to patient safety. *Compendium of Continuing Education in Dentistry (Jamesburg, N.J.: 1995)*, 37(10), 681-687; quiz 688.

Though uncommon, medical emergencies in the dental office are harrowing occurrences that can be the result of adverse drug reactions. Pharmacological antagonists have been developed for administration as reversal agents in emergency situations in which patients may have an untoward effect, typically caused by too much medication. Dental practitioners should be familiar with these agents to keep patients safe and help mitigate drug-induced medical emergencies. This article reviews the pharmacokinetic and pharmacodynamic principles of pharmacological antagonists; it emphasizes six specific reversal agents as they relate to the clinical practice of dentistry: naloxone, flumazenil, epinephrine, diphenhydramine, phentolamine, and atropine. Outside of emergency situations, the pharmacological antagonist phentolamine has been developed to reverse the effects of the vasoconstrictor in dental local anesthesia preparations when the effects of the agonist medication are no longer required. Such newer reversal agents are being considered for more routine use once the dental procedure is complete. This article is intended to assist dental practitioners who are familiar with pharmacological antagonists to be better able to help mitigate drug-induced medical emergencies should they occur.

Dotson, A. L., & Offner, H. (2017). Sex differences in the immune response to experimental stroke:

Implications for translational research. *Journal of Neuroscience Research*, 95(1-2), 437-446.

Ischemic stroke is a leading cause of death and disability in the United States. It is known that males and females respond differently to stroke. Depending on age, the incidence, prevalence, mortality rate, and disability outcome of stroke differ between the sexes. Females generally have strokes at older ages than males and, therefore, have a worse stroke outcome. There are also major differences in how the sexes respond to stroke at the cellular level. Immune response is a critical factor in determining the progress of neurodegeneration after stroke and is fundamentally different for males and females. Additionally, females respond to stroke therapies differently from males, yet they are often left out of the basic research that is focused on developing those therapies. With a resounding failure to translate stroke therapies from the bench to the bedside, it is clearer than ever that inclusion of both sexes in stroke studies is essential for future clinical success. This Mini-Review examines sex differences in the immune response to experimental stroke and its implications for therapy development. (c) 2016 Wiley Periodicals, Inc.

Duell, P. B., & Jialal, I. (2016). Modern management of familial hypercholesterolemia. *Metabolic Syndrome and Related Disorders*, 14(10), 463-467.

Familial hypercholesterolemia (FH) is a common genetic disorder that can manifest clinically as both the severe homozygous (HoFH) form that often presents in childhood and the commoner heterozygous (HeFH) form that is typically identified in adults. The majority of genetic causes are due to defects in low-density lipoprotein (LDL) receptor synthesis and action. Until recently, it was exceedingly difficult to achieve the goal of a 50% reduction in LDL-cholesterol or LDL-C < 70-100 in these patients. Established therapies include statins, niacin, bile-acid sequestrants, and ezetimibe in various combinations. The recent advent of monoclonal antibodies to PCSK9 (evolocumab and alirocumab) has revolutionized the management of FH and results in a substantial reduction in LDL-C and also reductions in Lp(a). In addition, the previous ushering in of antisense therapy against apoB (mipomersen) and inhibition of microsomal transfer protein (lomitapide) for use in HoFH greatly enhanced our ability to manage refractory hypercholesterolemia in these patients. Hence, the therapeutic landscape for this common

disorder has changed dramatically for these patients, with a strong promise for a reduction in cardiovascular events.

Durupinar, F., Kapadia, M., Deutsch, S., Neff, M., & Badler, N. I. (2016). PERFORM: Perceptual approach for adding OCEAN personality to human motion using laban movement analysis. *ACM Transactions on Graphics*, 36(1)

The research reported in this document was performed in connection with Contract Numbers W911NF-07-1-0216 and W911NF-10-2-0016 with the U.S. Army Research Laboratory. The views and conclusions contained in this document are those of the authors and should not be interpreted as presenting the official policies or position, either expressed or implied, of the U.S. Army Research Laboratory or the U.S. Government unless so designated by other authorized documents. Citation of manufacturers or trade names does not constitute an official endorsement or approval of the use thereof. The U.S. Government is authorized to reproduce and distribute reprints for Government purposes notwithstanding any copyright notation hereon. characters. The purpose and contribution of this work is to describe a formal, broadly applicable, procedural, and empirically grounded association between personality and body motion and apply this association to modify a given virtual human body animation that can be represented by these formal concepts. Because the body movement of virtual characters may involve different choices of parameter sets depending on the context, situation, or application, formulating a link from personality to body motion requires an intermediate step to assist generalization. For this intermediate step, we refer to Laban Movement Analysis, which is a movement analysis technique for systematically describing and evaluating human motion. We have developed an expressive human motion generation system with the help of movement experts and conducted a user study to explore how the psychologically validated OCEAN personality factors were perceived in motions with various Laban parameters. We have then applied our findings to procedurally animate expressive characters with personality, and validated the generalizability of our approach across different models and animations via another perception study. © 2016 ACM.

Ehrlich, J. R., Michelotti, M., Blachley, T. S., Zheng, K., Couper, M. P., Greenberg, G. M., et al. (2016). A two-year longitudinal assessment of ophthalmologists' perceptions after implementing an

electronic health record system. *Applied Clinical Informatics*, 7(4), 930-945.

Objectives: To understand the attitudes and perceptions of ophthalmologists toward an electronic health record (EHR) system, before and after its clinical implementation. Methods:

Ophthalmologists at a single large academic ophthalmology department were surveyed longitudinally before and after implementation of a new EHR system. The survey measured ophthalmologists' attitudes toward implementation of a new EHR. Questions focused on satisfaction, efficiency, and documentation. All attending physicians (between 56 and 61 at various time points) in the University of Michigan Department of Ophthalmology and Visual Sciences were surveyed. We plotted positive responses to survey questions and assessed whether perceptions followed a J-curve with an initial decrease followed by an increase surpassing pre-implementation levels. Results: Survey responses were received from 32 (52%) ophthalmologists pre-implementation, and 28 (46%) at 3 months, 35 (57%) at 7 months, 40 (71%) at 13 months and 39 (67%) at 24 months post-implementation. After EHR implementation respondents were more likely to express concerns about their ability to create high-quality documentation ($p < 0.01$) and the impact of an electronic health record on meaningful patient interaction ($p < 0.01$). Physicians did not report a significant change in the amount of time spent documenting outside of regular clinical work hours ($p = 0.54$) or on their clinic efficiency and workflow ($p = 0.97$). There was no significant change in overall job satisfaction during the study period ($p = 0.69$). We did not observe a J-curve for any of the survey responses analyzed.

Conclusions: As ophthalmology practices continue to transition to EHRs, adapting them to their specific culture and needs is important to maintain efficiency and user satisfaction. This study identifies areas of concern to ophthalmologists that may be addressed through education of physicians and customization of software as other practices move forward with EHR implementation. © Schattauer 2016.

Eisenberg, D. L., & Leslie, V. C. (2016). Threats to reproductive health care: Time for obstetrician-gynecologists to get involved. *American Journal of Obstetrics and Gynecology*,

To be healthy, support their families, and be productive members of their communities, women must have access to comprehensive reproductive health services including treatment of miscarriage and ectopic pregnancy and access to abortion, sterilization, and other contraceptive

methods. However, in the United States, hospitals and legislative bodies are erecting barriers and limiting access to these basic health care services. These barriers are caused by factors such as hospital mergers (specifically those that are religiously affiliated); federal, state, and local legislation; hospital policies; and business-related decisions are threatening reproductive health care. Such barriers, of which women are often not even aware, put women at real risk of harm. This commentary provides clinical examples of these harms and recommends ways that obstetrician-gynecologists can get involved to publicize the consequences of these barriers and, hopefully, prevent them from occurring or break them down to promote women's health.

Enriori, P. J., Chen, W., Garcia-Rudaz, M. C., Grayson, B. E., Evans, A. E., Comstock, S. M., et al.

(2016). α -Melanocyte stimulating hormone promotes muscle glucose uptake via melanocortin 5 receptors. *Molecular Metabolism*, 5(10), 807-822.

Objective Central melanocortin pathways are well-established regulators of energy balance. However, scant data exist about the role of systemic melanocortin peptides. We set out to determine if peripheral α -melanocyte stimulating hormone (α -MSH) plays a role in glucose homeostasis and tested the hypothesis that the pituitary is able to sense a physiological increase in circulating glucose and responds by secreting α -MSH. Methods We established glucose-stimulated α -MSH secretion using humans, non-human primates, and mouse models. Continuous α -MSH infusions were performed during glucose tolerance tests and hyperinsulinemic-euglycemic clamps to evaluate the systemic effect of α -MSH in glucose regulation. Complementary ex vivo and in vitro techniques were employed to delineate the direct action of α -MSH via the melanocortin 5 receptor (MC5R)-PKA axis in skeletal muscles. Combined treatment of non-selective/selective phosphodiesterase inhibitor and α -MSH was adopted to restore glucose tolerance in obese mice. Results Here we demonstrate that pituitary secretion of α -MSH is increased by glucose. Peripheral α -MSH increases temperature in skeletal muscles, acts directly on soleus and gastrocnemius muscles to significantly increase glucose uptake, and enhances whole-body glucose clearance via the activation of muscle MC5R and protein kinase A. These actions are absent in obese mice, accompanied by a blunting of α -MSH-induced cAMP levels in skeletal muscles of obese mice. Both selective and non-selective phosphodiesterase inhibition restores α -MSH induced skeletal muscle glucose uptake and improves glucose disposal in obese

mice. Conclusion These data describe a novel endocrine circuit that modulates glucose homeostasis by pituitary α -MSH, which increases muscle glucose uptake and thermogenesis through the activation of a MC5R-PKA-pathway, which is disrupted in obesity. © 2016 The Author(s)

Eshleman, A. J., Wolfrum, K. M., Reed, J. F., Kim, S. O., Swanson, T., Johnson, R. A., et al. (2016). Structure-activity relationships of substituted cathinones, with transporter binding, uptake and release. *The Journal of Pharmacology and Experimental Therapeutics*,
Synthetic cathinones are components of "bath salts" and have physical and psychological side effects including hypertension, paranoia, and hallucinations. Herein we report interactions of 20 "bath salt" components with human dopamine, serotonin, and norepinephrine transporters (hDAT, hSERT, and hNET, respectively) heterologously expressed in HEK 293 cells. Transporter inhibitors had nanomolar to micromolar affinities (K_i values) at radioligand binding sites, with relative affinities of hDAT>hNET>hSERT for alpha-PPP, alpha-PBP, alpha-PHP, PV-8, 3,4-MDPPP, 3,4-MDPBP, 4-MePPP, alpha-PVP, 4-MeO- alpha-PVP, alpha-PVT and pentedrone, and hDAT>hSERT>hNET for pentylone. Increasing the alpha-carbon chain length increased the affinity and potency of the alpha-pyrrolidinophenones. Uptake inhibitors had relative potencies of hDAT>hNET>hSERT except alpha-PPP and alpha-PVT, which had highest potencies at hNET. They did not induce [3H]neurotransmitter release. Substrates can enter presynaptic neurons via transporters, and the substrates methamphetamine (METH) and 3,4-methylenedioxymethylamphetamine (MDMA) are neurotoxic. We determined that 3-fluoro-, 4-bromo-, 4-chloro-methcathinone and 4-fluoroamphetamine were substrates at all three transporters; MDAI and 4-MEC were substrates primarily at hSERT and hNET, while ethylone and 5-methoxy-methylone were substrates only at hSERT and induced [3H]neurotransmitter release. Significant correlations between potencies for inhibition of uptake and for inducing release were observed for these and additional substrates. The excellent correlation of efficacy at stimulating release versus K_i/IC_{50} ratios suggested thresholds of binding/uptake ratios above which compounds were likely to be substrates. Based on their potencies at hDAT, most of these compounds have potential for abuse and addiction. 4-Bromomethcathinone, 4-MEC, 5-methoxy-

methylone, ethylone and MDAI, which have higher potency at hSERT than hDAT, may have empathogen psychoactivity.

Ferencik, M., Akhavein, R., & Hoffmann, U. (2016). The potential role of combined highly sensitive troponin and coronary computed tomography angiography in the evaluation of patients with suspected acute coronary syndrome in the emergency department. *Current Cardiovascular Imaging Reports*, 9(12)

The evaluation and triage of patients presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS) remains to be challenging despite available guidelines and clinical evidence. The current guidelines in the USA recommend clinical risk assessment based on cardiovascular risk factors followed by serial electrocardiograms and conventional cardiac troponin measurements, which are supplemented by advanced non-invasive cardiac testing in the majority of patients. This approach is safe, but leads to a lengthy work-up and high cost of care. There is clinical need for diagnostic strategies that will lead to rapid and reliable triage of patients with suspected ACS. In this review, we will summarize the experience and evidence for the use of highly sensitive troponin (hsTn) in the rapid and efficient evaluation of patients with suspected ACS. We will also review the available literature on the use of coronary computed tomography angiography (CTA) in the rapid evaluation of patients with suspected ACS. We will discuss the opportunities for the combined use of hsTn and coronary CTA in this population. Finally, we will outline the possible implementation of combined use of hsTn and coronary CTA in the evaluation of patients with suspected ACS in the ED. © 2016, Springer Science+Business Media New York.

Fischer, J. M., Calabrese, P. P., Miller, A. J., Munoz, N. M., Grady, W. M., Shibata, D., et al. (2016).

Single cell lineage tracing reveals a role for TgfbetaR2 in intestinal stem cell dynamics and differentiation. *Proceedings of the National Academy of Sciences of the United States of America*, 113(43), 12192-12197.

Intestinal stem cells (ISCs) are maintained by a niche mechanism, in which multiple ISCs undergo differential fates where a single ISC clone ultimately occupies the niche. Importantly, mutations continually accumulate within ISCs creating a potential competitive niche environment.

Here we use single cell lineage tracing following stochastic transforming growth factor beta receptor 2 (TgfbetaR2) mutation to show cell autonomous effects of TgfbetaR2 loss on ISC clonal dynamics and differentiation. Specifically, TgfbetaR2 mutation in ISCs increased clone survival while lengthening times to monoclonality, suggesting that Tgfbeta signaling controls both ISC clone extinction and expansion, independent of proliferation. In addition, TgfbetaR2 loss in vivo reduced crypt fission, irradiation-induced crypt regeneration, and differentiation toward Paneth cells. Finally, altered Tgfbeta signaling in cultured mouse and human enteroids supports further the in vivo data and reveals a critical role for Tgfbeta signaling in generating precursor secretory cells. Overall, our data reveal a key role for Tgfbeta signaling in regulating ISCs clonal dynamics and differentiation, with implications for cancer, tissue regeneration, and inflammation.

Fleseriu, M., Hashim, I. A., Karavitaki, N., Melmed, S., Murad, M. H., Salvatori, R., et al. (2016).

Hormonal replacement in hypopituitarism in adults: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, 101(11), 3888-3921.

OBJECTIVE: To formulate clinical practice guidelines for hormonal replacement in hypopituitarism in adults. **PARTICIPANTS:** The participants include an Endocrine Society-appointed Task Force of six experts, a methodologist, and a medical writer. The American Association for Clinical Chemistry, the Pituitary Society, 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 two systematic reviews 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 Pituitary Society, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

CONCLUSIONS: Using an evidence-based approach, this guideline addresses important clinical issues regarding the evaluation and management of hypopituitarism in adults, including appropriate biochemical assessments, specific therapeutic decisions to decrease the risk of co-

morbidities due to hormonal over-replacement or under-replacement, and managing hypopituitarism during pregnancy, pituitary surgery, and other types of surgeries.

Flood, S., Asplund, K., Hoffman, B., Nye, A., & Zuckerman, K. (2016). Fluoride supplementation adherence and barriers in a community without water fluoridation. *Academic Pediatrics*,

BACKGROUND: To prevent early childhood caries, the American Dental Association recommends oral fluoride supplementation for children in communities lacking water fluoridation who are at high caries risk. However, patient adherence to oral fluoride supplementation has not been studied in this population. This study assessed adherence to oral fluoride and barriers to adherence in a community lacking water fluoridation. METHODS: A self-administered survey was completed in a systematic sample of 209 parents of children ages 6 months to 4 years, during a primary care visit in an urban academic medical center. Participants reported frequency of administering oral fluoride to their children, as well as agreement or disagreement with proposed barriers to supplementation. Bivariate and multivariate analyses were used to assess adherence with oral supplementation and the association of barriers to supplementation and child receipt of fluoride on the day prior. RESULTS: Greater than half of parents either had not or did not know if their child had received fluoride on the day prior. Approximately 1 in 4 of parents had given fluoride 0 of the previous 7 days. Difficulty remembering to give fluoride and agreeing that the child does not need extra fluoride were associated with not receiving fluoride on the day prior. CONCLUSION: Adherence to oral fluoride supplementation in the primary care setting is low. Difficulty remembering to give fluoride daily is the greatest barrier to adherence. Further research on interventions to reduce common barriers is needed to increase fluoride administration and reduce early childhood caries in communities lacking water fluoridation.

Foquet, L., Wilson, E. M., Verhoye, L., Grompe, M., Leroux-Roels, G., Bial, J., et al. (2017). Successful engraftment of human hepatocytes in uPA-SCID and FRG(R) KO mice. *Methods in Molecular Biology (Clifton, N.J.)*, 1506, 117-130.

Mice with humanized chimeric liver are promising in vivo tools to evaluate the efficacy of novel compounds or vaccine induced antibodies directed against pathogens that infect the human liver.

In addition they can be used to study the human-type metabolism of medicinal compounds and hepatotoxicity.

Fu, X., Jeselsohn, R., Pereira, R., Hollingsworth, E. F., Creighton, C. J., Li, F., et al. (2016). FOXA1 overexpression mediates endocrine resistance by altering the ER transcriptome and IL-8 expression in ER-positive breast cancer. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(43), E6600-E6609.

Forkhead box protein A1 (FOXA1) is a pioneer factor of estrogen receptor alpha (ER)-chromatin binding and function, yet its aberration in endocrine-resistant (Endo-R) breast cancer is unknown. Here, we report preclinical evidence for a role of FOXA1 in Endo-R breast cancer as well as evidence for its clinical significance. FOXA1 is gene-amplified and/or overexpressed in Endo-R derivatives of several breast cancer cell line models. Induced FOXA1 triggers oncogenic gene signatures and proteomic profiles highly associated with endocrine resistance. Integrated omics data reveal IL8 as one of the most perturbed genes regulated by FOXA1 and ER transcriptional reprogramming in Endo-R cells. IL-8 knockdown inhibits tamoxifen-resistant cell growth and invasion and partially attenuates the effect of overexpressed FOXA1. Our study highlights a role of FOXA1 via IL-8 signaling as a potential therapeutic target in FOXA1-overexpressing ER-positive tumors.

Garaicoa, J. L., Fischer, C. L., Bates, A. M., Holloway, J., Avila-Ortiz, G., Guthmiller, J. M., et al. (2016). Promise of combining antifungal agents in denture adhesives to fight candida species infections. *Journal of Prosthodontics : Official Journal of the American College of Prosthodontists*, PURPOSE: Several complications may arise in patients wearing complete prosthetic appliances, including denture-associated infections and mucosal stomatitis due to Candida species. This study evaluated the activity of anti-Candida agents in denture adhesive and the cytotoxicities of these preparations for primary human gingival epithelial (GE) keratinocytes. MATERIALS AND METHODS: The anti-Candida activities of antimicrobial peptides, antimicrobial lipids, and antifungal agents against *C. albicans* ATCC 64124 or HMV4C were assessed in microdilution assays containing water or 1% denture adhesive. The minimal inhibitory concentrations (MIC) and the minimal bactericidal concentrations (MBC) were determined. The cytotoxicities of denture

adhesive compounded with these agents were assessed in 1.0×10^5 primary GE keratinocytes in LGM-3 media with resazurin. RESULTS: Lactoferricin B, SMAP28, sphingosine, dihydrosphingosine, and phytosphingosine in 1% denture adhesive lost antimicrobial activity for *C. albicans* (p 100.0 mug/ml) against primary human GE keratinocytes. CONCLUSIONS: Antimicrobial peptides and antimicrobial lipids had diminished activities in 1% adhesive, suggesting that components in adhesives may inactivate local innate immune factors in the oral cavity, possibly predisposing denture wearers to *Candida* species infections. More importantly, antifungal agents retained their anti-*C. albicans* activities in denture adhesive, strongly suggesting that antifungal agents could be candidates for inclusion in adhesive formulations and used as prescribed topical treatments for individuals with denture stomatitis.

Garritty, C., Stevens, A., Gartlehner, G., King, V., Kamel, C., & Cochrane Rapid Reviews Methods Group. (2016). Cochrane rapid reviews methods group to play a leading role in guiding the production of informed high-quality, timely research evidence syntheses. *Systematic Reviews*, 5(1), 184.

BACKGROUND: Policymakers and healthcare stakeholders are increasingly seeking evidence to inform the policymaking process, and often use existing or commissioned systematic reviews to inform decisions. However, the methodologies that make systematic reviews authoritative take time, typically 1 to 2 years to complete. Outside the traditional SR timeline, "rapid reviews" have emerged as an efficient tool to get evidence to decision-makers more quickly. However, the use of rapid reviews does present challenges. To date, there has been limited published empirical information about this approach to compiling evidence. Thus, it remains a poorly understood and ill-defined set of diverse methodologies with various labels. In recent years, the need to further explore rapid review methods, characteristics, and their use has been recognized by a growing network of healthcare researchers, policymakers, and organizations, several with ties to Cochrane, which is recognized as representing an international gold standard for high-quality, systematic reviews. PURPOSE: In this commentary, we introduce the newly established Cochrane Rapid Reviews Methods Group developed to play a leading role in guiding the production of rapid reviews given they are increasingly employed as a research synthesis tool to support timely evidence-informed decision-making. We discuss how the group was formed and outline the

group's structure and remit. We also discuss the need to establish a more robust evidence base for rapid reviews in the published literature, and the importance of promoting registration of rapid review protocols in an effort to promote efficiency and transparency in research.

CONCLUSION: As with standard systematic reviews, the core principles of evidence-based synthesis should apply to rapid reviews in order to minimize bias to the extent possible. The Cochrane Rapid Reviews Methods Group will serve to establish a network of rapid review stakeholders and provide a forum for discussion and training. By facilitating exchange, the group will strive to conduct research to advance the methods of rapid reviews.

Gibbs, S. E., Rocca, C. H., Bednarek, P., Thompson, K. M. J., Darney, P. D., & Harper, C. C. (2016).

Long-acting reversible contraception counseling and use for older adolescents and nulliparous women. *Journal of Adolescent Health, 59*(6), 703-709.

Purpose The majority of pregnancies during adolescence are unintended, and few adolescents use long-acting reversible contraception (LARC) due in part to health care providers' misconceptions about nulliparous women's eligibility for the intrauterine device. We examined differences in LARC counseling, selection, and initiation by age and parity in a study with a provider's LARC training intervention. **Methods** Sexually active women aged 18–25 years receiving contraceptive counseling (n = 1,500) were enrolled at 20 interventions and 20 control clinics and followed for 12 months. We assessed LARC counseling and selection, by age and parity, with generalized estimated equations with robust standard errors. We assessed LARC use over 1 year with Cox proportional hazards models with shared frailty for clustering. **Results** Women in the intervention had increased LARC counseling, selection, and initiation, with similar effects among older adolescent and nulliparous women, and among young adult and parous women. Across study arms, older adolescents were as likely as young adults to receive LARC counseling (adjusted odds ratio [aOR] = .85; 95% confidence interval [CI]: .63–1.15), select LARC (aOR = .86; 95% CI: .64–1.17), and use LARC methods (adjusted hazard ratio [aHR] = .94; 95% CI: .69–1.27). Nulliparous women were less likely to receive counseling (aOR = .57; 95% CI: .42–.79) and to select LARC (aOR = .53; 95% CI: .37–.75) than parous women, and they initiated LARC methods at lower rates (aHR = .65; 95% CI: .48–.90). Nulliparous women had similar rates of implant initiation but lower rates of intrauterine device initiation (aHR = .59; 95% CI: .41–.85). **Conclusions** Continued

efforts should be made to improve counseling and access to LARC methods for nulliparous women of all ages. © 2016 Society for Adolescent Health and Medicine

Gimenez-Roldan, S., & Spencer, P. S. (2016). Azanon's disease. A 19th century epidemic of
neurolethyrism in Spain. *Revue Neurologique*,

The cultivation and consumption of grasspea (*Lathyrus sativus*) in Spain probably dates back centuries, especially during times of famine when the neurotoxic potential of this legume was expressed in the form of a spastic paraparesis known as neurolethyrism. Little known outside the country, the epidemic of neurolethyrism in the years following the Spanish Civil War (1936-1939) came to affect more than a thousand people. In late 1872, during the Six Years Revolutionary Term, young Alejandro San Martin Satrustegui (1847-1908), then editor of the popular weekly *El Siglo Medico*, travelled to Azanon, a remote village in the province of Guadalajara, to clarify a so-far unknown disease. We analysed the original article published in 1873 by San Martin, as well as communications sent by *El Siglo Medico* readers reporting similar cases in many other Castilian provinces. San Martin's neurological findings in seven personally examined cases were astonishingly accurate; he concluded the subjects' neurological deficits resulted from injury to the lateral columns in the lower portion of the spinal cord. Description of the clinical findings provided both by San Martin, and by the readers of *El Siglo Medico*, leave no doubt as to the diagnosis of neurolethyrism. However, none suspected the patient's staple food was the determinant cause of the disease. San Martin proposed the eponym Azanon's disease for lack of a better name the same year (1873) in which Cantani in Italy introduced the term lathyrism. The epidemic of neurolethyrism that affected many Castilian towns represents one of the best-documented in Europe during the last third of the 19th century.

Gkourogianni, A., Andrew, M., Tyzinski, L., Crocker, M., Douglas, J., Dunbar, N., et al. (2016). Clinical characterization of patients with autosomal dominant short stature due to aggrecan mutations. *The Journal of Clinical Endocrinology and Metabolism*, , jc20163313.

CONTEXT: Heterozygous mutations in the Aggrecan gene (*ACAN*) cause autosomal dominant short stature with bone age (BA) acceleration, premature growth cessation and minor skeletal abnormalities. OBJECTIVE: Characterize the phenotypic spectrum, associated conditions and

response to growth-promoting therapies. DESIGN: Retrospective international cohort study. PATIENTS: Information from 103 individuals (57 female, 46 male) from 20 families with confirmed heterozygous ACAN mutations were included. METHODS: Families with autosomal dominant short stature and heterozygous ACAN mutations were identified and confirmed using whole-exome sequencing, targeted next generation sequencing, and/or Sanger sequencing. Clinical information was collected from medical records. RESULTS: Identified ACAN variants showed perfect co-segregation with phenotype. Adult individuals had mildly disproportionate short stature (median height: -2.8 SDS, range: -5.9 to -0.9) and histories of early growth cessation. The condition was frequently associated with early-onset osteoarthritis (12 families) and intervertebral disc disease (9 families). There was no apparent genotype-phenotype correlation between type of ACAN mutation and presence of joint complaints. During childhood, height was less affected (median height: -2.0 SDS, range: -4.2 to -0.6). In contrast to most children with short stature, the majority of children had advanced BA (BA - CA, median: +1.3y; range +0.0 to +3.7y) reflecting a reduction in remaining growth potential. Nineteen individuals had received GH with some evidence of increased growth velocity. CONCLUSIONS: Heterozygous ACAN mutations result in a phenotypic spectrum ranging from mild and proportionate short stature to a mild skeletal dysplasia with disproportionate short stature and brachydactyly. In several of the families, affected individuals developed early-onset osteoarthritis and degenerative disc disease requiring intervention, suggesting dysfunction of articular cartilage and intervertebral disc cartilage. Additional studies are needed to determine the optimal treatment strategy for these patients.

Goddard, E. T., Hill, R. C., Barrett, A., Betts, C., Guo, Q., Maller, O., et al. (2016). Quantitative extracellular matrix proteomics to study mammary and liver tissue microenvironments. *The International Journal of Biochemistry & Cell Biology*,
Normal epithelium exists within a dynamic extracellular matrix (ECM) that is tuned to regulate tissue specific epithelial cell function. As such, ECM contributes to tissue homeostasis, differentiation, and disease, including cancer. Though it is now recognized that the functional unit of normal and transformed epithelium is the epithelial cell and its adjacent ECM, we lack a basic understanding of tissue-specific ECM composition and abundance, as well as how physiologic

changes in ECM impact cancer risk and outcomes. While traditional proteomic techniques have advanced to robustly identify ECM proteins within tissues, methods to determine absolute abundance have lagged. Here, with a focus on tissues relevant to breast cancer, we utilize mass spectrometry methods optimized for absolute quantitative ECM analysis. Employing an extensive protein extraction and digestion method, combined with stable isotope labeled Quantitative conCATamer (QconCAT) peptides that serve as internal standards for absolute quantification of protein, we quantify 98 ECM, ECM-associated, and cellular proteins in a single analytical run. In rodent models, we applied this approach to the primary site of breast cancer, the normal mammary gland, as well as a common and particularly deadly site of breast cancer metastasis, the liver. We find that mammary gland and liver have distinct ECM abundance and relative composition. Further, we show mammary gland ECM abundance and relative compositions differ across the reproductive cycle, with the most dramatic changes occurring during the pro-tumorigenic window of weaning-induced involution. Combined, this work suggests ECM candidates for investigation of breast cancer progression and metastasis, particularly in postpartum breast cancers that are characterized by high metastatic rates. Finally, we suggest that with use of absolute quantitative ECM proteomics to characterize tissues of interest, it will be possible to reconstruct more relevant in vitro models to investigate tumor-ECM dynamics at higher resolution.

