

## References

Aggarwal, R. R., Beer, T. M., Weinberg, V. K., Higano, C., Taplin, M. E., Ryan, C. J., et al. (2014).

Intermittent chemotherapy as a platform for testing novel agents in patients with metastatic castration-resistant prostate cancer: A department of defense prostate cancer clinical trials consortium randomized phase II trial of intermittent docetaxel with prednisone with or without maintenance GM-CSF. *Clinical Genitourinary Cancer*,

BACKGROUND: Immunotherapy with granulocyte-macrophage colony-stimulating factor (GM-CSF), an agent that previously demonstrated antitumor activity, was evaluated within an intermittent chemotherapy framework of docetaxel with prednisone (D+P) in metastatic castration-resistant prostate cancer (mCRPC). PATIENTS AND METHODS: mCRPC patients with  $\geq 50\%$  prostate-specific antigen (PSA) decline after 6 cycles of D+P were randomized to either GM-CSF or observation (Obs). At disease progression (PD), D+P was reinitiated for 6 cycles followed by the same "off chemotherapy" regimen in patients eligible for chemotherapy interruption. The sequence was repeated until PD during chemotherapy, lack of PSA response to chemotherapy, or unacceptable toxicity. The primary end point was time to chemotherapy resistance (TTCR). RESULTS: Of 125 patients enrolled, 52 (42%) experienced  $\geq 50\%$  PSA decline on induction D+P and were randomized to GM-CSF (n = 27) or Obs (n = 25). The median time to PD was 3.3 months (95% confidence interval [CI], 2.4-3.5) and 1.5 months (95% CI, 1.5-2.4) during the initial course of GM-CSF and Obs, respectively. Twelve of 26 (46%) patients responded to a second course of D+P. Eleven randomized patients (21%) experienced PD during chemotherapy, precluding accurate assessment of TTCR. The remaining 41 randomized patients discontinued study for lack of PSA response to chemotherapy (n = 8), patient choice to not restart chemotherapy with PSA PD (n = 13), toxicity (n = 7), or study withdrawal (n = 13). CONCLUSION: Conducting a prospective study in mCRPC with maintenance immunotherapy within the framework of intermittent chemotherapy was feasible. The use of PSA instead of radiographic end points limited the number of evaluable patients. This study provides important insight into designing contemporary intermittent chemotherapy trials with maintenance immunotherapy in patients with advanced prostate cancer.

Aggarwal, R. R., Beer, T. M., Weinberg, V. K., Higano, C., Taplin, M. ., Ryan, C. J., et al. (2015).

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Ambardekar, A. V., Alluri, N., Patel, A. C., Lindenfeld, J., & Dorosz, J. L. (2015). Myocardial strain and strain rate from speckle-tracking echocardiography are unable to differentiate asymptomatic

biopsy-proven cellular rejection in the first year after cardiac transplantation. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography,*

**BACKGROUND:** Cellular rejection after cardiac transplantation is treatable with timely diagnosis. Because noninvasive methods for diagnosis are limited, surveillance endomyocardial biopsies are routinely performed in the first year after transplantation. The aim of this study was to test whether myocardial strain and strain rate as assessed by speckle-tracking echocardiography would be a sensitive noninvasive method for the detection of asymptomatic rejection. **METHODS:** Surveillance biopsies and echocardiograms obtained in the first year after transplantation were retrospectively reviewed, and patients with asymptomatic biopsy-proven cellular rejection were identified, as well as control transplantation patients without rejection or cardiac complications. Circumferential and longitudinal strain and strain rate were measured using Velocity Vector Imaging software from echocardiograms performed at three time points for patients with rejection-baseline (no rejection), rejection, and resolution (of rejection)-and three time points for control patients-baseline (within the first month after transplantation), 6 months, and 12 months after transplantation. **RESULTS:** Speckle-tracking strain and strain rate measurements were obtained from 30 patients with asymptomatic biopsy-proven rejection and 14 control transplantation patients. There were no significant differences in circumferential and longitudinal strain or strain rate between the baseline, rejection, and resolution studies. Furthermore, there were no significant differences in strain and strain rate in control transplantation patients during the first year after transplantation or compared with patients with rejection. **CONCLUSIONS:** Speckle-tracking analysis was unable to detect changes on serial studies from patients with asymptomatic rejection and thus cannot replace biopsy. Other noninvasive methods for the diagnosis of cellular-mediated rejection are needed.

Amman, B. R., Jones, M. E. B., Sealy, T. K., Uebelhoer, L. S., Schuh, A. J., Bird, B. H., et al. (2015).

Oral shedding of marburg virus in experimentally infected egyptian fruit bats (*Rousettus aegyptiacus*). *Journal of Wildlife Diseases*, 51(1), 113-124.

Marburg virus (Marburg marburgvirus; MARV) causes sporadic outbreaks of Marburg hemorrhagic fever (MHF) in Africa. The Egyptian fruit bat (*Rousettus aegyptiacus*) has been identified as a

natural reservoir based most-recently on the repeated isolation of MARV directly from bats caught at two locations in southwestern Uganda where miners and tourists separately contracted MHF from 2007–08. Despite learning much about the ecology of MARV through extensive field investigations, there remained unanswered questions such as determining the primary routes of virus shedding and the severity of disease, if any, caused by MARV in infected bats. To answer these questions and others, we experimentally infected captive-bred *R. aegyptiacus* with MARV under high (biosafety level 4) containment. These experiments have shown infection profiles consistent with *R. aegyptiacus* being a bona fide natural reservoir host for MARV and demonstrated routes of viral shedding capable of infecting humans and other animals.

Anderson, D. E., McKenna, K. A., Glynn, J. J., Marzec, U., Hanson, S. R., & Hinds, M. T. (2015).

Thrombotic responses of endothelial outgrowth cells to protein-coated surfaces. *Cells, Tissues, Organs*,

There is significant clinical need for viable small-diameter vascular grafts. While there are many graft biomaterials in development, few have been clinically successful. Evaluation of grafts with a clinically relevant model is needed to drive development. This work examined extracellular matrix coatings on the thrombotic phenotype of endothelial outgrowth cells (EOCs). EOCs were tested on flat plates and tubular grafts. Flat plate studies examined collagen I, collagen IV, fibronectin and alpha-elastin coatings. EOCs attached or proliferated more readily on collagen I and fibronectin surfaces as determined by total DNA. The production of activated protein C (APC) by EOCs was also dependent on the surface coating, with collagen I and fibronectin displaying a higher activity than both collagen IV and alpha-elastin on flat plate studies. Based on these results, only collagen I and fibronectin coatings were tested on expanded polytetrafluoroethylene (ePTFE) in the ex vivo model. Tubular samples showed significantly greater tissue factor pathway inhibitor gene expression on collagen I than on fibronectin. Platelet adhesion was not significantly different, but EOCs on collagen I produced significantly lower APC than on fibronectin, suggesting that differences exist between the flat plate and tubular cultures. Overall, while the hemostatic phenotype of EOCs displayed some differences, cell responses were largely independent of the matrix coating. EOCs adhered strongly to both fibronectin- and collagen-I-coated ePTFE grafts under ex vivo (100 ml/min) flow conditions suggesting the usefulness of this clinically relevant

cell source, testing modality, and shunt model for future work examining biomaterials and cell conditioning before implantation. (c) 2015 S. Karger AG, Basel.

Angier, H., Hoopes, M., Gold, R., Bailey, S. R., Cottrell, E. K., Heintzman, J., et al. (2015). An early look at rates of uninsured safety net clinic visits after the affordable care act. *Annals of Family Medicine*, 13(1), 10-16.

PURPOSE: The Affordable Care Act of 2010 supports marked expansions in Medicaid coverage in the United States. As of January 1, 2014, a total of 25 states and the District of Columbia expanded their Medicaid programs. We tested the hypothesis that rates of uninsured safety net clinic visits would significantly decrease in states that implemented Medicaid expansion, compared with states that did not. METHODS: We undertook a longitudinal observational study of coverage status for adult visits in community health centers, from 12 months before Medicaid expansion (January 1, 2013 to December 31, 2013) through 6 months after expansion (January 1, 2014 to June 30, 2014). We analyzed data from 156 clinics in the OCHIN practice-based research network, with a shared electronic health record, located in 9 states (5 expanded Medicaid coverage and 4 did not). RESULTS: Analyses were based on 333,655 nonpregnant adult patients and their 1,276,298 in-person billed encounters. Overall, clinics in the expansion states had a 40% decrease in the rate of uninsured visits in the postexpansion period and a 36% increase in the rate of Medicaid-covered visits. In contrast, clinics in the nonexpansion states had a significant 16% decline in the rate of uninsured visits but no change in the rate of Medicaid-covered visits. CONCLUSIONS: There was a substantial decrease in uninsured community health center visits and a significant increase in Medicaid-covered visits in study clinics in states that expanded Medicaid in 2014, whereas study clinics in states opting out of the expansion continued to have a high rate of uninsured visits. These findings suggest that Affordable Care Act-related Medicaid expansions have successfully decreased the number of uninsured safety net patients in the United States.

Ansell, S. M., Lesokhin, A. M., Borrello, I., Halwani, A., Scott, E. C., Gutierrez, M., et al. (2015). PD-1 blockade with nivolumab in relapsed or refractory hodgkin's lymphoma. *The New England Journal of Medicine*, 372(4), 311-319.

**BACKGROUND:** Preclinical studies suggest that Reed-Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection. In classic Hodgkin's lymphoma, alterations in chromosome 9p24.1 increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and promote their induction through Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling. We hypothesized that nivolumab, a PD-1-blocking antibody, could inhibit tumor immune evasion in patients with relapsed or refractory Hodgkin's lymphoma.

**METHODS:** In this ongoing study, 23 patients with relapsed or refractory Hodgkin's lymphoma that had already been heavily treated received nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks until they had a complete response, tumor progression, or excessive toxic effects. Study objectives were measurement of safety and efficacy and assessment of the PDL1 and PDL2 (also called CD274 and PDCD1LG2, respectively) loci and PD-L1 and PD-L2 protein expression. **RESULTS:** Of the 23 study patients, 78% were enrolled in the study after a relapse following autologous stem-cell transplantation and 78% after a relapse following the receipt of brentuximab vedotin. Drug-related adverse events of any grade and of grade 3 occurred in 78% and 22% of patients, respectively. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of progression-free survival at 24 weeks was 86%; 11 patients were continuing to participate in the study. Reasons for discontinuation included stem-cell transplantation (in 6 patients), disease progression (in 4 patients), and drug toxicity (in 2 patients). Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in PDL1 and PDL2 and increased expression of these ligands. Reed-Sternberg cells showed nuclear positivity of phosphorylated STAT3, indicative of active JAK-STAT signaling. **CONCLUSIONS:** Nivolumab had substantial therapeutic activity and an acceptable safety profile in patients with previously heavily treated relapsed or refractory Hodgkin's lymphoma. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT01592370.).

Api, A. M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M. L., et al. (2015). Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. *Food and Chemical Toxicology*,

The Research Institute for Fragrance Materials, Inc. (RIFM) has been engaged in the generation

and evaluation of safety data for fragrance materials since its inception over 45 years ago. Over time, RIFM's approach to gathering data, estimating exposure and assessing safety has evolved as the tools for risk assessment evolved. This publication is designed to update the RIFM safety assessment process, which follows a series of decision trees, reflecting advances in approaches in risk assessment and new and classical toxicological methodologies employed by RIFM over the past ten years. These changes include incorporating 1) new scientific information including a framework for choosing structural analogs, 2) consideration of the Threshold of Toxicological Concern (TTC), 3) the Quantitative Risk Assessment (QRA) for dermal sensitization, 4) the respiratory route of exposure, 5) aggregate exposure assessment methodology, 6) the latest methodology and approaches to risk assessments, 7) the latest alternatives to animal testing methodology and 8) environmental risk assessment. The assessment begins with a thorough analysis of existing data followed by in silico analysis, identification of 'read across' analogs, generation of additional data through in vitro testing as well as consideration of the TTC approach. If necessary, risk management may be considered.

Apigian, A. K., & Landry, G. J. (2015). Basic data underlying decision making in nonatherosclerotic causes of intermittent claudication. *Annals of Vascular Surgery*, 29(1), 138-153.

Although most cases of vasculogenic intermittent claudication are caused by atherosclerosis, there is an important minority of cases that are due to nonatherosclerotic causes. Because of their rarity and younger population affected, often without traditional atherosclerotic risk factors, there is frequently a significant delay in diagnosis of nonatherosclerotic peripheral arterial diseases by several months to years in some cases. Here, we review the literature on nonatherosclerotic causes of lower extremity claudication, symptoms, management including surgical and endovascular interventions, and outcomes. Conditions included are popliteal artery entrapment syndrome, cystic adventitial disease, pseudoxanthoma elasticum, persistent sciatic artery, fibromuscular disease, giant cell arteritis, iliac endofibrosis, neurogenic claudication, and chronic exertional compartment syndrome.

Archie Bouwer, H. G., Gregory, C. R., Wegmann, K. W., & Hinrichs, D. J. (2015). Absence of the memory response to encephalitogen following intergender adoptively transferred experimental

autoimmune encephalomyelitis. *Journal of Neuroimmunology*, 278, 194-199.

Animals that have recovered from adoptively transferred EAE develop clinical disease signs 2-3 days earlier than controls when challenged with encephalitogen. This may be due to the reactivation of donor-derived memory cells or stimulation of recipient-derived memory cells primed during the adoptive disease episode. In order to determine the origin of the memory cell subset, we used a donor-recipient model where donor cells are rejected in recipients following a course of adoptively transferred disease. Our results suggest the early onset of disease seen in recipients recovered from adoptively transferred disease and challenged with encephalitogen is due to the sustained presence of donor-derived memory cells.

Arttamangkul, S., Birdsong, W., & Williams, J. T. (2015). Does PKC activation increase the homologous desensitization of  $\mu$  opioid receptors? *British Journal of Pharmacology*, 172(2), 583-592.

**Background and Purpose** This study examined the role of agents known to activate PKC on morphine-induced desensitization of  $\mu$ -opioid receptors (MOP receptors) in brain slices containing locus coeruleus neurons. **Experimental Approach** Intracellular recordings were obtained from rat locus coeruleus neurons. Two measurements were used to characterize desensitization, the decline in hyperpolarization induced by application of a saturating concentration of agonist (acute desensitization) and the decrease in hyperpolarization induced by a subsaturating concentration of [Met]5enkephalin (ME) following washout of the saturating concentration (sustained desensitization). Internalization of MOP receptors was studied in brain slices prepared from transgenic mice expressing Flag-MOP receptors. The subcellular distribution of activated PKC was examined using a novel fluorescent sensor of PKC in HEK293 cells. **Key Results** The phorbol esters (PMA and PDBu) and muscarine increased acute desensitization induced by a saturating concentration of morphine and ME. These effects were not sensitive to staurosporine. Staurosporine did not block the decline in hyperpolarization induced by muscarine. PDBu and muscarine did not affect sustained desensitization induced by ME nor did phorbol esters or muscarine change the trafficking of MOP receptors induced by morphine or ME. The distribution of activated PKC measured in HEK293 cells differed depending on which phorbol ester was applied. **Conclusions and Implications** This study demonstrates a distinct difference in two

measurements that are often used to evaluate desensitization. The measure of decline correlated well with the reduction in peak amplitudes caused by PKC activators implicating the modification of other factors rather than MOP receptors. Linked Articles This article is part of a themed section on Opioids: New Pathways to Functional Selectivity. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2015.172.issue-2>.

Assaf, B. T., Knight, H. L., & Miller, A. D. (2015). Rhesus cytomegalovirus (macacine herpesvirus 3)–Associated facial neuritis in simian immunodeficiency Virus–Infected rhesus macaques (*Macaca mulatta*). *Veterinary Pathology*, 52(1), 217-223.

Peripheral neuropathies are common sequelae to human immunodeficiency virus (HIV) infection in humans and are due to a variety of mechanisms, including direct antiretroviral toxicity, HIV-mediated damage, immune-mediated disorders, and opportunistic viral infections. Rhesus macaques (*Macaca mulatta*) infected with simian immunodeficiency virus (SIV) remain the most consistent animal model for unraveling the pathogenesis of lentiviral-associated disease and its associated opportunistic infections. Rhesus cytomegalovirus (RhCMV) is the most common opportunistic viral infection in rhesus macaques infected with SIV and causes multiorgan pathology; however, its role in peripheral nerve pathology has not been explored. We have identified 115 coinfecting cases with SIV and RhCMV, of which 10 cases of RhCMV-associated facial neuritis were found (8.7% prevalence). Histologic lesions were consistent in all cases and ranged from partial to complete obliteration of the nerves of the tongue, lacrimal gland, and other facial tissues with a mixed inflammatory population of neutrophils and macrophages, of which the latter commonly contained intranuclear inclusion bodies. Luxol fast blue staining and myelin basic protein immunohistochemistry confirmed the progressive myelin loss in the peripheral nerves. Bielschowsky silver stain revealed progressive loss of axons directly related to the severity of inflammation. Double immunohistochemistry with spectral imaging analysis revealed RhCMV-infected macrophages directly associated with the neuritis, and there was no evidence to support RhCMV infection of Schwann cells. These results suggest that peripheral nerve damage is a bystander effect secondary to inflammation rather than a direct infection of Schwann cells and warrants further investigations into the pathogenesis of RhCMV-induced peripheral neuropathy.

Ataer-Cansizoglu, E., Kalpathy-Cramer, J., You, S., Keck, K., Erdogmus, D., & Chiang, M. F. (2015).

Analysis of underlying causes of inter-expert disagreement in retinopathy of prematurity diagnosis: Application of machine learning principles. *Methods of Information in Medicine*, 54(1), 93-102.

Objective: Inter-expert variability in imagebased clinical diagnosis has been demonstrated in many diseases including retinopathy of prematurity (ROP), which is a disease affecting low birth weight infants and is a major cause of childhood blindness. In order to better understand the underlying causes of variability among experts, we propose a method to quantify the variability of expert decisions and analyze the relationship between expert diagnoses and features computed from the images. Identification of these features is relevant for development of computer-based decision support systems and educational systems in ROP, and these methods may be applicable to other diseases where inter-expert variability is observed. Methods: The experiments were carried out on a dataset of 34 retinal images, each with diagnoses provided independently by 22 experts. Analysis was performed using concepts of Mutual Information (MI) and Kernel Density Estimation. A large set of structural features (a total of 66) were extracted from retinal images. Feature selection was utilized to identify the most important features that correlated to actual clinical decisions by the 22 study experts. The best three features for each observer © Schattauer 2015 *Methods Inf Med* 1/2015 were selected by an exhaustive search on all possible feature subsets and considering joint MI as a relevance criterion. We also compared our results with the results of Cohen's Kappa [36] as an inter-rater reliability measure. Results: The results demonstrate that a group of observers (17 among 22) decide consistently with each other. Mean and second central moment of arteriolar tortuosity is among the reasons of disagreement between this group and the rest of the observers, meaning that the group of experts consider amount of tortuosity as well as the variation of tortuosity in the image. Conclusion: Given a set of image-based features, the proposed analysis method can identify critical image-based features that lead to expert agreement and disagreement in diagnosis of ROP. Although tree-based features and various statistics such as central moment are not popular in the literature, our results suggest that they are important for diagnosis.

Austin, D., & Dinwoodie, I. H. (2015). Monomials and basin cylinders for network dynamics. *SIAM Journal on Applied Dynamical Systems*, 14(1), 25-42.

We describe methods to identify cylinder sets inside a basin of attraction for Boolean dynamics of biological networks. Such sets are used for designing regulatory interventions that make the system evolve towards a chosen attractor, for example initiating apoptosis in a cancer cell. We describe two algebraic methods for identifying cylinders inside a basin of attraction, one based on the Groebner fan that finds monomials that define cylinders and the other on primary decomposition. Both methods are applied to current examples of gene networks.

Bailey, S. R., O'Malley, J. P., Gold, R., Heintzman, J., Marino, M., & DeVoe, J. E. (2015). Receipt of diabetes preventive services differs by insurance status at visit. *American Journal of Preventive Medicine*, 48(2), 229-233.

Background: Lack of insurance is associated with suboptimal receipt of diabetes preventive care. One known reason for this is an access barrier to obtaining healthcare visits; however, little is known about whether insurance status is associated with differential rates of receipt of diabetes care during visits. Purpose: To examine the association between health insurance and receipt of diabetes preventive care during an office visit. Methods: This retrospective cohort study used electronic health record and Medicaid data from 38 Oregon community health centers. Logistic regression was used to test the association between insurance and receipt of four diabetes services during an office visit among patients who were continuously uninsured (n=1,117); continuously insured (n=1,466); and discontinuously insured (n=336) in 2006-2007. Generalized estimating equations were used to account for within-patient correlation. Data were analyzed in 2013. Results: Overall, continuously uninsured patients had lower odds of receiving services at visits when due, compared to those who were continuously insured (AOR=0.73, 95% CI=0.66, 0.80). Among the discontinuously insured, being uninsured at a visit was associated with lower odds of receipt of services due at that visit (AOR=0.77, 95% CI=0.64, 0.92) than being insured at a visit. Conclusions: Lack of insurance is associated with a lower probability of receiving recommended services that are due during a clinic visit. Thus, the association between being uninsured and receiving fewer preventive services may not be completely mediated by access to clinic visits.

Bakhtiani, P. A., El Youssef, J., Duell, A. K., Branigan, D. L., Jacobs, P. G., Lasarev, M. R., et al.

(2015). Factors affecting the success of glucagon delivered during an automated closed-loop system in type 1 diabetes. *Journal of Diabetes and its Complications*, 29(1), 93-98.

**Background** In bi-hormonal closed-loop systems for treatment of diabetes, glucagon sometimes fails to prevent hypoglycemia. We evaluated glucagon responses during several closed-loop studies to determine factors, such as gain factors, responsible for glucagon success and failure.

**Methods** We extracted data from four closed-loop studies, examining blood glucose excursions over the 50 min after each glucagon dose and defining hypoglycemic failure as glucose values  $< 70$  mg/dl. We evaluated several factors for association with rates of hypoglycemic failure or hyperglycemic excursion. These factors included age, weight, HbA1c, duration of diabetes, gender, automation of glucagon delivery, glucagon dose, proportional and derivative errors (PE and DE), insulin on board (IOB), night vs. day delivery, and point sensor accuracy. **Results** We analyzed a total of 251 glucagon deliveries during 59 closed-loop experiments performed on 48 subjects. Glucagon successfully maintained glucose within target (60-180 mg/dl) in 195 (78%) of instances with 40 (16%) hypoglycemic failures and 16 (6%) hyperglycemic excursions. A multivariate logistic regression model identified PE ( $p < 0.001$ ), DE ( $p < 0.001$ ), and IOB ( $p < 0.001$ ) as significant determinants of success in terms of avoiding hypoglycemia. Using a model of glucagon absorption and action, simulations suggested that the success rate for glucagon would be improved by giving an additional  $0.8 \mu\text{g/kg}$ . **Conclusion** We conclude that glucagon fails to prevent hypoglycemia when it is given at a low glucose threshold and when glucose is falling steeply. We also confirm that high IOB significantly increases the risk for glucagon failures. Tuning of glucagon subsystem parameters may help reduce this risk.

Banta-Wright, S. A., Kodadek, S. M., Steiner, R. D., & Houck, G. M. (2015). Challenges to

breastfeeding infants with phenylketonuria. *Journal of Pediatric Nursing*, 30(1), 219-226.

Breastfeeding duration for infants with phenylketonuria (PKU) is less than other full-term infants. However, no study has examined the challenges encountered by mothers' breastfeeding infants with PKU. In 75 mothers of a child with PKU, three categories of breastfeeding challenges were identified: common breastfeeding issues, breastfeeding and PKU, and no challenges. The common breastfeeding issues can be identified in the literature but for these mothers, the issues

are heightened due to frequent phenylalanine (Phe) monitoring. Even so, many mothers adapt breastfeeding to maintain desired Phe levels. A few mothers had no issues and were the exception, not the norm.

Barker, D. J. P. (2009). *The developmental origins of coronary heart disease* Oxford University Press.

This chapter discusses the developmental origins of coronary heart disease. The recent discovery that people who develop coronary heart disease (CHD) grew differently to other people during fetal life and childhood has led to a new 'developmental' model for the disease. Studies have shown an association between low birthweight and CHD. Low birthweight has also been shown to predict altered glucose tolerance in studies around the world.

Barrenas, F., Green, R. R., Thomas, M. J., Law, G. L., Proll, S. C., Engelmann, F., et al. (2015). Next generation sequencing reveals a controlled immune response to zaire ebola virus challenge in cynomolgus macaques immunized with VSVDeltaG/EBOVgp. *Clinical and Vaccine Immunology : CVI*,

Vesicular stomatitis virus expressing Zaire Ebola virus (EBOV) glycoprotein (VSVDeltaG/EBOVgp) could be used as a vaccine to meet the 2014 Ebola virus outbreak. To characterize host response to this vaccine, we used mRNA sequencing to analyze PBMC from cynomolgus macaques after VSVDeltaG/EBOVgp immunization and subsequent EBOV challenge. We found a controlled transcriptional response that transitioned to immune regulation as the EBOV was cleared. This observation supported the safety of the vaccine.

Barrett, T. W., Radha Shanmugam, N., Selvam, A. P., Kazmierczak, S. C., & Prasad, S. (2015). Novel nanomonitor ultra-sensitive detection of troponin T. *Clinica Chimica Acta; International Journal of Clinical Chemistry*,

BACKGROUND: Troponin is the preferred biomarker for diagnosing myocardial infarction. Point of care devices have not matched the sensitivity of laboratory-based methods for measuring troponin. The Nanomonitor is a novel point-of-care device that uses the change in electrical impedance that occurs when a biomarker binds to its antibody, which is then correlated to the concentration of the target biomarker. METHODS: Performance characteristics of the Nanomonitor were evaluated and compared to a standard laboratory-based method. RESULTS:

The limit of detection of the Nanomonior for troponin T was 0.0088ng/l. Total imprecision was 2.38% and 0.85% at troponin T concentrations of 73ng/l and 1800ng/l. The functional sensitivity (10% coefficient of variation) was 0.329ng/l. The linear regression had a slope of 0.996 (95% confidence interval, 0.991, 1.002),  $r=1.00$ , and an intercept of 15.88ng/l (95% confidence interval, -68.39ng/l, 100.15ng/l). The mean difference between the assays was -7.54ng/l, determined by Bland-Altman analysis. CONCLUSION: The Nanomonitor preliminary results have favorable performance characteristics for detecting troponin T in patient blood, provide results in 15min, and are portable. More research is needed.

Basso, L. R., Jr, Gast, C. E., Bruzual, I., & Wong, B. (2015). Identification and properties of plasma membrane azole efflux pumps from the pathogenic fungi *Cryptococcus gattii* and *Cryptococcus neoformans*. *The Journal of Antimicrobial Chemotherapy*,

OBJECTIVES: *Cryptococcus gattii* from the North American Northwest (NW) have higher azole MICs than do non-NW *C. gattii* or *Cryptococcus neoformans*. Since mechanisms of azole resistance in *C. gattii* are not known, we identified *C. gattii* and *C. neoformans* plasma membrane azole efflux pumps and characterized their properties. METHODS: The *C. gattii* R265 genome was searched for orthologues of known fungal azole efflux genes, expression of candidate genes was assessed by RT-PCR and the expressed genes' cDNAs were cloned and expressed in *Saccharomyces cerevisiae*. Azole MICs and intracellular [<sup>3</sup>H]fluconazole were measured in *C. gattii* and *C. neoformans* and in *S. cerevisiae* expressing each cDNA of interest, as was [<sup>3</sup>H]fluconazole uptake by post-Golgi vesicles (PGVs) isolated from *S. cerevisiae* *sec6-4* mutants expressing each cDNA of interest. RESULTS: Intracellular [<sup>3</sup>H]fluconazole concentrations were inversely correlated with fluconazole MICs only in 25 NW *C. gattii* strains. *S. cerevisiae* expressing three *C. gattii* cDNAs (encoded by orthologues of *C. neoformans* AFR1 and MDR1 and the previously unstudied gene AFR2) and their *C. neoformans* counterparts had higher azole MICs and lower intracellular [<sup>3</sup>H]fluconazole concentrations than did empty-vector controls. PGVs from *S. cerevisiae* expressing all six *Cryptococcus* cDNAs also accumulated more [<sup>3</sup>H]fluconazole than did controls, and [<sup>3</sup>H]fluconazole transport by all six transporters of interest was ATP dependent and was inhibited by excess unlabelled fluconazole, voriconazole, itraconazole and posaconazole. CONCLUSIONS: We conclude that *C. gattii* and *C. neoformans* AFR1, MDR1 and AFR2 encode ABC

transporters that pump multiple azoles out of *S. cerevisiae* cells, thereby causing azole resistance.

Baumert, M., Javorka, M., & Kabir, M. (2014). Joint symbolic dynamics for the assessment of cardiovascular and cardiorespiratory interactions. *Philosophical Topics*, 373(2034)

Beat-to-beat variations in heart period provide information on cardiovascular control and are closely linked to variations in arterial pressure and respiration. Joint symbolic analysis of heart period, systolic arterial pressure and respiration allows for a simple description of their shared short-term dynamics that are governed by cardiac baroreflex control and cardiorespiratory coupling. In this review, we discuss methodology and research applications. Studies suggest that analysis of joint symbolic dynamics provides a powerful tool for identifying physiological and pathophysiological changes in cardiovascular and cardiorespiratory control.

Bayestehtashk, A., Shafran, I., Coleman, K., & Robertson, N. (2014). Detecting vocalizations of individual monkeys in social groups. *Conference Proceedings : ...Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference, 2014*, 4775-4779.

Vocalization is an important clue in recognizing monkeys' behaviors. Previous studies have shown that the frequencies, the types and the lengths of vocalizations reveal significant information about social interactions in a group of monkeys. In this work, we describe a corpus of monkey vocalizations, recorded from Oregon National Primate Research Center with the goal of developing automatic methods for recognizing social behaviors of individuals in groups. The constraints of the problem necessitated using tiny low-power recorders, mounted on their collars. The recordings from each monkey's recorder nonetheless contains vocalizations from not only the monkey wearing the recorder but also its spatial neighbors. The devices recorded vocalizations for two consecutive days, 12 hours each day, from each monkey in the group. Like in sensor networks, low power recorders are unreliable and have sample loss over long durations. Furthermore, the recordings contain high-levels of background noise, including clanging of metal collars against cages and conversations of caretakers. These practical issues poses an interesting challenge in processing the recordings. In this paper, we investigate our automated approaches

to process the data efficiently, detect the vocalizations and align the recordings from the same sessions.

Belanger, A. Y., Cameron, M. H., Michlovitz, S. L., Bellew, J. W., & Freeman, L. (2015). On "the american physical therapy association's top five choosing wisely recommendations." white NT, delitto A, manal TJ, miller S. phys ther. doi: 10.2522/ptj.20140287. *Physical Therapy*, 95(1), 142-143.

Bennett, W. (1977). Pericardial effusions associated with minoxidil. *The Lancet*, 310(8052), 1356.

Bentley, M., Decker, H., Luisi, J., & Banker, G. (2015). A novel assay reveals preferential binding between rabs, kinesins, and specific endosomal subpopulations. *The Journal of Cell Biology*, Identifying the proteins that regulate vesicle trafficking is a fundamental problem in cell biology. In this paper, we introduce a new assay that involves the expression of an FKBP12-rapamycin-binding domain-tagged candidate vesicle-binding protein, which can be inducibly linked to dynein or kinesin. Vesicles can be labeled by any convenient method. If the candidate protein binds the labeled vesicles, addition of the linker drug results in a predictable, highly distinctive change in vesicle localization. This assay generates robust and easily interpretable results that provide direct experimental evidence of binding between a candidate protein and the vesicle population of interest. We used this approach to compare the binding of Kinesin-3 family members with different endosomal populations. We found that KIF13A and KIF13B bind preferentially to early endosomes and that KIF1A and KIF1Bbeta bind preferentially to late endosomes and lysosomes. This assay may have broad utility for identifying the trafficking proteins that bind to different vesicle populations.

Bethea, C. L., & Reddy, A. P. (2015). Ovarian steroids regulate gene expression related to DNA repair and neurodegenerative diseases in serotonin neurons of macaques. *Molecular Psychiatry*, Depression often accompanies the perimenopausal transition and it often precedes overt symptomology in common neurodegenerative diseases (NDDs, such as Alzheimer's, Parkinson's, Huntington, amyotrophic lateral sclerosis). Serotonin dysfunction is frequently found in the different etiologies of depression. We have shown that ovariectomized (Ovx) monkeys treated

with estradiol (E) for 28 days supplemented with placebo or progesterone (P) on days 14-28 had reduced DNA fragmentation in serotonin neurons of the dorsal raphe nucleus, and long-term Ovx monkeys had fewer serotonin neurons than intact controls. We questioned the effect of E alone or E+P (estradiol supplemented with progesterone) on gene expression related to DNA repair, protein folding (chaperones), the ubiquitin-proteasome, axon transport and NDD-specific genes in serotonin neurons. Ovx macaques were treated with placebo, E or E+P (n=3 per group) for 1 month. Serotonin neurons were laser captured and subjected to microarray analysis and quantitative real-time PCR (qRT-PCR). Increases were confirmed with qRT-PCR in five genes that code for proteins involved in repair of strand breaks and nucleotide excision. NBN1, PCNA (proliferating nuclear antigen), GADD45A (DNA damage-inducible), RAD23A (DNA damage recognition) and GTF2H5 (gene transcription factor 2H5) significantly increased with E or E+P treatment (all analysis of variance (ANOVA),  $P < 0.01$ ). Chaperone genes HSP70 (heat-shock protein 70), HSP60 and HSP27 significantly increased with E or E+P treatment (all ANOVA,  $P < 0.05$ ). HSP90 showed a similar trend. Ubiquitinase coding genes UBEA5, UBE2D3 and UBE3A (Parkin) increased with E or E+P (all ANOVA,  $P < 0.003$ ). Transport-related genes coding kinesin, dynein and dynactin increased with E or E+P treatment (all ANOVA,  $P < 0.03$ ). SCNA (alpha-synuclein) and ADAM10 (alpha-secretase) increased (both ANOVA,  $P < 0.02$ ) but PSEN1 (presenilin1) decreased (ANOVA,  $P < 0.02$ ) with treatment. APP decreased 10-fold with E or E+P administration. Newman-Keuls post hoc comparisons indicated variation in the response to E alone versus E+P across the different genes. In summary, E or E+P increased gene expression for DNA repair mechanisms in serotonin neurons, thereby rendering them less vulnerable to stress-induced DNA fragmentation. In addition, E or E+P regulated four genes encoding proteins that are often misfolded or malfunctioning in neuronal populations subserving overt NDD symptomology. The expression and regulation of these genes in serotonergic neurons invites speculation that they may mediate an underlying disease process in NDDs, which in turn may be ameliorated or delayed with timely hormone therapy in women. *Molecular Psychiatry* advance online publication, 20 January 2015; doi:10.1038/mp.2014.178.

Bethea, C. L., Reddy, A. P., Flowers, M., Shapiro, R. A., Colman, R. J., Abbott, D. H., et al. (2015).

*High fat diet decreases beneficial effects of estrogen on serotonin-related gene expression in*

*marmosets* Elsevier Inc.

The administration of estradiol-17 $\beta$  (E) to animal models after loss of ovarian steroid production has many beneficial effects on neural functions, particularly in the serotonin system in nonhuman primates (NHPs). E also has anorexic effects, although the mechanism of action is not well defined. In the US, obesity has reached epidemic proportions, and blame is partially directed at the Western style diet, which is high in fat and sugar. This study examined the interaction of E and diet in surgically menopausal nonhuman primates with a 2.  $\times$  2 block design. Marmosets (*Callithrix jacchus*; n= 4/group) were placed on control-low fat diet (LFD; 14%kcal from fat) or high fat diet (HFD; 28%kcal from fat) 1. month prior to ovariectomy (Ovx). Empty (placebo) or E-filled Silastic capsules were implanted immediately following Ovx surgery. Treatments extended 6. months. The established groups were: placebo. +. LFD, E. +. LFD, placebo. +. HFD, or E. +. HFD. At necropsy, the brain was flushed with saline and harvested. The midbrain was dissected and a small block containing the dorsal raphe nucleus was processed for qRT-PCR using Evagreen (Biotinum). Genes previously found to impact serotonin neural functions were examined. Results were compared with 2-way ANOVA followed by Bonferroni post-hoc tests or Cohen's D analysis. There was a significant effect of treatment on tryptophan hydroxylase 2 (TPH2) across the groups (. p=. 0.019). E stimulated TPH2 expression and HFD prevented E-stimulated TPH2 expression (. p<. 0.01). Treatment differentially affected monoamine oxidase B (MAO-B) across the groups (. p=. 0.05). E increased MAO-B with LFD, and this stimulatory effect was prevented by HFD (. p<. 0.05). There was a significant difference between treatments in corticotrophin releasing factor-receptor 2 (CRF-R2) expression (. p=. 0.012). E increased CRF-R2 and this stimulatory effect was blocked by HFD (. p<. 0.01). Regardless of diet, E increased Fev mRNA (. p=. 0.028) and decreased CRF-receptor 1 (CRF-R1) mRNA (. p=. 0.04). HFD suppressed urocortin 1 (UCN1; stresscopin) expression (. p=. 0.045) but E treatment had no effect. Monoamine oxidase A (MAO-A) was different due to treatment across the groups (. p=. 0.028). MAO-A was increased in the E. +. HFD group (. p<. 0.01) whereas previous studies showed E suppressed MAO-A in macaques. The serotonin reuptake transporter (SERT), the serotonin 1A receptor (5HT1A), estrogen receptor beta (ER $\beta$ ) and progesterin receptor (PR) expressions were not different between groups. Estrogen receptor alpha (ER $\alpha$ ) was undetectable. In summary, the data indicate that important actions of hormone therapy in the serotonin system may be lost in the context of a HFD.

Bleyer, A., Thomas, C. R., Jr., Baines, C., & Miller, A. B. (2015). Flawed assumptions used to defend screening mammography. *Cancer*, *121*(2), 320-321.