Graff, J. N., Alumkal, J. J., & Beer, T. M. (2016). Should chemotherapy be used in nonmetastatic prostate cancer? *JAMA Oncology*,

Graham, J. B., Swarts, J. L., Wilkins, C., Thomas, S., Green, R., Sekine, A., et al. (2016). A mouse model of chronic west nile virus disease. *PLoS Pathogens*, *12*(11), e1005996.

Infection with West Nile virus (WNV) leads to a range of disease outcomes, including chronic infection, though lack of a robust mouse model of chronic WNV infection has precluded identification of the immune events contributing to persistent infection. Using the Collaborative Cross, a population of recombinant inbred mouse strains with high levels of standing genetic variation, we have identified a mouse model of persistent WNV disease, with persistence of viral loads within the brain. Compared to lines exhibiting no disease or marked disease, the F1 cross

CC(032x013)F1 displays a strong immunoregulatory signature upon infection that correlates with restraint of the WNV-directed cytolytic response. We hypothesize that this regulatory T cell response sufficiently restrains the immune response such that a chronic infection can be maintained in the CNS. Use of this new mouse model of chronic neuroinvasive virus will be critical in developing improved strategies to prevent prolonged disease in humans.

Greene, T. T., Tokuyama, M., Knudsen, G. M., Kunz, M., Lin, J., Greninger, A. L., et al. (2016). A herpesviral induction of RAE-1 NKG2D ligand expression occurs through release of HDAC mediated repression. *Elife*, 5, 10.7554/eLife.14749.

Natural Killer (NK) cells are essential for control of viral infection and cancer. NK cells express NKG2D, an activating receptor that directly recognizes NKG2D ligands. These are expressed at low level on healthy cells, but are induced by stresses like infection and transformation. The physiological events that drive NKG2D ligand expression during infection are still poorly understood. We observed that the mouse cytomegalovirus encoded protein m18 is necessary and sufficient to drive expression of the RAE-1 family of NKG2D ligands. We demonstrate that RAE-1 is transcriptionally repressed by histone deacetylase inhibitor 3 (HDAC3) in healthy cells, and m18 relieves this repression by directly interacting with Casein Kinase II and preventing it from activating HDAC3. Accordingly, we found that HDAC inhibiting proteins from human herpesviruses induce human NKG2D ligand ULBP-1. Thus our findings indicate that virally mediated HDAC inhibition can act as a signal for the host to activate NK-cell recognition.

Hagen, M. W., Girdhar, G., Wainwright, J., & Hinds, M. T. (2016). Thrombogenicity of flow diverters in an ex vivo shunt model: Effect of phosphorylcholine surface modification. *Journal of Neurointerventional Surgery*,

BACKGROUND: Flow diverters offer a promising treatment for cerebral aneurysms. However, they have associated thromboembolic risks, mandating chronic dual antiplatelet therapy (DAPT).

Shield Technology is a phosphorylcholine surface modification of the Pipeline Embolization Device (PED) flow diverter, which has shown significant reductions in material thrombogenicity in vitro.

OBJECTIVE: To compare the thrombogenicity of PED, PED with Shield Technology (PED+Shield), and the Flow-Redirection Endoluminal Device (FRED)-with and without single antiplatelet therapy

and DAPT-under physiological flow. METHODS: An established non-human primate ex vivo arteriovenous shunt model of stent thrombosis was used. PED, PED+Shield, and FRED were tested without antiplatelet therapy, with acetylsalicylic acid (ASA) monotherapy, and with DAPT. Radiolabeled platelet deposition was quantified over 1 hour for each device and total fibrin deposition was also quantified. RESULTS: Cumulative statistical analysis showed significantly lower platelet deposition on PED compared with FRED. The same statistical model showed significant decreases in platelet deposition when ASA, clopidogrel, or Shield Technology was used. Direct comparisons of device performances within antiplatelet conditions showed consistent significant decreases in platelet accumulation on PED+Shield relative to FRED. PED+Shield showed significant reductions in platelet deposition compared with unmodified PED without antiplatelet therapy and with DAPT. PED accumulated minimal fibrin with and without Shield Technology. CONCLUSIONS: In this preclinical model, we have shown that the Shield Technology phosphorylcholine modification reduces the platelet-specific thrombogenicity of a flow diverter under physiologically relevant flow with and without DAPT. We have further identified increased fibrin-driven thrombogenicity associated with FRED relative to PED.

Halm, M. (2016). Making time for quiet. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses*, 25(6), 552-555.

Handelsman, Y., & Shapiro, M. D. (2016). Triglycerides, atherosclerosis, and cardiovascular outcome studies: Focus on omega-3 fatty acids. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, Despite improved atherosclerotic cardiovascular disease (ASCVD) outcomes with statin therapy, residual risk remains. Recent genetic insights provide further compelling evidence that triglycerides are in the causal pathway for the development of atherosclerosis, thereby renewing interest in targeting triglycerides to improve ASCVD outcomes. Fibrates, niacin, and omega-3 fatty acids (OM3FAs) are 3 classes of triglyceride-lowering drugs. Outcome studies with triglyceride-lowering agents have been inconsistent. With regard to OM3FAs, the Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS) showed that EPA significantly reduced major coronary events in statin-treated hypercholesterolemic patients. Regarding other

agents, extended-release niacin and fenofibrate are no longer recommended as statin add-on therapy (by some guidelines though not all) because of the lack of convincing evidence from outcome studies. Notably, subgroup analyses from outcome studies have generated the hypothesis that triglyceride lowering may provide benefit in statin-treated patients with persistent hypertriglyceridemia. Two ongoing outcome studies are testing this hypothesis in high-risk, statin-treated patients with triglyceride levels 200-500 mg/dL: the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCEIT) is evaluating EPA (icosapent ethyl) and the Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia study (STRENGTH) is evaluating omega-3-carboxylic acids (EPA plus docosahexaenoic acid). These studies will determine the role of triglyceride lowering in statin-treated patients with high-dose prescription OM3FAs in terms of improved ASCVD outcomes.

Hansen, L., Rosenkranz, S. J., Mularski, R. A., & Leo, M. C. (2016). Family perspectives on overall care in the intensive care unit. *Nursing Research*, 65(6), 446-454.

BACKGROUND: Family members' perspectives about satisfaction with care provided in the intensive care unit (ICU) have become an important part of quality assessment and improvement, but national and international differences may exist in care provided and family perspectives about satisfaction with care. **OBJECTIVE:** The purpose of the research was to understand family members' perspectives regarding overall care of medical patients receiving intensive care. **METHODS:** Family members of medical patients who remained 48 hours or more in two adult ICUS at two healthcare institutions in the U.S. Pacific Northwest took part by responding to the Family Satisfaction with Care in the Intensive Care Unit survey. Qualitative content analysis was used to identify major categories and subcategories in their complimentary (positive) or critical (negative) responses to open-ended questions. The number of comments in each category and subcategory was counted. **RESULTS:** Of 138 responding family members, 106 answered the open-ended questions. The 281 comments were more frequently complimentary (n = 126) than critical (n = 91). Three main categories (competent care, communication, and environment) and nine subcategories were identified. Comments about the subcategory of emotional/interrelational aspects of care occurred most frequently and were more positive than comments about practical aspects of care. **DISCUSSION:** Findings were similar to those reported

from other countries. Emotional/interrelational aspects of care were integral to family member satisfaction with care provided. Findings suggest that improving communication and decision-making, supporting family members, and caring for family loved ones as a person are important care targets. Initiatives to improve ICU care should include assessments from families and opportunity for qualitative analysis to refine care targets and assess changes.

Harris, R. A., Alcott, C. E., Sullivan, E. L., Takahashi, D., McCurdy, C. E., Comstock, S., et al. (2016). Genomic variants associated with resistance to high fat diet induced obesity in a primate model. *Scientific Reports*, 6, 36123.

Maternal obesity contributes to an increased risk of lifelong morbidity and mortality for both the mother and her offspring. In order to better understand the molecular mechanisms underlying these risks, we previously established and extensively characterized a primate model in *Macaca fuscata* (Japanese macaque). In prior studies we have demonstrated that a high fat, caloric dense maternal diet structures the offspring's epigenome, metabolome, and intestinal microbiome. During the course of this work we have consistently observed that a 36% fat diet leads to obesity in the majority, but not all, of exposed dams. In the current study, we sought to identify the genomic loci rendering resistance to obesity despite chronic consumption of a high fat diet in macaque dams. Through extensive phenotyping together with exon capture array and targeted resequencing, we identified three novel single nucleotide polymorphisms (SNPs), two in apolipoprotein B (APOB) and one in phospholipase A2 (PLA2G4A) that significantly associated with persistent weight stability and insulin sensitivity in lean macaques. By application of explicit orthogonal modeling (NOIA), we estimated the polygenic and interactive nature of these loci against multiple metabolic traits and their measures (i.e., serum LDL levels) which collectively render an obesity resistant phenotype in our adult female dams.

Harris, S. K., Roos, M. G., & Landry, G. J. (2016). Statin use in patients with peripheral arterial disease. *Journal of Vascular Surgery*, 64(6), 1881-1888.

BACKGROUND: Statins are recommended for use in patients with peripheral arterial disease (PAD) to reduce cardiovascular events and mortality. However, much of the data regarding benefits of statins stem from the cardiovascular literature. Here, we review the literature

regarding statin use specifically in patients with PAD regarding its effects on cardiovascular events and mortality, limb-related outcomes, statin use after endovascular interventions, statin dosing, and concerns about statins. METHODS: We performed a literature review using PubMed for literature after the year 2000. Search terms included "statins," "peripheral arterial disease," "peripheral vascular disease," "lipid-lowering medication," and "cardiovascular disease."

RESULTS: There is good evidence of statins lowering cardiovascular events and cardiovascular-related mortality in patients with PAD. Though revascularization rates were reduced with statins, amputation rates and amputation-free survival did not improve. Small randomized controlled trials show that patients taking statins can slightly improve pain-free walking distance or pain-free walking time, although the extent of the effect on quality of life is unclear. Statin use for patients undergoing endovascular interventions is recommended because of the reduction of postoperative cardiovascular events. Not enough data exist to support local effects of systemic statin therapy, such as prevention of restenosis. For statin dosing, there is little increased benefit to intense therapy compared with the adverse effects, whereas moderate-dose therapy has significant benefits with very few adverse effects. Adverse effects of moderate-dose statin therapy are rare and mild and are greatly outweighed by the cardiovascular benefits.

CONCLUSIONS: There is strong evidence to support use of statins in patients with PAD to reduce cardiovascular events and mortality. Use in patients undergoing open and endovascular interventions is also recommended. Statin use may reduce the need for revascularization, but reductions in amputation have not been shown. Moderate-dose statin therapy is safe, and the minor risks are greatly outweighed by benefits.

Hay, S., Zupancic, J. A., Flannery, D. D., Kirpalani, H., & Dukhovny, D. (2016). Should we believe in transfusion-associated enterocolitis? applying a GRADE to the literature. *Seminars in Perinatology*,

Numerous observational studies appear to demonstrate an association between packed red blood cell (pRBC) transfusions and necrotizing enterocolitis (NEC). However, the limited numbers of randomized controlled trials (RCTs) do not support a causal relationship between pRBC transfusion and NEC. We sought to determine the quality of the evidence behind transfusion-associated necrotizing enterocolitis (TANEC), and to formulate a GRADE-based recommendation

regarding transfusion practices to reduce the risk of TANEC. A systematic search including MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and clinical trials registries was performed for studies assessing the association between transfusion and NEC. Teams of two paired reviewers independently screened studies for eligibility, assessed risk of bias using the GRADE framework, and collected data from each eligible study. We examined studies for two time points following transfusion: within 48h if this was available, and otherwise at any time after transfusion. In total, 23 observational studies and three RCTs met inclusion criteria. The average rating for the quality of evidence of individual studies was between "very low" and "low." On pooling studies for GRADE review, we observed an inconsistency of results. This led to a final overall quality of "very low" for the evidence for an association between transfusions and necrotizing enterocolitis. The pooled outcome of NEC for observational/case control studies was an odds ratio of 1.13 (95% CI: 0.99-1.29) when TANEC was defined as occurring within 48 hours of transfusion. For NEC occurring at any time post-transfusion, the pooled OR was 1.95 (1.60-2.38). Conversely, the pooled outcome of NEC for the RCT data had an odds ratio of 0.6 (0.3, 1.21) with NEC being less frequent in the liberal transfusion group compared to the restrictive transfusion group. The overall quality of the evidence for TANEC is "very low," suggesting very little confidence in the effect estimate. RCT data tended toward apparent protection against NEC. The available evidence is not sufficient to support a practice recommendation around pRBC transfusions in the context of preventing the development of NEC.

Hayes, S. A., Zive, D., Ferrell, B., & Tolle, S. W. (2016). The role of advanced practice registered nurses in the completion of physician orders for life-sustaining treatment. *Journal of Palliative Medicine*,

BACKGROUND: The Physician Orders for Life-Sustaining Treatment (POLST) Paradigm records advance care planning for patients with advanced illness or frailty as actionable medical records. The National POLST Paradigm Task Force recommends that physicians, advanced practice registered nurses (APRNs), and physician assistants (PAs) be permitted to execute POLST forms. OBJECTIVE: To investigate the percentage of Oregon POLST forms signed by APRNs, and examine the obstacles faced by states attempting to allow APRNs to sign POLST forms. DESIGN: Cross-sectional. SETTING/SUBJECTS: 226,101 Oregon POLST Registry forms from 2010 to 2015.

MEASUREMENTS: POLST forms in the Oregon Registry were matched with signer type (MD, DO, APRN, PA). RESULTS: 226,101 POLST forms have been added to the Oregon POLST Registry from 2010 to 2015: 85.3% of forms were signed by a physician, 10.9% of forms were signed by an APRN, and 3.8% of forms were signed by a PA. From 2010 to 2015, the overall percentage of POLST forms signed by an APRN has increased from 9.0% in 2010 to 11.9% in 2015. Physicians are authorized signers in all 19 states with endorsed POLST Paradigm programs; 16 of these states also authorize APRN signature, and 3 states (LA, NY, and GA) allow only physicians to sign. CONCLUSIONS: More than 10% of Oregon POLST forms are signed by APRNs. Given the need for timely POLST form completion, ideally by a member of the interdisciplinary team who knows the patient's preferences best, these data support authorizing APRNs to complete POLST forms.

Hayward, A. D. (2016). Predicting outcomes after hip fracture. *Journal of General Internal Medicine,*

He, F., Verneris, M. R., Cooley, S., Blazar, B. R., MacMillan, M. L., Newell, L. F., et al. (2016). Low day +100 serum epidermal growth factor levels are associated with acute GvHD after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplantation,*

Heeman, P. A., Lunsford, R., McMillin, A., & Yaruss, J. S. (2016). Using clinician annotations to improve automatic speech recognition of stuttered speech. *17th Annual Conference of the International Speech Communication Association, INTERSPEECH 2016, , 08-12-September-2016.* pp. 2651-2655.

In treating people who stutter, clinicians often have their clients read a story in order to determine their stuttering frequency. As the client is speaking, the clinician annotates each disfluency. For further analysis of the client's speech, it is useful to have a word transcription of what was said. However, as these are realtime annotations, they are not always correct, and they usually lag where the actual disfluency occurred. We have built a tool that rescores a word lattice taking into account the clinician's annotations. In the paper, we describe how we incorporate the clinician's annotations, and the improvement over a baseline version. This approach of leveraging clinician annotations can be used for other clinical tasks where a word transcription is useful for further or richer analysis. Copyright © 2016 ISCA.

Heimer, G., Keratar, J. M., Riley, L. G., Balasubramaniam, S., Eyal, E., Pietikainen, L. P., et al. (2016).

MECR mutations cause childhood-onset dystonia and optic atrophy, a mitochondrial fatty acid synthesis disorder. *American Journal of Human Genetics*, 99(6), 1229-1244.

Mitochondrial fatty acid synthesis (mtFAS) is an evolutionarily conserved pathway essential for the function of the respiratory chain and several mitochondrial enzyme complexes. We report here a unique neurometabolic human disorder caused by defective mtFAS. Seven individuals from five unrelated families presented with childhood-onset dystonia, optic atrophy, and basal ganglia signal abnormalities on MRI. All affected individuals were found to harbor recessive mutations in MECR encoding the mitochondrial trans-2-enoyl-coenzyme A-reductase involved in human mtFAS. All six mutations are extremely rare in the general population, segregate with the disease in the families, and are predicted to be deleterious. The nonsense c.855T>G (p.Tyr285 *), c.247_250del (p.Asn83Hisfs *4), and splice site c.830+2_830+3insT mutations lead to C-terminal truncation variants of MECR. The missense c.695G>A (p.Gly232Glu), c.854A>G (p.Tyr285Cys), and c.772C>T (p.Arg258Trp) mutations involve conserved amino acid residues, are located within the cofactor binding domain, and are predicted by structural analysis to have a destabilizing effect. Yeast modeling and complementation studies validated the pathogenicity of the MECR mutations. Fibroblast cell lines from affected individuals displayed reduced levels of both MECR and lipoylated proteins as well as defective respiration. These results suggest that mutations in MECR cause a distinct human disorder of the mtFAS pathway. The observation of decreased lipoylation raises the possibility of a potential therapeutic strategy.

Heintzman, J., Bailey, S. R., Cowburn, S., Dexter, E., Carroll, J., & Marino, M. (2016). Pneumococcal

vaccination in low-income latinos: An unexpected trend in oregon community health centers.

Journal of Health Care for the Poor and Underserved, 27(4), 1733-1744.

Background. In cross-sectional studies, Latino and Spanish-speaking U.S. residents age 65 and over are less likely to receive pneumococcal vaccination than non-Hispanic Whites. Methods. We performed a time-to-event, cohort analysis, in 23 Oregon community health centers of low-income patients who turned 65 in the study period (2009–2013; n = 1,248). The outcome measure was receipt of PPSV-23 in the study period by race/ethnicity, preferred language, and insurance status. Results. Insured Latino patients were more likely to receive PPSV-23 than

insured non-Hispanic Whites (HR = 2.05, $p < .001$). Uninsured Latino seniors showed no difference from insured non-Hispanic Whites in PPSV-23 receipt (HR = 1.26, $p = .381$) unless they averaged fewer than one clinic visit yearly (HR = 1.80, $p = .001$). Conclusions. Low-income Latino seniors in Oregon community health centers were immunized against pneumococcus more frequently than insured non-Hispanic Whites, although this finding was mitigated in Latinos without insurance. This finding needs further research in order to reduce adult immunization disparities in the society at large. © Meharry Medical College.

Hoffman, K. A., Beltran, J., Ponce, J., Garcia-Fernandez, L., Calderon, M., Muench, J., et al. (2016).

Barriers to implementing screening, brief intervention and referral to treatment for substance use in HIV/AIDS health services in Peru. [Barreras para implementar el despistaje, intervenciones breves y referencia al tratamiento por problemas de consumo de alcohol y otras drogas en hospitales que atienden personas que viven con el VIH/SIDA en el Peru] *Revista Peruana De Medicina Experimental y Salud Publica*, 33(3), 432-437.

Objectives.: Screening and treatment for substance use among people living with HIV/AIDS (PLWHA) is highly recommended. Nevertheless, in Peru healthcare for PLWHA does not include a standardized or systematic assessment to identify substance use. The aim of this study was to assess the feasibility of implementing screening, brief intervention and referral to treatment (SBIRT) in healthcare settings attending people living with PLWHA. Materials and methods.: After providing training in SBIRT for PLWHA's healthcare personnel (including nurses and physicians) focus groups were conducted to explore knowledge, beliefs and perceived barriers to implementation and interviews were conducted to assess the barriers and facilitators of two tertiary hospitals in Lima, Peru. Results.: focus groups and interviews' thematic coding revealed three dimensions: 1) the unknown extent of substance use within PLWHA, 2) space and time limitations hinder completion of brief interventions during routine visits, and 3) insufficient access to substance use treatment appropriate for HIV patients. Conclusions.: Multiple barriers, including lack of awareness of substance use problems, limited space and time of providers, and lack of specialized services to refer patients for treatment make it difficult to implement SBIRT in the Peruvian healthcare system.

Holliday, E. B., Hampton, D. A., Thomas, C. R., Jr., & Rana, S. (2016). Prognostic value of the yale grading system for superior vena cava syndrome. *Annals of the American Thoracic Society*, 13(10), 1862-1865.

Holmes, J. M., Manh, V. M., Lazar, E. L., Beck, R. W., Birch, E. E., Kraker, R. T., et al. (2016). Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: A randomized clinical trial. *JAMA Ophthalmology*,

Importance: A binocular approach to treating anisometropic and strabismic amblyopia has recently been advocated. Initial studies have yielded promising results, suggesting that a larger randomized clinical trial is warranted. Objective: To compare visual acuity (VA) improvement in children with amblyopia treated with a binocular iPad game vs part-time patching. Design, Setting, and Participants: A multicenter, noninferiority randomized clinical trial was conducted in community and institutional practices from September 16, 2014, to August 28, 2015. Participants included 385 children aged 5 years to younger than 13 years with amblyopia (20/40 to 20/200, mean 20/63) resulting from strabismus, anisometropia, or both. Participants were randomly assigned to either 16 weeks of a binocular iPad game prescribed for 1 hour a day (190 participants; binocular group) or patching of the fellow eye prescribed for 2 hours a day (195 participants; patching group). Study follow-up visits were scheduled at 4, 8, 12, and 16 weeks. A modified intent-to-treat analysis was performed on participants who completed the 16-week trial. Interventions: Binocular iPad game or patching of the fellow eye. Main Outcomes and Measures: Change in amblyopic-eye VA from baseline to 16 weeks. Results: Of the 385 participants, 187 were female (48.6%); mean (SD) age was 8.5 (1.9) years. At 16 weeks, mean amblyopic-eye VA improved 1.05 lines (2-sided 95% CI, 0.85-1.24 lines) in the binocular group and 1.35 lines (2-sided 95% CI, 1.17-1.54 lines) in the patching group, with an adjusted treatment group difference of 0.31 lines favoring patching (upper limit of the 1-sided 95% CI, 0.53 lines). This upper limit exceeded the prespecified noninferiority limit of 0.5 lines. Only 39 of the 176 participants (22.2%) randomized to the binocular game and with log file data available performed more than 75% of the prescribed treatment (median, 46%; interquartile range, 20%-72%). In younger participants (aged 5 to <7 years) without prior amblyopia treatment, amblyopic-eye VA improved by a mean (SD) of 2.5 (1.5) lines in the binocular group and 2.8 (0.8) lines in the

patching group. Adverse effects (including diplopia) were uncommon and of similar frequency between groups. Conclusions and Relevance: In children aged 5 to younger than 13 years, amblyopic-eye VA improved with binocular game play and with patching, particularly in younger children (age 5 to <7 years) without prior amblyopia treatment. Although the primary noninferiority analysis was indeterminate, a post hoc analysis suggested that VA improvement with this particular binocular iPad treatment was not as good as with 2 hours of prescribed daily patching. Trial Registration: <http://www.clinicaltrials.gov> Identifier: NCT02200211.

Holton, K. F., Marshall, L. M., Shannon, J., Lapidus, J. A., Shikany, J. M., Bauer, D. C., et al. (2016).

Dietary antioxidants and longitudinal changes in lower urinary tract symptoms in elderly men: The osteoporotic fractures in men study. *European Urology Focus*, 2(3), 310-318.

Background Antioxidants can potentially alter the progression of lower urinary tract symptoms (LUTS) through anti-inflammatory mechanisms. Objective To determine if dietary antioxidants are associated with reduced likelihood of LUTS progression or increased likelihood of LUTS remission in untreated elderly men. Design, setting, and participants A prospective cohort study of 1670 US men aged 65–100 yr. Outcome measurements and statistical analysis Baseline variables included the American Urological Association Symptom Index, dietary intake assessed via a 69-item Block food frequency questionnaire (FFQ), demographics, lifestyle characteristics, quality of life (SF-12), and medication use. LUTS was assessed at four time points over a mean \pm standard deviation period of 6.9 ± 0.4 yr. Group-based trajectory modeling was performed for men without prostate cancer who did not undergo LUTS treatment with medication or surgery during follow-up ($n = 1670$). Analyses were stratified by LUTS symptoms at baseline. For men with mild baseline LUTS, we examined the likelihood of LUTS progression relative to LUTS stability. For men with moderate baseline LUTS, we analyzed the likelihood of both LUTS progression relative to LUTS stability and LUTS remission relative to progression. Odds ratios and 95% confidence intervals were estimated for quartiles of daily antioxidant intake using multivariable logistic regression. Results and limitations None of the dietary antioxidants (vitamin C, vitamin E, β -carotene, α -carotene, β -cryptoxanthin, lycopene, lutein/zeaxanthin) was associated with a lower probability of LUTS progression or LUTS remission. The study was limited by use of the brief Block FFQ, which contains only 69 food items and may have biased results

toward the null hypothesis because of nondifferential misclassification. Conclusions In this large cohort of US men, there were no significant associations between multiple dietary antioxidants and LUTS progression or remission over 7 yr. Patient summary In a large cohort of elderly men, there were no significant longitudinal associations between multiple dietary antioxidants and lower urinary tract symptoms (LUTS). Our data suggest that dietary antioxidant consumption may not influence the natural history of LUTS in older men. © 2015 European Association of Urology

Hoorn, E. J., & Ellison, D. H. (2016). Diuretic resistance. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation*,

Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic. The causes of diuretic resistance include poor adherence to drug therapy or dietary sodium restriction, pharmacokinetic issues, and compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic. To illustrate the pathophysiology and management of diuretic resistance, we describe a patient with nephrotic syndrome. This patient presented with generalized pitting edema and weight gain despite the use of oral loop diuretics. Nephrotic syndrome may cause mucosal edema of the intestine, limiting the absorption of diuretics. In addition, the patient's kidney function had deteriorated, impairing the tubular secretion of diuretics. He was admitted for intravenous loop diuretic treatment. However, this was ineffective, likely due to compensatory sodium reabsorption by other tubular segments. The combination of loop diuretics with triamterene, a blocker of the epithelial sodium channel, effectively reduced body weight and edema. Recent data suggest that plasmin in nephrotic urine can activate the epithelial sodium channel, potentially contributing to the diuretic resistance in this patient. This case is used to illustrate and review the mechanisms of, and possible interventions for, in diuretic resistance.

Hwang, T. S., Zhang, M., Bhavsar, K., Zhang, X., Campbell, J. P., Lin, P., et al. (2016). Visualization of 3 distinct retinal plexuses by projection-resolved optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmology*,

Importance: Projection artifacts in optical coherence tomography angiography (OCTA) blur the

retinal vascular plexuses together and limit visualization of the individual plexuses. Objective: To describe projection-resolved (PR) OCTA in eyes with diabetic retinopathy (DR) and healthy eyes.

Design, Setting, and Participants: In this case-control study, patients with DR and healthy controls were enrolled in this observational study from January 26, 2015, to December 4, 2015, at a tertiary academic center. Spectral-domain, 70-kHz OCT obtained 3 x 3-mm macular scans. The PR algorithm suppressed projection artifacts. A semiautomated segmentation algorithm divided PR-OCTA into superficial, intermediate, and deep retinal plexuses. Two masked graders examined 3-layer PR-OCTA and combined angiograms for nonperfusion and abnormal capillaries.

Main Outcomes and Measures: Retinal nonperfusion and capillary abnormalities and the diagnostic accuracy of detecting DR. Results: Twenty-nine eyes of 15 healthy individuals (mean [SD] age, 36.2 [13.4] years; 11 women) and 47 eyes of 29 patients with DR (mean [SD] age, 55.5 [11.9]; 10 women) underwent imaging. PR-OCTA revealed 3 distinct retinal plexuses in their known anatomical locations in all eyes. The intermediate and deep plexuses of healthy eyes revealed capillary networks of uniform density and caliber, whereas the superficial plexus revealed vessels in the familiar centripetal branching pattern. In eyes with DR, 3-layer PR-OCTA disclosed incongruent areas of nonperfusion and varied vessel caliber and density in the deeper plexuses. Masked grading of capillary nonperfusion on 3-layer PR-OCTA detected DR with 100% sensitivity (95% CI, 90.8%-100%) and 100% specificity (95% CI, 85.4%-100%). With unsegmented retinal angiograms, the sensitivity and specificity were 78.7% (95% CI, 63.9%-88.8%) and 100% (95% CI, 85.4%-100%), respectively (P = .002 for sensitivity). On 3-layer PR-OCTA, sensitivity was 72.2% (95% CI, 54.6%-85.2%) for severe nonproliferative DR and proliferative DR eyes with generalized nonperfusion in 2 or more individual plexuses, but on combined angiogram, sensitivity was 25.0% (95% CI, 12.7%-42.5%) for generalized nonperfusion (P < .001). PR-OCTA disclosed dilated vessels in the intermediate and deep plexuses in 23 eyes (100%) with proliferative DR, 13 eyes (100%) with severe nonproliferative DR, 8 eyes (73%) with mild to moderate nonproliferative DR, and 0 control eyes.