Bodhankar, S., Chen, Y., Lapato, A., Vandembark, A. A., Murphy, S. J., Saugstad, J. A., et al. (2014).

Regulatory CD8<sup>+</sup>CD122<sup>+</sup> T-cells predominate in CNS after treatment of experimental stroke in male mice with IL-10-secreting B-cells. *Metabolic Brain Disease*,

Clinical stroke induces inflammatory processes leading to cerebral and splenic injury and profound peripheral immunosuppression. IL-10 expression is elevated during major CNS diseases and limits inflammation in the brain. Recent evidence demonstrated that transfer of IL-10<sup>+</sup> B-cells reduced infarct volume in male C57BL/6J (wild-type, WT) recipient mice when given 24 h prior to or 4 h after middle cerebral artery occlusion (MCAO). The purpose of this study was to determine if passively transferred IL-10<sup>+</sup> B-cells can exert therapeutic and immunoregulatory effects when injected 24 h after MCAO induction in B-cell-sufficient male WT mice. The results demonstrated that IL-10<sup>+</sup> B-cell treated mice had significantly reduced infarct volumes in the ipsilateral cortex and hemisphere and improved neurological deficits vs. Vehicle-treated control mice after 60 min occlusion and 96 h of reperfusion. The MCAO-protected B-cell recipient mice had less splenic atrophy and reduced numbers of activated, inflammatory T-cells, decreased infiltration of T-cells and a less inflammatory milieu in the ischemic hemispheres compared with Vehicle-treated control mice. These immunoregulatory changes occurred in concert with the predominant appearance of IL-10-secreting CD8<sup>+</sup>CD122<sup>+</sup> Treg cells in both the spleen and the MCAO-affected brain hemisphere. This study for the first time demonstrates a major neuroprotective role for IL-10<sup>+</sup> B-cells in treating MCAO in male WT mice at a time point well beyond the ~4 h tPA treatment window, leading to the generation of a dominant IL-10<sup>+</sup>CD8<sup>+</sup>CD122<sup>+</sup> Treg population associated with spleen preservation and reduced CNS inflammation.

Bohanes, P., Rankin, C., Blanke, C. D., Winder, T., Ulrich, C. M., Smalley, S. R., et al. (2015).

Pharmacogenetic analysis of INT 0144 trial: Association of polymorphisms with survival and toxicity in rectal cancer patients treated with 5-FU and radiation. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

**Purpose:** We tested whether 18 polymorphisms in 16 genes (GSTP1, COX2, IL-10, EGFR, EGF, FGFR4, CCDN1, VEGFR2, VEGF, CXCR2, IL-8, MMP3, ICAM1, ERCC1, RAD51 and XRCC3) would predict disease-free-survival (DFS), Overall survival (OS) and toxicity in the INT0144 trial, which was designed to investigate different postoperative regimen of 5-FU-based chemoradiation in locally advanced rectal cancers: Arm1 consisted of bolus 5-FU followed by 5-FU protracted venous infusion (PVI) with radiotherapy; Arm2 was induction and concomitant PVI 5-FU with radiotherapy Arm3 was induction and concomitant bolus 5-FU with radiotherapy. **Experimental Design:** DNA from 746 stage II/III rectal patients enrolled in the SWOG S9304 phase III trial was analyzed. Genomic DNA was extracted from FFPE tumor tissue. The polymorphisms were analyzed using direct DNA-sequencing or PCR-RFLP. **Results:** GSTP1-Ile105Val (rs1695) was significantly associated with DFS and OS and its effect did not vary by treatment arm. The 5-year DFS and OS were 53% and 58%, respectively, for G/G, 66% and 72% for G/A and 57% and 66% for A/A patients. In Arm2, IL8-251A/A genotype (rs4073) was associated with a lower risk of toxicities ( $p=0.04$ ). The VEGFR2 H472Q Q/Q genotype (rs1870377) was associated with a higher risk of grade 3-5 proximal upper gastrointestinal tract (PUGIT) mucositis ( $p=0.04$ ) in Arm 2. However, in Arm 1 this genotype was associated with a lower risk of PUGIT mucositis ( $p=0.004$ ). **Conclusions:** rs1695 may be prognostic in patients with rectal cancer treated with adjuvant chemoradiation. rs4073 and rs1870377 may exhibit different associations with toxicity, according to the 5-FU schedule.

Braun, T. P., Maxson, J. E., Agarwal, A., Dunlap, J., Spurgeon, S. E., & Traer, E. (2014). Acute promyelocytic leukemia with JAK2 V617F and severe differentiation syndrome. *Leukemia Research Reports*, 4(1), 8-11.

Myeloproliferative neoplasms transformed into AML usually have a poor prognosis. We report a case of essential thrombocythemia with myelofibrosis that transformed into acute promyelocytic leukemia (APL) with both the t(15;17) translocation as well as the JAK2 V617F mutation.

Clinically, this case was notable for severe differentiation syndrome despite treatment with high-dose dexamethasone. Cytokine production by differentiating APL cells was not directly abrogated by JAK2 inhibitors in vitro, suggesting that JAK2 V617F enhances the hyperinflammatory response downstream of cytokines. JAK1/2 inhibitors may therefore dampen the inflammatory

cascade downstream of cytokine production, similar to glucocorticoids, and have a role in treating severe differentiation syndrome.

Braun, T. P., Maxson, J. E., Agarwal, A., Dunlap, J., Spurgeon, S. E., & Traer, E. (2015). Acute promyelocytic leukemia with JAK2 V617F and severe differentiation syndrome. *Leukemia Research Reports*, 4(1), 8-11.

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Broberg, C. S. (2015). Cardiac magnetic imaging of the patient with an atrial switch palliation for transposition of the great arteries. *Progress in Pediatric Cardiology*,

Patients with transposition of the great arteries treated with either a Mustard or Senning atrial switch palliation are often referred for assessment with cardiovascular magnetic resonance (CMR). Frequent indications for scanning include quantifying systemic right ventricular function, assessing patency of the venous pathways, finding baffle leaks, measuring systemic atrioventricular valve regurgitation, or detecting myocardial fibrosis. This review discusses the various techniques available for CMR imaging in this setting, an approach to obtaining reliable images, strategies and pitfalls to consider, and variations between centers to understand. The goal is to enable providers to obtain a thorough yet efficient study that adequately addresses the patient's clinical needs.

Brooks, V. L., Shi, Z., Holwerda, S. W., & Fadel, P. J. (2015). Obesity-induced increases in sympathetic nerve activity: Sex matters. *Autonomic Neuroscience: Basic and Clinical*, 187, 18-26.

Abundant evidence obtained largely from male human and animal subjects indicates that obesity increases sympathetic nerve activity (SNA), which contributes to hypertension development. However, recent studies that included women reported that the strong relationships between muscle SNA and waist circumference or body mass index (BMI) found in men are not present in overweight and obese women. A similar sex difference in the association between adiposity and hypertension development has been identified in animal models of obesity. In this brief review, we consider two possible mechanisms for this sex difference. First, visceral adiposity, leptin, insulin, and angiotensin II have been identified as potential culprits in obesity-induced sympathoexcitation in males. We explore if these factors wield the same impact in females. Second, we consider if sex differences in vascular reactivity to sympathetic activation contribute. Our survey of the literature suggests that premenopausal females may be able to resist obesity-induced sympathoexcitation and hypertension in part due to differences in adipose disposition as well as its muted inflammatory response and reduced production of pressor versus depressor components of the renin-angiotensin system. In addition, vascular responsiveness to increased SNA may be reduced. However, more importantly, we identify the urgent need for further study, not only of sex differences per se, but also of the mechanisms that may mediate these differences. This information is required not only to refine treatment options for obese premenopausal women but also to potentially reveal new therapeutic avenues in obese men and women.

Bumoko, G. M., Sadiki, N. H., Rwatambuga, A., Kayembe, K. P., Okitundu, D. L., Mumba Ngoyi, D., et al. (2015). Lower serum levels of selenium, copper, and zinc are related to neuromotor impairments in children with konzo. *Journal of the Neurological Sciences*,  
We assessed the relationship between key trace elements and neurocognitive and motor impairments observed in konzo, a motor neuron disease associated with cassava cyanogenic exposure in nutritionally challenged African children. Serum concentrations of iron, copper, zinc, selenium, and neurotoxic lead, mercury, manganese, cadmium, and cobalt were measured in 123 konzo children (mean age 8.53years) and 87 non-konzo children (mean age 9.07years) using inductively coupled plasma mass spectrometry (ICPMS). Concentrations of trace elements were compared and related to performance scores on the Kaufman Assessment Battery for Children,

2nd edition (KABC-II) for cognition and Bruininks-Oseretsky Test, 2nd edition (BOT-2) for motor proficiency. Children with konzo had low levels of selenium, copper, and zinc relative to controls. Selenium concentration significantly correlated with serum 8,12-iso-iPF<sub>2</sub>alpha-VI isoprostane (Spearman  $r=0.75$ ,  $p<0.01$ ) and BOT-2 scores ( $r=0.31$ ,  $p=0.00$ ) in children with konzo. Elemental deficiency was not associated with poor cognition. Mean (SD) urinary level of thiocyanate was 388.03 (221.75)  $\mu\text{mol/l}$  in non-konzo compared to 518.59 (354.19)  $\mu\text{mol/l}$  in konzo children ( $p<0.01$ ). Motor deficits associated with konzo may possibly be driven by the combined effects of cyanide toxicity and Se deficiency on prooxidant mechanisms. Strategies to prevent konzo may include dietary supplementation with trace elements, preferentially, those with antioxidant and cyanide-scavenging properties.

Burchett, M. A., McKenna, D. T., Selzer, D. J., Choi, J. H., & Mattar, S. G. (2014). Laparoscopic sleeve gastrectomy is safe and effective in elderly patients: A comparative analysis. *Obesity Surgery*, 25(2), 222-228.

Background: Laparoscopic sleeve gastrectomy (SG) is gaining widespread popularity as a definitive bariatric operation that provides satisfactory and durable weight loss as well as comorbidity resolution. Although SG is being increasingly offered to patients of all ages, there is a paucity of reported outcomes in patients  $\geq 62$  years of age. The purpose of this study was to perform a comparative analysis of the outcomes of SG in patients  $>62$  years versus a younger age group, with an emphasis on safety and efficacy. Methods: A retrospective analysis was performed from a prospectively collected database on patients who underwent SG from 2007 to 2012. All patients who were  $\geq 62$  years old were compared to those  $<62$  years. Results: There were 182 patients who underwent SG, 17 of whom were  $\geq 62$  years old. There were no significant differences in demographics or comorbidity characteristics between the groups. The mean follow-up was 1 year. There was no 30-day mortality in either group. The percent excess weight loss for the younger age group was  $44 \pm 21\%$  and the older group was  $44 \pm 25\%$ . The percent total body weight loss was  $22 \pm 10$  and  $21 \pm 10\%$ , respectively. Weight loss outcomes were maintained for up to 3 years. Comorbidity resolution and improvement rates were equivalent in both groups. Conclusions: SG is safe and effective in patients  $\geq 62$  years. Weight loss and the

beneficial effects on comorbidities are equivalent among elderly and younger patients. SG should be offered to elderly patients who are deemed to be appropriate candidates.

Burchill, L. J., Lameijer, H., Roos-Hesselink, J. W., Grewal, J., Ruys, T. P., Kulikowski, J. D., et al.

(2015). Pregnancy risks in women with pre-existing coronary artery disease, or following acute coronary syndrome. *Heart (British Cardiac Society)*,

OBJECTIVE: The objective of this study was to determine outcomes in pregnant women with pre-existing coronary artery disease (CAD) or following an acute coronary syndrome (ACS) including myocardial infarction (MI). BACKGROUND: The physiological changes of pregnancy can contribute to myocardial ischaemia. The pregnancy risk for women with pre-established CAD or a history of ACS/MI is not well studied. METHODS: This was a retrospective multicentre study. Adverse maternal cardiac, obstetric and fetal/neonatal events were examined. The primary outcome was a composite endpoint of cardiac arrest, ACS/MI, ventricular arrhythmia or congestive heart failure. The prevalence of new or progressive angina during pregnancy was also examined.

RESULTS: Fifty pregnancies in 43 women (mean age 35+/-5 years) were included. Coronary atherosclerosis (40%) and coronary thrombus (36%) were the most common underlying diagnoses. The primary outcome occurred in 10% (5/50) of pregnancies and included one maternal death secondary to cardiac arrest. Other events included ACS/MI (3/50) and heart failure (1/50). New or progressive angina occurred in 18% of pregnancies. Ischaemic complications of any type (new or progressive angina, ACS/MI, ventricular arrhythmia, cardiac arrest) occurred more commonly in women with coronary atherosclerosis compared with those without (50% vs 10%,  $p=0.003$ ). A high rate of adverse obstetric (16%) and fetal/neonatal (30%) events was observed. CONCLUSIONS: Pregnant women with pre-existing CAD or ACS/MI before pregnancy are at increased risk of adverse events during pregnancy. Those with coronary atherosclerosis are at highest risk of adverse maternal cardiac events due to myocardial ischaemia during pregnancy.

Burke, W., Appelbaum, P., Dame, L., Marshall, P., Press, N., Pyeritz, R., et al. (2015). The

translational potential of research on the ethical, legal, and social implications of genomics.

*Genetics in Medicine*, 17(1), 12-20.

Federally funded research on the ethical, legal, and social implications (ELSI) of genomics includes a programmatic charge to consider policy-relevant questions and to communicate findings in venues that help inform the policy-making process. In addressing this goal, investigators must consider the range of policies that are relevant to human genetics; how foundational research in bioethics, law, and the social sciences might inform those policies; and the potential professional issues that this translational imperative raises for ELSI investigators. We review these questions in light of experiences from a consortium of federally funded Centers of Excellence in ELSI Research, and offer a set of policy recommendations for program design and evaluation of ELSI research. We conclude that it would be a mistake to require that ELSI research programs demonstrate a direct impact on science or health policy; however, ELSI researchers can take steps to increase the relevance of their work to policy makers. Similarly, funders of ELSI research who are concerned with facilitating policy development can help by building cross-disciplinary translational research capacities, and universities can take steps to make policy-relevant research more rewarding for scholars in the humanities, social sciences, and law.

Büsch, K., Sonnenberg, A., & Bansback, N. (2014). Impact of inflammatory bowel disease on disability. *Current Gastroenterology Reports*, 16(10)

Inflammatory bowel disease can impact individuals at a young age, thus compromising their work productivity. Besides the inability to engage in gainful work, the concept of disability also relates to the patients' diminished ability to undertake household and social activities. A literature search was performed of recent literature, and all articles containing information about the impact of inflammatory bowel disease on disability or any work-related outcomes were included. Recent studies suggest that 9 to 19 % of inflammatory bowel disease patients suffer from short-term absences from work and 19 to 22 % are on long-term disability. Crohn's disease patients reported being more affected by their disease than ulcerative colitis patients. A comparison of results from different studies is difficult due to the lack of consensus on how to define and measure disability. Additional research is needed to better quantify disability in inflammatory bowel disease patients.

Caldwell, P., & Purtzer, M. A. (2015). Long-term learning in a short-term study abroad program: "are we really truly helping the community?". *Public Health Nursing*,  
Objective: To discover long-term learning outcomes in a short-term study abroad program. Students worked directly with community members to identify health issues, implement educational workshops addressing those issues, and evaluate health outcomes. Design and Sample: This is a qualitative, descriptive study. Thematic analysis was conducted using a written questionnaire completed one or more years postimmersion. The sample was 41 nursing students who participated in a 10-day immersion experience in remote Honduras. Results: Four themes emerged revealing evidence of long-term learning. Three of these themes, Embracing Other, Gaining Cultural Competencies, and Experiencing an Ethnocentric Shift, are supported in the literature. The fourth theme, Negotiating Ethical Dilemmas, offers a new finding. Conclusion: Although educators have questioned ethical consequences of study abroad programs, there is a paucity of literature indicating that students are the ones doing the questioning. Implications for educators and community members alike include facilitating dialog about collective worldviews related to global health ethics when designing study abroad programs.

Cameron, M., Coote, S., & Sosnoff, J. J. (2014). Whom to target for falls-prevention trials:

Recommendations from the international MS falls prevention research network. *International Journal of MS Care*, 16(4), 203-207.

Effective falls-prevention approaches for people with multiple sclerosis (MS) are needed. A significant challenge in studying falls-prevention programs for people with MS is deciding whom to include in trials. This article presents and discusses potential criteria for selecting participants for trials of falls-prevention interventions in MS. This narrative review reports on the inaugural meeting of the International MS Falls Prevention Research Network (IMSFPRN), which was held in March 2014 in Kingston, Ontario, Canada. Criteria considered were age, assistive device use, cognition, and fall history. The IMSFPRN reached consensus agreement to recommend that participants of all ages with varying levels of cognitive ability who are able to ambulate with or without assistance and who have a history of falling should be included in their future falls-prevention trials.

Campbell, A. N., Nunes, E. V., Pavlicova, M., Hatch-Maillette, M., Hu, M. C., Bailey, G. L., et al.

(2014). Gender-based outcomes and acceptability of a computer-assisted psychosocial intervention for substance use disorders. *Journal of Substance Abuse Treatment*,

BACKGROUND: Digital technologies show promise for increasing treatment accessibility and improving quality of care, but little is known about gender differences. This secondary analysis uses data from a multi-site effectiveness trial of a computer-assisted behavioral intervention, conducted within NIDA's National Drug Abuse Clinical Trials Network, to explore gender differences in intervention acceptability and treatment outcomes. METHODS: Men (n=314) and women (n=192) were randomly assigned to 12-weeks of treatment-as-usual (TAU) or modified TAU+Therapeutic Education System (TES), whereby TES substituted for 2hours of TAU per week. TES is composed of 62 Web-delivered, multimedia modules, covering skills for achieving and maintaining abstinence plus prize-based incentives contingent on abstinence and treatment adherence. Outcomes were: (1) abstinence from drugs and heavy drinking in the last 4weeks of treatment, (2) retention, (3) social functioning, and (4) drug and alcohol craving. Acceptability was the mean score across five indicators (i.e., interesting, useful, novel, easy to understand, and satisfaction). RESULTS: Gender did not moderate the effect of treatment on any outcome. Women reported higher acceptability scores at week 4 ( $p=.02$ ), but no gender differences were detected at weeks 8 or 12. Acceptability was positively associated with abstinence, but only among women ( $p=.01$ ). CONCLUSIONS: Findings suggest that men and women derive similar benefits from participating in a computer-assisted intervention, a promising outcome as technology-based treatments expand. Acceptability was associated with abstinence outcomes among women. Future research should explore characteristics of women who report less satisfaction with this modality of treatment and ways to improve overall acceptability.