Conclusions and Relevance: By presenting 3 retinal vascular plexuses distinctly, PR-OCTA reveals capillary abnormalities in deeper layers with clarity and may distinguish DR from healthy eyes and severe DR from mild DR with greater accuracy compared with conventional OCTA.

Iizuka, S., Abdullah, C., Buschman, M. D., Diaz, B., & Courtneidge, S. A. (2016). The role of tks adaptor proteins in invadopodia formation, growth and metastasis of melanoma. *Oncotarget*, Metastatic cancer cells are characterized by their ability to degrade and invade through extracellular matrix. We previously showed that the Tks adaptor proteins, Tks4 and Tks5, are required for invadopodia formation and/or function in Src-transformed fibroblasts and a number of human cancer cell types. In this study, we investigated the role of Tks adaptor proteins in melanoma cell invasion and metastasis. Knockdown of either Tks4 or Tks5 in both mouse and human melanoma cell lines resulted in a decreased ability to form invadopodia and degrade extracellular matrix. In addition, Tks-knockdown melanoma cells had decreased proliferation in a 3-dimensional type I collagen matrix, but not in 2-dimensional culture conditions. We also investigated the role of Tks proteins in melanoma progression in vivo using xenografts and experimental metastasis assays. Consistent with our in vitro results, reduction of Tks proteins markedly reduced subcutaneous melanoma growth as well as metastatic growth in the lung. We explored the clinical relevance of Tks protein expression in human melanoma specimens using a tissue microarray. Compared to non-malignant nevi, both Tks proteins were highly expressed in melanoma tissues. Moreover, metastatic melanoma cases showed higher expression of Tks5 than primary melanoma cases. Taken together, these findings suggest the importance of Tks adaptor proteins in melanoma growth and metastasis in vivo, likely via functional invadopodia formation.

Jaff, M. R., & Kaufman, J. (2016). A measured approach to vena cava filter use-respect rather than regret. *JAMA Cardiology*,

Jensen, J. T., Patil, E., Seguin, J., & Thurmond, A. (2016). Tubal patency during the menstrual cycle and during treatment with hormonal contraceptives: A pilot study in women. *Acta Radiologica (Stockholm, Sweden : 1987)*,

BACKGROUND: Hysterosalpingogram (HSG) evaluation of tubal patency is typically performed in the follicular phase, but data to support this timing are lacking. PURPOSE: To determine whether menstrual cycle phase or hormonal treatments affect observation of tubal patency during HSG. MATERIAL AND METHODS: Ten participants underwent repeated HSG examinations: during the follicular and luteal phase of a natural menstrual cycle; 30 days following continuous

administration of a combined oral contraceptive (COC); and 30 days after an intramuscular injection of depo medroxyprogesterone (DMPA) acetate. Participants with tubal blockade following DMPA had a fifth HSG 30 days following a second course of COCs. The primary outcome was tubal patency. RESULTS: All 10 participants demonstrated bilateral tubal patency (BTP) on at least one HSG examination during the study. One participant showed bilateral functional occlusion (FO) during the follicular phase examination, but BTP with the luteal phase, COC cycle, and DMPA exams. One participant with BTP discontinued participation and nine completed the COC HSG exam with BTP in seven, and one each with bilateral or unilateral FO. Seven participants completed the DMPA HSG with BTP in six and unilateral FO in one; BTP was seen in the final HSG after restarting the COC. CONCLUSION: This pilot study supports the luteal phase of natural cycles as the optimum time for evaluation of tubal patency. The occurrence of functional occlusion of the fallopian tube on HSG examination performed during the follicular phase and following contraceptive steroid treatment supports a role of hormonal action on the utero-tubal junction.

Jindai, K., Nielson, C. M., Vorderstrasse, B. A., & Quinones, A. R. (2016). Multimorbidity and functional limitations among adults 65 or older, NHANES 2005-2012. *Preventing Chronic Disease, 13*, E151.

INTRODUCTION: The development of functional limitations among adults aged 65 or older has profound effects on individual and population resources. Improved understanding of the relationship between functional limitations and co-occurring chronic diseases (multimorbidity) is an emerging area of interest. The objective of this study was to investigate the association between multimorbidity and functional limitations among community-dwelling adults 65 or older in the United States and explore factors that modify this association. METHODS: We conducted a cross-sectional analysis of adults aged 65 or older using data from the National Health and Nutrition Examination Survey (NHANES) from 2005 through 2012. We used negative binomial regression to estimate the association between multimorbidity (≥ 2 concurrent diseases) and functional limitations and to determine whether the association differed by sex or age. RESULTS: The prevalence of multimorbidity in this population was 67% (95% confidence interval [CI], 65%-68%). Each additional chronic condition was associated with an increase in the number of

functional limitations, and the association was stronger among those aged 75 or older than among those aged 65 to 74. For those aged 65 to 74, each additional chronic condition was associated with 1.35 (95% CI, 1.27-1.43) times the number of functional limitations for men and 1.62 times (95% CI, 1.31-2.02) the number of functional limitations for women. For those 75 or older, the associations increased to 1.71 (95% CI, 1.35-2.16) for men and 2.06 (95% CI, 1.51-2.81) for women for each additional chronic condition. CONCLUSION: Multimorbidity was associated with increases in functional limitations, and the associations were stronger among women than among men and among adults aged 75 or older than among those aged 65 to 74. These findings underscore the importance of addressing age and sex differences when formulating prevention strategies.

Jordan, J., Yarris, L. M., Santen, S. A., Guth, T. A., Rougas, S., Runde, D. P., et al. (2016). Creating a cadre of fellowship-trained medical educators, part II: A formal needs assessment to structure postgraduate fellowships in medical education scholarship and leadership. *Academic Medicine : Journal of the Association of American Medical Colleges*,

PURPOSE: Education leaders at the 2012 Academic Emergency Medicine Consensus Conference on education research proposed that dedicated postgraduate education scholarship fellowships (ESFs) might provide an effective model for developing future faculty as scholars. A formal needs assessment was performed to understand the training gap and inform the development of ESFs.

METHOD: A mixed-methods needs assessment was conducted of four emergency medicine national stakeholder groups in 2013: department chairs; faculty education/research leaders; existing education fellowship directors; and current education fellows/graduates. Descriptive statistics were reported for quantitative data. Qualitative data from semistructured interviews and free-text responses were analyzed using a thematic approach. RESULTS: Participants were 11/15 (73%) education fellowship directors, 13/20 (65%) fellows/graduates, 106/239 (44%) faculty education/research leaders, and a convenience sample of 26 department chairs. Department chairs expected new education faculty to design didactics (85%) and teach clinically (96%). Faculty education/research leaders thought new faculty were inadequately prepared for job tasks (83.7%) and that ESFs would improve the overall quality of education research (91.1%). Fellowship directors noted that ESFs provide skills, mentorship, and protected time for graduates

to become productive academicians. Current fellows/graduates reported pursuing an ESF to develop skills in teaching and research methodology. CONCLUSIONS: Stakeholder groups uniformly perceived a need for training in education theory, clinical teaching, and education research. These findings support dedicated, deliberate training in these areas. Establishment of a structure for scholarly pursuits prior to assuming a full-time position will effectively prepare new faculty. These findings may inform the development, implementation, and curricula of ESFs.

Junell, A., Thomas, J., Hawkins, L., Sklenar, J., Feldman, T., Henrikson, C. A., et al. (2016). Screening entire healthcare system ECG database: Association of deep terminal negativity of P wave in lead V1 and ECG referral with mortality. *International Journal of Cardiology*, 228, 219-224.

BACKGROUND: Each encounter of asymptomatic individuals with the healthcare system presents an opportunity for improvement of cardiovascular disease (CVD) awareness and sudden cardiac death (SCD) risk assessment. ECG sign deep terminal negativity of the P wave in V1 (DTNPV1) was shown to be associated with an increased risk of SCD in the general population. OBJECTIVE: To evaluate association of DTNPV1 with all-cause mortality and newly diagnosed atrial fibrillation (AFib) in the large tertiary healthcare system patient population. METHODS: Retrospective double cohort study compared two levels of exposure (automatically measured amplitude of P-prime (Pp) in V1): DTNPV1 (Pp from -100 μ V to -200 μ V) and ZeroPpV1 (Pp=0). An entire healthcare system (2010-2014) ECG database was screened. Medical records of children and patients with previously diagnosed AFib/atrial flutter (AFI), implanted pacemaker or cardioverter-defibrillator were excluded. DTNPV1 (n=3,413) and ZeroPpV1 (n=3,405) cohorts were matched by age and sex. Primary outcome was all-cause mortality. Secondary outcomes were newly diagnosed AFib/AFI. Median follow-up was 2.5 y. RESULTS: DTNPV1 was associated with all-cause mortality (HR 1.95(1.64-2.31); P<0.0001) and newly diagnosed AFib (HR 1.29(1.04-1.59); P=0.021) after adjustment for CVD, comorbidities, other ECG parameters, medications, and index ECG referral. Index ECG referral by a cardiologist was independently associated with 34% relative risk reduction of mortality (HR 0.66(0.52-0.84); P=0.001), as compared to ECG referral by a non-cardiologist. CONCLUSION: DTNPV1 is independently associated with twice higher risk of all-cause death, as compared to patients without P prime in V1. Life-saving effect of the index ECG referral by a cardiologist requires further study.

Jung, J. K., Wu, B., Kim, H., & Polsky, D. (2016). The effect of publicized quality information on home health agency choice. *Medical Care Research and Review*, 73(6), 703-723.

We examine consumers' use of publicized quality information in Medicare home health care markets, where consumer cost sharing and travel costs are absent. We report two findings. First, agencies with high quality scores are more likely to be preferred by consumers after the introduction of a public reporting program than before. Second, consumers' use of publicized quality information differs by patient group. Community-based patients have slightly larger responses to public reporting than hospital-discharged patients. Patients with functional limitations at the start of their care, at least among hospital-discharged patients, have a larger response to the reported functional outcome measure than those without functional limitations. In all cases of significant marginal effects, magnitudes are small. We conclude that the current public reporting approach is unlikely to have critical impacts on home health agency choice. Identifying and releasing quality information that is meaningful to consumers may help increase consumers' use of public reports. © The Author(s) 2016.

Kaner, J., & Schaack, S. (2016). Understanding ebola: The 2014 epidemic. *Globalization and Health*, 12(1)

Near the end of 2013, an outbreak of Zaire ebolavirus (EBOV) began in Guinea, subsequently spreading to neighboring Liberia and Sierra Leone. As this epidemic grew, important public health questions emerged about how and why this outbreak was so different from previous episodes. This review provides a synthetic synopsis of the 2014-15 outbreak, with the aim of understanding its unprecedented spread. We present a summary of the history of previous epidemics, describe the structure and genetics of the ebolavirus, and review our current understanding of viral vectors and the latest treatment practices. We conclude with an analysis of the public health challenges epidemic responders faced and some of the lessons that could be applied to future outbreaks of Ebola or other viruses. © 2016 The Author(s).

Karam, C., & Tramontozzi, L. A. (2016). Rapid screening for inflammatory neuropathies by standardized clinical criteria. *Neurology: Clinical Practice*, 6(5), 384-388.

Background: Delay in recognition and treatment of inflammatory neuropathies increases

morbidity and mortality. We have developed and standardized 3 clinical screening criteria that rapidly detect inflammatory neuropathies. Methods: We reviewed all patients with definite large fiber neuropathy in 2 different patient populations: 1 from a private neurology clinic and the other from a tertiary care center. Patients were divided into 2 groups: those with an inflammatory neuropathy and those with a noninflammatory neuropathy. We specifically noted the 3 key neuropathy characteristics: onset, distribution, and associated systemic features (ODS). We studied the sensitivity and specificity of ODS in differentiating between inflammatory and noninflammatory neuropathies. Results: A total of 206 patients were included: 51 from the private clinic and 155 from the tertiary care center. The sensitivity of using ODS in detecting an inflammatory neuropathy was 96% and the specificity was 85%. The positive predictive value of ODS was 0.8 and negative predictive value was 0.97. Conclusions: Rapid screening for inflammatory neuropathies by ODS clinical criteria is highly sensitive and has a high negative predictive value for noninflammatory neuropathies. ODS uses simple clinical criteria to rapidly screen for patients with a potentially treatable form of neuropathy and accelerate their diagnostic evaluation. Classification of evidence: This study provides Class IV evidence that 3 neuropathy characteristics-onset, distribution, and associated systemic features-accurately identify patients with inflammatory neuropathies. © 2016 American Academy of Neurology.

Kärnä, T., & Baptista, A. M. (2016). Water age in the Columbia River estuary. *Estuarine, Coastal and Shelf Science*,

The concept of water age is applied to the Columbia River estuary to investigate water renewing time scales. Water age tracers were implemented in a three-dimensional circulation model. The model was run for a nine month period in 2012, covering both high and low flow conditions. In the lower estuary renewing water age ranges from roughly 20 h during high flow season (typically April-June) to 70 h during lowest river discharge (typically September-October). The age of riverine water is strongly dependent on river discharge. Dense oceanic waters, in contrast, are always relatively young in the estuary (roughly 20 h) although their age does vary with tidal range and river discharge. Compared to the main channels, water age tends to be larger in the lateral bays throughout the simulation period; this is especially true under low flow and neap tides conditions when water age can exceed 120 h in the bays. During low flow conditions a

strong lateral circulation pattern emerges and leads to higher water age near Grays Bay. The maximal water age in the main channels is associated with mixed water mass (around 6-12 psu) located in front and above the salt wedge. The circulation model results are used to derive simple regression models that can be used to predict renewing water time scales without the need of a circulation model. © 2016 The Authors.

Kato, T. A., Teo, A. R., Tateno, M., Watabe, M., Kubo, H., & Kanba, S. (2016). Can "pokemon GO" rescue shut-ins (hikikomori) from their isolated world? *Psychiatry and Clinical Neurosciences*,

Kennedy, N. I., LaPrade, C. M., & LaPrade, R. F. (2017). Surgical management and treatment of the anterior cruciate Ligament/Posterolateral corner injured knee. *Clinics in Sports Medicine*, 36(1), 105-117.

Posterolateral knee injuries occur more commonly than in the past. These injuries most commonly occur concurrent with cruciate ligament tears. The main stabilizers of the posterolateral knee are the fibular collateral ligament, the popliteus tendon, and the popliteofibular ligament. These static stabilizers function to prevent increased varus, external rotation, and coupled posterolateral rotation of the knee. The most important clinical tests to diagnose posterolateral knee injuries are the varus stress test, posterolateral drawer, and dial tests. Varus stress radiographs are key objective means to diagnose these injuries. Anatomic-based reconstructions have been validated to restore stability and improve outcomes.

Kerr, W. C., Kaplan, M. S., Huguet, N., Caetano, R., Giesbrecht, N., & McFarland, B. H. (2016).

Economic recession, alcohol, and suicide rates: Comparative effects of poverty, foreclosure, and job loss. *American Journal of Preventive Medicine*,

INTRODUCTION: Suicide rates and the proportion of alcohol-involved suicides rose during the 2008-2009 recession. Associations between county-level poverty, foreclosures, and unemployment and suicide rates and proportion of alcohol-involved suicides were investigated.

METHODS: In 2015, National Violent Death Reporting System data from 16 states in 2005-2011 were utilized to calculate suicide rates and a measure of alcohol involvement in suicides at the county level. Panel models with year and state fixed effects included county-level measures of unemployment, foreclosure, and poverty rates. RESULTS: Poverty rates were strongly associated

with suicide rates for both genders and all age groups, were positively associated with alcohol involvement in suicides for men aged 45-64 years, and negatively associated for men aged 20-44 years. Foreclosure rates were negatively associated with suicide rates for women and those aged ≥ 65 years but positively related for those aged 45-64 years. Unemployment rate effects on suicide rates were mediated by poverty rates in all groups. CONCLUSIONS: Population risk of suicide was most clearly associated with county-level poverty rates, indicating that programs addressing area poverty should be targeted for reducing suicide risk. Poverty rates were also associated with increased alcohol involvement for men aged 45-64 years, indicating a role for alcohol in suicide for this working-aged group. However, negative associations between economic indicators and alcohol involvement were found for four groups, suggesting that non-economic factors or more general economic effects not captured by these indicators may have played a larger role in alcohol-related suicide increases.

Kesselheim, J. C., Agrawal, A. K., Bhatia, N., Cronin, A., Jubran, R., Kent, P., et al. (2016). Measuring pediatric hematology-oncology fellows' skills in humanism and professionalism: A novel assessment instrument. *Pediatric Blood & Cancer*,

BACKGROUND: Educators in pediatric hematology-oncology lack rigorously developed instruments to assess fellows' skills in humanism and professionalism. PROCEDURE: We developed a novel 15-item self-assessment instrument to address this gap in fellowship training. Fellows (N = 122) were asked to assess their skills in five domains: balancing competing demands of fellowship, caring for the dying patient, confronting depression and burnout, responding to challenging relationships with patients, and practicing humanistic medicine. An expert focus group predefined threshold scores on the instrument that could be used as a cutoff to identify fellows who need support. Reliability and feasibility were assessed and concurrent validity was measured using three established instruments: Maslach Burnout Inventory (MBI), Flourishing Scale (FS), and Jefferson Scale of Physician Empathy (JSPE). RESULTS: For 90 participating fellows (74%), the self-assessment proved feasible to administer and had high internal consistency reliability (Cronbach's alpha = 0.81). It was moderately correlated with the FS and MBI (Pearson's $r = 0.41$ and 0.4 , respectively) and weakly correlated with the JSPE (Pearson's $r = 0.15$). Twenty-eight fellows (31%) were identified as needing support. The self-

assessment had a sensitivity of 50% (95% confidence interval [CI]: 31-69) and a specificity of 77% (95% CI: 65-87) for identifying fellows who scored poorly on at least one of the three established scales. CONCLUSIONS: We developed a novel assessment instrument for use in pediatric fellowship training. The new scale proved feasible and demonstrated internal consistency reliability. Its moderate correlation with other established instruments shows that the novel assessment instrument provides unique, nonredundant information as compared to existing scales.

Kim, D. H., Kim, J., Kwon, J. S., Sandhu, J., Tontonoz, P., Lee, S. K., et al. (2016). Critical roles of the histone methyltransferase MLL4/KMT2D in murine hepatic steatosis directed by ABL1 and PPARgamma2. *Cell Reports*, 17(6), 1671-1682.

The pathophysiologic continuum of non-alcoholic fatty liver disease begins with steatosis. Despite recent advances in our understanding of the gene regulatory program directing steatosis, how it is orchestrated at the chromatin level is unclear. PPARgamma2 is a hepatic steatotic transcription factor induced by overnutrition. Here, we report that the histone H3 lysine 4 methyltransferase MLL4/KMT2D directs overnutrition-induced murine steatosis via its coactivator function for PPARgamma2. We demonstrate that overnutrition facilitates the recruitment of MLL4 to steatotic target genes of PPARgamma2 and their transactivation via H3 lysine 4 methylation because PPARgamma2 phosphorylated by overnutrition-activated ABL1 kinase shows enhanced interaction with MLL4. We further show that Pparg2 (encoding PPARgamma2) is also a hepatic target gene of ABL1-PPARgamma2-MLL4. Consistently, inhibition of ABL1 improves the fatty liver condition of mice with overnutrition by suppressing the pro-steatotic action of MLL4. Our results uncover a murine hepatic steatosis regulatory axis consisting of ABL1-PPARgamma2-MLL4, which may serve as a target of anti-steatosis drug development.

Kim, Y. -, Kim, R., Ferracane, J. L., & Lee, I. -. (2016). Influence of the compliance and layering method on the wall deflection of simulated cavities in bulk-fill composite restoration. *Operative Dentistry*, 41(6), e183-e194.

The aim of this study was to investigate the effects of the layering method and compliance on the wall deflection of simulated cavities in bulk-fill and conventional composite restorations and to

examine the relationships between the wall deflection and the polymerization shrinkage, flexural modulus, and polymerization shrinkage stress of composites. Six lightcured composites were used in this study. Two of these were conventional methacrylate-based composites (Filtek Z250 and Filtek Z350 XT Flowable [Z350F]), whereas four were bulk-fill composites (SonicFill, Tetric N-Ceram Bulk-Fill, SureFil SDR Flow [SDR], and Filtek Bulk-Fill). One hundred eighty aluminum molds simulating a mesio-occluso-distal cavity (6 W38 L34 D mm) were prepared and classified into three groups with mold wall thicknesses of 1, 2, and 3 mm. Each group was further subdivided according to the composite layering method (bulk or incremental layering). Linear variable differential transformer probes were used to measure the mold wall deflection of each composite (n=5) over a period of 2000 seconds (33.3 minutes). The polymerization shrinkage, flexural modulus, and polymerization shrinkage stress of the six composites were also measured. All groups with bulk filling exhibited significantly higher deflection compared with groups with incremental layering. The deflection decreased as mold wall thickness increased. The highest and lowest polymerization shrinkage stresses were recorded for Z350F (5.07 MPa) and SDR (1.70 MPa), respectively. The correlation between polymerization shrinkage and the mold wall deflection decreased with increasing wall thickness. On the other hand, the correlation between flexural modulus and the mold wall deflection increased with increasing wall thickness. For all groups, wall deflection correlated strongly with polymerization shrinkage stress.

Kolivras, A., & Thompson, C. (2016). Primary scalp alopecia: New histopathological tools, new concepts and a practical guide to diagnosis. *Journal of Cutaneous Pathology*,
The diagnosis of primary scalp alopecia remains one of the most challenging fields in dermatopathology. In this review, we would like to connect the established classification of primary alopecia into scarring (cicatricial) and non-scarring (non-cicatricial) with current concepts. We introduce a simplified pathway for the diagnosis of the most common causes of alopecia, including a discussion of tissue processing techniques and use of immunohistochemistry.

Kopp, R. P., Chevinsky, M., Bernstein, M., Bosl, G., Motzer, R., Bajorin, D., et al. (2016). Bilateral testicular germ cell tumors in the era of multimodal therapy. *Urology*,

OBJECTIVES: To characterize the incidence, presentation, management, and relapse of a large population of bilateral testicular germ cell tumors (TGCT) from a single institution. **METHODS:** We identified bilateral TGCT diagnosed between 1/1989 and 2/2014. We categorized synchronous and metachronous TGCT, noting time between 1st and 2nd TGCT, histology [seminoma vs. nonseminoma (NSGCT)], stage and treatments. Kaplan Meier survival estimates characterized relapse. **RESULTS:** Of 5,132 TGCT patients, 128 (2.5%) had bilateral TGCT. Bilateral TGCT increased over time-1.7% in 1989-1994 up to 3.8% in 2010-2/2014. The 35 (27%) synchronous TGCT had 20 (57%) concordant seminoma, 5 (14%) concordant NSGCT, and 10 (29%) discordant. The 93 (73%) metachronous cases had median time interval to 2nd TGCT of 73 months (range 5 months to 28.6 years). Compared to 1st TGCT, 39 (42%) had discordant histology, 29 (31%) concordant seminoma, and 25 (27%) concordant NSGCT. Stage at 1st tumor was statistically similar to second TGCT (2nd stage I/II/III in 69%/22%/10%). Increasing duration between 1st and 2nd TGCT was not associated with higher stage (II/III) at second TGCT ($p=0.09$). Treatment at 1st tumor was not associated with stage at 2nd tumor. Relapse following bilateral diagnosis was 16.8% (95%CI 10.5-26.2%) at 5 years. **CONCLUSIONS:** Incidence of bilateral TGCT increased with >25% of metachronous TGCT presenting ≥ 10 years after 1st TGCT; possible causes include increased survivorship and/or referral bias. Stage was statistically similar at 1st and 2nd tumor; stage at 2nd tumor was not associated with time interval between tumors or prior treatment modality at 1st tumor.

Krey, J. F., Krystofiak, E. S., Dumont, R. A., Vijayakumar, S., Choi, D., Rivero, F., et al. (2016).

Plastin 1 widens stereocilia by transforming actin filament packing from hexagonal to liquid. *The Journal of Cell Biology*, 215(4), 467-482.

With their essential role in inner ear function, stereocilia of sensory hair cells demonstrate the importance of cellular actin protrusions. Actin packing in stereocilia is mediated by cross-linkers of the plastin, fascin, and espin families. Although mice lacking espin (ESPN) have no vestibular or auditory function, we found that mice that either lacked plastin 1 (PLS1) or had nonfunctional fascin 2 (FSCN2) had reduced inner ear function, with double-mutant mice most strongly affected. Targeted mass spectrometry indicated that PLS1 was the most abundant cross-linker in vestibular stereocilia and the second most abundant protein overall; ESPN only accounted for

approximately 15% of the total cross-linkers in bundles. Mouse utricle stereocilia lacking PLS1 were shorter and thinner than wild-type stereocilia. Surprisingly, although wild-type stereocilia had random liquid packing of their actin filaments, stereocilia lacking PLS1 had orderly hexagonal packing. Although all three cross-linkers are required for stereocilia structure and function, PLS1 biases actin toward liquid packing, which allows stereocilia to grow to a greater diameter.

Lam, M. K., Bayne, A. P., Thomas, G. A., & Austin, J. C. (2016). Invasive high-grade upper tract urothelial carcinoma in a 14 year-old girl. *Urology*,

We present an unusual pediatric case of invasive upper tract urothelial carcinoma with an associated genetic predisposition. A 14 year-old female presented with intermittent right flank pain, and was found to have a poorly functioning hydronephrotic right kidney. Laparoscopic nephrectomy was performed. Pathology demonstrated upper tract urothelial carcinoma, and she subsequently underwent completion ureterectomy. Genetic studies demonstrated a double-hit constitutional deletion of a DNA mismatch repair protein, revealing a rare Lynch syndrome variant known as Constitutional Mismatch Repair Deficiency Syndrome (CMMRD). This disease places her at high risk for multiple malignancies, including upper tract urothelial carcinoma.

Landry, G. J., Shukla, R., Rahman, A., Azarbal, A. F., Mitchell, E. L., Liem, T. K., et al. (2016).

Demographic and echocardiographic predictors of anatomic site and outcomes of surgical interventions for cardiogenic limb emboli. *Vascular Medicine (London, England)*, 21(6), 528-534.

We sought to determine if symptomatic cardiogenic limb emboli have a random distribution or if there are demographic or echocardiographic factors that predict site of embolization, limb salvage and mortality. Upper (UE) and lower extremity (LE) emboli were evaluated over a 16-year period (1996-2012). Demographic (age, gender, smoking, medical comorbidities) and echocardiographic data were analyzed to determine predictors of embolic site. All symptomatic patients underwent surgical revascularization. Limb salvage and mortality were compared with Kaplan-Meier analysis. A total of 161 patients with symptomatic cardiogenic emboli were identified: 56 UE and 105 LE. The female-to-male ratio for UE emboli (70%:30%) was significantly higher than for LE emboli (47%:53%, $p=0.008$). No other demographic factors were statistically different. Upper extremity patients were more likely to have atrial fibrillation (50% vs 29.8%, $p=0.028$), while LE patients

had a higher percentage of aortic or mitral valvular disease or intracardiac thrombus (71.4% vs 52.5%, $p=0.038$). The 30-day limb salvage was higher for UE compared to LE (100% vs 88%, $p=0.008$). There was a trend toward higher 30-day mortality in the LE group (14% vs 5%, $p=0.11$). Survival at 1, 3, and 5 years were similar (UE: 62.2%, 44.2%, 35.3%; LE: 69.1%, 47.5%, 30.3%; $p=ns$). Upper extremity emboli are more frequent in women and patients with atrial fibrillation. Lower extremity emboli are more frequent in the presence of valvular disease or intracardiac thrombus, and are associated with increased 30-day limb loss and mortality. These findings suggest gender- and cardiac-specific differences in patterns of blood flow leading to preferential sites of peripheral embolization.

Leichtling, G. J., Irvine, J. M., Hildebran, C., Cohen, D. J., Hallvik, S. E., & Deyo, R. A. (2016).