Cani, A. K., Hovelson, D. H., McDaniel, A. S., Sadis, S., Haller, M. J., Yadati, V., et al. (2015). Next-gen sequencing exposes frequent MED12 mutations and actionable therapeutic targets in phyllodes tumors. *Molecular Cancer Research : MCR*,

Phyllodes tumors are rare fibroepithelial tumors with variable clinical behavior accounting for a small subset of all breast neoplasms, yet little is known about the genetic alterations that drive tumor initiation and/or progression. Here targeted next generation sequencing (NGS) was used to

identify somatic alterations in formalin fixed paraffin embedded (FFPE) patient specimens from malignant, borderline and benign cases. NGS revealed mutations in mediator complex subunit 12 (MED12) affecting the G44 hotspot residue in the majority (67%) of cases spanning all three histological grades. In addition, loss-of-function mutations in p53 (TP53) as well as deleterious mutations in the tumor suppressors retinoblastoma (RB1) and neurofibromin 1 (NF1) were identified exclusively in malignant tumors. High-level copy number alterations (CNAs) were nearly exclusively confined to malignant tumors, including potentially clinically actionable gene amplifications in IGF1R and EGFR. Taken together, this study defines the genomic landscape underlying phyllodes tumor development, suggests potential molecular correlates to histologic grade, expands the spectrum of human tumors with frequent recurrent MED12 mutations, and identifies IGF1R and EGFR as potential therapeutic targets in malignant cases. Implications: Integrated genomic sequencing and mutational profiling provides insight into the molecular origin of phyllodes tumors and indicates potential druggable targets in malignant disease.

Chang, H., Zhou, Y., Borowsky, A., Barner, K., Spellman, P., & Parvin, B. (2014). Stacked predictive sparse decomposition for classification of histology sections. *International Journal of Computer Vision*,

Image-based classification of histology sections, in terms of distinct components (e.g., tumor, stroma, normal), provides a series of indices for histology composition (e.g., the percentage of each distinct components in histology sections), and enables the study of nuclear properties within each component. Furthermore, the study of these indices, constructed from each whole slide image in a large cohort, has the potential to provide predictive models of clinical outcome. For example, correlations can be established between the constructed indices and the patients' survival information at cohort level, which is a fundamental step towards personalized medicine. However, performance of the existing techniques is hindered as a result of large technical variations (e.g., variations of color/textures in tissue images due to non-standard experimental protocols) and biological heterogeneities (e.g., cell type, cell state) that are always present in a large cohort. We propose a system that automatically learns a series of dictionary elements for representing the underlying spatial distribution using stacked predictive sparse decomposition. The learned representation is then fed into the spatial pyramid matching framework with a linear

support vector machine classifier. The system has been evaluated for classification of distinct histological components for two cohorts of tumor types. Throughput has been increased by using of graphical processing unit (GPU), and evaluation indicates a superior performance results, compared with previous research.

Choo, E. K., Beauchamp, G., Beaudoin, F. L., Bernstein, E., Bernstein, J., Bernstein, S. L., et al. (2014). A research agenda for gender and substance use disorders in the emergency department. *Academic Emergency Medicine*, 21(12), 1438-1446.

For many years, gender differences have been recognized as important factors in the etiology, pathophysiology, comorbidities, and treatment needs and outcomes associated with the use of alcohol, drugs, and tobacco. However, little is known about how these gender-specific differences affect ED utilization; responses to ED-based interventions; needs for substance use treatment and barriers to accessing care among patients in the ED; or outcomes after an alcohol-, drug-, or tobacco-related visit. As part of the 2014 Academic Emergency Medicine consensus conference on "Gender-Specific Research in Emergency Care: Investigate, Understand and Translate How Gender Affects Patient Outcomes," a breakout group convened to generate a research agenda on priority questions related to substance use disorders.

Christen, W. G., Glynn, R. J., Gaziano, J. M., Darke, A. K., Crowley, J. J., Goodman, P. J., et al.

(2015). Age-related cataract in men in the selenium and vitamin e cancer prevention trial eye endpoints study: A randomized clinical trial. *JAMA Ophthalmology*, 133(1), 17-24.

**IMPORTANCE:** Observational studies suggest a role for dietary nutrients such as vitamin E and selenium in cataract prevention. However, the results of randomized clinical trials of vitamin E supplements and cataract have been disappointing and are not yet available for selenium.

**OBJECTIVE:** To test whether long-term supplementation with selenium and vitamin E affects the incidence of cataract in a large cohort of men. **DESIGN, SETTING, AND PARTICIPANTS:** The Selenium and Vitamin E Cancer Prevention Trial (SELECT) Eye Endpoints Study was an ancillary study of the Southwest Oncology Group-coordinated SELECT, a randomized placebo-controlled 4-arm trial of selenium and vitamin E conducted among 35 533 men, 50 years and older for African American participants and 55 years and older for all other men, at 427 participating sites in the

United States, Canada, and Puerto Rico. A total of 11 267 SELECT participants from 128 SELECT sites participated in the SELECT Eye Endpoints ancillary study. INTERVENTIONS: Individual supplements of selenium (200 µg per day from L-selenomethionine) and vitamin E (400 IU per day of all rac- $\alpha$ -tocopheryl acetate). MAIN OUTCOMES AND MEASURES: Incident cataract was defined as a lens opacity, age related in origin, and responsible for a reduction in best-corrected visual acuity to 20/30 or worse based on self-reports confirmed by medical record review. Cataract extraction was defined as the surgical removal of an incident cataract. RESULTS: During a mean (SD) of 5.6 (1.2) years of treatment and follow-up, 389 cases of cataract were documented. There were 185 cataracts in the selenium group and 204 in the no selenium group (hazard ratio, 0.91; 95%CI, 0.75-1.11; P = .37). For vitamin E, there were 197 cases in the treated group and 192 in the placebo group (hazard ratio, 1.02; 95%CI, 0.84-1.25; P = .81). Similar results were observed for cataract extract. CONCLUSIONS AND RELEVANCE: These data from a large cohort of apparently healthy men indicate that long-term daily supplementation with selenium and/or vitamin E is unlikely to have a large beneficial effect on age-related cataract. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT00784225.

Colin Partridge, J., Robertson, K. R., Rogers, E. E., Landman, G. O., Allen, A. J., & Caughey, A. B. (2015). Resuscitation of neonates at 23 weeks' gestational age: A cost-effectiveness analysis. *Journal of Maternal-Fetal and Neonatal Medicine*, 28(2), 121-130.

Objective: Resuscitation of infants at 23 weeks' gestation remains controversial; clinical practices vary. We sought to investigate the cost effectiveness of resuscitation of infants born 23 0/7-23 6/7 weeks' gestation. Design: Decision-analytic modeling comparing universal and selective resuscitation to non-resuscitation for 5176 live births at 23 weeks in a theoretic U.S. cohort. Estimates of death (77%) and disability (64-86%) were taken from the literature. Maternal and combined maternal-neonatal utilities were applied to discounted life expectancy to generate QALYs. Incremental cost-effectiveness ratios were calculated, discounting costs and QALYs. Main outcomes included number of survivors, their outcome status and incremental cost-effectiveness ratios for the three strategies. A cost-effectiveness threshold of \$100000/QALY was utilized. Results: Universal resuscitation would save 1059 infants: 138 severely disabled, 413 moderately impaired and 508 without significant sequelae. Selective resuscitation would save 717 infants: 93

severely disabled, 279 moderately impaired and 343 without significant sequelae. For mothers, non-resuscitation is less expensive (\$19.9 million) and more effective (127844 mQALYs) than universal resuscitation (\$1.2 billion; 126574 mQALYs) or selective resuscitation (\$845 million; 125966 mQALYs). For neonates, both universal and selective resuscitation were cost-effective, resulting in 22256 and 15134 nQALYS, respectively, versus 247 nQALYS for non-resuscitation. In sensitivity analyses, universal resuscitation was cost-effective from a maternal perspective only at utilities for neonatal death <0.42. When analyzed from a maternal-neonatal perspective, universal resuscitation was cost-effective when the probability of neonatal death was <0.95. Conclusions: Over wide ranges of probabilities for survival and disability, universal and selective resuscitation strategies were not cost-effective from a maternal perspective. Both strategies were cost-effective from a maternal-neonatal perspective. This study offers a metric for counseling and decision-making for extreme prematurity. Our results could support a more permissive response to parental requests for aggressive intervention at 23 weeks' gestation.

Connelly, K. J., Larson, E. A., Marks, D. L., & Klein, R. F. (2015). Neonatal estrogen exposure results in biphasic age-dependent effects on the skeletal development of male mice. *Endocrinology*, 156(1), 193-202.

Peak bone mass, one of the most important predictors for fracture risk later in life, is attained during puberty and adolescence and influenced by neonatal and pubertal sex-specific gonadal hormones and GH-IGF-I secretion patterns. This study examined the effects of brief neonatal estrogen (NE) exposure on growth and skeletal development in C57BL/6J mice. A single injection of 100- $\mu$ g estradiol or vehicle was administered on the first day of life. Growth parameters were monitored and skeletal phenotyping performed at 16 weeks in female mice and at 4 and 16 weeks in male mice. NE exposure negatively impacted adult femoral length in both sexes, but adult body weight, areal bone density, and bone strength in female mice were unaffected. In contrast, somatic growth was attenuated in estrogen-exposed male mice throughout the study period. At the prepubertal time point, the estrogen-exposed males exhibited higher bone mineral density, cortical volume, and cortical thickness compared with controls. However, by the time of peak bone mass acquisition, the early skeletal findings had reversed; estrogen-exposed mice had lower bone density with reduced cross-sectional area, cortical volume, and cortical thickness,

resulting in cortical bone that were less resistant to fracture. NE exposure also resulted in reduced testicular volume and lower circulating IGF-

I. Male mice exposed to estrogen on the first day of life experience age-dependent changes in skeletal development. Prepubertal animals experience greater endocortical bone acquisition as a result of estrogen exposure. However, by adulthood, continued developmental changes result in overall reduced skeletal integrity

Cotter, F., Bowler, S., Mulkern, V., & McCarty, D. (2012). *Practice improvement collaboratives: An overview* Taylor and Francis.

The Center for Substance Abuse Treatment created Practice Improvement Collaboratives (PICs) to promote implementation of evidence-based practices for the treatment of alcohol and drug dependence through partnerships of practitioners, investigators, policy makers and consumers. Early implementation experiences within 11 PICs are examined and factors that facilitated and inhibited program maturation are identified. Case studies, structured interviews and a review of presentations and reports were used to document developmental processes. Successful development consistently required environmental adaptation, construction of formal organizational structures and processes, recruitment and retention of membership, and implementation of activities that fostered the mission of the Collaboratives. The Collaboratives provide a useful model for promoting the application of research-based innovations to practice and policy in the treatment of alcohol and drug abuse and dependence.

Cronise, K., & Crabbe, J. C. (2005). *Murine models of substance and alcohol dependence: Unraveling genetic complexities* Humana Press Inc.

Most behavioral traits operate on a phenotypic and genetic continuum, i.e., the phenotypic output is quantitative based on the genetic input. No one gene is either necessary or sufficient to account for the observed phenotype; rather, a collection of genes is responsible. This phenotypic and genetic complexity is particularly evident in psychological disorders. For instance, first-degree relatives of schizophrenics have a 9% risk for a diagnosis, whereas the risk drops to 2% for a third-degree relative (1. These findings suggest that many genes contribute, and as the proportion of shared genes increases among relatives, so does the likelihood of shared diagnosis.

Regardless of commonalities among genotypes, phenotypic expression may vary significantly in the frequency and severity of symptoms. This further supports the contention that several genes contribute to the trait, each with small effects.

Crowell, T. A., Berry, S. A., Fleishman, J. A., LaRue, R. W., Korthuis, P. T., Nijhawan, A. E., et al.

(2014). Impact of hepatitis co-infection on healthcare utilization among persons living with HIV. *Journal of Acquired Immune Deficiency Syndromes (1999)*,

Hepatitis B (HBV) and hepatitis C (HCV) co-infection are increasingly important sources of morbidity among HIV-infected persons. We determined associations between hepatitis co-infection and healthcare utilization among HIV-infected adults at four U.S. sites during 2006-2011. Outpatient HIV visits did not differ by hepatitis serostatus and decreased over time. Mental health visits were more common among HIV/HCV co-infected persons than among HIV mono-infected (IRR 1.27 [1.08-1.50]). Hospitalization rates were higher among all hepatitis-infected groups than among HIV mono-infected (HIV/HBV IRR 1.23 [1.05-1.44], HIV/HCV 1.22 [1.10-1.36], HIV/HBV/HCV 1.31 [1.02-1.68]). These findings may inform the design of clinical services and allocation of resources.

Davare, M. A., & Tognon, C. E. (2015). Detecting and targeting oncogenic fusion proteins in the

genomic era. *Biology of the Cell / Under the Auspices of the European Cell Biology Organization*,

The advent of widespread cancer genome sequencing has accelerated our understanding of the molecular aberrations underlying malignant disease at an unprecedented rate. Coupling the large number of bioinformatic methods that have been developed to locate breakpoints in the genome with increased sequence read length and a deeper understanding of coding region function has enabled the rapid identification of novel chromosomal rearrangements that encode actionable oncogenic fusion proteins. Using examples of fusion proteins found in liquid and solid tumors, this review highlights major concepts that have arisen in our understanding of cancer pathogenesis through the study of oncogenic fusion proteins. We provide an overview of recently developed methods to identify potential fusion proteins from next-generation sequencing data, describe the validation of oncogenic potential of candidate fusion proteins, and discuss the role of targeted

therapies in treating cancers driven by fusion oncoproteins. This article is protected by copyright.  
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Deans, A. R., Lewis, S. E., Huala, E., Anzaldo, S. S., Ashburner, M., Balhoff, J. P., et al. (2015).

Finding our way through phenotypes. *PLoS Biology*, 13(1), e1002033.

Despite a large and multifaceted effort to understand the vast landscape of phenotypic data, their current form inhibits productive data analysis. The lack of a community-wide, consensus-based, human- and machine-interpretable language for describing phenotypes and their genomic and environmental contexts is perhaps the most pressing scientific bottleneck to integration across many key fields in biology, including genomics, systems biology, development, medicine, evolution, ecology, and systematics. Here we survey the current phenomics landscape, including data resources and handling, and the progress that has been made to accurately capture relevant data descriptions for phenotypes. We present an example of the kind of integration across domains that computable phenotypes would enable, and we call upon the broader biology community, publishers, and relevant funding agencies to support efforts to surmount today's data barriers and facilitate analytical reproducibility.

Deconde, A. S., Barton, M. D., Mace, J. C., & Smith, T. L. (2015). Can sinus anatomy predict quality of life outcomes and operative times of endoscopic frontal sinus surgery? *American Journal of Otolaryngology - Head and Neck Medicine and Surgery*, 36(1), 13-19.

Purpose Endoscopic sinus surgery (ESS) can manipulate sinus anatomy, but with limitations due to skull base and orbit anatomy. These anatomical structures dictate the maximal extent of ESS in the frontal recess and may limit surgical extent or operative duration. This study investigates the impact of these anatomical constraints on operative time and quality-of-life (QOL) outcomes. Materials and methods Patients with medically refractory chronic rhinosinusitis undergoing Draf IIa frontal sinus surgery were prospectively enrolled. Anatomic measurements of the frontal sinus anatomy were collected during computed tomography review and included: widest distance between the frontal beak and posterior table, narrowest point in the ethmoid bed, Keros height, presence of an anterior ethmoid artery on a mesentery, and presence of inter-sinus septal cells. Primary outcomes included mean operative time and improvement in SinoNasal Outcome Test

(SNOT-22) survey scores. Results 63 adult participants were enrolled and followed 13.8 (5.2) months on average. The ethmoid bed mean width was 7.2 (1.4) mm, the mean distance from frontal beak to the posterior table at widest was 9.0 (2.7) mm, and mean Keros height was 5.1 (1.8) mm. 49/63 (83.1%) of participants had inter-sinus septal cells and 30/63(50.8%) had anterior ethmoid arteries on a mesentery. Mean operative time was 121.5 (44.0) min while SNOT-22 scores significantly ( $p < 0.050$ ). Conclusions Frontal sinus surgery is an effective treatment for a range of frontal and ethmoid sinus anatomy. Further study with larger sample size and measures of more restricted anatomy might elucidate treatment limitations of ESS.

Deconde, A. S., Mace, J. C., Alt, J. A., Soler, Z. M., Orlandi, R. R., & Smith, T. L. Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. *International Forum of Allergy and Rhinology*, 5(1), 36-45.

Background: Chronic rhinosinusitis (CRS) has been defined as inflammation of the paranasal sinuses lasting at least 12 weeks with corresponding 2 or more "cardinal symptoms" that include: (1) nasal obstruction; (2) thick nasal discharge; (3) facial pain/pressure; and (4) reduction or loss of sense of smell. Although prior studies have investigated symptoms of CRS after sinus surgery, none have compared the outcomes of these specific symptoms to ongoing medical therapy. Methods: Patients with CRS were prospectively enrolled into a multi-institutional, comparative effectiveness, cohort study. Subjects elected either continued medical management or endoscopic sinus surgery (ESS). Baseline characteristics and objective clinical findings were collected. Cardinal symptoms of CRS were operationalized by 4 questions on the 22-item Sino-Nasal Outcome Test (SNOT-22). Symptom improvement was evaluated in subjects with at least 6-month follow-up. Results: A total of 342 subjects were enrolled, with 69 (20.2%) electing continued medical management, whereas 273 (79.8%) elected ESS. Subjects electing surgical therapy were more likely to have a higher baseline aggregate SNOT-22 score (44.3 (18.9) vs 53.6 (18.8);  $p < 0.001$ ). All subjects improved across all cardinal symptoms; however, subjects undergoing ESS were significantly more likely ( $p \leq 0.013$ ) to experience improvement in thick nasal discharge (odds ratio [OR] = 4.36), facial pain/pressure (OR = 3.56), and blockage/congestion of nose (OR = 2.76). Subjects with nasal polyposis were significantly more likely to report complete resolution of smell/taste following ESS compare to medical management

(23.8% vs 4.0%;  $p = 0.026$ ). Conclusion: Across a large population, surgical management is more effective at resolving the cardinal symptoms of CRS than ongoing medical management with the exception of sense of smell/taste.

DeLoughery, T. G. (2014). The author replies. *New England Journal of Medicine*, 371(26), 2537.

DeVoe, J. E., Marino, M., Angier, H., O'Malley, J. P., Crawford, C., Nelson, C., et al. (2015). Effect of expanding medicaid for parents on children's health insurance coverage: Lessons from the oregon experiment. *JAMA Pediatrics*, 169(1), e143145.