Clinicians' use of prescription drug monitoring programs in clinical practice and decision-making. *Pain Medicine (Malden, Mass.)*,

OBJECTIVES: Little is known about clinicians' use of prescription drug monitoring program (PDMP) profiles in decision-making. The objective of this qualitative study was to understand how clinicians use, interpret, and integrate PDMP profiles with other information in making clinical decisions. DESIGN : Qualitative interviews of clinician PDMP users. SETTING: Oregon registrants in the state's PDMP. SUBJECTS: Thirty-three clinicians practicing in primary care, emergency medicine, pain management, psychiatry, dentistry, and surgery. METHODS: We conducted semistructured telephone interviews with PDMP users. A multidisciplinary team used a grounded theory approach to identify patterns of PDMP use and how PDMP profiles influence clinical decisions. RESULTS: PDMP use varied from consistent monitoring to checking the PDMP only on suspicion of misuse, with inconsistent use reported particularly among short-term prescribers. Primary care clinicians reported less routine use with existing pain patients than with new patients. In response to worrisome PDMP profiles with new patients, participants reported declining to prescribe, except in the case of acute, verifiable conditions. Long-term prescribers reported sometimes continuing prescriptions for existing patients depending on perceived patient intent, honesty, and opioid misuse risk. Some long-term prescribers reported discharging patients from their practices due to worrisome PDMP profiles; others expressed strong ethical grounds for retaining patients but discontinuing controlled substances. CONCLUSION: Greater

consistency is needed in use of PDMP in monitoring existing patients and in conformity to guidelines against discharging patients from practice. Research is needed to determine optimal approaches to interpreting PDMP profiles in relation to clinical judgment, patient screeners, and other information.

Levy, J. M., Mace, J. C., Smith, T. L., & Soler, Z. M. (2016). Influence of interpersonal traits on patient outcomes in the treatment of chronic rhinosinusitis. *International Forum of Allergy & Rhinology*,

BACKGROUND: Patient-reported outcome measures (PROMs) measure health states in chronic rhinosinusitis (CRS) and have become the dominant metrics of treatment outcomes. Interpersonal traits (IPTs) are patient-specific factors that include personality type, perceived social support, and trust in physicians. The association of IPTs on treatment outcomes among patients with CRS has not been described previously, and IPTs may represent major clinical factors influencing treatment outcomes. METHODS: Adult patients electing medical or surgical treatment for recalcitrant CRS were prospectively enrolled into a multi-institutional, observational outcomes study. Validated measures of IPTs, including the Big Five Inventory-10 Short Version (BFI-10), Multidimensional Scale of Perceived Social Support (MSPSS), and the Trust in Physician Scale (TPS), were completed and compared with PROMs, which included the 22-item SinoNasal Outcome Test (SNOT-22), the Medical Outcomes Study Short Form-6D (SF-6D), and the Patient Health Questionnaire-2 (PHQ-2). RESULTS: Three hundred fifty-four participants were included and followed for an average (+/- standard deviation) of 16.3 (+/-4.8) months. Significant within-subject improvement in mean PROM scores was reported (all $p < 0.050$). Significant, but weak, absolute correlations were reported between baseline TPS scores and improvement in SNOT-22, SF-6D, and PHQ-2 total scores ($p < 0.050$; $r \leq 0.138$). CONCLUSION: Personality type and perceived social support do not associate with improvement after treatment for CRS. However, increased trust in physicians is weakly associated with greater posttreatment improvement. Further study is needed to examine the relationship between physician trust, patient satisfaction, and treatment outcomes among patients with CRS.

Levy, J. M., & Smith, T. L. (2016). Is aspirin desensitization indicated for the treatment recalcitrant chronic rhinosinusitis with nasal polyposis in aspirin-exacerbated respiratory disease? *The Laryngoscope*,

Lindly, O. J., Chavez, A. E., & Zuckerman, K. E. (2016). Unmet health services needs among US children with developmental disabilities: Associations with family impact and child functioning. *Journal of Developmental and Behavioral Pediatrics : JDBP*, 37(9), 712-723.

OBJECTIVE: To determine associations of unmet needs for child or family health services with (1) adverse family financial and employment impacts and (2) child behavioral functioning problems among US children with autism spectrum disorder (ASD), developmental delay (DD), and/or intellectual disability (ID). METHOD: This was a secondary analysis of parent-reported data from the 2009 to 2010 National Survey of Children with Special Health Care Needs linked to the 2011 Survey of Pathways to Diagnosis and Services. The study sample (n = 3,518) represented an estimated 1,803,112 US children aged 6 to 17 years with current ASD, DD, and/or ID (developmental disabilities). Dependent variables included adverse family financial and employment impacts, as well as child behavioral functioning problems. The independent variables of interest were unmet need for (1) child health services and (2) family health services. Multivariable logistic regression models were fit to examine associations. RESULTS: Unmet need for child and family health services, adverse family financial and employment impacts, and child behavioral functioning problems were prevalent among US children with developmental disabilities. Unmet needs were associated with an increased likelihood of adverse family employment and financial impacts. Unmet needs were associated with an increased likelihood of child behavioral functioning problems the following year; however, this association was not statistically significant. CONCLUSION: Unmet needs are associated with adverse impacts for children with developmental disabilities and their families. Increased access to and coordination of needed health services following ASD, DD, and/or ID diagnosis may improve outcomes for children with developmental disabilities and their families.

Loo, C. P., Snyder, C. M., & Hill, A. B. (2016). Blocking virus replication during acute murine cytomegalovirus infection paradoxically prolongs antigen presentation and increases the CD8+ T

cell response by preventing type I IFN-dependent depletion of dendritic cells. *Journal of Immunology (Baltimore, Md.: 1950)*,

Increasing amounts of pathogen replication usually lead to a proportionate increase in size and effector differentiation of the CD8+ T cell response, which is attributed to increased Ag and inflammation. Using a murine CMV that is highly sensitive to the antiviral drug famciclovir to modulate virus replication, we found that increased virus replication drove increased effector CD8+ T cell differentiation, as expected. Paradoxically, however, increased virus replication dramatically decreased the size of the CD8+ T cell response to two immunodominant epitopes. The decreased response was due to type I IFN-dependent depletion of conventional dendritic cells and could be reproduced by specific depletion of dendritic cells from day 2 postinfection or by sterile induction of type I IFN. Increased virus replication and type I IFN specifically inhibited the response to two immunodominant epitopes that are known to be dependent on Ag cross-presented by DCs, but they did not inhibit the response to "inflationary" epitopes whose responses can be sustained by infected nonhematopoietic cells. Our results show that type I IFN can suppress CD8+ T cell responses to cross-presented Ag by depleting cross-presenting conventional dendritic cells.

Loomans, B., & Hilton, T. (2016). Extended resin composite restorations: Techniques and procedures. *Operative Dentistry, 41*, S58-S67.

This article gives an overview of the state of the art of different restorative treatment procedures and techniques needed for placing extended posterior resin composite restorations. Clinical aspects related to the procedure are discussed and reviewed based on the current literature, such as the use of proper adhesive restorative materials, use of liners and bases, moisture control, reconstruction of proximal contacts, extended resin composite restorations, and techniques to address restoring teeth with deep subgingival margins.

Luna, S. L., Brown, D. I., Eghlidi, D. H., Kohama, S. G., & Urbanski, H. F. (2017). Locomotor activity and the expression of orexin A and orexin B in aged female rhesus macaques. *Neurobiology of Aging, 50*, 1-4.

Reduced activity has been linked to age-associated physiological changes but the underlying root

cause is unclear. The goal of the present study was to compare the orexin neuronal system of old (23–29 years) female rhesus macaques with either active or sedentary 24-hour locomotor activity patterns. Using immunohistochemistry, we counted the number of orexin A and orexin B neurons in the lateral hypothalamic area of each animal. Overall, we observed no difference in the distribution pattern or number of either orexin A or orexin B immune-positive neurons between animals in the 2 groups. Thus, reduced activity in the elderly is unlikely to stem from a loss of orexin neuronal perikarya in the lateral hypothalamic area. This, however, does not rule out the possibility that the reduced activity stems from reduced orexin neuronal projections to arousal centers of the brain, such as the locus coeruleus, or from attenuated release of orexin. © 2016 Elsevier Inc.

Lund, A. W. (2016). The lung's defensive line. *Science Translational Medicine*, 8(365), 365ec184.

Lund, A. W. (2016). Rethinking lymphatic vessels and antitumor immunity. *Trends in Cancer*, 2(10), 548-551.

Lymphatic vessels facilitate fluid homeostasis, immune cell trafficking, and lipid transport, and contribute to solid tumor progression as routes of metastasis. Given new evidence that lymphatic vessels both correlate with intratumoral lymphocytes and directly suppress immune function, I reevaluate the passive lymphatic vessel paradigm and discuss its relevance to antitumor immunity. © 2016 Elsevier Inc.

Lunsford, R., Heeman, P. A., & Rennie, E. (2016). Measuring turn-taking offsets in human-human dialogues. *17th Annual Conference of the International Speech Communication Association, INTERSPEECH 2016, , 08-12-September-2016*. pp. 2895-2899.

This paper examines the pauses, gaps and overlaps associated with turn-taking in order to better understand how people engage in this activity, which should lead to more natural and effective spoken dialogue systems. This paper makes three advances in studying these durations. First, we take into account the type of turn-taking event, carefully treating interruptions, dual starts, and delayed backchannels, as these can make it appear that turn-taking is more disorderly than it really is. Second, we do not view turn-transitions in isolation, but consider turntransitions and turn-continuations together, as equal alternatives of what could have occurred. Third, we use the

distributions of turn-transition and turn-continuation offsets (gaps, overlaps, and pauses) to shed light on the extent to which turn-taking is negotiated by the two conversants versus controlled by the current speaker. Copyright © 2016 ISCA.

Lusardi, T. A., Phillips, J. I., Wiedrick, J. T., Harrington, C. A., Lind, B., Lapidus, J. A., et al. (2016).

MicroRNAs in human cerebrospinal fluid as biomarkers for alzheimer's disease. *Journal of Alzheimer's Disease : JAD*,

BACKGROUND: Currently available biomarkers of Alzheimer's disease (AD) include cerebrospinal fluid (CSF) protein analysis and amyloid PET imaging, each of which has limitations. The discovery of extracellular microRNAs (miRNAs) in CSF raises the possibility that miRNA may serve as novel biomarkers of AD. OBJECTIVE: Investigate miRNAs in CSF obtained from living donors as biomarkers for AD. METHODS: We profiled miRNAs in CSF from 50 AD patients and 49 controls using TaqMan(R) arrays. Replicate studies performed on a subset of 32 of the original CSF samples verified 20 high confidence miRNAs. Stringent data analysis using a four-step statistical selection process including log-rank and receiver operating characteristic (ROC) tests, followed by random forest tests, identified 16 additional miRNAs that discriminate AD from controls. Multimarker modeling evaluated linear combinations of these miRNAs via best-subsets logistic regression, and computed area under the ROC (AUC) curve ascertained classification performance. The influence of ApoE genotype on miRNA biomarker performance was also evaluated. RESULTS: We discovered 36 miRNAs that discriminate AD from control CSF. 20 of these retested in replicate studies verified differential expression between AD and controls. Stringent statistical analysis also identified these 20 miRNAs, and 16 additional miRNA candidates. Top-performing linear combinations of 3 and 4 miRNAs have AUC of 0.80-0.82. Addition of ApoE genotype to the model improved performance, i.e., AUC of 3 miRNA plus ApoE4 improves to 0.84. CONCLUSIONS: CSF miRNAs can discriminate AD from controls. Combining miRNAs improves sensitivity and specificity of biomarker performance, and adding ApoE genotype improves classification.

Lyons, K. S., Miller, L. M., & McCarthy, M. J. (2016). The roles of dyadic appraisal and coping in couples with lung cancer. *Journal of Family Nursing*, 22(4), 493-514.

Given the high symptom burden and low survivability of lung cancer, patients and their spouses have been found to experience poor mental health. The current study examined the roles of dyadic appraisal and dyadic coping on the mental health of 78 couples living with non-small cell lung cancer. Multilevel modeling revealed that spouses, on average, reported significantly worse mental health than patients. Dyadic appraisal and dyadic coping played important roles in predicting mental health, controlling for known developmental and contextual covariates. Dyadic appraisal of the patient's pain and fatigue was significantly associated with spouse mental health, albeit in opposite directions. Dyadic coping significantly predicted patient mental health. The study underlines the need to incorporate routine screening of both patient and spouse mental health, and highlights the complex role of appraisal within the couple in a life-threatening context. Viewing the couple as a unit, rather than separate individuals, raises important awareness about the role of disparate illness appraisals and coping strategies within the dyad on the health of both members. Nurses are particularly well situated to engage in a collaborative family-focused approach to the couple with cancer that promotes communication and health.

Markham, C. M., Craig Rushing, S., Jessen, C., Gorman, G., Torres, J., Lambert, W. E., et al. (2016).

Internet-based delivery of evidence-based health promotion programs among American Indian and Alaska Native youth: A case study. *JMIR Research Protocols*, 5(4), e225.

BACKGROUND: American Indian and Alaska Native (AI/AN) youth face multiple health challenges compared to other racial/ethnic groups, which could potentially be ameliorated by the dissemination of evidence-based adolescent health promotion programs. Previous studies have indicated that limited trained personnel, cultural barriers, and geographic isolation may hinder the reach and implementation of evidence-based health promotion programs among AI/AN youth. Although Internet access is variable in AI/AN communities across the United States, it is swiftly and steadily improving, and it may provide a viable strategy to disseminate evidence-based health promotion programs to this underserved population. **OBJECTIVE:** We explored the potential of using the Internet to disseminate evidence-based health promotion programs on multiple health topics to AI/AN youth living in diverse communities across 3 geographically dispersed regions of the United States. Specifically, we assessed the Internet's potential to increase the reach and implementation of evidence-based health promotion programs for AI/AN

youth, and to engage AI/AN youth. METHODS: This randomized controlled trial was conducted in 25 participating sites in Alaska, Arizona, and the Pacific Northwest. Predominantly AI/AN youth, aged 12-14 years, accessed 6 evidence-based health promotion programs delivered via the Internet, which focused on sexual health, hearing loss, alcohol use, tobacco use, drug use, and nutrition and physical activity. Adult site coordinators completed computer-based education inventory surveys, connectivity and bandwidth testing to assess parameters related to program reach (computer access, connectivity, and bandwidth), and implementation logs to assess barriers to implementation (program errors and delivery issues). We assessed youths' perceptions of program engagement via ratings on ease of use, understandability, credibility, likeability, perceived impact, and motivational appeal, using previously established measures. RESULTS: Sites had sufficient computer access and Internet connectivity to implement the 6 programs with adequate fidelity; however, variable bandwidth (ranging from 0.24 to 93.5 megabits per second; mean 25.6) and technical issues led some sites to access programs via back-up modalities (eg, uploading the programs from a Universal Serial Bus drive). The number of youth providing engagement ratings varied by program (n=40-191; 48-60% female, 85-90% self-identified AI/AN). Across programs, youth rated the programs as easy to use (68-91%), trustworthy (61-89%), likeable (59-87%), and impactful (63-91%). Most youth understood the words in the programs (60-83%), although some needed hints to complete the programs (16-49%). Overall, 37-66% of the participants would recommend the programs to a classmate, and 62-87% found the programs enjoyable when compared to other school lessons. CONCLUSIONS: Findings demonstrate the potential of the Internet to enhance the reach and implementation of evidence-based health promotion programs, and to engage AI/AN youth. Provision of back-up modalities is recommended to address possible connectivity or technical issues. The dissemination of Internet-based health promotion programs may be a promising strategy to address health disparities for this underserved population. TRIAL REGISTRATION: Clinicaltrials.gov NCT01303575; <https://clinicaltrials.gov/ct2/show/NCT01303575> (Archived by WebCite at <http://www.webcitation.org/6m7DO4g7c>).

Martin, I. (2016). Caspase-2: Divide and conquer. *Science Translational Medicine*, 8(363)

Martin, M., Vanichseni, S., Suntharasamai, P., Sangkum, U., Mock, P. A., Chaipung, B., et al. (2016).

Factors associated with the uptake of and adherence to HIV pre-exposure prophylaxis in people who have injected drugs: An observational, open-label extension of the bangkok tenofovir study. *The Lancet.HIV*,

BACKGROUND: Results of the randomised, double-blind, placebo-controlled Bangkok Tenofovir Study (BTS) showed that taking tenofovir daily as pre-exposure prophylaxis (PrEP) can reduce the risk of HIV infection by 49% in people who inject drugs. In an extension to the trial, participants were offered 1 year of open-label tenofovir. We aimed to examine the demographic characteristics, drug use, and risk behaviours associated with participants' uptake of and adherence to PrEP. METHODS: In this observational, open-label extension of the BTS (NCT00119106), non-pregnant, non-breastfeeding, HIV-negative BTS participants, all of whom were current or previous injecting drug users at the time of enrolment in the BTS, were offered daily oral tenofovir (300 mg) for 1 year at 17 Bangkok Metropolitan Administration drug-treatment clinics. Participant demographics, drug use, and risk behaviours were assessed at baseline and every 3 months using an audio computer-assisted self-interview. HIV testing was done monthly and serum creatinine was assessed every 3 months. We used logistic regression to examine factors associated with the decision to take daily tenofovir as PrEP, the decision to return for at least one PrEP follow-up visit, and greater than 90% adherence to PrEP. FINDINGS: Between Aug 1, 2013, and Aug 31, 2014, 1348 (58%) of the 2306 surviving BTS participants returned to the clinics, 33 of whom were excluded because they had HIV (n=27) or grade 2-4 creatinine results (n=6). 798 (61%) of the 1315 eligible participants chose to start open-label PrEP and were followed up for a median of 335 days (IQR 0-364). 339 (42%) participants completed 12 months of follow-up; 220 (28%) did not return for any follow-up visits. Participants who were 30 years or older (odds ratio [OR] 1.8, 95% CI 1.4-2.2; $p < 0.0001$), injected heroin (OR 1.5, 1.1-2.1; $p = 0.007$), or had been in prison (OR 1.7, 1.3-2.1; $p < 0.0001$) during the randomised trial were more likely to choose PrEP than were those without these characteristics. Participants who reported injecting heroin or being in prison during the 3 months before open-label enrolment were more likely to return for at least one open-label follow-up visit than those who did not report injecting heroin (OR 3.0, 95 % CI 1.3-7.3; $p = 0.01$) or being in prison (OR 2.3, 1.4-3.7; $p = 0.0007$). Participants who injected midazolam or were in prison during open-

label follow-up were more likely to be greater than 90% adherent than were those who did not inject midazolam (OR 2.2, 95% CI 1.2-4.3; $p=0.02$) or were not in prison (OR 4.7, 3.1-7.2; $p<0.0001$). One participant tested positive for HIV, yielding an HIV incidence of 2.1 (95% CI 0.05-11.7) per 1000 person-years. No serious adverse events related to tenofovir use were reported. INTERPRETATION: More than 60% of returning, eligible BTS participants started PrEP, which indicates that a substantial proportion of PWID who are knowledgeable about PrEP might be interested in taking it. Participants who had injected heroin or been in prison were more likely to choose to take PrEP, suggesting that participants based their decision to take PrEP, at least in part, on their perceived risk of incident HIV infection. FUNDING: US Centers for Disease Control and Prevention and the Bangkok Metropolitan Administration.

Martinez, J. M., Groot, J. A., Curtis, D. C., Allison, C. L., Marquardt, P. C., Holmes, A. N., et al. (2016). Effective reduction of acute ethanol withdrawal by the tetracycline derivative, tigecycline, in female and male DBA/2J mice. *Alcoholism, Clinical and Experimental Research*, 40(12), 2499-2505.

BACKGROUND: Alcohol use disorder (AUD) is a spectrum disorder characterized by mild to severe symptoms, including potential withdrawal signs upon cessation of consumption. Approximately five hundred thousand patients with AUD undergo clinically relevant episodes of withdrawal annually (New Engl J Med, 2003, 348, 1786). Recent evidence indicates potential for drugs that alter neuroimmune pathways as new AUD therapies. We have previously shown the immunomodulatory drugs, minocycline and tigecycline, were effective in reducing ethanol (EtOH) consumption in both the 2-bottle choice and drinking-in-the-dark paradigms. Here, we test the hypothesis that tigecycline, a tetracycline derivative, will reduce the severity of EtOH withdrawal symptoms in a common acute model of alcohol withdrawal (AWD) using a single anesthetic dose of EtOH in seizure sensitive DBA/2J (DBA) mice. METHODS: Naive adult female and male DBA mice were given separate injections of 4 g/kg i.p. EtOH with vehicle or tigecycline (0, 20, 40, or 80 mg/kg i.p.). The 80 mg/kg dose was tested at 3 time points (0, 4, and 7 hours) post EtOH treatment. Handling-induced convulsions (HICs) were measured before and then over 12 hours following EtOH injection. HIC scores and areas under the curve were tabulated. In separate mice, blood EtOH concentrations (BECs) were measured at 2, 4, and 7 hours postinjection of 4 g/kg i.p.

EtOH in mice treated with 0 and 80 mg/kg i.p. tigecycline. RESULTS: AWD symptom onset, peak magnitude, and overall HIC severity were reduced by tigecycline drug treatment compared to controls. Tigecycline treatment was effective regardless of timing throughout AWD, with earlier treatment showing greater efficacy. Tigecycline showed a dose-responsive reduction in acute AWD convulsions, with no sex differences in efficacy. Importantly, tigecycline did not affect BECs over a time course of elimination. CONCLUSIONS: Tigecycline effectively reduced AWD symptoms in DBA mice at all times and dosages tested, making it a promising lead compound for development of a novel pharmacotherapy for AWD. Further studies are needed to determine the mechanism of tigecycline action.

Matsuhisa, M., Koyama, M., Cheng, X., Sumi, M., Riddle, M. C., Bolli, G. B., et al. (2016). Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension). *Diabetes Research and Clinical Practice*, 122, 133-140. Aims To evaluate the efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100) in adults with type 1 diabetes in Japan over 12 months. Methods EDITION JP 1 was a multicentre, randomised, open-label phase 3 study. Following a 6-month on-treatment period, participants continued to receive Gla-300 or Gla-100 once daily, plus mealtime insulin, over a 6-month open-label extension phase. HbA1c, hypoglycaemia, body weight and adverse events were assessed. Results Overall, 114/122 (93%) and 114/121 (94%) of participants in the Gla-300 and Gla-100 group, respectively, completed the 6-month extension phase. Glycaemic control was sustained in both groups up to month 12 (mean HbA1c: Gla-300, 7.9% [62 mmol/mol]; Gla-100, 7.8% [62 mmol/mol]). Annualised rates of hypoglycaemia were lower with Gla-300 versus Gla-100; significantly for nocturnal confirmed (<3.0 mmol/L [<54 mg/dL]) or severe hypoglycaemia (2.39 and 3.85 events per participant-year; rate ratio: 0.62 [0.39–0.97]). No between-treatment differences in mean body weight change or adverse events were observed. Conclusion Over 12 months' treatment, participants with type 1 diabetes receiving Gla-300 achieved sustained glycaemic control and experienced less nocturnal hypoglycaemia that was confirmed (<3.0 mmol/L [<54 mg/dL]) or severe compared with Gla-100, supporting the 6-month results. © 2016 Elsevier Ireland Ltd

McCarty, D., Rieckmann, T., Baker, R. L., & McConnell, K. J. (2016). The perceived impact of 42 CFR part 2 on coordination and integration of care: A qualitative analysis. *Psychiatric Services (Washington, D.C.)*, , appips201600138.

OBJECTIVE: Title 42 of the Code of Federal Regulations Part 2 (42 CFR Part 2) controls the release of patient information about treatment for substance use disorders. In 2016, the Substance Abuse and Mental Health Services Administration (SAMHSA) released a proposed rule to update the regulations, reduce provider burdens, and facilitate information exchange. Oregon's Medicaid program (Oregon Health Plan) altered the financing and structure of medical, dental, and behavioral care to promote greater integration and coordination. A qualitative analysis examined the perceived impact of 42 CFR Part 2 on care coordination and integration. METHODS: Interviews with 76 stakeholders (114 interviews) conducted in 2012-2015 probed the processes of integrating behavioral health into primary care settings in Oregon and assessed issues associated with adherence to 42 CFR Part 2. RESULTS: Respondents expressed concerns that the regulations caused legal confusion, inhibited communication and information sharing, and required updating. Addiction treatment directors noted the challenges of obtaining patient consent to share information with primary care providers. CONCLUSIONS: The confidentiality regulations were perceived as a barrier to care coordination and integration. The Oregon Health Authority, therefore, requested regulatory changes. SAMHSA's proposed revisions permit a general consent to an entire health care team and allow inclusion of substance use disorder information within health information exchanges, but they mandate data segmentation of diagnostic and procedure codes related to substance use disorders and restrict access only to parties with authorized consent, possibly adding barriers to the coordination and integration of addiction treatment with primary care.

McClintic, S. M., Wilson, L. B., & Campbell, J. P. (2016). Novel macular findings on optical coherence tomography in incontinentia pigmenti. *JAMA Ophthalmology*, 134(11), e162751.

Meshorer, T., & Heeman, P. A. (2016). Using past speaker behavior to better predict turn transitions. *17th Annual Conference of the International Speech Communication Association, INTERSPEECH 2016*, , 08-12-September-2016. pp. 2900-2904.

This paper explores using a summary of past speaker behavior to better predict turn transitions. We computed two types of summary features that represent the current speaker's past turn-taking behavior: relative turn length and relative floor control. Relative turn length measures the current turn length so far (in time and words) relative to the speaker's average turn length. Relative floor control measures the speaker's control of the conversation floor (in time and words) relative to the total conversation length. The features are recomputed for each dialog act based on past turns of the speaker within the current conversation. Using the switchboard corpus, we trained two models to predict turn transitions: one with just local features (e.g., current speech act, previous speech act) and one that added the summary features. Our results shows that using the summary features improve turn transitions prediction. Copyright © 2016 ISCA.

Meyza, K. Z., Bartali, I. B., Monfils, M. H., Panksepp, J. B., & Knapska, E. (2016). The roots of empathy: Through the lens of rodent models. *Neuroscience and Biobehavioral Reviews*, Empathy is a phenomenon often considered dependent on higher-order emotional control and an ability to relate to the emotional state of others. It is, by many, attributed only to species having well-developed cortical circuits capable of performing such complex tasks. However, over the years, a wealth of data has been accumulated showing that rodents are capable not only of sharing emotional states of their conspecifics, but also of prosocial behavior driven by such shared experiences. The study of rodent empathic behaviors is only now becoming an independent research field. Relevant animal models allow precise manipulation of neural networks, thereby offering insight into the foundations of empathy in the mammalian brains. Here we review the data on empathic behaviors in rat and mouse models, their neurobiological and neurophysiological correlates, and the factors influencing these behaviors. We discuss how simple rodent models of empathy enhance our understanding of how brain controls empathic behaviors.

Mitin, T., & Thomas, C. R., Jr. (2016). Prophylactic cranial irradiation for extensive-stage small cell lung cancer: Authors' reply. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*, 11(12), e152.

Mohammadi, S. H., & Kain, A. (2016). A voice conversion mapping function based on a stacked joint-autoencoder. *17th Annual Conference of the International Speech Communication Association, INTERSPEECH 2016, , 08-12-September-2016*. pp. 1647-1651.

In this study, we propose a novel method for training a regression function and apply it to a voice conversion task. The regression function is constructed using a Stacked Joint-Autoencoder (SJAE). Previously, we have used a more primitive version of this architecture for pre-training a Deep Neural Network (DNN). Using objective evaluation criteria, we show that the lower levels of the SJAE perform best with a low degree of jointness, and higher levels with a higher degree of jointness. We demonstrate that our proposed approach generates features that do not suffer from the averaging effect inherent in backpropagation training. We also carried out subjective listening experiments to evaluate speech quality and speaker similarity. Our results show that the SJAE approach has both higher quality and similarity than a SJAE+DNN approach, where the SJAE is used for pre-training a DNN, and the fine-tuned DNN is then used for mapping. We also present the system description and results of our submission to Voice Conversion Challenge 2016. Copyright © 2016 ISCA.

Morey, K. E., Vega, R., Cassidy, P. M., Buser, G. L., Rayar, J. K., Myers, J. A., et al. (2016). Evaluation of the carba NP test in oregon, 2013. *Antimicrobial Agents and Chemotherapy*, Carbapenem-resistant Enterobacteriaceae (CRE) are an urgent public health threat. We evaluated the capacity of the Carba NP test to detect carbapenemase production in 206 isolates: 143 Enterobacteriaceae identified by Oregon's CRE surveillance in 2013 and 63 known carbapenemase-positive organisms. Overall, test sensitivity and specificity were 89% (59/66; 95% CI 81-97%) and 100% (140/140; 95% CI 98-100%), respectively. All KPC, NDM-1, VIM, and IMP-producers but no (0/7) OXA-48-like strains were Carba NP-positive prior to a post-hoc protocol modification. We subsequently incorporated Carba NP into Oregon's CRE screening algorithm.

Morimoto, M., Myung, C., Beirnes, K., Choi, K., Asakura, Y., Bokenkamp, A., et al. (2016). Increased wnt and notch signaling: A clue to the renal disease in schimke immuno-osseous dysplasia? *Orphanet Journal of Rare Diseases*, 11(1), 149.