**IMPORTANCE:** In the United States, health insurance is not universal. Observational studies show an association between uninsured parents and children. This association persisted even after expansions in child-only public health insurance. Oregon's randomized Medicaid expansion for adults, known as the Oregon Experiment, created a rare opportunity to assess causality between parent and child coverage. **OBJECTIVE:** To estimate the effect on a child's health insurance coverage status when (1) a parent randomly gains access to health insurance and (2) a parent obtains coverage. **DESIGN, SETTING, AND PARTICIPANTS:** Oregon Experiment randomized natural experiment assessing the results of Oregon's 2008 Medicaid expansion. We used generalized estimating equation models to examine the longitudinal effect of a parent randomly selected to apply for Medicaid on their child's Medicaid or Children's Health Insurance Program (CHIP) coverage (intent-to-treat analyses). We used per-protocol analyses to understand the impact on children's coverage when a parent was randomly selected to apply for and obtained Medicaid. Participants included 14 409 children aged 2 to 18 years whose parents participated in the Oregon Experiment. **EXPOSURES:** For intent-to-treat analyses, the date a parent was selected to apply for Medicaid was considered the date the child was exposed to the intervention. In per-protocol analyses, exposure was defined as whether a selected parent obtained Medicaid. **MAIN OUTCOMES AND MEASURES:** Children's Medicaid or CHIP coverage, assessed monthly and in 6-month intervals relative to their parent's selection date. **RESULTS:** In the immediate period after selection, children whose parents were selected to apply significantly increased from 3830 (61.4%) to 4152 (66.6%) compared with a nonsignificant change from 5049 (61.8%) to 5044 (61.7%) for children whose parents were not selected to apply. Children whose parents were

randomly selected to apply for Medicaid had 18% higher odds of being covered in the first 6 months after parent's selection compared with children whose parents were not selected (adjusted odds ratio [AOR] = 1.18; 95% CI, 1.10-1.27). The effect remained significant during months 7 to 12 (AOR = 1.11; 95% CI, 1.03-1.19); months 13 to 18 showed a positive but not significant effect (AOR = 1.07; 95% CI, 0.99-1.14). Children whose parents were selected and obtained coverage had more than double the odds of having coverage compared with children whose parents were not selected and did not gain coverage (AOR = 2.37; 95% CI, 2.14-2.64).

CONCLUSIONS AND RELEVANCE: Children's odds of having Medicaid or CHIP coverage increased when their parents were randomly selected to apply for Medicaid. Children whose parents were selected and subsequently obtained coverage benefited most. This study demonstrates a causal link between parents' access to Medicaid coverage and their children's coverage.

Deyo, R. A. (2015). Fusion surgery for lumbar degenerative disc disease: Still more questions than answers. *The Spine Journal : Official Journal of the North American Spine Society*, 15(2), 272-274.

COMMENTARY ON: Yoshihara H, Yoneoka D. National trends in the surgical treatment for lumbar degenerative disc disease: United States, 2000 to 2009. *Spine J* 2015;15:265-71 (in this issue).

Deyo, R. A., Von Korff, M., & Duhkoop, D. (2015). Opioids for low back pain. *BMJ (Clinical Research Ed.)*, 350, g6380.

Back pain affects most adults, causes disability for some, and is a common reason for seeking healthcare. In the United States, opioid prescription for low back pain has increased, and opioids are now the most commonly prescribed drug class. More than half of regular opioid users report back pain. Rates of opioid prescribing in the US and Canada are two to three times higher than in most European countries. The analgesic efficacy of opioids for acute back pain is inferred from evidence in other acute pain conditions. Opioids do not seem to expedite return to work in injured workers or improve functional outcomes of acute back pain in primary care. For chronic back pain, systematic reviews find scant evidence of efficacy. Randomized controlled trials have high dropout rates, brief duration (four months or less), and highly selected patients. Opioids seem to have short term analgesic efficacy for chronic back pain, but benefits for function are less clear.

The magnitude of pain relief across chronic non-cancer pain conditions is about 30%. Given the brevity of randomized controlled trials, the long term effectiveness and safety of opioids are unknown. Loss of long term efficacy could result from drug tolerance and emergence of hyperalgesia. Complications of opioid use include addiction and overdose related mortality, which have risen in parallel with prescription rates. Common short term side effects are constipation, nausea, sedation, and increased risk of falls and fractures. Longer term side effects may include depression and sexual dysfunction. Screening for high risk patients, treatment agreements, and urine testing have not reduced overall rates of opioid prescribing, misuse, or overdose. Newer strategies for reducing risks include more selective prescription of opioids and lower doses; use of prescription monitoring programs; avoidance of co-prescription with sedative hypnotics; and reformulations that make drugs more difficult to snort, smoke, or inject.

Di Martino, A., Fair, D. A., Kelly, C., Satterthwaite, T. D., Castellanos, F. X., Thomason, M. E., et al. (2014). Unraveling the miswired connectome: A developmental perspective. *Neuron*, *83*(6), 1335-1353.

The vast majority of mental illnesses can be conceptualized as developmental disorders of neural interactions within the connectome, or developmental miswiring. The recent maturation of pediatric in vivo brain imaging is bringing the identification of clinically meaningful brain-based biomarkers of developmental disorders within reach. Even more auspicious is the ability to study the evolving connectome throughout life, beginning in utero, which promises to move the field from topological phenomenology to etiological nosology. Here, we scope advances in pediatric imaging of the brain connectome as the field faces the challenge of unraveling developmental miswiring. We highlight promises while also providing a pragmatic review of the many obstacles ahead that must be overcome to significantly impact public health.

Donley, N., Smith, L., & Thayer, M. J. (2015). ASAR15, A cis-acting locus that controls chromosome-wide replication timing and stability of human chromosome 15. *PLoS Genetics*, *11*(1), e1004923. DNA replication initiates at multiple sites along each mammalian chromosome at different times during each S phase, following a temporal replication program. We have used a Cre/loxP-based strategy to identify cis-acting elements that control this replication-timing program on individual

human chromosomes. In this report, we show that rearrangements at a complex locus at chromosome 15q24.3 result in delayed replication and structural instability of human chromosome 15. Characterization of this locus identified long, RNA transcripts that are retained in the nucleus and form a "cloud" on one homolog of chromosome 15. We also found that this locus displays asynchronous replication that is coordinated with other random monoallelic genes on chromosome 15. We have named this locus ASynchronous replication and Autosomal RNA on chromosome 15, or ASAR15. Previously, we found that disruption of the ASAR6 lincRNA gene results in delayed replication, delayed mitotic condensation and structural instability of human chromosome 6. Previous studies in the mouse found that deletion of the Xist gene, from the X chromosome in adult somatic cells, results in a delayed replication and instability phenotype that is indistinguishable from the phenotype caused by disruption of either ASAR6 or ASAR15. In addition, delayed replication and chromosome instability were detected following structural rearrangement of many different human or mouse chromosomes. These observations suggest that all mammalian chromosomes contain similar cis-acting loci. Thus, under this scenario, all mammalian chromosomes contain four distinct types of essential cis-acting elements: origins, telomeres, centromeres and "inactivation/stability centers", all functioning to promote proper replication, segregation and structural stability of each chromosome.

Dotson, A. L., Wang, J., Saugstad, J., Murphy, S. J., & Offner, H. (2015). Splenectomy reduces infarct volume and neuroinflammation in male but not female mice in experimental stroke. *Journal of Neuroimmunology*, 278, 289-298.

The peripheral immune response contributes to neurodegeneration after stroke yet little is known about how this process differs between males and females. The current study demonstrates that splenectomy prior to experimental stroke eliminates sex differences in infarct volume and activated brain monocytes/microglia. In the periphery of both sexes, activated T cells correlate directly with stroke outcome while monocytes are reduced by splenectomy only in males. This study provides new information about the sex specific mechanisms of the peripheral immune response in neurodegeneration after stroke and demonstrates the need for representation of both sexes in basic and clinical stroke research.

DuBois, B. N., Atrio, J., Stanczyk, F. Z., & Cherala, G. (2015). Increased exposure of norethindrone in HIV + women treated with ritonavir-boosted atazanavir therapy. *Contraception*, *91*(1), 71-75.

Objective: Pharmacokinetics of norethindrone in combination oral contraceptive regimen are well described among HIV + women treated with ritonavir-boosted protease inhibitor therapies; however, such characterization is lacking in women using progestin-only contraception. Our objective is to characterize pharmacokinetics of norethindrone in HIV + women using ritonavir-boosted atazanavir treatment during progestin-only contraceptive regimens. Study design: An open-label, prospective, nonrandomized trial to characterize the pharmacokinetics of norethindrone in HIV + women receiving ritonavir-boosted atazanavir (n= 10; treatment group) and other antiretroviral therapy known to not alter norethindrone levels (n= 17; control group) was conducted. Following informed consent, women were instructed to take a single daily fixed oral dose of 0.35 mg norethindrone and 300 mg/100 mg atazanavir/ritonavir for 22 days. On day 22, serial blood samples were collected by venous catheter at 0, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h. Whole blood was processed to collect serum and stored at - 20°C until later analysis using radioimmunoassay. Pharmacokinetic parameters were estimated using noncompartmental method. Results: In the treatment group, compared to the control group, an increase in area under the curve<sub>0-24</sub> (16.69 h\*ng/mL vs. 25.20 h\*ng/mL; p<.05) and maximum serum concentration (2.09 ng/mL vs. 3.19 ng/mL; p<.05), decrease (25%-40%) in apparent volume of distribution and apparent clearance, and unaltered half-life were observed. Conclusion(s): Our findings suggest that progestin-only contraceptives, unlike combination oral contraceptives, benefit from drug-drug interaction and achieve higher levels of exposure. Further studies are needed to establish whether pharmacokinetic interaction leads to favorable clinical outcomes. Implications: Norethindrone-based progestin-only contraceptives, unlike combination oral contraceptives, exhibit greater drug exposure when co-administered with ritonavir-boosted atazanavir regimen and thus may not warrant a category 3 designation by the World Health Organization. Prospective studies are needed to confirm whether pharmacokinetic interaction results in favorable clinical outcomes.

Edelman, A., Alemayehu, T., Gebrehiwot, Y., Kidenemariam, S., & Getachew, Y. (2015). Addressing unmet need by expanding access to safe second trimester medical abortion services in ethiopia,

2010-2014. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 128(2), 177-178.

Edmundson, E., Jr., & McCarty, D. (2012). *Implementing evidence-based practices for treatment of alcohol and drug disorders* Taylor and Francis.

"Implementing Evidence-Based Practices for Treatment of Alcohol and Drug Disorders" provides managers and clinicians with results from Practice Improvement Collaboratives (PIC) that demonstrate how substance abuse treatment can be improved by increasing the exchange of knowledge between community-based service providers and the research community. The book examines improvement collaboratives and mentoring strategies for adopting and using evidence-based practices. Contributors address how to determine the best treatment processes to serve clients, how to deal with the hurdles faced in preparing and training counsellors, and how to affect the needed changes in agency activities. This unique professional resource responds to an Institute of Medicine report that found a substantial disconnect between research and practice in treatment for drug and alcohol dependence. Focusing on how to make the changes necessary to support the adoption and use of evidence-based practices, the book documents the activities of four sites to illustrate how investigators and treatment practitioners worked together to implement evidence-based practices. Contributors examine the development and early implementation of Practice Improvement Collaboratives, the investigator-provider-policymaker model, Motivational Enhancement Therapy, the use of Opinion Leaders in training, and targeted strategies that take into account the differences in clinician demographics and training.

"Implementing Evidence-Based Practices for Treatment of Alcohol and Drug Disorders" is an essential tool for alcohol and drug counsellors, directors of alcohol and drug treatment clinics, and instructors in counsellor training and academic programs.

Edmundson, E., Jr., & McCarty, D. (2012). Preface. *Implementing Evidence-Based Practices for Treatment of Alcohol and Drug Disorders*, 24, xv-xviii.

Eriksson, J., Evans, D. S., Nielson, C. M., Shen, J., Srikanth, P., Hochberg, M., et al. (2015). Limited clinical utility of a genetic risk score for the prediction of fracture risk in elderly subjects. *Journal of Bone and Mineral Research*, 30(1), 184-194.

It is important to identify the patients at highest risk of fractures. A recent large-scale meta-Analysis identified 63 autosomal singlenucleotide polymorphisms (SNPs) associated with bone mineral density (BMD), of which 16 were also associated with fracture risk. Based on these findings, two genetic risk scores (GRS63 and GRS16) were developed. Our aim was to determine the clinical usefulness of these GRSs for the prediction of BMD, BMD change, and fracture risk in elderly subjects. We studied two male (Osteoporotic Fractures in Men Study [MrOS] US, MrOS Sweden) and one female (Study of Osteoporotic Fractures [SOF]) large prospective cohorts of older subjects, looking at BMD, BMD change, and radiographically and/or medically confirmed incident fractures (8067 subjects, 2185 incident nonvertebral or vertebral fractures). GRS63 was associated with BMD ( $\cong 3\%$  of the variation explained) but not with BMD change. Both GRS63 and GRS16 were associated with fractures. After BMD adjustment, the effect sizes for these associations were substantially reduced. Similar results were found using an unweighted GRS63 and an unweighted GRS16 compared with those found using the corresponding weighted risk scores. Only minor improvements in C-statistics (AUC) for fractures were found when the GRSs were added to a base model (age, weight, and height), and no significant improvements in C-statistics were found when they were added to a model further adjusted for BMD. Net reclassification improvements with the addition of the GRSs to a base model were modest and substantially attenuated in BMD-Adjusted models. GRS63 is associated with BMD, but not BMD change, suggesting that the genetic determinants of BMD differ from those of BMD change. When BMD is known, the clinical utility of the two GRSs for fracture prediction is limited in elderly subjects.

Farquhar, S. A., Ryder, M., Henderlong, D., Lowe, R. A., & Amann, T. (2014). Listening to consumer perspectives to inform addictions and housing-related practice and research. *Global Journal of Community Psychology Practice*, 5(1), 1-14.

The study, funded by the Northwest Health Foundation of Portland, Oregon and the National Institute on Drug Abuse (NIDA), was conducted as part of the HEARTH collaborative (Housing, Employment and Recovery Together for Health). HEARTH, established in 2010, is a community-academic partnership involving partners from Portland State University (PSU), Oregon Health and Science University (OHSU), and Central City Concern (CCC). Using the approaches of community-

based participatory research (CBPR), these diverse stakeholders collaborated to co-develop research of direct relevance to the local community and to national academic and policy communities. This study employed qualitative methods and community-based participatory research principles to solicit personal experiences with housing, employment, and recovery programs. We recruited interview participants via CCC-operated housing programs, including Alcohol and Drug Free Community Housing (ADFC), family housing, transitional housing, and non-ADFC (low barrier) housing units. The manuscript presents interview themes based on the five broad categories of interview questions: housing, employment programs, recovery programs, definitions of recovery, and definitions of success. Co-authors describe recommendations for practice and research protocol based on our findings. Our results highlight the importance of involving consumers in the development, data collection, and analysis of research, and present the unique perspectives of those who experience homelessness, recovery, and the programs designed to assist them.

Farrens, D. L. (2005). *Structural dynamics of the signal termination process in rhodopsin* Springer Japan.

This review will provide an overview of what is known, and what is not known, about the visual signal termination process in mammalian vision. The focus will be on the role of structure and dynamic changes in the primary mammalian photo-transducer rhodopsin, and the protein that attenuates rhodopsin signaling, arrestin. Although this review focuses on mammalian photoreceptor proteins, analogous mechanisms may be used in the phototransduction pathways of other organisms.

Feeny, D., Garner, R., Bernier, J., Thompson, A., McFarland, B. H., Huguet, N., et al. (2014). Physical activity matters: Associations among body mass index, physical activity, and health-related quality of life trajectories over 10 years. *Journal of Physical Activity and Health*, 11(7), 1265-1275.

Background: The objective of this study was to assess the associations among body mass index (BMI), leisure time physical activity (LTPA) and health-related quality of life (HRQL) trajectories among adults. Methods: Self-reported data were drawn from the Canadian National Population

Health Survey, with respondents being interviewed every 2 years between 1996-97 and 2006-07. Using growth curve modeling, HRQL trajectories for individuals aged 18 and over were associated with measures of BMI and LTPA. Growth models were constructed separately for males and females. Results: Findings suggested that, for males, BMI categories had little impact on baseline HRQL, and no impact on the rate of change in HRQL. Among women, higher BMI categories were associated with significantly lower baseline HRQL. However, BMI had no impact on the rate of change of HRQL. Conversely, for both men and women and regardless of BMI category, LTPA had significant impacts on baseline HRQL, as well as the rate of change in HRQL. Individuals who were inactive or sedentary had much steeper declines in HRQL as they aged, as compared with individuals who were active in their leisure time. Conclusions: The results underscore the importance of LTPA in shaping trajectories of HRQL.

Ferrecchia, C. E., Ducore, R. M., Colgin, L. M. A., & Lewis, A. D. (2015). Spontaneous nocardial brain abscess in a juvenile rhesus macaque (*macaca mulatta*). *Journal of Medical Primatology*, *44*(1), 45-48.

Background: A juvenile rhesus macaque presented with blindness, ataxia, and head tilt. Methods: Postmortem gross and microscopic examination, histochemical staining and bacterial culture were performed. Results: *Nocardia* sp. was identified as the etiologic agent of a primary pneumonia with secondary cerebral abscessation. Conclusions: Nocardiosis should be a differential diagnosis for patients with neurologic disease.

Finlayson, M., Cattaneo, D., Cameron, M., Coote, S., Matsuda, P. N., Peterson, E., et al. (2014).

Applying the RE-AIM framework to inform the development of a multiple sclerosis falls-prevention intervention. *International Journal of MS Care*, *16*(4), 192-197.

Successfully addressing the problem of falls among people with multiple sclerosis (MS) will require the translation of research findings into practice change. This process is not easy but can be facilitated by using frameworks such as RE-AIM during the process of planning, implementing, and evaluating MS falls-prevention interventions. RE-AIM stands for Reach, Effectiveness, Adoption, Implementation, and Maintenance. Since its initial publication in 1999, the RE-AIM framework has become widely recognized across a range of disciplines as a valuable tool to guide

thinking about the development and evaluation of interventions intended for widespread dissemination. For this reason, it was selected by the International MS Falls Prevention Research Network to structure initial discussions with clinicians, people with MS, and representatives of professional and MS societies about the factors we need to consider in the development of an MS falls-prevention intervention for multisite testing that we hope will someday be disseminated widely. Through a combination of small-group work and large-group discussion, participants discussed four of the five RE-AIM elements. A total of 17 recommendations were made to maximize the reach (n = 3), adoption (n = 5), implementation (n = 4), and maintenance (n = 5) of the intervention the Network is developing. These recommendations are likely to be useful for any MS rehabilitation researcher who is developing and testing interventions that he or she hopes will be widely disseminated.

Fischer, C. R., Braaksma, B., Peters, A., Weinreb, J. H., Nalbandian, M., Spivak, J. M., et al. (2014).

Outcomes and complications of the midline anterior approach 3 years after lumbar spine surgery. *Advances in Orthopedics*, 2014, 142604.

Objective. The purpose of this study was to evaluate a new questionnaire to assess outcomes related to the midline anterior lumbar approach and to identify risk factors for negative patient responses. Methods. A retrospective review of 58 patients who underwent anterior lumbar surgery at a single institution for either degenerative disc disease or spondylolisthesis in 2009 was performed. The outcome measures included our newly developed Anterior Lumbar Surgery Questionnaire (ALSQ), ODI, and EQ-5D. Results. There were 58 patients available for followup, 27 women and 31 men. The average age at surgery was 50.8 years, with an average followup of 2.92 years. The average change in ODI was 34.94 (22.7) and EQ-5D was 0.28 (0.29). The rate of complications with the anterior approach was 10.3% and there was one male patient (3.2%) with retrograde ejaculation. Determination of the effectiveness of the new ALSQ revealed that it significantly correlated to the EQ-5D and ODI ( $P < 0.05$ ). Smoking was associated with a negative response on thirteen questions. BMP use was not associated with a negative response on any sexual function questions. Conclusions. Our new Anterior Lumbar Surgery Questionnaire determines patient perceived complications related to the midline anterior lumbar surgical approach.