BACKGROUND: Schimke immuno-osseous dysplasia (SIOD) is a multisystemic disorder caused by biallelic mutations in the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin, subfamily A-like 1 (SMARCAL1) gene. Changes in gene expression underlie the arteriosclerosis and T-cell immunodeficiency of SIOD; therefore, we hypothesized that SMARCAL1 deficiency causes the focal segmental glomerulosclerosis (FSGS) of SIOD by altering renal gene expression. We tested this hypothesis by gene expression analysis of an SIOD patient kidney and verified these findings through immunofluorescent analysis in additional SIOD patients and a genetic interaction analysis in *Drosophila*. **RESULTS:** We found increased expression of components and targets of the Wnt and Notch signaling pathways in the SIOD patient kidney, increased levels of unphosphorylated beta-catenin and Notch1 intracellular domain in the glomeruli of most SIOD patient kidneys, and genetic interaction between the *Drosophila* SMARCAL1 homologue Marcal1 and genes of the Wnt and Notch signaling pathways. **CONCLUSIONS:** We conclude that increased Wnt and Notch activity result from SMARCAL1 deficiency and, as established causes of FSGS, contribute to the renal disease of most SIOD patients. This further clarifies the pathogenesis of SIOD and will hopefully direct potential therapeutic approaches for SIOD patients.

Munoz-Calvo, M. T., Barrios, V., Pozo, J., Chowen, J. A., Martos-Moreno, G. A., Hawkins, F., et al. (2016). Treatment with recombinant human insulin-like growth factor-1 improves growth in patients with PAPP-A2 deficiency. *The Journal of Clinical Endocrinology and Metabolism*, 101(11), 3879-3883.

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-1 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-1 (rhIGF-1) twice daily for 1 year. There was a clear increase in growth velocity and height in both siblings. Bioactive IGF-1

was increased, and spontaneous GH secretion was diminished after acute administration of rhIGF-1, whereas serum total IGF-1 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-1 improves growth in patients with PAPP-A2 deficiency.

Muñoz-Calvo, M. T., Barrios, V., Pozo, J., Chowen, J. A., Martos-Moreno, G. Á., Hawkins, F., et al. (2016). Treatment with recombinant human insulin-like growth factor-1 improves growth in patients with PAPP-A2 deficiency. *Journal of Clinical Endocrinology and Metabolism*, *101*(11), 3879-3883.

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-1 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 µg/kg) of recombinant human IGF-1 (rhIGF-1) twice daily for 1 year. There was a clear increase in growth velocity and height in both siblings. Bioactive IGF-1 was increased, and spontaneous GH secretion was diminished after acute administration of rhIGF-1, whereas serum total IGF-1 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-1 improves growth in patients with PAPP-A2 deficiency. (*J Clin Endocrinol Metab* 101: 3879-3883, 2016). Copyright © 2016 by the Endocrine Society.

Murphy, M. J., Halow, N. G., Royer, P. A., & Hennebold, J. D. (2016). Leukemia inhibitory factor is necessary for ovulation in female rhesus macaques. *Endocrinology*, *157*(11), 4378-4387. Although the requirement of pituitary-derived LH for ovulation is well documented, the intrafollicular paracrine and autocrine processes elicited by LH necessary for follicle rupture are not fully understood. Evaluating a published rhesus macaque periovulatory transcriptome database revealed that mRNA encoding leukemia inhibitory factor (LIF) and its downstream

signaling effectors are up-regulated in the follicle after animals receive an ovulatory stimulus (human chorionic gonadotropin [hCG]). Follicular LIF mRNA and protein levels are below the limit of detection before the administration of hCG but increase significantly 12 hours thereafter. Downstream LIF receptor (LIFR) signaling components including IL-6 signal transducer, the receptor associated Janus kinase 1, and the transcription factor signal transducer and activator of transcription 3 also exhibit increased expression in the rhesus macaque follicle 12 hours after administration of an ovulatory hCG bolus. A laparoscopic ovarian evaluation 72 hours after the injection of a LIF antagonist (soluble LIFR) into the rhesus macaque preovulatory follicle and hCG administration revealed blocking LIF action prevented ovulation (typically occurs 36-44 h after hCG). Moreover, ovaries removed 52 hours after both hCG and intrafollicular soluble LIFR administration confirmed ovulation was blocked as evidenced by the presence of an intact follicle and a trapped cumulus-oocyte complex. These findings give new insight into the role of LIF in the primate ovary and could lead to the development of new approaches for the control of fertility.

Naithani, S., Preece, J., D'Eustachio, P., Gupta, P., Amarasinghe, V., Dharmawardhana, P. D., et al. (2016). Plant reactome: A resource for plant pathways and comparative analysis. *Nucleic Acids Research*,

Plant Reactome (<http://plantreactome.gramene.org/>) is a free, open-source, curated plant pathway database portal, provided as part of the Gramene project. The database provides intuitive bioinformatics tools for the visualization, analysis and interpretation of pathway knowledge to support genome annotation, genome analysis, modeling, systems biology, basic research and education. Plant Reactome employs the structural framework of a plant cell to show metabolic, transport, genetic, developmental and signaling pathways. We manually curate molecular details of pathways in these domains for reference species *Oryza sativa* (rice) supported by published literature and annotation of well-characterized genes. Two hundred twenty-two rice pathways, 1025 reactions associated with 1173 proteins, 907 small molecules and 256 literature references have been curated to date. These reference annotations were used to project pathways for 62 model, crop and evolutionarily significant plant species based on gene homology. Database users can search and browse various components of the database, visualize curated baseline expression of pathway-associated genes provided by the Expression Atlas and

upload and analyze their Omics datasets. The database also offers data access via Application Programming Interfaces (APIs) and in various standardized pathway formats, such as SBML and BioPAX.

Nanes, B. A., Grimsley-Myers, C. M., Cadwell, C. M., Robinson, B. S., Lowery, A. M., Vincent, P. A., et al. (2016). p120-catenin regulates VE-cadherin endocytosis and degradation induced by the kaposi sarcoma associated ubiquitin ligase K5. *Molecular Biology of the Cell*,
Vascular endothelial (VE)-cadherin undergoes constitutive internalization driven by a unique endocytic motif that also serves as a p120-catenin (p120) binding site. p120 binding masks the motif, stabilizing the cadherin at cell junctions. This mechanism allows constitutive VE-cadherin endocytosis and recycling to contribute to adherens junction dynamics without resulting in junction disassembly. Here, we identify an additional motif that drives VE-cadherin endocytosis and pathological junction disassembly associated with the endothelial-derived tumor Kaposi sarcoma. Human herpesvirus 8, which causes Kaposi sarcoma, expresses the MARCH family ubiquitin ligase K5. We report that K5 targets two membrane-proximal VE-cadherin lysine residues for ubiquitination, driving endocytosis and down-regulation of the cadherin. K5-induced VE-cadherin endocytosis does not require the constitutive endocytic motif. However, K5-induced VE-cadherin endocytosis is associated with displacement of p120 from the cadherin, and p120 protects VE-cadherin from K5. Thus, multiple context-dependent signals drive VE-cadherin endocytosis, but p120 binding to the cadherin juxtamembrane domain acts as a master regulator guarding cadherin stability.

Nelson, J. W., Sklenar, J., Barnes, A. P., & Minnier, J. (2016). The START app: A web-based RNAseq analysis and visualization resource. *Bioinformatics (Oxford, England)*,
Transcriptional profiling using RNA sequencing (RNAseq) has emerged as a powerful methodology to quantify global gene expression patterns in various contexts from single cells to whole tissues. The tremendous amount of data generated by this profiling technology presents a daunting challenge in terms of effectively visualizing and interpreting results. Convenient and intuitive data interfaces are critical for researchers to easily upload, analyze and visualize their RNAseq data. We designed the START (Shiny Transcriptome Analysis Resource Tool) App with these

requirements in mind. This application has the power and flexibility to be resident on a local computer or serve as a web-based environment, enabling easy sharing of data between researchers and collaborators. AVAILABILITY AND IMPLEMENTATION: Source Code for the START App is written entirely in R and can be freely available to download at <https://github.com/jminnier/STARTapp> with the code licensed under GPLv3. It can be launched on any system that has R installed. The START App is also hosted on <https://kcvl.shinyapps.io/START> for researchers to temporarily upload their data. CONTACT: minnier@ohsu.edu.

Nettleton, W., & King, V. (2016). The risk of MI and ischemic stroke with combined oral contraceptives. *American Family Physician*, 94(9), 691-692.

Nyendak, M., Swarbrick, G. M., Duncan, A., Cansler, M., Huff, E. W., Hokey, D., et al. (2016).

Adenovirally-induced polyfunctional T cells do not necessarily recognize the infected target: Lessons from a phase I trial of the AERAS-402 vaccine. *Scientific Reports*, 6, 36355.

The development of a vaccine for Mycobacterium tuberculosis (Mtb) has been impeded by the absence of correlates of protective immunity. One correlate would be the ability of cells induced by vaccination to recognize the Mtb-infected cell. AERAS-402 is a replication-deficient serotype 35 adenovirus containing DNA expressing a fusion protein of Mtb antigens 85A, 85B and TB10.4. We undertook a phase I double-blind, randomized placebo controlled trial of vaccination with AERAS-402 following BCG. Analysis of the vaccine-induced immune response revealed strong antigen-specific polyfunctional CD4+ and CD8+ T cell responses. However, analysis of the vaccine-induced CD8+ T cells revealed that in many instances these cells did not recognize the Mtb-infected cell. Our findings highlight the measurement of vaccine-induced, polyfunctional T cells may not reflect the extent or degree to which these cells are capable of identifying the Mtb-infected cell and correspondingly, the value of detailed experimental medicine studies early in vaccine development.

O'Daniel, J. M., McLaughlin, H. M., Amendola, L. M., Bale, S. J., Berg, J. S., Bick, D., et al. (2016). A survey of current practices for genomic sequencing test interpretation and reporting processes in US laboratories. *Genetics in Medicine : Official Journal of the American College of Medical*

Genetics,

PURPOSE: While the diagnostic success of genomic sequencing expands, the complexity of this testing should not be overlooked. Numerous laboratory processes are required to support the identification, interpretation, and reporting of clinically significant variants. This study aimed to examine the workflow and reporting procedures among US laboratories to highlight shared practices and identify areas in need of standardization. **METHODS:** Surveys and follow-up interviews were conducted with laboratories offering exome and/or genome sequencing to support a research program or for routine clinical services. The 73-item survey elicited multiple choice and free-text responses that were later clarified with phone interviews. **RESULTS:** Twenty-one laboratories participated. Practices highly concordant across all groups included consent documentation, multiperson case review, and enabling patient opt-out of incidental or secondary findings analysis. Noted divergence included use of phenotypic data to inform case analysis and interpretation and reporting of case-specific quality metrics and methods. Few laboratory policies detailed procedures for data reanalysis, data sharing, or patient access to data. **CONCLUSION:** This study provides an overview of practices and policies of experienced exome and genome sequencing laboratories. The results enable broader consideration of which practices are becoming standard approaches, where divergence remains, and areas of development in best practice guidelines that may be helpful. *Genet Med* advance online publication 03 November 2016 *Genetics in Medicine* (2016); doi:10.1038/gim.2016.152.

Olsen, R. H., Weber, S. J., Akinyeke, T., & Raber, J. (2016). Enhanced cued fear memory following post-training whole body irradiation of 3-month-old mice. *Behavioural Brain Research*, 319, 181-187.

Typically, in studies designed to assess effects of irradiation on cognitive performance the animals are trained and tested for cognitive function following irradiation. Little is known about post-training effects of irradiation on cognitive performance. In the current study, 3-month-old male mice were irradiated with X-rays 24h following training in a fear conditioning paradigm and cognitively tested starting two weeks later. Average motion during the extinction trials, measures of anxiety in the elevated zero maze, and body weight changes over the course of the study were assessed as well. Exposure to whole body irradiation 24h following training in a fear conditioning

resulted in greater freezing levels 2 weeks after training. In addition, motion during both contextual and cued extinction trials was lower in irradiated than sham-irradiated mice. In mice trained for cued fear conditioning, activity levels in the elevated zero maze 12 days after sham-irradiation or irradiation were also lower in irradiated than sham-irradiated mice. Finally, the trajectory of body weight changes was affected by irradiation, with lower body weights in irradiated than sham-irradiated mice, with the most profound effect 7 days after training. These effects were associated with reduced c-Myc protein levels in the amygdala of the irradiated mice. These data indicate that whole body X ray irradiation of mice at 3 months of age causes persistent alterations in the fear response and activity levels in a novel environment, while the effects on body weight seem more transient.

Onega, T., Smith, M., Miglioretti, D. L., Carney, P. A., Geller, B. A., Kerlikowske, K., et al. (2016).

Radiologist agreement for mammographic recall by case difficulty and finding type. *Journal of the American College of Radiology : JACR*, 13(11S), e72-e79.

PURPOSE: The aim of this study was to assess agreement of mammographic interpretations by community radiologists with consensus interpretations of an expert radiology panel to inform approaches that improve mammographic performance. **METHODS:** From 6 mammographic registries, 119 community-based radiologists were recruited to assess 1 of 4 randomly assigned test sets of 109 screening mammograms with comparison studies for no recall or recall, giving the most significant finding type (mass, calcifications, asymmetric density, or architectural distortion) and location. The mean proportion of agreement with an expert radiology panel was calculated by cancer status, finding type, and difficulty level of identifying the finding at the patient, breast, and lesion level. Concordance in finding type between study radiologists and the expert panel was also examined. For each finding type, the proportion of unnecessary recalls, defined as study radiologist recalls that were not expert panel recalls, was determined. **RESULTS:** Recall agreement was 100% for masses and for examinations with obvious findings in both cancer and noncancer cases. Among cancer cases, recall agreement was lower for lesions that were subtle (50%) or asymmetric (60%). Subtle noncancer findings and benign calcifications showed 33% agreement for recall. Agreement for finding responsible for recall was low, especially for architectural distortions (43%) and asymmetric densities (40%). Most unnecessary

recalls (51%) were asymmetric densities. CONCLUSIONS: Agreement in mammographic interpretation was low for asymmetric densities and architectural distortions. Training focused on these interpretations could improve the accuracy of mammography and reduce unnecessary recalls.

Parker, K. N., & Brummel, B. J. (2016). Examining the curvilinear relationship between income and job and pay satisfaction. *Journal of Personnel Psychology, 15*(4), 164-173.

Previous research has shown that income is related to both job satisfaction and pay satisfaction. However, this research has assumed that these relationships are linear. The current study investigated whether the relationship between income and job and pay satisfaction might be better understood using curvilinear models. Self-report data was obtained from 25,465 working adults in the US using a company rating web site, www.careerbliss.com. Results indicated that the relationship between income and job satisfaction was linear. However, income and pay satisfaction were found to have a significant curvilinear relationship such that people began reporting decreased pay satisfaction above income levels of \$260,000. Additionally, supplementary analyses demonstrated that other facets of job satisfaction also had significant curvilinear relationships with income. © 2016 Hogrefe Publishing.

Patel, Z. M., Thamboo, A., Rudmik, L., Nayak, J. V., Smith, T. L., & Hwang, P. H. (2016). Surgical therapy vs continued medical therapy for medically refractory chronic rhinosinusitis: A systematic review and meta-analysis. *International Forum of Allergy & Rhinology,*

BACKGROUND: The currently accepted treatment paradigm of treating chronic rhinosinusitis (CRS) first with appropriate medical therapy (AMT) and then with surgery if patients are refractory to AMT, has been criticized for lack of evidence. The objective of this study was to reassess the literature and establish the highest level of evidence possible regarding further management of CRS patients refractory to AMT. METHODS: This study was a systematic review (SR) with meta-analysis (MA). Adult CRS patients who received AMT and then underwent either medical or surgical therapy in moderate to high level prospective studies were included. Outcomes assessed were disease-specific quality of life (QOL), nasal endoscopy, health-state utility, missed work days, change in cardinal symptoms of CRS, economic impact, and adverse

events. RESULTS: A total of 970 manuscripts were identified; 6 studies were ultimately included in the SR with 5 included in the MA. Compared to continued medical therapy, endoscopic sinus surgery (ESS) significantly improved patient-based QOL scores ($p < 0.00001$) and nasal endoscopy scores ($p < 0.00001$). Difference in missed work days depended heavily on patient choice of intervention. Unpooled analysis showed improvements in olfaction, health utility scores, and cost-effectiveness. CONCLUSION: On meta-analysis, for CRS patients refractory to AMT, ESS significantly improves objective endoscopic scoring outcomes vs continued medical therapy alone. In patients with refractory CRS who have significant reductions in baseline QOL, ESS results in significant improvements. Continued medical therapy appears to maintain outcomes in patients with less severe baseline QOL. Unpooled analysis demonstrates improvement in health utility, olfaction, and cost-effectiveness following ESS compared to continued medical therapy alone, in medically refractory CRS.

Pham, A. N., Bubalo, J. S., & Lewis, J. S.,II. (2016). Posaconazole tablet formulation at 400 milligrams daily achieves desired minimum serum concentrations in adult patients with a hematologic malignancy or stem cell transplant. *Antimicrobial Agents and Chemotherapy*, 60(11), 6945-6947. We describe our experience using the posaconazole 400-mg delayed-release tablet formulation once daily in 20 patients with hematologic malignancy or hematopoietic stem cell transplant who were unable to attain prespecified target minimum serum (trough) concentrations for treatment or prophylaxis of invasive fungal infection. The higher dose allowed the majority of patients to achieve prespecified target trough concentrations without incurring additional toxicities. Copyright © 2016, American Society for Microbiology. All Rights Reserved.

Pina, M. M., & Cunningham, C. L. (2016). Ethanol-seeking behavior is expressed directly through an extended amygdala to midbrain neural circuit. *Neurobiology of Learning and Memory*, 137, 83-91.

Abstinent alcohol-dependent individuals experience an enduring sensitivity to cue-induced craving and relapse to drinking. There is considerable evidence indicating that structures within the midbrain and extended amygdala are involved in this process. Individually, the ventral tegmental area (VTA) and the bed nucleus of the stria terminalis (BNST) have been shown to modulate cue-

induced ethanol-seeking behavior. It is hypothesized that cue-induced seeking is communicated through a direct projection from the BNST to VTA. In the current experiments, an intersectional viral strategy was used in DBA/2J mice to selectively target and inhibit BNST projections to the VTA during a test of ethanol conditioned place preference (CPP). Inhibitory designer receptors exclusively activated by designer drugs (hM4Di DREADDs) were expressed in VTA-projecting BNST (BNST-VTA) cells by infusing a retrograde herpes-simplex virus encoding cre recombinase (HSV-Cre) into VTA and a cre-inducible adeno-associated virus encoding hM4Di (AAV-DIO-hM4Di) into BNST. Before testing the expression of preference, clozapine-N-oxide (CNO) was peripherally administered to activate hM4Di receptors and selectively inhibit these cells. Ethanol CPP expression was blocked by CNO-mediated inhibition of BNST-VTA cells. A follow-up study revealed this effect was specific to CNO activation of hM4Di as saline- and CNO-treated mice infused with a control vector (HSV-GFP) in place of HSV-Cre showed significant CPP. These findings establish a role for a direct BNST input to VTA in cue-induced ethanol-seeking behavior.

Plate, J. F., Wohler, A. D., Brown, M. L., Sun, D., Fino, N. F., & Lang, J. E. (2016). Factors associated with range of motion recovery following manipulation under anesthesia. *Surgical Technology International, XXIX*, 295-301.

INTRODUCTION: Stiffness and loss of motion following total knee arthroplasty (TKA) is a complex and multifactorial complication that may require manipulation under anesthesia (MUA). However, patient and surgical factors that potentially influence the development of knee stiffness following TKA are not fully understood. The purpose of this study was to identify patient and surgical factors that may influence range of motion loss following TKA by assessing a cohort of patients that underwent MUA and comparing them to a matched cohort of patients without complications.

MATERIALS AND METHODS: The joints registry was searched for patients who underwent MUA following primary TKA between 2004 and 2013. Demographic and surgical information was obtained from the electronic medical record including range of motion (ROM), comorbidities and timing of MUA. Patients who underwent MUA were then double-matched by baseline (prior to primary TKA) knee ROM to patients who underwent primary TKA with normal postoperative range of motion recovery during the same time period. **RESULTS:** Fifty-two patients (fifty-six knees) (66% female, mean BMI 32.4 kg/m²) underwent MUA after TKA during the study period. MUA

was performed a mean of 13.6 weeks after primary TKA. Study patients were double-matched by baseline flexion (mean 107 masculine+/-2 masculine) to 111 patients (112 knees) with a similar mean baseline flexion (104 masculine+/-2 masculine, p=0.138). Patients requiring MUA were younger (mean age 56 vs. 64 years, p50 mL, and any complication during the hospital stay were not found to be associated with an increased risk of requiring MUA. CONCLUSION: Younger patients with more comorbidities and a history of previous knee surgery were found to have significantly higher risk for developing stiffness and loss of motion requiring MUA after primary TKA in the current study. Patients with this risk profile need to be counseled regarding the risk for postoperative knee stiffness and range of motion loss possibly requiring MUA after primary TKA.

Prasad, V., & Rajkumar, S. V. (2016). Conflict of interest in academic oncology: Moving beyond the blame game and forging a path forward. *Blood Cancer Journal*, 6(11), e489.

Price, J. R., Guran, L. A., Gregory, W. T., & McDonagh, M. S. (2016). Nitrofurantoin vs other prophylactic agents in reducing recurrent urinary tract infections in adult women: A systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology*, 215(5), 548-560. BACKGROUND: The clinical and financial burden from bladder infections is significant. Daily antibiotic use is the recommended strategy for recurrent urinary tract infection prevention. Increasing antibiotic resistance rates, however, require immediate identification of innovative alternative prophylactic therapies. This systematic review aims to provide guidance on gaps in evidence to guide future research. OBJECTIVE: The objective of this review was to provide current pooled estimates of randomized control trials comparing the effects of nitrofurantoin vs other agents in reducing recurrent urinary tract infections in adult, nonpregnant women and assess relative adverse side effects. DATA SOURCES: Data sources included the following: MEDLINE, Jan. 1, 1946, to Jan. 31, 2015; Cochrane Central Register of Controlled Trials the Cochrane Database of Systematic Reviews, and web sites of the National Institute for Clinical Excellence, and the National Guideline Clearinghouse from 2000 to 2015. Randomized control trials of women with recurrent urinary tract infections comparing nitrofurantoin with any other treatment were included. STUDY DESIGN: A protocol for the study was developed a priori. Published guidance was followed for assessment of study quality. All meta-analyses were

performed using random-effects models with Stats Direct Software. Dual review was used for all decisions and data abstraction. RESULTS: Twelve randomized control trials involving 1063 patients were included. One study that had a serious flaw was rated poor in quality, one study rated good, and the remainder fair. No significant differences in prophylactic antibiotic treatment with nitrofurantoin and norfloxacin, trimethoprim, sulfamethoxazole/trimethoprim, methamine hippurate, estriol, or cefaclor were found in clinical or microbiological cure in adult nonpregnant women with recurrent urinary tract infections (9 randomized control trials, 673 patients, relative risk ratio, 1.06; 95% confidence interval, 0.89-1.27; I2, 65%; and 12 randomized control trials, 1063 patients, relative risk ratio, 1.06; 95% confidence interval, 0.90-1.26; I2, 76%, respectively). Duration of prophylaxis also did not have a significant impact on outcomes. There was a statistically significant difference in overall adverse effects, with nitrofurantoin resulting in greater risk than other prophylactic treatments (10 randomized control trials, 948 patients, relative risk ratio, 2.17; 95% confidence interval, 1.34-3.50; I2, 61%). Overall, the majority of nitrofurantoin adverse effects were gastrointestinal, with a significant difference for withdrawals (12 randomized control trials, 1063 patients, relative risk ratio, 2.14; 95% confidence interval, 1.28-3.56; I2, 8%). CONCLUSION: Nitrofurantoin had similar efficacy but a greater risk of adverse events than other prophylactic treatments. Balancing the risks of adverse events, particularly gastrointestinal symptoms, with potential benefits of decreasing collateral ecological damage should be considered if selecting nitrofurantoin.

Quinn, C., Moore, S. A., Bardakjian, T. M., & Karam, C. (2016). Clinical reasoning: A 30-year-old man with progressive weakness and atrophy. *Neurology*, *87*(19), e227-e230.

Raber, J., Davis, M. J., Pfankuch, T., Rosenthal, R., Doctrow, S. R., & Moulder, J. E. (2016). Mitigating effect of EUK-207 on radiation-induced cognitive impairments. *Behavioural Brain Research*, The brain could be exposed to irradiation as part of a nuclear accident, radiological terrorism (dirty bomb scenario) or a medical radiological procedure. In the context of accidents or terrorism, there is considerable interest in compounds that can mitigate radiation-induced injury when treatment is initiated a day or more after the radiation exposure. As it will be challenging to determine the radiation exposure an individual has received within a relatively short time frame,

it is also critical that the mitigating agent does not negatively affect individuals, including emergency workers, who might be treated, but who were not exposed. Alterations in hippocampus-dependent cognition often characterize radiation-induced cognitive injury. The catalytic ROS scavenger EUK-207 is a member of the class of metal-containing salen manganese (Mn) complexes that suppress oxidative stress, including in the mitochondria, and have been shown to mitigate radiation dermatitis, promote wound healing in irradiated skin, and mitigate vascular injuries in irradiated lungs. As the effects of EUK-207 against radiation injury in the brain are not known, we assessed the effects of EUK-207 on sham-irradiated animals and the ability of EUK-207 to mitigate radiation-induced cognitive injury. The day following irradiation or sham-irradiation, the mice started to receive EUK-207 and were cognitively tested 3 months following exposure. Mice irradiated at a dose of 15Gy showed cognitive impairments in the water maze probe trial. EUK-207 mitigated these impairments while not affecting cognitive performance of sham-irradiated mice in the water maze probe trial. Thus, EUK-207 has attractive properties and should be considered an ideal candidate to mitigate radiation-induced cognitive injury.

Raju, T. N., Pemberton, V. L., Saigal, S., Blaisdell, C. J., Moxey-Mims, M., Buist, S., et al. (2016). Long-term healthcare outcomes of preterm birth: An executive summary of a conference sponsored by the national institutes of health. *The Journal of Pediatrics*,

Rennie, E., Lunsford, R., & Heeman, P. A. (2016). The discourse marker "so" in turn-taking and turn-releasing behavior. *17th Annual Conference of the International Speech Communication Association, INTERSPEECH 2016, , 08-12-September-2016*. pp. 1280-1284.

Although so is a recognized discourse marker, little work has explored its uses in turn-taking, especially when it is not followed by additional speech. In this paper we explore the use of the discourse marker so as it pertains to turn-taking and turnreleasing. Specifically, we compare the duration and intensity of so when used to take a turn, mid-utterance, and when releasing a turn. We found that durations of turn-retaining tokens are generally shorter than turn-releases; we also found that turnretaining tokens tend to be lower in intensity than the following speech. These trends of turn-taking behavior alongside certain lexical and prosodic features may prove useful for the development of speech-recognition software. Copyright © 2016 ISCA.

Riley, A. R., Wagner, D. V., Tudor, M. E., Zuckerman, K. E., & Freeman, K. A. (2016). A survey of parents' perceptions and utilization of time-out in comparison to empirical evidence. *Academic Pediatrics,*

OBJECTIVE: To assess parents' perceptions and utilization of Time-out (TO) in contrast to empirical indications and examine the relationship between reported implementation procedures and perceived effectiveness. METHODS: We surveyed parents of preschool and school-aged children (N=401, aged 15 months-10 years) at well-child visits with regards to their awareness, perception, and usage of TO. Parents were specifically surveyed regarding TO components that have been empirically evaluated or pertain directly to its underlying behavioral principles. Descriptive analyses, group comparisons, and correlational analyses were used to characterize responses and evaluate the relationship between TO administration variation and perceived effectiveness. RESULTS: Most parents (76.8%) reported using TO in response to misbehavior, but a large majority of these parents (84.9%) reported implementing TO in a manner counter to empirical evidence. Parents who endorsed TO as effective varied significantly from those who did not on key implementation components (e.g., use of a single warning). Further, several reported implementation practices were correlated with perceived effectiveness and challenging child behavior. For example, requiring a child to be calm before ending TO was positively correlated with perceived effectiveness. CONCLUSIONS: These results cement TO as a widely disseminated practice, but cast doubt on the fidelity with which it is typically implemented. Better methods of educating parents on evidence-based discipline are needed.

Roengvoraphoj, M., Yan, S., Lansigan, F., Chapman, M. S., & Danilov, A. V. (2016). Acute inflammatory skin reaction during neutrophil recovery after antileukemic therapy. *Cutis, 98*(4), E13-E15.