Fleseriu, M., & Petersenn, S. (2015). Medical therapy for Cushing's disease: Adrenal steroidogenesis inhibitors and glucocorticoid receptor blockers. *Pituitary*,

Morbidity and mortality in Cushing's disease (CD) patients are increased if patients are not appropriately treated. Surgery remains the first line therapy, however the role of medical therapy has become more prominent in patients when biochemical remission is not achieved/or recurs after surgery, while waiting effects of radiation therapy or when surgery is contraindicated. Furthermore, use of preoperative medical therapy has been also recognized. In addition to centrally acting therapies (reviewed elsewhere in this special issue), adrenal steroidogenesis inhibitors, and glucocorticoid receptor antagonists are frequently used. A PubMed search of all original articles or abstracts detailing medical therapy in CD, published within 12 months (2013-2014), were identified and pertinent data extracted. Although not prospectively studied, ketoconazole and metyrapone have been the most frequently used medical therapies. A large retrospective ketoconazole study showed that almost half of patients who continued on ketoconazole therapy achieved biochemical control and clinical improvement; however almost 20% discontinued ketoconazole due to poor tolerability. Notably, hepatotoxicity was usually mild and resolved after drug withdrawal. Etomidate remains the only drug available for intravenous use. A new potent inhibitor of both aldosterone synthase and 11beta-hydroxylase, following the completion of a phase II study LCI699 is being studied in a large phase III with promising results. Mifepristone, a glucocorticoid receptor antagonist, has been approved for hyperglycemia associated with Cushing's syndrome based on the results of a prospective study where it produced in the majority of patients' significant clinical and metabolic improvement. Absence of both a biochemical marker for remission and/or diagnosis of adrenal insufficiency remain, however, a limiting factor. Patient characteristics and preference should guide the choice between different medications in the absence of clinical trials comparing any of these therapies. Despite significant progress, there is still a need for a medical therapy that is more effective and with less adverse effects for patients with CD.

Fong, L., Carroll, P., Weinberg, V., Chan, S., Lewis, J., Corman, J., et al. (2014). Activated lymphocyte recruitment into the tumor microenvironment following preoperative sipuleucel-T for localized prostate cancer. *Journal of the National Cancer Institute*, 106(11), 10.1093/jnci/dju268. Print

2014 Nov.

**BACKGROUND:** Sipuleucel-T is a US Food and Drug Administration-approved immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Its mechanism of action is not fully understood. This prospective trial evaluated the direct immune effects of systemically administered sipuleucel-T on prostatic cancer tissue in the preoperative setting. **METHODS:** Patients with untreated localized prostate cancer were treated on an open-label Phase II study of sipuleucel-T prior to planned radical prostatectomy (RP). Immune infiltrates in RP specimens (posttreatment) and in paired pretreatment biopsies were evaluated by immunohistochemistry (IHC). Correlations between circulating immune response and IHC were assessed using Spearman rank order. **RESULTS:** Of the 42 enrolled patients, 37 were evaluable. Adverse events were primarily transient, mild-to-moderate and infusion related. Patients developed T cell proliferation and interferon-gamma responses detectable in the blood following treatment. Furthermore, a greater-than-three-fold increase in infiltrating CD3(+), CD4(+) FOXP3(-), and CD8(+) T cells was observed in the RP tissues compared with the pretreatment biopsy (binomial proportions: all  $P < .001$ ). This level of T cell infiltration was observed at the tumor interface, and was not seen in a control group consisting of 12 concurrent patients who did not receive any neoadjuvant treatment prior to RP. The majority of infiltrating T cells were PD-1(+) and Ki-67(+), consistent with activated T cells. Importantly, the magnitude of the circulating immune response did not directly correlate with T cell infiltration within the prostate based upon Spearman's rank order correlation. **CONCLUSIONS:** This study is the first to demonstrate a local immune effect from the administration of sipuleucel-T. Neoadjuvant sipuleucel-T elicits both a systemic antigen-specific T cell response and the recruitment of activated effector T cells into the prostate tumor microenvironment.

Freeman, K. A., & Eagle, R. F. (2011). *Single-subject research designs* Taylor and Francis.

Fu, Y., Rope, R., Fargue, S., Cohen, H. T., Holmes, R. P., & Cohen, D. M. (2015). A mutation creating an out-of-frame alternative translation initiation site in the GRHPR 5'UTR causing primary hyperoxaluria type II. *Clinical Genetics*,

Primary hyperoxaluria type II is a recessive genetic disorder caused by mutations in the GRHPR

gene. Although several dozen mutations have been described, all affect coding or transcript splicing. A man suspected of having primary hyperoxaluria type II was heterozygous for a novel single-nucleotide deletion (c.694delC) in GRHPR affecting Gln232, which introduced a pre-mature termination (p.Gln232Argfs\*3). Two 5'untranslated region (UTR) variants of unknown significance were also noted. We show that these two variants occur in cis, on the opposite allele, and introduce - immediately upstream of the canonical translation initiation site - a novel out-of-frame translational start site. In vitro studies using the GRHPR 5'UTR fused to a luciferase reporter show that the variant start site pre-empted initiation at the canonical translational start site, and this was corroborated within the broader context of 1.3kb of the GRHPR proximal promoter. This latter mechanism may be underappreciated in general; reports of clinically significant functional variation of this type are extremely rare.

Fukazawa, Y., Lum, R., Okoye, A. A., Park, H., Matsuda, K., Bae, J. Y., et al. (2015). B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers. *Nature Medicine*,  
Chronic-phase HIV and simian immunodeficiency virus (SIV) replication is reduced by as much as 10,000-fold in elite controllers (ECs) compared with typical progressors (TPs), but sufficient viral replication persists in EC tissues to allow viral sequence evolution and induce excess immune activation. Here we show that productive SIV infection in rhesus monkey ECs, but not TPs, is markedly restricted to CD4+ follicular helper T (TFH) cells, suggesting that these EC monkeys' highly effective SIV-specific CD8+ T cells can effectively clear productive SIV infection from extrafollicular sites, but their relative exclusion from B cell follicles prevents their elimination of productively infected TFH cells. CD8+ lymphocyte depletion in EC monkeys resulted in a dramatic re-distribution of productive SIV infection to non-TFH cells, with restriction of productive infection to TFH cells resuming upon CD8+ T cell recovery. Thus, B cell follicles constitute 'sanctuaries' for persistent SIV replication in the presence of potent anti-viral CD8+ T cell responses, potentially complicating efforts to cure HIV infection with therapeutic vaccination or T cell immunotherapy.

Gatter, K. (2015). Pathology and malpractice. *American Journal of Clinical Pathology*, 143(2), 311-312.

Gebara, M. A., Lipsey, K. L., Karp, J. F., Nash, M. C., Iaboni, A., & Lenze, E. J. (2014). Cause or effect? selective serotonin reuptake inhibitors and falls in older adults: A systematic review. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*,

A 2012 update of the Beers criteria categorizes selective serotonin reuptake inhibitors (SSRIs) as potentially inappropriate medications in all older adults based on fall risk. The application of these recommendations, not only to frail nursing home residents, but to all older adults, may lead to changes in health policy or clinical practice with harmful consequences. A systematic review of studies on the association between SSRIs and falls in older adults was conducted to examine the evidence for causation. Twenty-six studies met the inclusion criteria. The majority of studies were observational and suggest an association between SSRIs and falls. The direction of the relationship-causation or effect-cannot be discerned from this type of study. Standardized techniques for determining likely causation were then used to see if there was support for the hypothesis that SSRIs lead to falls. This analysis did not suggest causation was likely. There is no Level 1 evidence that SSRIs cause falls. Therefore, changes in the current treatment guidelines or policies on the use of SSRIs in older adults based on fall risk may not be justified at this time given the lack of an established evidence base. Given its significance to public health, well-designed experimental studies are required to address this question definitively.

Geltzeiler, C. B., Young, J. I., Diggs, B. S., Keyashian, K., Deveney, K., Lu, K. C., et al. (2015).

Strictureplasty for treatment of crohn's disease: An ACS-NSQIP database analysis. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract*,

INTRODUCTION: Strictureplasty is an alternative to resection for treatment of Crohn's disease (CD) strictures. It preserves bowel length, and specialized centers report favorable outcomes. Strictureplasty rates, however, are thought to be low, and it was recently removed from required cases for colon and rectal surgery residents. We examined operative characteristics, and trends in its use using a large national database. MATERIALS AND METHODS: We examined the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database from 2005 to 2012, identifying patients with CD who underwent strictureplasty. We identified patient characteristics, outcome variables, and trends in utilization of strictureplasty.

RESULTS: A total of 9172 patients underwent surgery for CD. Two hundred fifty-six (2.8 %) underwent strictureplasty. Median preoperative albumin was 3.6. Preoperative steroid use and weight loss rates were 39 and 8 %. Rates of wound infection and organ space infection were 11 and 4 %. Rate of reoperation was 6 %. Outcomes did not change significantly over time (all p = NS). The proportion of CD operations that included a strictureplasty decreased from 5.1 to 1.7 % (OR 0.902 with each additional year, 95 % CI (0.852, 0.960), p < 0.001). CONCLUSION: Strictureplasty as treatment for CD is decreasing in the ACS-NSQIP database. Infectious complications and reoperation rates following strictureplasty are low and have not changed over time.

Genta, R. M., & Sonnenberg, A. (2015). Characteristics of the gastric mucosa in patients with intestinal metaplasia. *The American Journal of Surgical Pathology*,  
Gastric intestinal metaplasia (IM) occurs in response to different injuries, some of which involve increased risk for gastric cancer, whereas others may not. The background in which IM arises has not been systematically investigated. This study was designed to determine the relative prevalence of the histopathologic conditions of the gastric mucosa associated with IM in a large cohort. We extracted from a database patients who had undergone esophagogastroduodenoscopy with gastric biopsies between January 2008 and December 2013 in endoscopy centers throughout the United States. For each subject we recorded demographic, clinical, and histopathologic information. We stratified patients according to the presence of IM and compared the prevalence of *Helicobacter pylori* infection, reactive gastropathy, minimal inflammatory and gastropathy changes, mucosal atrophy, gastric polyps, cancer, and lymphoma in the 2 groups. IM, present in 8.4% of the 810,821 unique patients, increased with age and was more common in male than in female individuals. Compared with other Americans, East Asian ancestry was associated with a 5-fold risk for IM. *Helicobacter* gastritis and its sequelae were present in 42.2% of patients with IM, and reactive gastropathy in 17.3%. In >50% of patients under the age of 30 and in 26% of older adults, foci of IM occurred in an almost normal gastric mucosa. Thus, approximately half of the patients with IM had no histopathologic evidence of current or previous *Helicobacter* gastritis, whereas almost one fifth had a background of reactive gastropathy. Longitudinal studies are

needed to determine the relative risk for gastric cancer in patients with IM associated and not with Helicobacter infection.

George, R., Kovak, K., & Cox, S. L. (2015). Aligning policy to promote cascade genetic screening for prevention and early diagnosis of heritable diseases. *Journal of Genetic Counseling*, Cascade genetic screening is a methodology for identifying and testing close blood relatives of individuals at increased risk for heritable conditions and follows a sequential process, minimizing testing costs and the number of family members who need to be tested. It offers considerable potential for cost savings and increased awareness of heritable conditions within families. CDC-classified Tier 1 genomic applications for hereditary breast and ovarian cancer syndrome (HBOC), Lynch Syndrome (LS), and familial hypercholesterolemia (FH) are recommended for clinical use and support the use of cascade genetic screening. Most individuals are unaware of their increased risk for heritable conditions such as HBOC, LS, and FH. Consistent implementation of cascade genetic screening could significantly increase awareness and prevention of heritable conditions. Limitations to effective implementation of cascade genetic screening include: insufficient genetic risk assessment and knowledge by a majority of healthcare providers without genetics credentials; a shortage of genetic specialists, especially in rural areas; a low rate of reimbursement for comprehensive genetic counseling services; and an individual focus on prevention by clinical guidelines and insurance coverage. The family-centric approach of cascade genetic screening improves prevention and early diagnosis of heritable diseases on a population health level. Cascade genetic screening could be better supported and augmented through changes in health policy.

Ghindilis, A. L., Smith, M. W., Simon, H. M., Seoudi, I. A., Yazvenko, N. S., Murray, I. A., et al. (2015). Restriction cascade exponential amplification (RCEA) assay with an attomolar detection limit: A novel, highly specific, isothermal alternative to qPCR. *Scientific Reports*, 5, 7737. An alternative to qPCR was developed for nucleic acid assays, involving signal rather than target amplification. The new technology, Restriction Cascade Exponential Amplification (RCEA), relies on specific cleavage of probe-target hybrids by restriction endonucleases (REase). Two mutant REases for amplification (Ramp), S17C BamHI and K249C EcoRI, were conjugated to

oligonucleotides, and immobilized on a solid surface. The signal generation was based on: (i) hybridization of a target DNA to a Ramp-oligonucleotide probe conjugate, followed by (ii) specific cleavage of the probe-target hybrid using a non-immobilized recognition REase. The amount of Ramp released into solution upon cleavage was proportionate to the DNA target amount. Signal amplification was achieved through catalysis, by the free Ramp, of a restriction cascade containing additional oligonucleotide-conjugated Ramp and horseradish peroxidase (HRP). Colorimetric quantification of free HRP indicated that the RCEA achieved a detection limit of 10 aM ( $10^{-17}$  M) target concentration, or approximately 200 molecules, comparable to the sensitivity of qPCR-based assays. The RCEA assay had high specificity, it was insensitive to non-specific binding, and detected target sequences in the presence of foreign DNA. RCEA is an inexpensive isothermal assay that allows coupling of the restriction cascade signal amplification with any DNA target of interest.

Goy, E. R., Bohlig, A., Carter, J., & Ganzini, L. (2015). Identifying predictors of hospice eligibility in patients with parkinson disease. *American Journal of Hospice and Palliative Medicine*, 32(1), 29-33.

This study aims to improve recognition of hospice eligibility for patients with Parkinson disease (PD) by ascertaining which variables have a higher probability of occurring uniquely in 6 to 12 months before death when compared to 18 to 24 months before death. Participants were 339 patients who died who were diagnosed with PD or Parkinsonism and treated with dopaminergic prescriptions for at least 3 years in northwestern US Veterans Affairs medical centers. A range of indicators were compared across 3 time periods (30-36 months, 24-18 months, and 12-6 months before death) using within-subjects repeated measures design. Results indicate that body mass index less than 18, alone or combined with a shift in prescribing (when benefits of dopaminergic medications no longer outweigh their risk of side effects), may signal appropriate timing for hospice referral.

Gubner, N. R., Cunningham, C. L., & Phillips, T. J. (2015). Nicotine enhances the locomotor stimulating but not the conditioned rewarding effect of ethanol in DBA/2J mice. *Alcoholism, Clinical and Experimental Research*, 39(1), 64-72.

BACKGROUND: One hypothesis to explain the high rate of nicotine and alcohol (ethanol [EtOH]) co-abuse is that these drugs have enhanced rewarding effects when taken together. The goal of this work was to use the conditioned place preference (CPP) procedure to determine whether nicotine would enhance the development of EtOH-induced CPP. METHODS: The conditioned rewarding effects of nicotine (1 or 2 mg/kg of nicotine tartrate), EtOH (1 g/kg), and nicotine plus EtOH in combination were assessed using a well-established CPP procedure chosen specifically for examining alterations in the development of EtOH-induced CPP by nicotine. In addition, the reference dose procedure was used to directly compare the conditioned rewarding effect of EtOH versus nicotine plus EtOH. DBA/2J mice were used because they are an inbred strain that has repeatedly been shown to develop CPP to EtOH. RESULTS: Neither dose of nicotine alone produced CPP, whereas EtOH did, using the standard EtOH CPP procedure. The magnitude of EtOH-induced CPP was not affected by co-administration of 1 mg/kg nicotine, but 2 mg/kg nicotine interfered with the development of EtOH-induced CPP. Using the reference dose procedure, there was no significant preference or aversion for either nicotine + EtOH dose combination versus EtOH alone. However, combined nicotine and EtOH had a larger effect on locomotor activity, during the conditioning trials, compared to their additive effect when given alone, consistent with previous data. CONCLUSIONS: These data do not support the hypothesis that nicotine enhances the conditioned rewarding effect of EtOH. This finding differs from the combined locomotor stimulant effects of nicotine and EtOH that were observed in this study and in our previously published work, and suggests that combined stimulant effects of nicotine and EtOH do not predict enhanced reward.

Gubner, N. R., McKinnon, C. S., & Phillips, T. J. (2014). Effects of varenicline on ethanol-induced conditioned place preference, locomotor stimulation, and sensitization. *Alcoholism, Clinical and Experimental Research*, 38(12), 3033-3042.

BACKGROUND: Varenicline, a partial nicotinic acetylcholine receptor (nAChR) agonist, is a promising new drug for the treatment of alcohol (ethanol [EtOH]) dependence. Varenicline has been approved by the Food and Drug Administration as a smoking cessation therapeutic and has also been found to reduce EtOH consumption in humans and animal models of alcohol use. These studies examined the hypotheses that varenicline attenuates the stimulant and sensitizing effects

of EtOH and reduces the motivational effects of EtOH-associated cues. The goal was to determine whether these effects of varenicline contribute to its pharmacotherapeutic effects for alcohol dependence. In addition, effects of varenicline on acute stimulation and/or on the acquisition of sensitization would suggest a role for nAChR involvement in these effects of EtOH. METHODS: Dose-dependent effects of varenicline on the expression of EtOH-induced conditioned place preference (CPP), locomotor activation, and behavioral sensitization were examined. These measures model motivational effects of EtOH-associated cues, euphoric or stimulatory effects of EtOH, and EtOH-induced neuroadaptation. All studies used DBA/2J mice, an inbred strain with high sensitivity to these EtOH-related effects. RESULTS: Varenicline did not significantly attenuate the expression of EtOH-induced CPP. Varenicline reduced locomotor activity and had the most pronounced effect in the presence of EtOH, with the largest effect on acute EtOH-induced locomotor stimulation and a trend for varenicline to attenuate the expression of EtOH-induced sensitization. CONCLUSIONS: Because varenicline did not attenuate the expression of EtOH-induced CPP, it may not be effective at reducing the motivational effects of EtOH-associated cues. This outcome suggests that reductions in the motivational effects of EtOH-associated cues may not be involved in how varenicline reduces EtOH consumption. However, varenicline did have effects on locomotor behavior and significantly attenuated acute EtOH-induced locomotor stimulation. In humans who drink while taking varenicline, it might similarly reduce stimulant responses and have an impact on continued drinking. General sedative effects in such individuals should be carefully considered.

Gupta, K., Sabry, H. A., Dogan, A., Coppa, N. D., McMenomey, S., Delashaw, J. B., et al. (2015).

Classification of middle fossa floor dehiscence syndromes. *Journal of Neurosurgery*, , 1-7.