Rose, M. B., Domes, C., Farooqi, M., & Crawford, D. C. (2016). A prospective randomized comparison of two distinct allogenic tissue constructs for anterior cruciate ligament reconstruction. *The Knee,* BACKGROUND: Conduct a prospective randomized study to compare clinical outcomes of anterior cruciate ligament (ACL) reconstruction using quadrupled hamstring tendon (HT) allograft or doubled tibialis anterior (TA) allograft. Limited level 1 data exist comparing outcomes of different

soft tissue allograft constructs for ACL reconstruction. We hypothesized no difference would exist in the patient reported outcomes (PRO), arthrometric testing, or rate of re-rupture between the two constructs. METHODS: Ninety eight subjects undergoing primary ACL reconstruction were randomized to HT (n=47) or TA (n=51) allograft. Subjects completed validated (PRO) measures pre-operatively, and six months and two years post-operatively. Arthrometric testing was performed at six months to assess integrity of the reconstruction. RESULTS: Fifty-eight percent of subjects (57/98) completed a two-year follow up. Allograft re-tear rates were similar between groups (6.2% HT vs. 4.0% TA, respectively, $p=1.0$). The relative risk of re-tear in the HT group was 1.5 compared to the TA group ($p=0.7$). The TA group improved significantly more on the physical portion of the VR-12 ($p=0.046$) and Lysholm score ($p=0.014$) compared to the HT group. There was no difference in the change from baseline for the other PRO scores at two years. CONCLUSIONS: Our data indicate no difference in graft failure rate and similar improvement from baseline in most PRO scores between treatment groups after two years. Based on these findings, TA allograft appears to provide a reliable and satisfactory option for patients who elect to undergo allograft ACL reconstruction.

Roselli, C. E., Amodei, R., Gribbin, K. P., Corder, K., Stormshak, F., & Estill, C. T. (2016). Excess testosterone exposure alters hypothalamic-pituitary-testicular axis dynamics and gene expression in sheep fetuses. *Endocrinology*, *157*(11), 4234-4245.

Prenatal exposure to excess androgen may result in impaired adult fertility in a variety of mammalian species. However, little is known about what feedback mechanisms regulate gonadotropin secretion during early gestation and how they respond to excess T exposure. The objective of this study was to determine the effect of exogenous exposure to T on key genes that regulate gonadotropin and GnRH secretion in fetal male lambs as compared with female cohorts. We found that biweekly maternal testosterone propionate (100 mg) treatment administered from day 30 to day 58 of gestation acutely decreased ($P < .05$) serum LH concentrations and reduced the expression of gonadotropin subunit mRNA in both sexes and the levels of GnRH receptor mRNA in males. These results are consistent with enhanced negative feedback at the level of the pituitary and were accompanied by reduced mRNA levels for testicular steroidogenic enzymes, suggesting that Leydig cell function was also suppressed. The expression of kisspeptin 1 mRNA, a

key regulator of GnRH neurons, was significantly greater ($P < .01$) in control females than in males and reduced ($P < .001$) in females by T exposure, indicating that hypothalamic regulation of gonadotropin secretion was also affected by androgen exposure. Although endocrine homeostasis was reestablished 2 weeks after maternal testosterone propionate treatment ceased, additional differences in the gene expression of GnRH, estrogen receptor-beta, and kisspeptin receptor (G protein coupled receptor 54) emerged between the treatment cohorts. These changes suggest the normal trajectory of hypothalamic-pituitary axis development was disrupted, which may, in turn, contribute to negative effects on fertility later in life.

Safdar, N., Sengupta, S., Musuuza, J. S., Juthani-Mehta, M., Drees, M., Abbo, L. M., et al. (2016).

Status of the prevention of multidrug-resistant organisms in international settings: A survey of the society for healthcare epidemiology of america research network. *Infection Control and Hospital Epidemiology*, , 1-8.

OBJECTIVE To examine self-reported practices and policies to reduce infection and transmission of multidrug-resistant organisms (MDRO) in healthcare settings outside the United States.

DESIGN Cross-sectional survey. **PARTICIPANTS** International members of the Society for Healthcare Epidemiology of America (SHEA) Research Network. **METHODS** Electronic survey of infection control and prevention practices, capabilities, and barriers outside the United States and Canada. Participants were stratified according to their country's economic development status as defined by the World Bank as low-income, lower-middle-income, upper-middle-income, and high-income. **RESULTS** A total of 76 respondents (33%) of 229 SHEA members outside the United States and Canada completed the survey questionnaire, representing 30 countries. Forty (53%) were high-, 33 (43%) were middle-, and 1 (1%) was a low-income country. Country data were missing for 2 respondents (3%). Of the 76 respondents, 64 (84%) reported having a formal or informal antibiotic stewardship program at their institution. High-income countries were more likely than middle-income countries to have existing MDRO policies (39/64 [61%] vs 25/64 [39%], $P=.003$) and to place patients with MDRO in contact precautions (40/72 [56%] vs 31/72 [44%], $P=.05$). Major barriers to preventing MDRO transmission included constrained resources (infrastructure, supplies, and trained staff) and challenges in changing provider behavior.

CONCLUSIONS In this survey, a substantial proportion of institutions reported encountering

barriers to implementing key MDRO prevention strategies. Interventions to address capacity building internationally are urgently needed. Data on the infection prevention practices of low income countries are needed. *Infect Control Hosp Epidemiol.* 2016:1-8.

Schellino, R., Trova, S., Cimino, I., Farinetti, A., Jongbloets, B. C., Pasterkamp, R. J., et al. (2016).

Opposite-sex attraction in male mice requires testosterone-dependent regulation of adult olfactory bulb neurogenesis. *Scientific Reports*, 6

Opposite-sex attraction in most mammals depends on the fine-tuned integration of pheromonal stimuli with gonadal hormones in the brain circuits underlying sexual behaviour. Neural activity in these circuits is regulated by sensory processing in the accessory olfactory bulb (AOB), the first central station of the vomeronasal system. Recent evidence indicates adult neurogenesis in the AOB is involved in sex behaviour; however, the mechanisms underlying this function are unknown. By using Semaphorin 7A knockout (Sema7A ko) mice, which show a reduced number of gonadotropin-releasing-hormone neurons, small testicles and subfertility, and wild-type males castrated during adulthood, we demonstrate that the level of circulating testosterone regulates the sex-specific control of AOB neurogenesis and the vomeronasal system activation, which influences opposite-sex cue preference/attraction in mice. Overall, these data highlight adult neurogenesis as a hub for the integration of pheromonal and hormonal cues that control sex-specific responses in brain circuits. © The Author(s) 2016.

Schenning, K. J., Noguchi, K. K., Martin, L. D., Manzella, F. M., Cabrera, O. H., Dissen, G. A., et al.

(2016). Isoflurane exposure leads to apoptosis of neurons and oligodendrocytes in 20- and 40-day old rhesus macaques. *Neurotoxicology and Teratology*,

Previously we reported that a 5-hour exposure of 6-day-old (P6) rhesus macaques to isoflurane triggers robust neuron and oligodendrocyte apoptosis. In an attempt to further describe the window of vulnerability to anesthetic neurotoxicity, we exposed P20 and P40 rhesus macaques to 5h of isoflurane anesthesia or no exposure (control animals). Brains were collected 3h later and examined immunohistochemically to analyze neuronal and glial apoptosis. Brains exposed to isoflurane displayed neuron and oligodendrocyte apoptosis distributed throughout cortex and white matter, respectively. When combining the two age groups (P20+P40), the animals exposed

to isoflurane had 3.6 times as many apoptotic cells as the control animals. In the isoflurane group, approximately 66% of the apoptotic cells were oligodendrocytes and 34% were neurons. In comparison, in our previous studies on P6 rhesus macaques, approximately 52% of the dying cells were glia and 48% were neurons. In conclusion, the present data suggest that the window of vulnerability for neurons is beginning to close in the P20 and P40 rhesus macaques, but continuing for oligodendrocytes.

Scherber, R. M., Geyer, H. L., Dueck, A. C., Kosiorek, H. E., Finazzi, G., Cavazzina, R., et al. (2016).

The potential role of hematocrit control on symptom burden among polycythemia vera patients: Insights from the CYTO-PV and MPN-SAF patient cohorts. *Leukemia & Lymphoma*, , 1-7.

Current guidelines suggest that polycythemia vera (PV) patients maintain a strict hematocrit less than 45%. However, to date, little is known about the relationship between HCT control and PV-related symptom burden. In this study, PV patient data was analyzed from the CYTO PV trial (n = 224) and the MPN-SAF study cohort (n = 645). No significant differences in symptom burden were seen at the 6 and 12 month follow-up when evaluating prospective hematocrit control in the CYTO PV cohort. Patients in the MPN-SAF cohort with a worst item score of greater than 5/10 on the Myeloproliferative Neoplasm Symptom Total Symptom Score had a significantly lower mean hematocrit (p = .0376). These findings suggest a relationship between traditional aggressive therapy for PV and increased symptom burden with prolonged therapy. Thus, symptom burden should be considered when contemplating the choice of therapy in the second-line setting for PV.

Schild, C., Reed, E. A., Hingston, T., Dennis, C. H., & Wilson, A. C. (2016). Neighborhood

characteristics: Influences on pain and physical function in youth at risk for chronic pain. *Children (Basel, Switzerland)*, 3(4), E35.

Neighborhood features such as community socioeconomic status, recreational facilities, and parks have been correlated to the health outcomes of the residents living within those neighborhoods, especially with regard to health-related quality of life, body mass index, and physical activity. The interplay between one's built environment and one's perceptions may affect physical health, well-being, and pain experiences. In the current study, neighborhood characteristics and attitudes about physical activity were examined in a high-risk (youths with a parent with chronic pain) and

low-risk (youths without a parent with chronic pain) adolescent sample. There were significant differences in neighborhood characteristics between the high-risk (n = 62) and low-risk (n = 77) samples (ages 11-15), with low-risk participants living in residences with more walkability, closer proximity to parks, and higher proportion of neighborhood residents having college degrees. Results indicate that neighborhood features (e.g., walkability and proximity to parks), as well as positive attitudes about physical activity were correlated with lower levels of pain and pain-related disability, and higher performance in physical functioning tests. These findings suggest that the built environment may contribute to pain outcomes in youth, above and beyond the influence of family history of pain.

Seshadri, C., Thuong, N. T., Mai, N. T., Bang, N. D., Chau, T. T., Lewinsohn, D. M., et al. (2016). A polymorphism in human MR1 is associated with mRNA expression and susceptibility to tuberculosis. *Genes and Immunity*,

The MR1 antigen-presenting system is conserved among mammals and enables T cells to recognize small molecules produced by bacterial pathogens, including *Mycobacterium tuberculosis* (M.tb). However, it is not known whether MR1-mediated antigen presentation is important for protective immunity against mycobacterial disease. We hypothesized that genetic control of MR1 expression correlates with clinical outcomes of tuberculosis infection. We performed an MR1 candidate gene association study and identified an intronic single-nucleotide polymorphism (rs1052632) that was significantly associated with susceptibility to tuberculosis in a discovery and validation cohort of Vietnamese adults with tuberculosis. Stratification by site of disease revealed that rs1052632 genotype GG was strongly associated with the development of meningeal tuberculosis (odds ratio=2.99; 95% confidence interval (CI) 1.64-5.43; P=0.00006). Among patients with meningeal disease, absence of the G allele was associated with an increased risk of death (hazard ratio=3.86; 95% CI 1.49-9.98; P=0.005). Variant annotation tools using public databases indicate that rs1052632 is strongly associated with MR1 gene expression in lymphoblastoid cells (P=0.004) and is located within a transcriptional enhancer in epithelial keratinocytes. These data support a role for MR1 in the pathogenesis of human tuberculosis by revealing that rs1052632 is associated with MR1 gene expression and susceptibility to

tuberculosis in Vietnam. *Genes and Immunity* advance online publication, 24 November 2016; doi:10.1038/gene.2016.41.

Sexson, K., Lindauer, A., & Harvath, T. A. (2016). Administration of subcutaneous injections. *The American Journal of Nursing*, 116(12), 49-52.

This article is the second in a series, Supporting Family Caregivers: No Longer Home Alone, published in collaboration with the AARP Public Policy Institute. Results of focus groups conducted as part of the AARP Public Policy Institute's No Longer Home Alone video project supported evidence that family caregivers aren't being given the information they need to manage the complex care regimens of their family members. This series of articles and accompanying videos aims to help nurses provide caregivers with the tools they need to manage their family member's medications. Each article explains the principles nurses should consider and reinforce with caregivers and is accompanied by a video for the caregiver to watch. The second video can be accessed at <http://links.lww.com/AJN/A75>.

Shearer, T. R., Chamberlain, W. D., Fujii, A., & Azuma, M. (2016). Selecting fuchs patients for drug trials involving endothelial cell proliferation. *European Journal of Ophthalmology*, 26(6), 536-539.

PURPOSE: Fuchs endothelial corneal dystrophy (FECD) might be managed by drug treatment before becoming severe enough to require surgery. For a clinical trial of such a drug, we hypothesize that selecting an adequate number of patients with FECD with only moderately compromised cell densities will be challenging. Thus, the purpose of the present study was to measure the prevalence of patients with FECD exhibiting moderately decreased corneal cell densities. METHODS: A retrospective data mining study (cross-sectional study) was performed on patient charts presenting at a large US northwestern academic health center by searching for diagnosis ICD-9 code 371.57 and Fuchs corneal dystrophies, including those with prior cataract surgeries and/or existing glaucoma. Patients with prior corneal transplants were excluded. Noncontact specular photomicroscopic data (Topcon 2000) were obtained from the central region whenever possible, and individual eyes were grouped according to cell density (cells/mm²): severe (1,500). RESULTS: The values for 98 eyes from 61 patients with FECD were as follows (mean +/- SD): corneal thickness 573 +/- 59 μ m, cell size 627 +/- 336 μ m²/cell, coefficient

of variation 23 ± 7 , and density $1,883 \pm 703$ cells/mm². The moderate subgroup with cell density values averaging $1,184 \pm 212$ (26) comprised 27% of the total FECD patient pool.

CONCLUSIONS: Only approximately 1 out of 4 patients with FECD will show moderately compromised corneal cell densities. A moderate level of damage may be optimal for clinical trials for testing topical drugs on endothelial cell viability. Thus, investigators will need to initially screen a fourfold excess of all patients with FECD.

Simmons, K. B., Edelman, A. B., Fu, R., & Jensen, J. T. (2016). Tamoxifen for the treatment of breakthrough bleeding with the etonogestrel implant: A randomized controlled trial.

Contraception,

OBJECTIVE: The etonogestrel (ENG) subdermal implant can cause frequent breakthrough bleeding in some users. The objective of this study was to evaluate whether a short course of tamoxifen reduces bleeding/spotting days compared to placebo in ENG implant users. **STUDY DESIGN:** In this double-blind trial, we randomized ENG implant users with frequent or prolonged bleeding or spotting to tamoxifen 10 mg or placebo twice daily for 7 days, to be started after 3 consecutive days of bleeding/spotting. Treatment was repeated as needed up to three times in 180 days. Subjects completed a daily text message bleeding diary. A sample size of 56 provided 80% power to detect a difference of 6 days of bleeding/spotting per 30 days by two-sample t test. Ovulation was monitored by urinary metabolites of progesterone. **RESULTS:** From March 2014 to February 2015, 56 women enrolled. Fifty-one completed at least 30 days of follow up, and 34 completed 180 days. Compared to women randomized to placebo, women randomized to tamoxifen reported 5 fewer days of bleeding/spotting over 30 days (95% confidence interval [CI] -9.9 to -0.05, $p=.05$), and 15.2 more continuous bleeding-free days (95% CI 2.8-27.5 days, $p=.02$) after first use of study drug. Conclusions could not be drawn after 30 days due to higher-than-expected dropout. No ovulation was detected. **CONCLUSION:** First use of tamoxifen by ENG implant users reduces bleeding/spotting days and provides a longer cessation of bleeding/spotting than placebo, without compromising ovulation suppression. Further study is needed to determine whether this effect is maintained with repeat use. **IMPLICATIONS:** Women with frequent ENG implant-related breakthrough bleeding may experience a reduction in bleeding/spotting days and an increase in continuous bleeding-free days in the month following

first use of tamoxifen. This short course of tamoxifen was well tolerated with bleeding cessation noted within a median of 5 days.

Sittig, D. F., Wright, A., Ash, J., & Singh, H. (2016). New unintended adverse consequences of electronic health records. *Yearbook of Medical Informatics*, (1)(1), 7-12.

Although the health information technology industry has made considerable progress in the design, development, implementation, and use of electronic health records (EHRs), the lofty expectations of the early pioneers have not been met. In 2006, the Provider Order Entry Team at Oregon Health & Science University described a set of unintended adverse consequences (UACs), or unpredictable, emergent problems associated with computer-based provider order entry implementation, use, and maintenance. Many of these originally identified UACs have not been completely addressed or alleviated, some have evolved over time, and some new ones have emerged as EHRs became more widely available. The rapid increase in the adoption of EHRs, coupled with the changes in the types and attitudes of clinical users, has led to several new UACs, specifically: complete clinical information unavailable at the point of care; lack of innovations to improve system usability leading to frustrating user experiences; inadvertent disclosure of large amounts of patient-specific information; increased focus on computer-based quality measurement negatively affecting clinical workflows and patient-provider interactions; information overload from marginally useful computer-generated data; and a decline in the development and use of internally-developed EHRs. While each of these new UACs poses significant challenges to EHR developers and users alike, they also offer many opportunities. The challenge for clinical informatics researchers is to continue to refine our current systems while exploring new methods of overcoming these challenges and developing innovations to improve EHR interoperability, usability, security, functionality, clinical quality measurement, and information summarization and display.

Skalet, A. H., Li, Y., Lu, C. D., Jia, Y., Lee, B., Husvogt, L., et al. (2016). Optical coherence tomography angiography characteristics of iris melanocytic tumors. *Ophthalmology*,
PURPOSE: To evaluate tumor vasculature with optical coherence tomography angiography (OCTA) in malignant iris melanomas and benign iris lesions. DESIGN: Cross-sectional

observational clinical study. PARTICIPANTS: Patients with iris lesions and healthy volunteers. METHODS: Eyes were imaged using OCTA systems operating at 1050- and 840-nm wavelengths. Three-dimensional OCTA scans were acquired. Iris melanoma patients treated with radiation therapy were imaged again after I-125 plaque brachytherapy at 6 and 18 months. MAIN OUTCOME MEASURES: OCT and OCTA images, qualitative evaluation of iris and tumor vasculature, and quantitative vessel density. RESULTS: One eye each of 8 normal volunteers and 9 patients with iris melanomas or benign iris lesions, including freckles, nevi, and an iris pigment epithelial (IPE) cyst, were imaged. The normal iris has radially oriented vessels within the stroma on OCTA. Penetration of flow signal in normal iris depended on iris color, with best penetration seen in light to moderately pigmented irides. Iris melanomas demonstrated tortuous and disorganized intratumoral vasculature. In 2 eyes with nevi there was no increased vascularity; in another, fine vascular loops were noted near an area of ectropion uveae. Iris freckles and the IPE cyst did not have intrinsic vascularity. The vessel density was significantly higher within iris melanomas (34.5%±9.8%, $P < 0.05$) than in benign iris nevi (8.0%±1.4%) or normal irides (8.0%±1.2%). Tumor regression after radiation therapy for melanomas was associated with decreased vessel density. OCTA at 1050 nm provided better visualization of tumor vasculature and penetration through thicker tumors than at 840 nm. But in very thick tumors and highly pigmented lesions even 1050-nm OCTA could not visualize their full thickness. Interpretable OCTA images were obtained in 82% of participants in whom imaging was attempted. CONCLUSIONS: This is the first demonstration of OCTA in iris tumors. OCTA may provide a dye-free, no-injection, cost-effective method for monitoring a variety of tumors, including iris melanocytic lesions, for growth and vascularity. This could be helpful in evaluating tumors for malignant transformation and response to treatment. Penetration of the OCT beam remains a limitation for highly pigmented tumors, as does the inability to image the entire iris in a single field.

Skalsky, R. L. (2017). Analysis of viral and cellular MicroRNAs in EBV-infected cells. *Methods in Molecular Biology (Clifton, N.J.)*, 1532, 133-146.

MicroRNAs are small, noncoding RNAs that posttranscriptionally regulate gene expression. The discovery of this relatively new mode of gene regulation as well as studies showing the prognostic

value of viral and cellular miRNAs as biomarkers, such as in cancer progression, has stimulated the development of many methods to characterize miRNAs. EBV encodes 25 viral precursor microRNAs within its genome that are expressed during lytic and latent infection. In addition to viral miRNAs, EBV infection induces the expression of specific cellular oncogenic miRNAs, such as miR-155, miR-146a, miR-21, and others, that can contribute to the persistence of latently infected cells. This chapter describes several current techniques used to identify and detect the expression of viral and cellular miRNAs in EBV-infected cells.

Smith, J. W., Rogers, R. B., Jeon, S., Rubakhin, S. S., Wang, L., Sweedler, J. V., et al. (2016). Carrot solution culture bioproduction of uniformly labeled ^{13}C -lutein and in vivo dosing in non-human primates. *Experimental Biology and Medicine (Maywood, N.J.)*,

Lutein is a xanthophyll abundant in nature and most commonly present in the human diet through consumption of leafy green vegetables. With zeaxanthin and meso-zeaxanthin, lutein is a component of the macular pigment of the retina, where it protects against photooxidation and age-related macular degeneration. Recent studies have suggested that lutein may positively impact cognition throughout the lifespan, but outside of the retina, the deposition, metabolism, and function(s) of lutein are poorly understood. Using a novel botanical cell culture system (*Daucus carota*), the present study aimed to produce a stable isotope lutein tracer for use in future investigations of dietary lutein distribution and metabolism. Carrot cultivars were initiated into liquid solution culture, lutein production conditions optimized, and uniformly labeled ^{13}C -glucose was provided as the sole media carbon source for four serial growth cycles. Lutein yield was 2.58 ± 0.24 microg/g, and mass spectrometry confirmed high enrichment of ^{13}C : 64.9% of lutein was uniformly labeled and 100% of lutein was labeled on at least 37 of 40 possible carbons. Purification of carrot extracts yielded a lutein dose of 1.92 mg with $96.0 \pm 0.60\%$ purity. ^{13}C -lutein signals were detectable in hepatic extracts of an adult rhesus macaque monkey (*Macaca mulatta*) dosed with ^{13}C -lutein, but not in hepatic samples collected from control animals. This novel botanical biofactory approach can be used to produce sufficient quantities of highly enriched and pure ^{13}C -lutein doses for use in tracer studies investigating lutein distribution, metabolism, and function.

Snowden, J. M., Muoto, I., Darney, B. G., Quigley, B., Tomlinson, M. W., Neilson, D., et al. (2016).

Oregon's hard-stop policy limiting elective early-term deliveries: Association with obstetric procedure use and health outcomes. *Obstetrics and Gynecology*, 128(6), 1389-1396.

OBJECTIVE: To evaluate the association of Oregon's hard-stop policy limiting early elective deliveries (before 39 weeks of gestation) and the rate of elective early-term inductions and cesarean deliveries and associated maternal-neonatal outcomes. METHODS: This was a population-based retrospective cohort study of Oregon births between 2008 and 2013 using vital statistics data and multivariable logistic regression models. Our exposure was the Oregon hard-stop policy, defined as the time periods prepolicy (2008-2010) and postpolicy (2012-2013). We included all term or postterm, cephalic, nonanomalous, singleton deliveries (N=181,034 births). Our primary outcomes were induction of labor and cesarean delivery at 37 or 38 weeks of gestation without a documented indication on the birth certificate (ie, elective early term delivery). Secondary outcomes included neonatal intensive care unit admission, stillbirth, macrosomia, chorioamnionitis, and neonatal death. RESULTS: The rate of elective inductions before 39 weeks of gestation declined from 4.0% in the prepolicy period to 2.5% during the postpolicy period ($P<.001$); a similar decline was observed for elective early-term cesarean deliveries (from 3.4% to 2.1%; $P<.001$). There was no change in neonatal intensive care unit admission, stillbirth, or assisted ventilation prepolicy and postpolicy, but chorioamnionitis did increase (from 1.2% to 2.2%, $P<.001$; adjusted odds ratio 1.94, 95% confidence interval 1.80-2.09). CONCLUSIONS: Oregon's statewide policy to limit elective early-term delivery was associated with a reduction in elective early-term deliveries, but no improvement in maternal or neonatal outcomes.

Son, J., Miller, W. M., Tossone, K., Butcher, F., & Kuo, K. (2016). The impact of interprofessional student-led reproductive health education on youths in juvenile detention. *Journal of Pediatric and Adolescent Gynecology*,

STUDY OBJECTIVE: To assess the effects of an interprofessional student-led comprehensive sexual education curriculum in improving the reproductive health literacy among at-risk youths in detention. DESIGN: Setting, and Participants: We performed a prospective cohort study involving 134 incarcerated youth and an interprofessional team of 23 medical, nursing, and social work

students, who participated in a comprehensive reproductive health curriculum over the course of 3 days. INTERVENTION AND MAIN OUTCOME MEASURES: Basic reproductive health knowledge, confidence in condom use with a new partner, and self-efficacy with regards to contraception use and sexual autonomy were assessed prior to and following completion of the curriculum. We also assessed the student teachers' level of comfort with teaching reproductive health to adolescents and their perception of interprofessionalism. RESULTS: Incarcerated youth demonstrated a statistically significant increase in knowledge regarding sexually transmitted infections as well as self-reported confidence in condom use ($p = 0.002$). Self-efficacy in contraception use and sexual autonomy did not show significant improvement. Qualitative analysis of student teachers' surveys revealed theme categories regarding perception of youth, perception of self in teaching youth, perception of interacting with youth, and perception of working in interprofessional teams. CONCLUSIONS: Our program may represent a mutually beneficial community relationship to improve reproductive health literacy in this high-risk youth population.

Sonnenberg, A. (2016). Cry wolf and inflate medical urgency to expedite consult resolution through gastrointestinal endoscopy. *European Journal of Gastroenterology & Hepatology*,
BACKGROUND AND AIMS: To expedite a consult resolution, referring physicians sometimes inflate the urgency and need for endoscopic workup. The aim of the present decision analysis was to study the impact of inflationary indication on the expected benefits to gastroenterologists and referring physicians. METHODS: The study aims were pursued in terms of game theory and medical decision analysis using decision trees. Different outcomes associated with true versus false urgent indication in immediate versus delayed endoscopy were ranked according to different preference schemes of gastroenterologists versus referring physicians. RESULTS: The decision analysis shows that inflating the urgency of indication for endoscopy reduces the benefit from the perspective of gastroenterologists and referring physicians alike. Raising the level of false urgent indications results in a lost opportunity for immediate endoscopy among patients with true urgent indications and, thus, diminishes the overall benefit of endoscopy. By comparison, all other influences play only a marginal role. For referring physicians, the small benefit of expediting nonurgent endoscopies by exaggerated claims does not compensate for the concomitant loss of truly needed endoscopy slots. For gastroenterologists, a small benefit derived from delaying

endoscopies in patients with false urgent endoscopies rapidly wears off as inflationary indications become common practice. CONCLUSION: An underlying communication problem between referring physicians and gastroenterologists needs to be resolved by educating referring physicians about the operative exigencies of endoscopy units and about the true appearance of alarm symptoms in common digestive diseases.

Sonnenberg, A., Turner, K. O., Spechler, S. J., & Genta, R. M. (2016). The influence of helicobacter pylori on the ethnic distribution of barrett's metaplasia. *Alimentary Pharmacology & Therapeutics*,

BACKGROUND: Environmental risk factors associated with ethnicity may contribute to the occurrence of Barrett's metaplasia. AIM: Our aim was to investigate the interaction between ethnicity and Helicobacter pylori infection in the occurrence of Barrett's metaplasia among patients undergoing oesophago-gastro-duodenoscopy. METHODS: The Miraca Life Sciences Database is an electronic repository of histopathological patient records. A case-control study evaluated the influence of age, gender, ethnicity and histological diagnosis of H. pylori on the occurrence of Barrett's metaplasia. RESULTS: The total study population comprised 596 479 subjects, of whom 76 475 harboured a diagnosis of Barrett's metaplasia. Male sex, age and H. pylori infection in declining order exerted the strongest influence on the occurrence of BM. In comparison with the population comprising Caucasians and African Americans, Barrett's metaplasia was less common among subjects of African (OR = 0.09, 95% CI = 0.01-0.43), Middle Eastern (0.26, 0.20-0.34), East Asian (0.35, 0.31-0.40), Indian (0.39, 0.32-0.47), Hispanic (0.62, 0.59-0.64) or Jewish descent (0.50, 0.45-0.54), but more common among subjects of Northern European descent (1.14, 1.03-1.26). With the exception of Jews and Northern Europeans, all other ethnic subgroups were characterised by a higher prevalence of H. pylori than the comparison group. A low prevalence of H. pylori was significantly associated with a high prevalence of Barrett's metaplasia ($R^2 = 0.82$, $P < 0.001$), as well as dysplasia or oesophageal adenocarcinoma ($R^2 = 0.81$, $P < 0.001$). CONCLUSION: Our analysis reveals an inverse relationship between the prevalence of Barrett's metaplasia and H. pylori gastritis among different ethnic groups within the United States.

Sontag, R. L., Nakayasu, E. S., Brown, R. N., Niemann, G. S., Sydor, M. A., Sanchez, O., et al.

(2016). Identification of novel host interactors of effectors secreted by salmonella and citrobacter. *Msystems*, 1(4), e00032-15. eCollection 2016 Jul-Aug.

Many pathogenic bacteria of the family Enterobacteriaceae use type III secretion systems to inject virulence proteins, termed "effectors," into the host cell cytosol. Although host-cellular activities of several effectors have been demonstrated, the function and host-targeted pathways of most of the effectors identified to date are largely undetermined. To gain insight into host proteins targeted by bacterial effectors, we performed coaffinity purification of host proteins from cell lysates using recombinant effectors from the Enterobacteriaceae intracellular pathogens *Salmonella enterica* serovar Typhimurium and *Citrobacter rodentium*. We identified 54 high-confidence host interactors for the *Salmonella* effectors GogA, GtgA, GtgE, SpvC, SrfH, SseL, SspH1, and SssB collectively and 21 interactors for the *Citrobacter* effectors EspT, NleA, NleG1, and NleK. We biochemically validated the interaction between the SrfH *Salmonella* protein and the extracellular signal-regulated kinase 2 (ERK2) host protein kinase, which revealed a role for this effector in regulating phosphorylation levels of this enzyme, which plays a central role in signal transduction. **IMPORTANCE** During infection, pathogenic bacteria face an adverse environment of factors driven by both cellular and humoral defense mechanisms. To help evade the immune response and ultimately proliferate inside the host, many bacteria evolved specialized secretion systems to deliver effector proteins directly into host cells. Translocated effector proteins function to subvert host defense mechanisms. Numerous pathogenic bacteria use a specialized secretion system called type III secretion to deliver effectors into the host cell cytosol. Here, we identified 75 new host targets of *Salmonella* and *Citrobacter* effectors, which will help elucidate their mechanisms of action.

Sosa, E., Kim, R., Rojas, E. J., Hosohama, L., Hennebold, J. D., Orwig, K. E., et al. (2016). An integration-free, virus-free rhesus macaque induced pluripotent stem cell line (riPSC89) from embryonic fibroblasts. *Stem Cell Research*, 17(2), 444-447.

We generated a rhesus macaque induced pluripotent stem cell (riPSC) line, riPSC89, from rhesus embryonic fibroblasts (REFs). Fibroblasts were expanded from the skin of a rhesus macaque embryo at embryonic day 47. REFs and riPSCs had a normal male (42, XY) karyotype. The

riPSC89 line was positive for markers of self-renewal including OCT4, NANOG, TRA-1-81 and SSEA4. Pluripotency was demonstrated through the generation of teratomas using transplantation into immunocompromised mice. The riPSC89 line may be a useful non-human primate resource to uncover developmental origins of disease, or used as a basic model to understand lineage specification in the primate embryo.

Soto, P. L., Hiranita, T., Xu, M., Hursh, S. R., Grandy, D. K., & Katz, J. L. (2016). Dopamine D(2)-like receptors and behavioral economics of food reinforcement. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, 41(4), 971-978.

Previous studies suggest dopamine (DA) D2-like receptor involvement in the reinforcing effects of food. To determine contributions of the three D2-like receptor subtypes, knockout (KO) mice completely lacking DA D2, D3, or D4 receptors (D2R, D3R, or D4R KO mice) and their wild-type (WT) littermates were exposed to a series of fixed-ratio (FR) food-reinforcement schedules in two contexts: an open economy with additional food provided outside the experimental setting and a closed economy with all food earned within the experimental setting. A behavioral economic model was used to quantify reinforcer effectiveness with food pellets obtained as a function of price (FR schedule value) plotted to assess elasticity of demand. Under both economies, as price increased, food pellets obtained decreased more rapidly (ie, food demand was more elastic) in DA D2R KO mice compared with WT littermates. Extinction of responding was studied in two contexts: by eliminating food deliveries and by delivering food independently of responding. A hyperbolic model quantified rates of extinction. Extinction in DA D2R KO mice occurred less rapidly compared with WT mice in both contexts. Elasticity of food demand was higher in DA D4R KO than WT mice in the open, but not closed, economy. Extinction of responding in DA D4R KO mice was not different from that in WT littermates in either context. No differences in elasticity of food demand or extinction rate were obtained in D3R KO mice and WT littermates. These results indicate that the D2R is the primary DA D2-like receptor subtype mediating the reinforcing effectiveness of food.

Spuls, P. I., Gerbens, L. A., Simpson, E., Apfelbacher, C. J., Chalmers, J. R., Thomas, K. S., et al. (2016). POEM a core instrument to measure symptoms in clinical trials: A HOME statement. *The*

British Journal of Dermatology,

BACKGROUND: The Harmonising Outcome Measures for Eczema (HOME) initiative has defined four core outcome domains for a core outcome set (COS) to be measured in all atopic eczema (AE) trials to ensure cross-trial comparison: clinical signs, symptoms, quality of life and long-term control. **OBJECTIVES:** The aim of this paper is to report on the consensus process that was used to select the core instrument to consistently assess symptoms in all future AE trials.

METHODS: Following the HOME roadmap, two systematic reviews were performed which identified three instruments that had sufficient evidence of validity, reliability, and feasibility to be considered for the final COS. **RESULTS:** At the 4th international HOME meeting there was broad consensus among all stakeholders that the Patient-Oriented Eczema Measure (POEM) should be used as the core instrument (87.5% agreed, 9.4% unsure, 3.1% disagreed). **CONCLUSIONS:** All relevant stakeholders are encouraged to use POEM as the chosen instrument to measure the core domain of symptoms in all future AE clinical trials. Other instruments of interest can be used in addition to POEM. This article is protected by copyright. All rights reserved.

Stark, D., Rosenberg, A. R., Johnston, D., Knight, K., Caperon, L., Uleryk, E., et al. (2016). Patient-reported measures of hearing loss and tinnitus in pediatric cancer and hematopoietic stem cell transplantation: A systematic review. *Journal of Speech, Language, and Hearing Research : JSLHR*, 59(5), 1247-1252.

Purpose: We identified studies that described use of any patient-reported outcome scale for hearing loss or tinnitus among children and adolescents and young adults (AYAs) with cancer or hematopoietic stem cell transplantation (HSCT) recipients. **Method:** In this systematic review, we performed electronic searches of OvidSP MEDLINE, EMBASE, and PsycINFO to August 2015. We included studies if they used any patient-reported scale of hearing loss or tinnitus among children and AYAs with cancer or HSCT recipients. Only English language publications were included. Two reviewers identified studies and abstracted data. **Results:** There were 953 studies screened; 6 met eligibility criteria. All studies administered hearing patient-reported outcomes only once, after therapy completion. None of the studies described the psychometric properties of the hearing-specific component. Three instruments (among 6 studies) were used: Health Utilities Index (Barr et al., 2000; Fu et al., 2006; Kennedy et al., 2014), Hearing Measurement Scales

(Einar-Jon et al., 2011; Einarsson et al., 2011), and the Tinnitus Questionnaire for Auditory Brainstem Implant (Soussi & Otto, 1994). All had limitations, precluding routine use for hearing assessment in this population. Conclusions: We identified few studies that included hearing patient-reported measures for children and AYA cancer and HSCT patients. None are ideal to take forward into future studies. Future work should focus on the creation of a new psychometrically sound instrument for hearing outcomes in this population.

Stovall, S., Midgett, M., Thornburg, K., & Rugonyi, S. (2016). Changes in dynamic embryonic heart wall motion in response to outflow tract banding measured using video densitometry. *Journal of Biomedical Optics*, 21(11), 116003.

Sultana, S., Agrawal, P., Elhabian, S. Y., Whitaker, R. T., Rashid, T., Blatt, J. E., et al. (2016). In Shekhar R., et al(Eds.), *Towards a statistical shape-aware deformable contour model for cranial nerve identification* Springer Verlag.

This paper presents a cranial nerve segmentation technique that combines a 3D deformable contour and a 3D contour Statistical Shape Model (SSM). A set of training data for the construction of the 3D contour shape model is produced using a 1-simplex based discrete deformable contour model where the centerline identification proceeds by optimizing internal and external forces. Point-correspondence for the training dataset is performed using an entropybased energy minimization of particles on the centerline curve. The resulting average shape is used as a prior knowledge, which is incorporated into the 1-simplex as a reference shape model, making the approach stable against low resolution and image artifacts during segmentation using MRI data. Shape variability is shown using the first 3 modes of variation. The segmentation result is validated quantitatively, with ground truth provided by an expert. © Springer International Publishing AG 2016.

Taha, A. A., & Westlake, C. (2016). Palestinian nurses' lived experiences working in the occupied west bank. *International Nursing Review*,

BACKGROUND: Since the construction of the separation wall between Israel and the West Bank, Palestinians living in occupied West Bank have endured intense conflict, and severe restrictions on people's movement, trade and healthcare access, all of which resulted in spiralling poverty.

These issues have created challenges for nurses that, to date, have not been explored. AIM: To explore the lived experience of Palestinian nurses working in the occupied West Bank. METHODS: Qualitative phenomenological study using interviews with Palestinian nurses working in public hospitals in the West Bank. FINDINGS: Seventeen nurses were interviewed. Despite ongoing experiences of trauma and humiliation, personal/professional role conflicts, political workplace bias and blurred role boundaries, these nurses persevered because of their commitment to caring and sense of moral duty to 'the people of this land'. DISCUSSION: Nurses in conflict areas are subject to layers of trauma. Palestinian nurses in the West Bank not only experience ongoing personal trauma, loss and humiliation of living in a conflict zone but they also experience additional professional trauma. CONCLUSION: The findings provide first-person reports of the unique challenges of nurses working in the occupied West Bank. IMPLICATIONS FOR NURSING PRACTICE: Understanding the experiences of nurses working in occupied territories provides authentic information for local authorities and the global healthcare community. Practice improvements must be addressed and implemented. IMPLICATIONS FOR HEALTH POLICY: Local and global organizations that mobilize support, invest in human capital, and protect human rights in areas of conflict may benefit from understanding the experiences of nurses in this study.

Tang, M., Li, Y., Chamberlain, W., Louie, D. J., Schallhorn, J. M., & Huang, D. (2016). Differentiating keratoconus and corneal warpage by analyzing focal change patterns in corneal topography, pachymetry, and epithelial thickness maps. *Investigative Ophthalmology and Visual Science*, 57(9Special Issue), OCT544-OCT549.

PURPOSE. To differentiate between keratoconus and contact lens-related corneal warpage by combining focal change patterns in anterior corneal topography, pachymetry, and epithelial thickness maps. METHODS. Pachymetry and epithelial thickness maps of normal, keratoconus, and warpage, and forme fruste keratoconus (FFK) eyes were obtained from a Fourier-domain optical coherence tomography (OCT). Epithelial pattern standard deviation (PSD) was calculated and combined with two novel indices, the Warpage Index and the Anterior Ectasia Index, to differentiate between normal, keratoconus, and warpage eyes. The values of the three parameters were compared between groups. RESULTS. The study included 22 normal, 31 keratoconic, 11 warpage, and 8 FFK eyes. The epithelial PSD was normal (0.041) for 100% of

keratoconic eyes, 81.8% of warpage eyes, and 87.5% of FFK eyes. The Anterior Ectasia Index of normal eyes (1.66 ± 0.74) was significantly lower than that for the keratoconus eyes (17.5 ± 7.17), the warpage eyes (2.98 ± 1.69), and the FFK eyes (6.95 ± 5.86). The Warpage Index was positive in all warpage eyes and negative for all keratoconic and FFK eyes except three wearing rigid gas-permeable contact lens. CONCLUSIONS. The epithelial PSD can distinguish normal from keratoconus or warpage, but does not distinguish between these two conditions. The Anterior Ectasia Index is abnormal in keratoconus but not warpage. The Warpage Index is positive for warpage and negative for keratoconus, except in cases where keratoconus and warpage coexist. Together, the three parameters are strong tripartite discriminators of normal, keratoconus, and warpage. © 2016, Association for Research in Vision and Ophthalmology Inc. All rights reserved.

Tateno, M., Skokauskas, N., Kato, T. A., Teo, A. R., & Guerrero, A. P. (2016). New game software (pokemon go) may help youth with severe social withdrawal, hikikomori. *Psychiatry Research*,

Tereshchenko, L. G., Kim, E. D., Oehler, A., Meoni, L. A., Ghafoori, E., Rami, T., et al. (2016).

Electrophysiologic substrate and risk of mortality in incident hemodialysis. *Journal of the American Society of Nephrology : JASN*, 27(11), 3413-3420.

The single leading cause of mortality on hemodialysis is sudden cardiac death. Whether measures of electrophysiologic substrate independently associate with mortality is unknown. We examined measures of electrophysiologic substrate in a prospective cohort of 571 patients on incident hemodialysis enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease Study. A total of 358 participants completed both baseline 5-minute and 12-lead electrocardiogram recordings on a nondialysis day. Measures of electrophysiologic substrate included ventricular late potentials by the signal-averaged electrocardiogram and spatial mean QRS-T angle measured on the averaged beat recorded within a median of 106 days (interquartile range, 78-151 days) from dialysis initiation. The cohort was 59% men, and 73% were black, with a mean \pm -SD age of 55 \pm -13 years. Transthoracic echocardiography revealed a mean \pm -SD ejection fraction of 65.5% \pm -12.0% and a mean \pm -SD left ventricular mass index of 66.6 \pm -22.3 g/m².7 During 864.6 person-years of follow-up, 77 patients died; 35 died from cardiovascular causes, of which 15 were sudden cardiac deaths. By Cox regression analysis, QRS-T angle \geq 75

degrees significantly associated with increased risk of cardiovascular mortality (hazard ratio, 2.99; 95% confidence interval, 1.31 to 6.82) and sudden cardiac death (hazard ratio, 4.52; 95% confidence interval, 1.17 to 17.40) after multivariable adjustment for demographic, cardiovascular, and dialysis factors. Abnormal signal-averaged electrocardiogram measures did not associate with mortality. In conclusion, spatial QRS-T angle but not abnormal signal-averaged electrocardiogram significantly associates with cardiovascular mortality and sudden cardiac death independent of traditional risk factors in patients starting hemodialysis.

Thornburg, K. L., Kolahi, K., Pierce, M., Valent, A., Drake, R., & Louey, S. (2016). Biological features of placental programming. *Placenta, 48 Suppl 1*, S47-S53.

The placenta is a key organ in programming the fetus for later disease. This review outlines nine of many structural and physiological features of the placenta which are associated with adult onset chronic disease. 1) Placental efficiency relates the placental mass to the fetal mass. Ratios at the extremes are related to cardiovascular disease risk later in life. 2) Placental shape predicts a large number of disease outcomes in adults but the regulators of placental shape are not known. 3) Non-human primate studies suggest that at about mid-gestation, the placenta becomes less plastic and less able to compensate for pathological stresses. 4) Recent studies suggest that lipids have an important role in regulating placental metabolism and thus the future health of offspring. 5) Placental inflammation affects nutrient transport to the fetus and programs for later disease. 6) Placental insufficiency leads to inadequate fetal growth and elevated risks for later life disease. 7) Maternal height, fat and muscle mass are important in combination with placental size and shape in predicting adult disease. 8) The placenta makes a host of hormones that influence fetal growth and are related to offspring disease. Unfortunately, our knowledge of placental growth and function lags far behind that of other organs. An investment in understanding placental growth and function will yield enormous benefits to human health because it is a key player in the origins of the most expensive and deadly chronic diseases that humans face.

Tilden, E. L., Snowden, J. M., Caughey, A. B., & Lowe, N. K. (2016). Reframing US maternity care: Lessons learned from end-of-life care. *Journal of Midwifery and Women's Health*,

Traer, E., Martinez, J., Javidi-Sharifi, N., Agarwal, A., Dunlap, J., English, I., et al. (2016). FGF2 from marrow microenvironment promotes resistance to FLT3 inhibitors in acute myeloid leukemia.

Cancer Research,

Potent FLT3 inhibitors, such as quizartinib (AC220), have shown promise in treating acute myeloid leukemia (AML) containing FLT3 internal tandem duplication (ITD) mutations. However, responses are not durable and resistance develops within months. In this study, we outline a two-step model of resistance whereby extrinsic microenvironmental proteins FLT3 ligand (FL) and fibroblast growth factor 2 (FGF2) protect FLT3-ITD+ MOLM14 cells from AC220, providing time for subsequent accumulation of ligand-independent resistance mechanisms. FL directly attenuated AC220 inhibition of FLT3, consistent with previous reports. Conversely, FGF2 promoted resistance through activation of FGFR1 and downstream MAPK effectors; these resistant cells responded synergistically to combinatorial inhibition of FGFR1 and FLT3. Removing FL or FGF2 from ligand-dependent resistant cultures transiently restored sensitivity to AC220, but accelerated acquisition of secondary resistance via reactivation of FLT3 and RAS/MAPK signaling. FLT3-ITD AML patients treated with AC220 developed increased FGF2 expression in marrow stromal cells, which peaked prior to overt clinical relapse and detection of resistance mutations. Overall, these results support a strategy of early combination therapy to target early survival signals from the bone marrow microenvironment, in particular FGF2, to improve the depth of response in FLT3-ITD AML. *Cancer Res; 76(22); 1-12. (c)2016 AACR.*

Turner, R. B., Valcarlos, E., Won, R., Chang, E., & Schwartz, J. (2016). Impact of infectious diseases consultation on clinical outcomes of patients with staphylococcus aureus bacteremia in a community health system. *Antimicrobial Agents and Chemotherapy, 60(10), 5682-5687.*

Staphylococcus aureus bacteremia (SAB) causes high rates of morbidity and death. Several studies in academic health settings have demonstrated that consultations from infectious diseases specialists improve the quality of care and clinical outcomes for SAB. Few data that describe the impact in resource-limited settings such as community hospitals are available. This retrospective cohort study evaluated the adherence to quality-of-care indicators and the clinical outcomes for SAB in a five-hospital community health system (range of 95 to 272 available beds per hospital), for patients with versus without infectious diseases consultation (IDC). IDC was

provided if requested by the attending physician. The primary outcome was the incidence of treatment failure, defined as 30-day in-hospital death or 90-day SAB recurrence. Other outcomes included adherence to quality-of-care indicators. A total of 473 adult patients with SAB were included, with 369 (78%) receiving IDC. We identified substantial differences in baseline characteristics between the IDC group and the no-IDC group, including greater incidences of complicated bacteremia and intravenous drug users in the IDC group, with similar rates of severe illness (measured by Pitt bacteremia scores). Adherence to quality-of-care indicators was greater for patients with IDC ($P < 0.001$). After adjustment for other predicting variables, IDC was associated with a lower rate of treatment failure (adjusted odds ratio, 0.42 [95% confidence interval, 0.20 to 0.86]; $P = 0.018$). IDC provided better quality of care and better clinical outcomes for patients with SAB who were treated at small, resource-limited, community hospitals. Copyright © 2016, American Society for Microbiology. All Rights Reserved.

Tusch, E. S., Alperin, B. R., Holcomb, P. J., & Daffner, K. R. (2016). Increased early processing of task-irrelevant auditory stimuli in older adults. *PLoS One*, 11(11), e0165645.

The inhibitory deficit hypothesis of cognitive aging posits that older adults' inability to adequately suppress processing of irrelevant information is a major source of cognitive decline. Prior research has demonstrated that in response to task-irrelevant auditory stimuli there is an age-associated increase in the amplitude of the N1 wave, an ERP marker of early perceptual processing. Here, we tested predictions derived from the inhibitory deficit hypothesis that the age-related increase in N1 would be 1) observed under an auditory-ignore, but not auditory-attend condition, 2) attenuated in individuals with high executive capacity (EC), and 3) augmented by increasing cognitive load of the primary visual task. ERPs were measured in 114 well-matched young, middle-aged, young-old, and old-old adults, designated as having high or average EC based on neuropsychological testing. Under the auditory-ignore (visual-attend) task, participants ignored auditory stimuli and responded to rare target letters under low and high load. Under the auditory-attend task, participants ignored visual stimuli and responded to rare target tones. Results confirmed an age-associated increase in N1 amplitude to auditory stimuli under the auditory-ignore but not auditory-attend task. Contrary to predictions, EC did not modulate the N1 response. The load effect was the opposite of expectation: the N1 to task-

irrelevant auditory events was smaller under high load. Finally, older adults did not simply fail to suppress the N1 to auditory stimuli in the task-irrelevant modality; they generated a larger response than to identical stimuli in the task-relevant modality. In summary, several of the study's findings do not fit the inhibitory-deficit hypothesis of cognitive aging, which may need to be refined or supplemented by alternative accounts.

Tusch, E. S., Alperin, B. R., Ryan, E., Holcomb, P. J., Mohammed, A. H., & Daffner, K. R. (2016).

Changes in neural activity underlying working memory after computerized cognitive training in older adults. *Frontiers in Aging Neuroscience*, *8*, 255.

Computerized cognitive training (CCT) may counter the impact of aging on cognition, but both the efficacy and neurocognitive mechanisms underlying CCT remain controversial. In this study, 35 older individuals were randomly assigned to Cogmed adaptive working memory (WM) CCT or an active control CCT, featuring five weeks of five approximately 40 min sessions per week. Before and after the 5-week intervention, event-related potentials were measured while subjects completed a visual n-back task with three levels of demand (0-back, 1-back, 2-back). The anterior P3a served as an index of directing attention and the posterior P3b as an index of categorization/WM updating. We hypothesized that adaptive CCT would be associated with decreased P3 amplitude at low WM demand and increased P3 amplitude at high WM demand. The adaptive CCT group exhibited a training-related increase in the amplitude of the anterior P3a and posterior P3b in response to target stimuli across n-back tasks, while subjects in the active control CCT group demonstrated a post-training decrease in the anterior P3a. Performance did not differ between groups or sessions. Larger overall P3 amplitudes were strongly associated with better task performance. Increased post-CCT P3 amplitude correlated with improved task performance; this relationship was especially robust at high task load. Our findings suggest that adaptive WM training was associated with increased orienting of attention, as indexed by the P3a, and the enhancement of categorization/WM updating processes, as indexed by the P3b. Increased P3 amplitude was linked to improved performance; however, there was no direct association between adaptive training and improved performance.

Uhrlaub, J. L., Pulko, V., DeFilippis, V. R., Broeckel, R., Streblow, D. N., Coleman, G. D., et al. (2016).

Dysregulated TGF- β production underlies the age-related vulnerability to chikungunya virus. *PLoS Pathogens*, 12(10)

Chikungunya virus (CHIKV) is a re-emerging global pathogen with pandemic potential, which causes fever, rash and debilitating arthralgia. Older adults over 65 years are particularly susceptible to severe and chronic CHIKV disease (CHIKVD), accounting for >90% of all CHIKV-related deaths. There are currently no approved vaccines or antiviral treatments available to limit chronic CHIKVD. Here we show that in old mice excessive, dysregulated TGF β production during acute infection leads to a reduced immune response and subsequent chronic disease. Humans suffering from CHIKV infection also exhibited high TGF β levels and a pronounced age-related defect in neutralizing anti-CHIKV antibody production. In vivo reduction of TGF β levels minimized acute joint swelling, restored neutralizing antibody production and diminished chronic joint pathology in old mice. This study identifies increased and dysregulated TGF β secretion as one key mechanism contributing to the age-related loss of protective anti-CHIKV-immunity leading to chronic CHIKVD. © 2016 Uhrlaub et al.

Veerappan, M., El-Hage-Sleiman, A. M., Tai, V., Chiu, S. J., Winter, K. P., Stinnett, S. S., et al.

(2016). Optical coherence tomography reflective drusen substructures predict progression to geographic atrophy in age-related macular degeneration. *Ophthalmology*, 123(12), 2554-2570.

PURPOSE: Structural and compositional heterogeneity within drusen comprising lipids, carbohydrates, and proteins have been previously described. We sought to detect and define phenotypic patterns of drusen heterogeneity in the form of optical coherence tomography-reflective drusen substructures (ODS) and examine their associations with age-related macular degeneration (AMD)-related features and AMD progression. DESIGN: Retrospective analysis in a prospective study. PARTICIPANTS: Patients with intermediate AMD (n = 349) enrolled in the multicenter Age-Related Eye Disease Study 2 (AREDS2) ancillary spectral-domain optical coherence tomography (SD OCT) study. METHODS: Baseline SD OCT scans of 1 eye per patient were analyzed for the presence of ODS. Cross-sectional and longitudinal associations of ODS presence with AMD-related features visible on SD OCT and color photographs, including drusen volume, geographic atrophy (GA), and preatrophic features, were evaluated for the entire

macular region. Similar associations were also made locally within a 0.5-mm-diameter region around individual ODS and corresponding control region without ODS in the same eye. MAIN OUTCOME MEASURES: Preatrophy SD OCT changes and GA, central GA, and choroidal neovascularization (CNV) from color photographs. RESULTS: Four phenotypic subtypes of ODS were defined: low reflective cores, high reflective cores, conical debris, and split drusen. Among the 349 participants, there were 307 eligible eyes and 74 (24%) had at least 1 ODS. The ODS at baseline were associated with (1) greater macular drusen volume at baseline ($P < 0.001$), (2) development of preatrophic changes at year 2 ($P = 0.001-0.01$), and (3) development of macular GA ($P = 0.005$) and preatrophic changes at year 3 ($P = 0.002-0.008$), but not development of CNV. The ODS at baseline in a local region were associated with (1) presence of preatrophy changes at baseline ($P = 0.02-0.03$) and (2) development of preatrophy changes at years 2 and 3 within the region ($P = 0.008-0.05$). CONCLUSIONS: Optical coherence tomography-reflective drusen substructures are optical coherence tomography-based biomarkers of progression to GA, but not to CNV, in eyes with intermediate AMD. Optical coherence tomography-reflective drusen substructures may be a clinical entity helpful in monitoring AMD progression and informing mechanisms in GA pathogenesis.

Wang, Y., Galivo, F., Pelz, C., Haft, A., Lee, J., Kim, S. K., et al. (2016). Efficient generation of pancreatic β -like cells from the mouse gallbladder. *Stem Cell Research*, 17(3), 587-596.

Direct reprogramming is a promising approach for the replacement of β cells in diabetes. Reprogramming of cells originating from the endodermal lineage, such as acinar cells in the pancreas, liver cells and gallbladder cells has been of particular interest because of their developmental proximity to β cells. Our previous work showed that mouse gallbladder epithelium can be partially reprogrammed in vitro to generate islet-like cells (rGBC1). Here, the reprogramming protocol was substantially improved, yielding cells (rGBC2) closer to functional β cells than the 1st generation method with higher conversion efficiency and insulin expression. In addition to insulin synthesis and processing, rGBC2 presented many hallmark features of β cells, including insulin secretion in response to high glucose stimulation. Gene expression analysis indicated that rGBC2 clustered closer with β cells and had a metabolic gene expression profile resembling neonatal β cells. When transplanted into immune-deficient animals, rGBC2 were

stable for at least 5 months and further matured in vivo. Taken together, this approach provides further understanding of endodermal lineage conversion and potential for development of cell replacement therapy for type 1 diabetes patients. © 2016 The Authors

Wang, Y. J., Golson, M. L., Schug, J., Traum, D., Liu, C., Vivek, K., et al. (2016). Single-cell mass cytometry analysis of the human endocrine pancreas. *Cell Metabolism*, 24(4), 616-626.

The human endocrine pancreas consists of multiple cell types and plays a critical role in glucose homeostasis. Here, we apply mass cytometry technology to measure all major islet hormones, proliferative markers, and readouts of signaling pathways involved in proliferation at single-cell resolution. Using this innovative technology, we simultaneously examined baseline proliferation levels of all endocrine cell types from birth through adulthood, as well as in response to the mitogen harmine. High-dimensional analysis of our marker protein expression revealed three major clusters of beta cells within individuals. Proliferating beta cells are confined to two of the clusters. © 2016 Elsevier Inc.

Welling, L., Bernstein, L. E., Berry, G. T., Burlina, A. B., Eyskens, F., Gautschi, M., et al. (2016).

International clinical guideline for the management of classical galactosemia: Diagnosis, treatment, and follow-up. *Journal of Inherited Metabolic Disease*,

Classical galactosemia (CG) is an inborn error of galactose metabolism. Evidence-based guidelines for the treatment and follow-up of CG are currently lacking, and treatment and follow-up have been demonstrated to vary worldwide. To provide patients around the world the same state-of-the-art in care, members of The Galactosemia Network (GalNet) developed an evidence-based and internationally applicable guideline for the diagnosis, treatment, and follow-up of CG. The guideline was developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. A systematic review of the literature was performed, after key questions were formulated during an initial GalNet meeting. The first author and one of the working group experts conducted data-extraction. All experts were involved in data-extraction. Quality of the body of evidence was evaluated and recommendations were formulated. Whenever possible recommendations were evidence-based, if not they were based on expert opinion. Consensus was reached by multiple conference calls, consensus rounds via e-mail and a final

consensus meeting. Recommendations addressing diagnosis, dietary treatment, biochemical monitoring, and follow-up of clinical complications were formulated. For all recommendations but one, full consensus was reached. A 93 % consensus was reached on the recommendation addressing age at start of bone density screening. During the development of this guideline, gaps of knowledge were identified in most fields of interest, foremost in the fields of treatment and follow-up.

Wen, H., Hubbard, J. M., Wang, W. C., & Brehm, P. (2016). Fatigue in rapsyn-deficient zebrafish reflects defective transmitter release. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 36(42), 10870-10882.