OBJECT Middle fossa floor dehiscence (MFFD) can present as multiple syndromes depending on dehiscence location, tissue herniation, and dural integrity. The authors propose a classification system for MFFD with the potential to guide clinical decision making. METHODS A retrospective analysis of the electronic medical records (years 1995-2012) of patients who had undergone temporal craniotomy for the surgical repair of an MFFD syndrome at a single institution was undertaken. Reviewed data included demographic, operative, presentation, and outcome details. Middle fossa floor dehiscence was classified as follows: Class A, bony dehiscence without

herniation of the brain and/or meninges; Class B, herniation of the brain and/or meninges through the middle fossa floor without CSF leakage; Class C, dehiscence with CSF leakage without meningitis; or Class D, dehiscence with meningitis. RESULTS Fifty-one patients, 22 males and 29 females, were included in the analysis. The mean age was 48.7 +/- 15.5 years, mean body mass index was 32.65 +/- 6.86 kg/m<sup>2</sup>, and mean symptom duration was 33 +/- 42 months. Seven patients underwent repeat surgery for symptomatic recurrence; therefore, there were 58 surgical encounters. Repair included bony reconstruction with hydroxyapatite with or without resection of encephaloceles and/or repair of a dural defect. According to the MFFD classification system described, 15, 8, 27, and 8 cases were categorized as Class A, B, C, and D, respectively. The prevalence of hearing loss was 87%, 63%, and 70% in Classes A, B, and C, respectively. Vestibular symptoms were more prevalent in Class A. Seven patients reported persistent symptoms at the last follow-up. Transient complications were similar in each classification (13%-25%), and a single permanent complication related to anesthesia was observed. There were no mortalities or severe neurological morbidities in the series. CONCLUSIONS Middle fossa floor dehiscence has a spectrum of clinical presentations. A classification system may help to clarify the diagnosis and guide therapy. Surgery, the mainstay of treatment, is safe and well tolerated.

Guseh, S. H., Feinberg, B. B., Dawood, H. Y., Yamamoto, H. S., Fichorova, R. N., & Burwick, R. M. (2014). Urinary excretion of C5b-9 is associated with the anti-angiogenic state in severe preeclampsia. *American Journal of Reproductive Immunology*,  
Problem: Severe preeclampsia has been independently linked to complement dysregulation and angiogenic imbalance; however, the relationship between complement and angiogenic factors in human pregnancy is unclear. Method of study: Utilizing existing biomarkers, our study sought to better understand this relationship in active disease. We performed a case-control study, enrolling 25 cases with severe preeclampsia, 25 controls with chronic hypertension, and 25 healthy controls without hypertension. Levels of complement components (C3a, C5a, and C5b-9) and angiogenic markers [basic fibroblast growth factor (bFGF), placental growth factor (PlGF), vascular endothelial growth factor (VEGF), and soluble fms-like tyrosine kinase-1 (sFlt-1)] were measured simultaneously. Results: Compared to both hypertensive and non-hypertensive

controls, severe preeclampsia was associated with increased plasma sFlt-1, decreased plasma VEGF and PlGF, decreased urinary PlGF, and increased urinary C5b-9. Urinary marker C5b-9 correlated strongly with the anti-angiogenic condition. In subjects with detectable urinary excretion of C5b-9, median plasma levels of sFlt-1 were significantly greater (32,029 versus 4556 pg/mL,  $P < 0.0001$ ) and levels of PlGF (15.6 versus 226 pg/mL,  $P < 0.0001$ ) and VEGF (119 versus 153 pg/mL,  $P = 0.001$ ) were significantly lower. Conclusion: More so than plasma complement markers, urinary C5b-9 may be a useful measure to link complement dysregulation with angiogenic imbalance in severe preeclampsia.

Haar, S., Givon-Mayo, R., Barmack, N. H., Yakhnitsa, V., & Donchin, O. (2015). Spontaneous activity does not predict morphological type in cerebellar interneurons. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 35(4), 1432-1442.

The effort to determine morphological and anatomically defined neuronal characteristics from extracellularly recorded physiological signatures has been attempted with varying success in different brain areas. Recent studies have attempted such classification of cerebellar interneurons (CINs) based on statistical measures of spontaneous activity. Previously, such efforts in different brain areas have used supervised clustering methods based on standard parameterizations of spontaneous interspike interval (ISI) histograms. We worried that this might bias researchers toward positive identification results and decided to take a different approach. We recorded CINs from anesthetized cats. We used unsupervised clustering methods applied to a nonparametric representation of the ISI histograms to identify groups of CINs with similar spontaneous activity and then asked how these groups map onto different cell types. Our approach was a fuzzy C-means clustering algorithm applied to the Kullback-Leibler distances between ISI histograms. We found that there is, in fact, a natural clustering of the spontaneous activity of CINs into six groups but that there was no relationship between this clustering and the standard morphologically defined cell types. These results proved robust when generalization was tested to completely new datasets, including datasets recorded under different anesthesia conditions and in different laboratories and different species (rats). Our results suggest the importance of an unsupervised approach in categorizing neurons according to their extracellular activity. Indeed, a reexamination of such categorization efforts throughout the brain may be necessary. One

important open question is that of functional differences of our six spontaneously defined clusters during actual behavior.

Habashi-Daniel, A., Roberts, J. L., Desai, N., & Thompson, C. T. (2014). Absence of catagen/telogen phase and loss of cytokeratin 15 expression in hair follicles in lichen planopilaris. *Journal of the American Academy of Dermatology*, 71(5), 969-972.

**BACKGROUND:** Lichen planopilaris (LPP) is a lymphocyte-mediated cicatricial alopecia mostly involving the bulge region of the hair follicle. The origin of LPP is unknown. Therapy for LPP often does not prevent disease progression. We describe histologic and immunohistologic features that aid in diagnosis and provide an explanation for disease progression in LPP. **OBJECTIVE:** We sought to demonstrate a decrease in the number of catagen-/telogen-phase follicles and to confirm the loss of cytokeratin 15 (CK15) expression in the stem cells of LPP-affected follicles. **METHODS:** In all, 144 LPP cases were retrieved; 55 cases were stained immunohistochemically, targeting the CK15 antigen with 40 cases ultimately analyzed for CK15 expression. **RESULTS:** Catagen/telogen phase was significantly decreased or absent in all cases of LPP, a novel clue useful in histologic diagnostics. The loss of CK15+ stem cells in most affected follicles in LPP was also confirmed, with unaffected follicles retaining CK15+ stem cells. **LIMITATIONS:** Limited tissue for analysis remained in the clinical sample tissue blocks. **CONCLUSION:** Damaged follicles that have lost their CK15+ stem cells disappear when they enter catagen phase. CK15+ stem cell loss explains the clinical observation that LPP progresses despite immunosuppressive therapies. Finally, the absence of catagen/telogen hair follicles is a helpful diagnostic clue for LPP.

Hajar, T., Leshem, Y. A., Hanifin, J. M., Nedorost, S. T., Lio, P. A., Paller, A. S., et al. (2015). A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses. *Journal of the American Academy of Dermatology*,

**BACKGROUND:** The National Eczema Association has received increasing numbers of patient inquiries regarding "steroid addiction syndrome," coinciding with the growing presence of social media dedicated to this topic. Although many of the side effects of topical corticosteroids (TCS) are addressed in guidelines, TCS addiction is not. **OBJECTIVE:** We sought to assess the current evidence regarding addiction/withdrawal. **METHODS:** We performed a systematic review of the

current literature. RESULTS: Our initial search yielded 294 results with 34 studies meeting inclusion criteria. TCS withdrawal was reported mostly on the face and genital area (99.3%) of women (81.0%) primarily in the setting of long-term inappropriate use of potent TCS. Burning and stinging were the most frequently reported symptoms (65.5%) with erythema being the most common sign (92.3%). TCS withdrawal syndrome can be divided into papulopustular and erythematous subtypes, with the latter presenting with more burning and edema. LIMITATIONS: Low quality of evidence, variability in the extent of data, and the lack of studies with rigorous steroid addiction methodology are limitations. CONCLUSIONS: TCS withdrawal is likely a distinct clinical adverse effect of TCS misuse. Patients and providers should be aware of its clinical presentation and risk factors.

Hanish, L. D., Hill, A., Gosney, S., Fabes, R. A., & Lynn Martin, C. (2011). *Girls, boys, and bullying in preschool: The role of gender in the development of bullying* Taylor and Francis.

Hanlon, S. D., Behzad, A. R., Sakai, L. Y., & Burns, A. R. (2015). Corneal stroma microfibrils. *Experimental Eye Research*,

Elastic tissue was first described well over a hundred years ago and has since been identified in nearly every part of the body. In this review, we examine elastic tissue in the corneal stroma with some mention of other ocular structures which have been more thoroughly described in the past. True elastic fibers consist of an elastin core surrounded by fibrillin microfibrils. However, the presence of elastin fibers is not a requirement and some elastic tissue is comprised of non-elastin-containing bundles of microfibrils. Fibers containing a higher relative amount of elastin are associated with greater elasticity and those without elastin, with structural support. Recently it has been shown that the microfibrils, not only serve mechanical roles, but are also involved in cell signaling through force transduction and the release of TGF-beta. A well characterized example of elastin-free microfibril bundles (EFMBs) is found in the ciliary zonules which suspend the crystalline lens in the eye. Through contraction of the ciliary muscle they exert enough force to reshape the lens and thereby change its focal point. It is believed that the molecules comprising these fibers do not turn-over and yet retain their tensile strength for the life of the animal. The mechanical properties of the cornea (strength, elasticity, resiliency) would suggest

that EFMBs are present there as well. However, many authors have reported that, although present during embryonic and early postnatal development, EFMBs are generally not present in adults. Serial-block-face imaging with a scanning electron microscope enabled 3D reconstruction of elements in murine corneas. Among these elements were found fibers that formed an extensive network throughout the cornea. In single sections these fibers appeared as electron dense patches. Transmission electron microscopy provided additional detail of these patches and showed them to be composed of fibrils ( approximately 10nm diameter). Immunogold evidence clearly identified these fibrils as fibrillin EFMBs and EFMBs were also observed with TEM (without immunogold) in adult mammals of several species. Evidence of the presence of EFMBs in adult corneas will hopefully pique an interest in further studies that will ultimately improve our understanding of the cornea's biomechanical properties and its capacity to repair.

Hartung, D. M., Middleton, L., Markwardt, S., Williamson, K., & Ketchum, K. (2015). Changes in long-acting  $\beta$ -agonist utilization after the FDA's 2010 drug safety communication. *Clinical Therapeutics*, 37(1), 114-123.

Purpose: In February 2010, the US Food and Drug Administration (FDA) issued new recommendations for the safe use of long-acting  $\beta$ -agonists (LABAs) in patients with asthma. The objective of this study was to determine the impact of the FDA's 2010 safety advisory on LABA utilization. Methods: Using administrative data from the Oregon Medicaid program, we performed an interrupted time series regression to evaluate changes in the trend in new LABA prescriptions before and after the FDA's 2010 advisory. Trends in incident fills were examined among those with and without an asthma diagnosis code and previous respiratory controller medication use; trends were also assessed according to patient age. Findings: The average age of the 8646 study patients was 37 years, 53% had a diagnosis of asthma, 21% had no respiratory diagnosis, and 32% had not used a respiratory controller medication in the recent past. The trend in new LABA prescriptions declined by 0.09 new start per 10,000 patients per month (95% CI, -0.19 to -0.01) after the FDA's advisory. Among those with a diagnosis of asthma, there was an immediate drop of 0.48 (95% CI, -0.93 to -0.03) and a 0.10 (95% CI, - 0.13 to -0.06) decline in the monthly rate of new starts per 10,000 patients. Immediately after the FDA's advisory, we observed a statistically significant 4.7% increase (95% CI, 0.8 to 8.7) in the proportion of new LABA starts

with history of previous respiratory controller medication use. Utilization of LABAs did not change in those without a diagnosis of asthma. Implications: The FDA's 2010 advisory was associated with modest reductions in LABA utilization overall and in ways highlighted in their recommendations.

Heinricher, M. M. (2008). *Pain* Humana Press Inc.

Hendrickson, R. G. (2015). Painful and petechial rash after injecting black tar heroin. *Clinical Toxicology (Philadelphia, Pa.)*, , 1-2.

A painful petechial rash developed in a patient after the subcutaneous or intravenous injection of reported black tar heroin. Additional history and the appearance of the skin lesion suggested otherwise.

Henry, J. A., Frederick, M., Sell, S., Griest, S., & Abrams, H. (2015). Validation of a novel combination hearing aid and tinnitus therapy device. *Ear and Hearing*, 36(1), 42-52.

OBJECTIVES: Most patients with tinnitus also have hearing loss. Hearing aids have been well-documented to provide amelioration for both hearing and tinnitus problems. Some hearing aids have built-in noise/sound generators that are intended to provide added benefit to patients with tinnitus. It has not been proven, however, whether these "combination instruments" are more effective for tinnitus management than hearing aids alone. The purpose of this study was to collect initial data addressing this question. DESIGN: Thirty individuals meeting study requirements (bothersome tinnitus, hearing aid candidate, and no use of hearing aids for the previous 12 months) were enrolled. All participants initially completed the primary outcome questionnaire (Tinnitus Functional Index [TFI]) and then returned to be fitted with combination instruments. The hearing aid portion of the devices was adjusted to optimize hearing ability. Participants were then randomized to either the experimental group (n = 15) or the control group (n = 15). The experimental group had the noise feature of the instruments activated and adjusted to achieve optimal relief from tinnitus. The control group did not have the noise portion activated. Following the hearing aid fitting, all study participants also received brief tinnitus counseling. Participants returned 1 to 2 weeks later for a follow-up appointment to confirm proper fit of the instruments and to make any necessary programming adjustments. Additionally,

they returned 3 months after the fitting to complete the TFI, which also concluded their participation in the study. RESULTS: Both groups revealed significant improvement, as indicated by reductions in mean TFI index scores. Differences between groups at 3 months were not statistically significant. However, the experimental group showed a mean reduction in the TFI score that was 6.4 points greater than that for the control group. The difference approached significance ( $p = 0.09$ ), suggesting that a larger group of participants may have resulted in a significant difference between groups. This possibility is tempered by the fact that effect sizes, which control for variation, were very similar between groups. CONCLUSION: Results of this study suggest that the use of hearing aids alone or hearing aids plus the use of sound generators both provide significant benefit with respect to alleviating effects of tinnitus. A larger controlled clinical trial is needed to obtain more definitive results regarding the two configurations of hearing aids.

Heppner, K. M., Kirigiti, M., Secher, A., Paulsen, S. J., Buckingham, R., Pyke, C., et al. (2015).

Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (*macaca mulatta*) brain. *Endocrinology*, *156*(1), 255-267.

Glucagon-like peptide-1 (GLP-1) is released from endocrine L-cells lining the gut in response to food ingestion. However, GLP-1 is also produced in the nucleus of the solitary tract, where it acts as an anorectic neurotransmitter and key regulator of many autonomic and neuroendocrine functions. The expression and projections of GLP-1-producing neurons is highly conserved between rodent and primate brain, although a few key differences have been identified. The GLP-1 receptor (GLP-1R) has been mapped in the rodent brain, but no studies have described the distribution of GLP-1Rs in the nonhuman primate central nervous system. Here, we characterized the distribution of GLP-1R mRNA and protein in the adult macaque brain using in situ hybridization, radioligand receptor autoradiography, and immunohistochemistry with a primate specific GLP-1R antibody. Immunohistochemistry demonstrated that the GLP-1R is localized to cell bodies and fiber terminals in a very selective distribution throughout the brain. Consistent with the functional role of the GLP-1R system, we find the highest concentration of GLP-1R-immunoreactivity present in select hypothalamic and brainstem regions that regulate feeding, including the paraventricular and arcuate hypothalamic nuclei, as well as the area postrema,

nucleus of the solitary tract, and dorsal motor nucleus of the vagus. Together, our data demonstrate that GLP-1R distribution is highly conserved between rodent and primate, although a few key species differences were identified, including the amygdala, where GLP-1R expression is much higher in primate than in rodent.

Hernandez, K. O., Woodall, K. D., & Simon-Dack, S. L. (2015). Left hemispheric contributions to temporal perception: A resting electroencephalographic study. *Neuroreport*, *26*(3), 163-166.

Beta brain wave frequencies, theta brain wave frequencies, and interhemispheric transfer rates were investigated in individuals to explore components of time perception. Research suggests that the left hemisphere is highly involved in attention and language, which are important components of temporal processing mechanisms. Resting state electroencephalography was used to evaluate the relationship between right and left hemispheric brain wave frequencies and performance on a duration-discrimination task and an interhemispheric transfer rate task. A stepwise multiple regression was used to investigate the absolute spectral power of right minus left hemispheric activation for each frequency (alpha, beta, gamma, theta) at each of eight paired electrode locations onto d' data for a temporal discrimination task. Higher absolute spectral power in parietal and temporal left electrodes was predictive of better performance on the duration-discrimination task. Right-to-left interhemispheric transfer approached a significant correlation with performance on the duration-discrimination task. Our results indicate that sensitivity on a temporal task is positively correlated with beta and theta brain wave frequencies, and negatively correlated with right-to-left interhemispheric transfer rates. The current study provides support for a left hemispheric advantage for temporal processing; this provides further explanation of temporal processing mechanisms and where deficits may occur in clinical populations.

Herzig, D. O., & Tsikitis, V. L. (2015). Molecular markers for colon diagnosis, prognosis and targeted therapy. *Journal of Surgical Oncology*, *111*(1), 96-102.

Colorectal adenocarcinoma (CRC), the second leading cancer-related death in the United States, remains a global public health issue. Sporadic CRC is considered the result of sequential mucosal changes from normal colonic mucosa to adenocarcinoma. Efforts in understanding the molecular

pathways leading to CRC tumorigenesis may lead to identifying novel, individually tailored therapeutic targets for patients. In this review, we focus on well-published prognostic and predictive markers in CRC and examine their role in clinical practice.

Hinson, H. E., Puybasset, L., Weiss, N., Perlberg, V., Benali, H., Galanaud, D., et al. (2015).

Neuroanatomical basis of paroxysmal sympathetic hyperactivity: A diffusion tensor imaging analysis. *Brain Injury*, , 1-7.

Abstract Primary objective: Paroxysmal sympathetic hyperactivity (PSH) is observed in a sub-set of patients with moderate-to-severe traumatic brain injury (TBI). The neuroanatomical basis of PSH is poorly understood. It is hypothesized that PSH is linked to changes in connectivity within the central autonomic network. Research design: Retrospective analysis in a sub-set of patients from a multi-centre, prospective cohort study Methods and procedures: Adult patients who were <3 weeks after severe TBI were enrolled and screened for PSH using a standard definition.

Patients underwent multimodal MRI, which included quantitative diffusion tensor imaging. Main outcomes and results: Principal component analysis (PCA) was used to resolve the set of tracts into components. Ability to predict PSH was evaluated via area under the receiver operating characteristic (AUROC) and tree-based classification analyses. Among 102 enrolled patients, 16 met criteria for PSH. The first principle component was significantly associated ( $p = 0.024$ , AUROC = 0.867) with PSH status even after controlling for age and admission GCS. In a classification tree analysis, age, GCS and decreased FA in the splenium of the corpus callosum and in the right posterior limb of the internal capsule discriminated PSH vs no PSH with an AUROC of 0.933. Conclusions: Disconnection involving the posterior corpus callosum and of the posterior limb of the internal capsule may play a role in the pathogenesis or expression of PSH.