Rapsyn-deficient myasthenic syndrome is characterized by a weakness in voluntary muscle contraction, a direct consequence of greatly reduced synaptic responses that result from poorly clustered acetylcholine receptors. As with other myasthenic syndromes, the general muscle weakness is also accompanied by use-dependent fatigue. Here, we used paired motor neuron target muscle patch-clamp recordings from a rapsyn-deficient mutant line of zebrafish to explore for the first time the mechanisms causal to fatigue. We find that synaptic responses in mutant fish can follow faithfully low-frequency stimuli despite the reduced amplitude. This is in part helped by a compensatory increase in the number of presynaptic release sites in the mutant fish. In response to high-frequency stimulation, both wild-type and mutant neuromuscular junctions depress to steady-state response levels, but the latter shows exaggerated depression. Analysis of the steady-state transmission revealed that vesicle reloading and release at individual release sites is significantly slower in mutant fish during high-frequency activities. Therefore, reductions in postsynaptic receptor density and compromised presynaptic release collectively serve to reduce synaptic strength to levels that fall below the threshold for muscle action potential generation, thus accounting for use-dependent fatigue. Our findings raise the possibility that defects in motor neuron function may also be at play in other myasthenic syndromes that have been mapped to mutations in muscle-specific proteins. SIGNIFICANCE STATEMENT: Use-dependent fatigue accompanies many neuromuscular myasthenic syndromes, including muscle rapsyn deficiency. Here, using a rapsyn-deficient line of zebrafish, we performed paired motor neuron target muscle patch-clamp recordings to investigate the mechanisms causal to this

phenomenon. Our findings indicate that the reduced postsynaptic receptor density resulting from defective rapsyn contributes to weakness, but is not solely responsible for use-dependent fatigue. Instead, we find unexpected involvement of altered transmitter release from the motor neuron. Specifically, slowed reloading of vesicle release sites leads to augmented synaptic depression during repeated action potentials. Even at moderate stimulus frequencies, the depression levels for evoked synaptic responses fall below the threshold for the generation of muscle action potentials. The associated contraction failures are manifest as use-dependent fatigue.

Williams, A. N. (2016). Diagnostic evaluation in aspirin-exacerbated respiratory disease. *Immunology and Allergy Clinics of North America*, 36(4), 657-668.

Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical condition characterized by chronic sinusitis with nasal polyps, asthma, and hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Distinguishing AERD from other forms of chronic sinusitis, asthma, and NSAID reactivity has important clinical implications for management. The clinical history is helpful, but not adequate for confirming the diagnosis of AERD, in most cases. Diagnostic provocation challenge remains the only way to confirm or exclude the diagnosis of AERD. This article discusses the utility of the clinical history and the current evidence regarding measures that optimize the safety of performing diagnostic NSAID provocation challenges. © 2016 Elsevier Inc.

Willson, D. F., Hoot, M., Khemani, R., Carrol, C., Kirby, A., Schwarz, A., et al. (2016). Pediatric ventilator-associated infections: The ventilator-associated INfection study. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*,

OBJECTIVE: Suspected ventilator-associated infection is the most common reason for antibiotics in the PICU. We sought to characterize the clinical variables associated with continuing antibiotics after initial evaluation for suspected ventilator-associated infection and to determine whether clinical variables or antibiotic treatment influenced outcomes. DESIGN: Prospective, observational cohort study conducted in 47 PICUs in the United States, Canada, and Australia. Two hundred twenty-nine pediatric patients ventilated more than 48 hours undergoing respiratory secretion

cultures were enrolled as "suspected ventilator-associated infection" in a prospective cohort study, those receiving antibiotics of less than or equal to 3 days were categorized as "evaluation only," and greater than 3 days as "treated." Demographics, diagnoses, comorbidities, culture results, and clinical data were compared between evaluation only and treated subjects and between subjects with positive versus negative cultures. SETTING: PICUs in 47 hospitals in the United States, Canada, and Australia. SUBJECTS: All patients undergoing respiratory secretion cultures during the 6 study periods. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Treated subjects differed from evaluation-only subjects only in frequency of positive cultures (79% vs 36%; $p < 0.0001$). Subjects with positive cultures were more likely to have chronic lung disease, tracheostomy, and shorter PICU stay, but there were no differences in ventilator days or mortality. Outcomes were similar in subjects with positive or negative cultures irrespective of antibiotic treatment. Immunocompromise and higher Pediatric Logistic Organ Dysfunction scores were the only variables associated with mortality in the overall population, but treated subjects with endotracheal tubes had significantly lower mortality. CONCLUSIONS: Positive respiratory cultures were the primary determinant of continued antibiotic treatment in children with suspected ventilator-associated infection. Positive cultures were not associated with worse outcomes irrespective of antibiotic treatment although the lower mortality in treated subjects with endotracheal tubes is notable. The necessity of continuing antibiotics for a positive respiratory culture in suspected ventilator-associated infection requires further study.

Wilmot, B., Fry, R., Smeester, L., Musser, E. D., Mill, J., & Nigg, J. T. (2016). Methyloomic analysis of salivary DNA in childhood ADHD identifies altered DNA methylation in VIPR2. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 57(2), 152-160.

BACKGROUND: Peripheral epigenetic marks hold promise for understanding psychiatric illness and may represent fingerprints of gene-environment interactions. We conducted an initial examination of CpG methylation variation in children with or without attention-deficit/hyperactivity disorder (ADHD). METHODS: Children age 7-12 were recruited, screened, evaluated and assigned to ADHD or non-ADHD groups by defined research criteria. Two independent age-matched samples were examined, a discovery set ($n = 92$, all boys, half control, half ADHD) and a confirmation set ($n = 20$, half ADHD, all boys). 5-methylcytosine levels were

quantified in salivary DNA using the Illumina 450 K HumanMethylation array. Genes for which multiple probes were nominally significant and had a beta difference of at least 2% were evaluated for biological relevance and prioritized for confirmation and sequence validation. Gene pathways were explored and described. RESULTS: Two genes met the criteria for confirmation testing, VIPR2 and MYT1L; both had multiple probes meeting cutoffs and strong biological relevance. Probes on VIPR2 passed FDR correction in the confirmation set and were confirmed through bisulfite sequencing. Enrichment analysis suggested involvement of gene sets or pathways related to inflammatory processes and modulation of monoamine and cholinergic neurotransmission. CONCLUSIONS: Although it is unknown to what extent CpG methylation seen in peripheral tissue reflect transcriptomic changes in the brain, these initial results indicate that peripheral DNA methylation markers in ADHD may be promising and suggest targeted hypotheses for future study in larger samples.

Wilson, D. G., Harris, S. K., Peck, H., Hart, K., Jung, E., Azarbal, A. F., et al. (2016). Patterns of care in hospitalized vascular surgery patients at end of life. *JAMA Surgery*,
Importance: There is limited literature reporting circumstances surrounding end-of-life care in vascular surgery patients. Objective: To identify factors driving end-of-life decisions in vascular surgery patients. Design, Setting, and Participants: In this cohort study, medical records were reviewed for all vascular surgery patients at a tertiary care university hospital who died during their hospitalization from 2005 to 2014. Main Outcomes and Measures: Patient, family, and hospitalization variables potentially important to influencing end-of-life decisions. Results: Of 111 patients included (67 [60%] male; median age, 75 [range, 24-94] years), 81 (73%) were emergent vs 30 (27%) elective admissions. Only 15 (14%) had an advance directive. Of the 81 (73%) patients placed on comfort care, 31 (38%) had care withheld or withdrawn despite available medical options, 15 (19%) had an advance directive, and 28 (25%) had a palliative care consultation. The median time from palliative care consultation to death was 10 hours (interquartile range, 3.36-66 hours). Comparing the 31 patients placed on comfort care despite available medical options with an admission diagnosis-matched cohort, we found that more than 5 days admitted to the intensive care unit (odds ratio [OR], 4.11; 95% CI, 1.59-10.68; $P < .001$), more than 5 days requiring ventilator support (OR, 9.45; 95% CI, 3.41-26.18; $P < .001$),

new renal failure necessitating dialysis (OR, 14.48; 95% CI, 3.69-56.86; $P < .001$), and new respiratory failure necessitating tracheostomy (OR, 23.92; 95% CI, 2.80-204; $P < .001$) correlated with transition to comfort care. Conclusions and Relevance: Palliative care consultations may be underused at the end of life. A large percentage of patients were transitioned to comfort measures despite available treatment, yet few presented with advance directives. In high-risk patients, discussions regarding extended stays in the intensive care unit, prolonged ventilator management, and possible dialysis and tracheostomy should be communicated with patients and families at time of hospitalization and advance directives solicited.

Wineland, A., Menezes, M. D., Shimony, J. S., Shinawi, M. S., Hullar, T. E., & Hirose, K. (2016).

Prevalence of semicircular canal hypoplasia in patients with CHARGE syndrome: 3C syndrome. *JAMA Otolaryngology-- Head & Neck Surgery*,

Importance: CHARGE syndrome refers to a syndrome involving coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary disorders, and ear anomalies.

However, Verloes revised the characteristics of CHARGE syndrome in 2005 to define this syndrome more broadly. Deficiency of the semicircular canals is now a major criterion for CHARGE syndrome. Objective: To characterize patients with CHARGE syndrome at our center using Verloes' criteria and to reevaluate the nomenclature for this condition. Design, Setting, and Participants: We performed a medical chart review of patients with CHARGE syndrome and reviewed their temporal bone imaging studies at a tertiary care children's hospital affiliated with Washington University in St Louis. Two authors independently reviewed each imaging study (A.W. and K.H.). Radiologic studies, physical findings, genetic tests, and other diagnostic tests were included. Patients with no temporal bone imaging studies were excluded. Results: Eighteen children were included in this study; 13 children (72%) were male, and the mean (median; range) age of patients at the time of inner ear imaging studies was 2 years (4.5 years; 8 months to 8 years). Coloboma was present in 13 patients (72%) and choanal atresia in 5 (28%); semicircular canal anomalies were present in all patients. Additionally, 13 patients (72%) were diagnosed as having hindbrain anomalies, 17 (94%) as having endocrine disorders, 17 (94%) as having mediastinal organ malformations, and all as having middle or external ear abnormalities

and development delay. Cleft lip and cleft palate were found in 6 of 14 patients (43%) who did not have choanal atresia. We tested 16 patients for mutations in the CHD7 gene; 10 were positive (63%) for mutations, 4 (25%) were negative, and 2 (13%) were inconclusive.

Conclusions and Relevance: Semicircular canal anomalies were the most consistent finding in our patients with CHARGE syndrome. Given the high prevalence of semicircular canal hypoplasia and importance of imaging for diagnosing CHARGE syndrome, we propose changing the term CHARGE syndrome to 3C syndrome to emphasize the importance of the semicircular canals and to recall the 3 major criteria for diagnosis: coloboma, choanal atresia, and semicircular canal anomaly. The nomenclature would also reference the 3 semicircular canals in each ear. This new name for CHARGE syndrome would provide a mnemonic and focus the disease on the most important clinical criteria for diagnosis.

Wolf, D. P., Morey, R., Kang, E., Ma, H., Hayama, T., Laurent, L. C., et al. (2016). Embryonic stem cells derived by somatic cell nuclear transfer: A horse in the race? *Stem Cells*, Embryonic stem cells (ESC) hold promise for the treatment of human medical conditions but are allogeneic. Here, we consider the differences between autologous pluripotent stem cells produced by nuclear transfer (NT-ESCs) and transcription factor-mediated, induced pluripotent stem cells (iPSCs) that impact the desirability of each of these cell types for clinical use. The derivation of NT-ESCs is more cumbersome and requires donor oocytes; however, the use of oocyte cytoplasm as the source of reprogramming factors is linked to a key advantage of NT-ESCs—the ability to replace mutant mitochondrial DNA in a patient cell (due to either age or inherited disease) with healthy donor mitochondria from an oocyte. Moreover, in epigenomic and transcriptomic comparisons between isogenic iPSCs and NT-ESCs, the latter produced cells that more closely resemble bona fide ESCs derived from fertilized embryos. Thus, although NT-ESCs are more difficult to generate than iPSCs, the ability of somatic cell nuclear transfer to replace aged or diseased mitochondria and the closer epigenomic and transcriptomic similarity between NT-ESCs and bona fide ESCs may make NT-ESCs superior for future applications in regenerative medicine. © 2016 AlphaMed Press.

Wu, B. C., Patel, E. D., & Ortega-Loayza, A. G. (2016). Drug-induced pyoderma gangrenosum: A model to understand the pathogenesis of pyoderma gangrenosum. *The British Journal of Dermatology*,

Pyoderma gangrenosum (PG) is a rare auto-inflammatory condition in which the alteration of neutrophil function and the innate immune response play key roles in its pathogenesis. Cases of PG have been reported in patients being treated with certain medications, which may help us to understand some of the possible pathways involved in the etiology of PG. The aim of this review is to review the cases of PG triggered by certain drugs and try to thoroughly understand the pathogenesis of the disease. To accomplish this, a PubMed search was completed using the following words: pyoderma gangrenosum, neutrophilic dermatosis, pathophysiology, drug-induced pyoderma gangrenosum. In total, we found 43 cases of drug-induced pyoderma gangrenosum. Most of them were caused by colony stimulating factors and small molecule inhibitors of tyrosine kinase. We propose that drugs induce PG through various mechanisms such as dysfunctional neutrophil migration and function, dysregulated inflammatory response, promotion of keratinocyte apoptosis and alteration of epigenetics mechanism. PG is a rare condition with complex pathophysiology and drug-induced cases are even more scarce; this is the main limitation of this review. Understanding the possible mechanisms of drug-induced PG, via abnormal neutrophil migration and function, abnormal inflammation, keratinocyte apoptosis and alteration of epigenetic mechanisms would help to better understand the pathogenesis of PG and ultimately to optimize targeted therapy. This article is protected by copyright. All rights reserved.

Xu, C., Zhang, B., Wang, Y., Shao, Q., Zhou, W., Fan, D., et al. (2016). Effects of sulfidation, magnetization, and oxygenation on azo dye reduction by zerovalent iron. *Environmental Science & Technology*, 50(21), 11879-11887.

Applications of zerovalent iron (ZVI) for water treatment under aerobic conditions include sequestration of metals (e.g., in acid mine drainage) and decolorization of dyes (in wastewaters from textile manufacturing). The processes responsible for contaminant removal can be a complex mixture of reduction, oxidation, sorption, and coprecipitation processes, which are further complicated by the dynamics of oxygen intrusion, mixing, and oxide precipitation. To better understand such systems, the removal of an azo dye (Orange I) by micron-sized granular

ZVI at neutral pH was studied in open (aerobic) stirred batch reactors, by measuring the kinetics of Orange I decolorization and changes in "geochemical" properties (DO, Fe(II), and Eh), with and without two treatments that might improve the long-term performance of this system: sulfidation by pretreatment with sulfide and magnetization by application of a weak magnetic field (WMF). The results show that the changes in solution chemistry are coupled to the dynamics of oxygen intrusion, which was modeled as analogous to dissolved oxygen sag curves. Both sulfidation and magnetization increased Orange I removal rates 2.4-71.8-fold, but there was little synergistic benefit to applying both enhancements together. Respike experiments showed that the enhancement from magnetization carries over from magnetization to sulfidation, but not the reverse.

Yarema, M. C., Green, J. P., Sivilotti, M. L., Johnson, D. W., Nettel-Aguirre, A., Victorino, C., et al. (2016). Can a serum acetaminophen concentration obtained less than 4 hours post-ingestion determine which patients do not require treatment with acetylcysteine? *Clinical Toxicology (Philadelphia, Pa.)*, , 1-7.

CONTEXT: The interpretation of acetaminophen concentrations obtained prior to 4 hours after an acute, single overdose remains unclear. Patient care decisions in the Emergency Department could be accelerated if such concentrations could reliably exclude the need for treatment.

OBJECTIVE: To determine the agreement between a serum acetaminophen concentration obtained less than 4 hours after an acute ingestion and the subsequent 4 + hour concentration, and the predictive accuracy of early concentrations for identifying patients with potentially toxic exposures. METHODS: A secondary analysis of patients admitted for acetaminophen poisoning at one of the 34 hospitals in eight Canadian cities from 1980 to 2005. We examined serum acetaminophen concentrations obtained less than 4 hours post-ingestion, and again 4 or more hours post-ingestion. For the diagnostic accuracy analysis, we specified a cutpoint of 100 mug/mL (662 mumol/L) obtained between 2 and 4 hours and a subsequent 4 to 20 hour acetaminophen concentration above the nomogram treatment line of 150 mug/mL (993 mumol/L). RESULTS: Of 2454 patients identified, 879 (36%) had a subsequent acetaminophen concentration above the nomogram treatment line. The 2-4 hour concentration demonstrated a sensitivity of 0.96 [95% CI; 0.94, 0.97] and a negative likelihood ratio of 0.070 [0.048, 0.10].

Coingested opioids reduced this sensitivity to 0.91 [0.83, 0.95], and antimuscarinics to 0.86 [0.72, 0.94]. Only very low to undetectable acetaminophen concentrations prior to 4 hours reliably excluded a subsequent concentration over the treatment line. CONCLUSIONS: Applying an acetaminophen concentration cutpoint of 100 mug/mL (662 mumol/L) at 2-4 hours after an acute ingestion as a threshold for repeat testing and/or treatment would occasionally miss potentially toxic exposures. Absorption of acetaminophen is only slightly delayed by coingested opioids or antimuscarinics. Our analysis validates the practice of not retesting when the first post-ingestion acetaminophen concentration is below the lower limit of quantification.

Yoon, Y. M., Storm, K. J., Kamimae-Lanning, A. N., Goloviznina, N. A., & Kurre, P. (2016).

Endogenous DNA damage leads to p53-independent deficits in replicative fitness in fetal murine *Fancd2*^{-/-} hematopoietic stem and progenitor cells. *Stem Cell Reports*, 7(5), 840-853.

Our mechanistic understanding of Fanconi anemia (FA) pathway function in hematopoietic stem and progenitor cells (HSPCs) owes much to their role in experimentally induced DNA crosslink lesion repair. In bone marrow HSPCs, unresolved stress confers p53-dependent apoptosis and progressive cell attrition. The role of FA proteins during hematopoietic development, in the face of physiological replicative demand, remains elusive. Here, we reveal a fetal HSPC pool in *Fancd2*^{-/-} mice with compromised clonogenicity and repopulation. Without experimental manipulation, fetal *Fancd2*^{-/-} HSPCs spontaneously accumulate DNA strand breaks and RAD51 foci, associated with a broad transcriptional DNA-damage response, and constitutive activation of ATM as well as p38 stress kinase. Remarkably, the unresolved stress during rapid HSPC pool expansion does not trigger p53 activation and apoptosis; rather, it constrains proliferation.

Collectively our studies point to a role for the FA pathway during hematopoietic development and provide a new model for studying the physiological function of FA proteins. © 2016 The Author(s)

Yu, Q., Cai, H., Zhang, Y., He, Y., Chen, L., Merritt, J., et al. (2016). Negative regulation of ectoine uptake and catabolism in *Sinorhizobium meliloti*: Characterization of the *EhuR* gene. *Journal of Bacteriology*,

Ectoine has osmoprotective effects on *Sinorhizobium meliloti* that differ from its effects in other bacteria. Ectoine does not accumulate in *S. meliloti* cells; instead, it is degraded. The products of

the ehuABCD-eutABCDE operon were previously discovered to be responsible for the uptake and catabolism of ectoine in *S. meliloti*. However, the mechanism by which ectoine is involved in the regulation of the ehuABCD-eutABCDE operon remains unclear. EhuR, which is upstream of and oriented in the same direction as the ehuABCD-eutABCDE operon, encodes a member of the MocR/GntR family of transcriptional regulators. Quantitative RT-PCR and promoter-lacZ reporter fusion experiments revealed that EhuR represses the transcription of the ehuABCD-eutABCDE operon, but this repression is inhibited in the presence of ectoine. Electrophoretic mobility shift and DNase I footprinting assays revealed that EhuR bound specifically to the DNA regions overlapping the -35 region of the ehuA promoter and the +1 region of the ehuR promoter. Surface plasmon resonance further demonstrated a direct interaction between EhuR and both promoters, although EhuR was found to have a higher affinity for the ehuA promoter than for the ehuR promoter. In vitro, DNA binding by EhuR could be directly inhibited by a degradation product of ectoine. Our work demonstrates that EhuR is an important negative transcriptional regulator involved in the regulation of ectoine uptake and catabolism and is likely regulated by one or more end products of ectoine catabolism. **IMPORTANCE:** *Sinorhizobium meliloti* is an important soil bacterium, that displays symbiotic interactions with legume hosts. Ectoine serves as a key osmoprotectant for *S. meliloti*. However, ectoine does not accumulate in the cell; rather, it is degraded. In this study, we characterized the transcriptional regulation of the operon responsible for ectoine uptake and catabolism in *S. meliloti*. We identified and characterized the transcriptional repressor EhuR, which is the first MocR/GntR family member found to be involved in the regulation of compatible solute uptake and catabolism. More importantly, we demonstrated for the first time that an ectoine catabolic end product could modulate EhuR DNA binding activity. Therefore, this work provides new insights into the unique mechanism of ectoine-induced osmoprotection in *S. meliloti*.

Zahid, H. M., Ferdous, M. Z., Ohara, H., Isomura, M., & Nabika, T. (2016). Effect of p22phox depletion on sympathetic regulation of blood pressure in SHRSP: Evaluation in a new congenic strain. *Scientific Reports*, 6

Oxidative stress in the rostral ventrolateral medulla (RVLM), a sympathetic center in the brainstem, was implicated in the regulation of sympathetic activity in various hypertensive

models including stroke-prone spontaneously hypertensive rats (SHRSP). In this study, we evaluated the role of the NADPH oxidases (NOX) in the blood pressure (BP) regulation in RVLM in SHRSP. The P22PHOX-depleted congenic SHRSP (called SP.MES) was constructed by introducing the mutated p22phox gene of Matsumoto Eosinophilic Shinshu rat. BP response to glutamate (Glu) microinjection into RVLM was compared among SHRSP, SP.MES, SHR and Wistar Kyoto (WKY); the response to Glu microinjection was significantly greater in SHRSP than in SP.MES, SHR and WKY. In addition, tempol, losartan and apocynin microinjection reduced the response to Glu significantly only in SHRSP. The level of oxidative stress, measured in the brainstem using lucigenin and dihydroethidium, was reduced in SP.MES than in SHRSP. BP response to cold stress measured by telemetry system was also blunted in SP.MES when compared with SHRSP. The results suggested that oxidative stress due to the NOX activation in RVLM potentiated BP response to Glu in SHRSP, which might contribute to the exaggerated response to stress in this strain. © The Author(s) 2016.

Zanganeh, S., Hutter, G., Spitler, R., Lenkov, O., Mahmoudi, M., Shaw, A., et al. (2016). Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. *Nature Nanotechnology*, 11(11), 986-994.

Until now, the Food and Drug Administration (FDA)-approved iron supplement ferumoxytol and other iron oxide nanoparticles have been used for treating iron deficiency, as contrast agents for magnetic resonance imaging and as drug carriers. Here, we show an intrinsic therapeutic effect of ferumoxytol on the growth of early mammary cancers, and lung cancer metastases in liver and lungs. In vitro, adenocarcinoma cells co-incubated with ferumoxytol and macrophages showed increased caspase-3 activity. Macrophages exposed to ferumoxytol displayed increased mRNA associated with pro-inflammatory Th1-type responses. In vivo, ferumoxytol significantly inhibited growth of subcutaneous adenocarcinomas in mice. In addition, intravenous ferumoxytol treatment before intravenous tumour cell challenge prevented development of liver metastasis. Fluorescence-activated cell sorting (FACS) and histopathology studies showed that the observed tumour growth inhibition was accompanied by increased presence of pro-inflammatory M1 macrophages in the tumour tissues. Our results suggest that ferumoxytol could be applied 'off

label' to protect the liver from metastatic seeds and potentiate macrophage-modulating cancer immunotherapies.

Zhen, J., Antonio, T., Jacob, J. C., Grandy, D. K., Reith, M. E., Dutta, A. K., et al. (2016). Efficacy of hybrid tetrahydrobenzo[d]thiazole based aryl piperazines D-264 and D-301 at D(2) and D(3) receptors. *Neurochemical Research*, 41(1-2), 328-339.

In elucidating the role of pharmacodynamic efficacy at D3 receptors in therapeutic effectiveness of dopamine receptor agonists, the influence of study system must be understood. Here two compounds with D3 over D2 selectivity developed in our earlier work, D-264 and D-301, are compared in dopamine receptor-mediated G-protein activation in striatal regions of wild-type and D2 receptor knockout mice and in CHO cells expressing D2 or D3 receptors. In caudate-putamen of D2 knockout mice, D-301 was ~3-fold more efficacious than D-264 in activating G-proteins as assessed by [(35)S]GTPgammaS binding; in nucleus accumbens, D-301 stimulated G-protein activation whereas D-264 did not. In contrast, the two ligands exerted similar efficacy in both regions of wild-type mice, suggesting both ligands activate D2 receptors with similar efficacy. In D2 and D3 receptor-expressing CHO cells, D-264 and D-301 appeared to act in the [(35)S]GTPgammaS assay as full agonists because they produced maximal stimulation equal to dopamine. Competition for [(3)H]spiperone binding was then performed to determine Ki/EC50 ratios as an index of receptor reserve for each ligand. Action of D-301, but not D-264, showed receptor reserve in D3 but not in D2 receptor-expressing cells, whereas dopamine showed receptor reserve in both cell lines. Galphao1 is highly expressed in brain and is important in D2-like receptor-G protein coupling. Transfection of Galphao1 in D3- but not D2-expressing CHO cells led to receptor reserve for D-264 without altering receptor expression levels. D-301 and dopamine exhibited receptor reserve in D3-expressing cells both with and without transfection of Galphao1. Altogether, these results indicate that D-301 has greater intrinsic efficacy to activate D3 receptors than D-264, whereas the two compounds act on D2 receptors with similar intrinsic efficacy. These findings also suggest caution in interpreting Emax values from functional assays in receptor-transfected cell models without accounting for receptor reserve.

Zilberman-Rudenko, J., Sylman, J. L., Lakshmanan, H. H. S., McCarty, O. J. T., & Maddala, J. (2016).

Dynamics of blood flow and thrombus formation in a multi-bypass microfluidic ladder network. *Cellular and Molecular Bioengineering*, , 1-14.

The reaction dynamics of a complex mixture of cells and proteins, such as blood, in branched circulatory networks within the human microvasculature or extravascular therapeutic devices such as extracorporeal oxygenation machine (ECMO) remains ill-defined. In this report we utilize a multi-bypass microfluidics ladder network design with dimensions mimicking venules to study patterns of blood platelet aggregation and fibrin formation under complex shear. Complex blood fluid dynamics within multi-bypass networks under flow were modeled using COMSOL. Red blood cells and platelets were assumed to be non-interacting spherical particles transported by the bulk fluid flow, and convection of the activated coagulation factor II, thrombin, was assumed to be governed by mass transfer. This model served as the basis for predicting formation of local shear rate gradients, stagnation points and recirculation zones as dictated by the bypass geometry. Based on the insights from these models, we were able to predict the patterns of blood clot formation at specific locations in the device. Our experimental data was then used to adjust the model to account for the dynamical presence of thrombus formation in the biorheology of blood flow. The model predictions were then compared to results from experiments using recalcified whole human blood. Microfluidic devices were coated with the extracellular matrix protein, fibrillar collagen, and the initiator of the extrinsic pathway of coagulation, tissue factor. Blood was perfused through the devices at a flow rate of 2 $\mu\text{L}/\text{min}$, translating to physiologically relevant initial shear rates of 300 and 700 s^{-1} for main channels and bypasses, respectively. Using fluorescent and light microscopy, we observed distinct flow and thrombus formation patterns near channel intersections at bypass points, within recirculation zones and at stagnation points. Findings from this proof-of-principle ladder network model suggest a specific correlation between microvascular geometry and thrombus formation dynamics under shear. This model holds potential for use as an integrative approach to identify regions susceptible to intravascular thrombus formation within the microvasculature as well as extravascular devices such as ECMO.

© 2016 Biomedical Engineering Society

Zive, D., & Daya, M. (2016). Witness status: A new definition for out-of-hospital cardiac arrest? *Resuscitation, 109*, A8-A9.

Zonies, D., & Merkel, M. (2016). Advanced extracorporeal therapy in trauma. *Current Opinion in Critical Care, 22*(6), 578-583.

PURPOSE OF REVIEW: The purpose is to review the current application of extracorporeal life support (ECLS) in trauma patients. In addition, programmatic development is described. RECENT FINDINGS: ECLS use is increasing among trauma patients. Several recent studies among trauma patients report survival rates of 65-79%. Despite the high bleeding risk, extracorporeal membrane oxygenation (ECMO) may be safely implemented in trauma patients based on a strict protocol-driven policy. Early implementation may improve overall outcomes. Alternative anticoagulants and heparin free periods may be well tolerated in trauma patients at high risk of hemorrhage. SUMMARY: ECMO is becoming a more routine option in severely injured trauma patients that develop severe respiratory failure. Well tolerated implementation and program development is possible among regional trauma centers. Although clinical knowledge gaps exist, ECMO is a promising treatment in this high-risk population.