Hogarth, P. (2015). Neurodegeneration with brain iron accumulation: Diagnosis and management.

*Journal of Movement Disorders*, 8(1), 1-13.

Neurodegeneration with brain iron accumulation (NBIA) encompasses a group of inherited disorders that share the clinical features of an extrapyramidal movement disorder accompanied by varying degrees of intellectual disability and abnormal iron deposition in the basal ganglia. The genetic basis of ten forms of NBIA is now known. The clinical features of NBIA range from rapid

global neurodevelopmental regression in infancy to mild parkinsonism with minimal cognitive impairment in adulthood, with wide variation seen between and within the specific NBIA subtype. This review describes the clinical presentations, imaging findings, pathologic features, and treatment considerations for this heterogeneous group of disorders.

Horner-Johnson, W., Keys, C. B., Henry, D., Yamaki, K., Watanabe, K., Oi, F., et al. (2015). Staff attitudes towards people with intellectual disabilities in Japan and the United States. *Journal of Intellectual Disability Research : JIDR*,

**BACKGROUND:** Staff attitudes may affect choices available to persons with intellectual disabilities (ID). This study examined attitudes towards people with ID among staff working with people with ID in Japan and the United States. **METHOD:** Attitudes of staff working with people with ID in Japan and the United States were compared using the Community Living Attitudes Scale, Intellectual Disabilities Form. Responses were examined via multivariate analysis of variance. **RESULTS:** In unadjusted analyses, Japanese staff exhibited a greater tendency towards Sheltering and Exclusion of people with ID and lower endorsement of Empowerment and Similarity of people with ID. After controlling for covariates, the country effect was no longer significant for Sheltering and Exclusion. Age and education were significantly associated with attitudes in the adjusted model. **CONCLUSIONS:** While attitudes in Japan appeared less supportive of community inclusion of people with ID, some of the differences between countries were attributable to other staff characteristics such as age and education. Findings provide new information about how attitudes of staff in each country compare with each other.

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Walker, S. J., et al. (2015). It still hurts: Altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Molecular Psychiatry*,

The mu-opioid receptor (MOR) system, well known for dampening physical pain, is also hypothesized to dampen 'social pain.' We used positron emission tomography scanning with the selective MOR radioligand [<sup>11</sup>C]carfentanil to test the hypothesis that MOR system activation (reflecting endogenous opioid release) in response to social rejection and acceptance is altered in medication-free patients diagnosed with current major depressive disorder (MDD, n=17)

compared with healthy controls (HCs, n=18). During rejection, MDD patients showed reduced endogenous opioid release in brain regions regulating stress, mood and motivation, and slower emotional recovery compared with HCs. During acceptance, only HCs showed increased social motivation, which was positively correlated with endogenous opioid release in the nucleus accumbens, a reward structure. Altered endogenous opioid activity in MDD may hinder emotional recovery from negative social interactions and decrease pleasure derived from positive interactions. Both effects may reinforce depression, trigger relapse and contribute to poor treatment outcomes. *Molecular Psychiatry* advance online publication, 20 January 2015; doi:10.1038/mp.2014.185.

Huckans, M., Fuller, B., Wheaton, V., Jaehnert, S., Ellis, C., Kolessar, M., et al. (2015). A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. *Journal of Psychosomatic Research*, 78(2), 184-192.

Objective: To prospectively evaluate for changes in objective cognitive performance (attention, memory, and executive function) and psychiatric symptom severity (depression, anxiety, fatigue, and pain) in patients before, during and after interferon-alpha based therapy (IFN) for chronic hepatitis C virus infection (HCV). Methods: 33 HCV. + adults were evaluated two months before IFN initiation (baseline), three months into IFN, and six months following IFN termination (IFN. + Group). 31 HCV. + adults who did not undergo IFN therapy were evaluated at baseline and six months later (IFN. - Group). At each evaluation, participants completed the Neuropsychological Assessment Battery (NAB) Attention, Memory and Executive Functions Modules, the Beck Depression Inventory, Second Edition (BDI), Generalized Anxiety Disorder Inventory (GADI), Fatigue Severity Scale (FSS), and Brief Pain Inventory (BPI). Results: Compared with the IFN. - Group, the IFN. + Group experienced significantly ( $p < .005$ ) increased symptoms of depression, anxiety, fatigue and pain during IFN therapy relative to baseline. In the IFN. + Group, psychiatric symptoms generally returned to baseline levels following IFN termination. Sustained viral response was associated with significantly lower depression and fatigue. No significant changes in cognitive performance were observed. Conclusions: During IFN, patients with HCV evidence significantly increased psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain. These psychiatric symptoms are generally short-term and

remit following IFN termination, with increased benefit if viral clearance is achieved. However, IFN is not associated with significant declines in objective cognitive performance during or following IFN.

Huffman, C., Stacey, B. R., Tuchman, M., Burbridge, C., Li, C., Parsons, B., et al. (2015). Efficacy and safety of pregabalin in the treatment of patients with painful diabetic peripheral neuropathy and pain on walking. *Clinical Journal of Pain*,

OBJECTIVES:: This randomized, double-blind, placebo-controlled, multicenter, 2-period crossover study (two 6-week treatment periods separated by a 2-week washout period) evaluated efficacy and safety of pregabalin (150–300 mg/d) for treatment of pain and pain on walking in patients with painful diabetic peripheral neuropathy (DPN) who experienced pain while walking.

METHODS:: Co-primary efficacy endpoints were (1) mean pain score (last 7 daily pain diary scores, 0–10 numeric rating scale [(NRS)] at end of each treatment period and (2) DPN pain on walking (0–10 NRS immediately after walking 50 feet (15.2 m) on flat surface). Secondary endpoints included other pain parameters, patient-reported sleep, health-related quality of life, and safety measures. RESULTS:: Two hundred three patients were treated (pregabalin, n=198; placebo, n=186), with no statistically significant treatment difference for pregabalin versus placebo in the co-primary efficacy endpoints, mean DPN pain (P=0.0659) and mean DPN pain on walking (P=0.4120). A carryover effect was observed. Analysis of co-primary endpoints for period 1 showed significant treatment difference for DPN pain (P=0.0338) and DPN pain on walking (P=0.0011). Treatment with pregabalin resulted in significant improvements versus placebo on prespecified patient global impression of change (end of period 1; P=0.0020), and sleep interference rating scale (end of period 2; P=0.0105). Adverse events were more frequent with pregabalin than with placebo and caused discontinuation in 13 (6.6%) pregabalin patients versus 5 (2.7%) placebo patients. DISCUSSION:: Failure to meet the co-primary objectives may be related to carryover effect from period 1 to period 2, lower pregabalin dose (150–300 mg/d), and/or placebo response in painful DPN.

Hughes, H. K., Korthis, P. T., Saha, S., Egly, S., Sharp, V., Cohn, J., et al. (2015). A mixed methods study of patient-provider communication about opioid analgesics. *Patient Education and*

### *Counseling,*

**OBJECTIVE:** To describe patient-provider communication about opioid pain medicine and explore how these discussions affect provider attitudes toward patients. **METHODS:** We audio-recorded 45 HIV providers and 423 patients in routine outpatient encounters at four sites across the country. Providers completed post-visit questionnaires assessing their attitudes toward patients. We identified discussions about opioid pain management and analyzed them qualitatively. We used logistic regression to assess the association between opioid discussion and providers' attitudes toward patients. **RESULTS:** 48 encounters (11% of the total sample) contained substantive discussion of opioid-related pain management. Most conversations were initiated by patients (n=28, 58%) and ended by the providers (n=36, 75%). Twelve encounters (25%) contained dialog suggesting a difference of opinion or conflict. Providers more often agreed than disagreed to give the prescription (50% vs. 23%), sometimes reluctantly; in 27% (n=13) of encounters, no decision was made. Fewer than half of providers (n=20, 42%) acknowledged the patient's experience of pain. Providers had a lower odds of positive regard for the patient (adjusted OR=0.51, 95% CI: 0.27-0.95) when opioids were discussed. **CONCLUSIONS:** Pain management discussions are common in routine outpatient HIV encounters and providers may regard patients less favorably if opioids are discussed during visits. The sometimes-adversarial nature of these discussions may negatively affect provider attitudes toward patients. **PRACTICE IMPLICATIONS:** Empathy and pain acknowledgment are tools that clinicians can use to facilitate productive discussions of pain management.

Hussain, M., Carducci, M. A., Slovin, S., Cetnar, J., Qian, J., McKeegan, E. M., et al. (2014). Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer. *Investigational New Drugs*, 32(5), 904-912.

**Summary:** Androgen receptor-mediated transcription is directly coupled with the induction of DNA damage, and castration-resistant tumor cells exhibit increased activity of poly (ADP-ribose) polymerase (PARP)-1, a DNA repair enzyme. This study assessed the efficacy and safety of low dose oral PARP inhibitor veliparib (ABT-888) and temozolomide (TMZ) in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer (mCRPC) in a single-arm, open-label, pilot study. Patients with mCRPC progressing on at least one docetaxel-based therapy and

prostate specific antigen (PSA)  $\geq 2$  ng/mL were treated with veliparib 40 mg twice daily on days 1-7 and TMZ once daily (150 mg/m<sup>2</sup>/day cycle 1; if well tolerated then 200 mg/m<sup>2</sup>/day cycle 2 onwards) on days 1-5 q28 days. Patients received 2 (median) treatment cycles (range, 1-9). The primary endpoint was confirmed PSA response rate (decline  $\geq 30$  %). Twenty-six eligible patients were enrolled, 25 evaluable for PSA response. Median baseline PSA was 170 ng/mL. Two patients had a confirmed PSA response (8.0 %; 95 % CI: 1.0-26.0), 13 stable PSA, and 10 PSA progression. The median progression-free survival was 9 weeks (95 % CI: 7.9-17) and median overall survival 39.6 weeks (95 % CI: 26.6-not estimable). The most frequent treatment-emergent adverse events (AEs) were thrombocytopenia (77 %), anemia (69 %), fatigue (50 %), neutropenia (42 %), nausea (38 %), and constipation (23 %). Grade 3/4 AEs occurring in > 10 % of patients were thrombocytopenia (23 %) and anemia (15 %). Veliparib and TMZ combination was well tolerated but with modest activity. Biomarker analysis supported the proof of concept that this combination has some antitumor activity in mCRPC.

Idris, A. H., Guffey, D., Pepe, P. P., Brown, S. P., Brooks, S. C., Callaway, C. W., et al. (2015). Chest compression rates and survival following out-of-hospital cardiac arrest. *Critical Care Medicine*,  
OBJECTIVE:: Guidelines for cardiopulmonary resuscitation recommend a chest compression rate of at least 100 compressions/min. A recent clinical study reported optimal return of spontaneous circulation with rates between 100 and 120/min during cardiopulmonary resuscitation for out-of-hospital cardiac arrest. However, the relationship between compression rate and survival is still undetermined. DESIGN:: Prospective, observational study. SETTING:: Data is from the Resuscitation Outcomes Consortium Prehospital Resuscitation Impedance threshold device and Early versus Delayed analysis clinical trial. PARTICIPANTS:: Adults with out-of-hospital cardiac arrest treated by emergency medical service providers. INTERVENTIONS:: None.  
MEASUREMENTS MAIN RESULTS:: Data were abstracted from monitor-defibrillator recordings for the first five minutes of emergency medical service cardiopulmonary resuscitation. Multiple logistic regression assessed odds ratio for survival by compression rate categories ( $n=140$ ), both unadjusted and adjusted for sex, age, witnessed status, attempted bystander cardiopulmonary resuscitation, location of arrest, chest compression fraction and depth, first rhythm, and study site. Compression rate data were available for 10,371 patients; 6,399 also had chest compression

fraction and depth data. Age (mean +/- SD) was 67 +/- 16 years. Chest compression rate was 111 +/- 19 per minute, compression fraction was 0.70 +/- 0.17, and compression depth was 42 +/- 12 mm. Circulation was restored in 34%; 9% survived to hospital discharge. After adjustment for covariates without chest compression depth and fraction (n = 10,371), a global test found no significant relationship between compression rate and survival (p = 0.19). However, after adjustment for covariates including chest compression depth and fraction (n = 6,399), the global test found a significant relationship between compression rate and survival (p = 0.02), with the reference group (100-119 compressions/min) having the greatest likelihood for survival. CONCLUSIONS: After adjustment for chest compression fraction and depth, compression rates between 100 and 120 per minute were associated with greatest survival to hospital discharge.

Ishikawa, Y., Boudko, S., & Bachinger, H. P. (2015). Ziploc-ing the structure: Triple helix formation is coordinated by rough endoplasmic reticulum resident PPIases. *Biochimica Et Biophysica Acta*,  
BACKGROUND: Protein folding is crucial for proteins' specific functions and is facilitated by various types of enzymes and molecular chaperones. The peptidyl prolyl cis/trans isomerases (PPIase) are one of these families of enzymes. They ubiquitously exist inside the cell and there are eight PPIases in the rough endoplasmic reticulum (rER), a compartment where the folding of most secreted proteins occurs. SCOPE OF REVIEW: We review the functional and structural aspects of individual rER resident PPIases. Furthermore, we specifically discuss the role of these PPIases during collagen biosynthesis, since collagen is the most abundant protein in humans, is synthesized in the rER, and contains a proportionally high number of proline residues. MAJOR CONCLUSIONS: The rER resident PPIases recognize different sets of substrates and facilitate their folding. Although they are clearly catalysts for protein folding, they also have more broad and multifaceted functions. We propose that PPIases coordinate collagen biosynthesis in the rER. GENERAL SIGNIFICANCE: This review expands our understanding of collagen biosynthesis by explaining the influence of novel indirect mechanisms of regulating folding and this is also explored for PPIases. We also suggest future directions of research to obtain a better understanding of collagen biosynthesis and functions of PPIases in the rER. This article is part of a Special Issue entitled Proline-directed Foldases: Cell Signaling Catalysts and Drug Targets.

Isom, J. (1970). Dog licks man. *The Lancet*, 295(7653), 955.

Jahangir, E., Lipworth, L., Edwards, T. L., Kabagambe, E. K., Mumma, M. T., Mensah, G. A., et al.

(2015). Smoking, sex, risk factors and abdominal aortic aneurysms: A prospective study of 18 782 persons aged above 65 years in the southern community cohort study. *Journal of Epidemiology and Community Health*,

BACKGROUND: Abdominal aortic aneurysm (AAA) is a leading cause of death in the USA. We evaluated the incidence and predictors of AAA in a prospectively followed cohort. METHODS: We calculated age-adjusted AAA incidence rates (IR) among 18 782 participants aged  $\geq 65$  years in the Southern Community Cohort Study who received Medicare coverage from 1999-2012, and assessed predictors of AAA using multivariable Cox proportional hazards models, overall and stratified by sex, adjusting for demographic, lifestyle, socioeconomic, medical and other factors. HRs and 95% CIs were calculated for AAA in relation to factors ascertained at enrolment.

RESULTS: Over a median follow-up of 4.94 years, 281 cases were identified. Annual IR was 153/100 000, 401, 354 and 174 among blacks, whites, men and women, respectively. AAA risk was lower among women (HR 0.48, 95% CI 0.36 to 0.65) and blacks (HR 0.51, 95% CI 0.37 to 0.69). Smoking was the strongest risk factor (former: HR 1.91, 95% CI 1.27 to 2.87; current: HR 5.55, 95% CI 3.67 to 8.40), and pronounced in women (former: HR 3.4, 95% CI 1.83 to 6.31; current: HR 9.17, 95% CI 4.95 to 17). A history of hypertension (HR 1.44, 95% CI 1.04 to 2.01) and myocardial infarction or coronary artery bypass surgery (HR 1.9, 95% CI 1.37 to 2.63) was negatively associated, whereas a body mass index  $\geq 25$  kg/m<sup>2</sup> (HR 0.72; 95% CI 0.53 to 0.98) was protective. College education (HR 0.6, 95% CI 0.37 to 0.97) and black race (HR 0.44, 95% CI 0.28 to 0.67) were protective among men. CONCLUSIONS: Smoking is a major risk factor for incident AAA, with a strong and similar association between men and women. Further studies are needed to evaluate benefits of ultrasound screening for AAA among women smokers.

Jensen, K. K., & Sohaey, R. (2015). Antenatal sonographic diagnosis of choledochal cyst: Case report and imaging review. *Journal of Clinical Ultrasound*,

In this report, we present the antenatal two- and three-dimensional sonographic findings from a fetus with choledochal cyst as well as confirmatory postnatal MRI. A delayed diagnosis of

choledochal cyst is common, leading to significant morbidity and mortality. Visualizing bile ducts entering a right upper quadrant cyst is pathognomonic, and early diagnosis can facilitate definitive treatment with Roux-en-Y hepaticojejunostomy.

Johnson, A. R., Crouch, B., & Zane Horowitz, B. (2014). Discrepancies in reported US pricing information for digoxin-fab. *Clinical Toxicology*, 53(1), 71.

Kallmes, D. F., Hanel, R., Lopes, D., Boccardi, E., Bonafé, A., Cekirge, S., et al. (2015). International retrospective study of the pipeline embolization device: A multicenter aneurysm treatment study. *American Journal of Neuroradiology*, 36(1), 108-115.

Background and Purpose: Flow diverters are increasingly used in the endovascular treatment of intracranial aneurysms. Our aim was to determine neurologic complication rates following Pipeline Embolization Device placement for intracranial aneurysm treatment in a real-world setting. Materials and Methods: We retrospectively evaluated all patients with intracranial aneurysms treated with the Pipeline Embolization Device between July 2008 and February 2013 in 17 centers worldwide. We defined 4 subgroups: internal carotid artery aneurysms of  $\geq 10$  mm, ICA aneurysms of  $< 10$  mm, other anterior circulation aneurysms, and posterior circulation aneurysms. Neurologic complications included spontaneous rupture, intracranial hemorrhage, ischemic stroke, permanent cranial neuropathy, and mortality. Comparisons were made with t tests or ANOVAs for continuous variables and the Pearson  $\chi^2$  or Fisher exact test for categorical variables. Results: In total, 793 patients with 906 aneurysms were included. The neurologic morbidity and mortality rate was 8.4% (67/793), highest in the posterior circulation group (16.4%, 9/55) and lowest in the ICA  $< 10$ -mm group (4.8%, 14/294) ( $P = .01$ ). The spontaneous rupture rate was 0.6% (5/793). The intracranial hemorrhage rate was 2.4% (19/793). Ischemic stroke rates were 4.7% (37/793), highest in patients with posterior circulation aneurysms (7.3%, 4/55) and lowest in the ICA  $< 10$ -mm group (2.7%, 8/294) ( $P = .16$ ). Neurologic mortality was 3.8% (30/793), highest in the posterior circulation group (10.9%, 6/55) and lowest in the anterior circulation ICA  $< 10$ -mm group (1.4%, 4/294) ( $P < .01$ ). Conclusions: Aneurysm treatment with the Pipeline Embolization Device is associated with the lowest complication rates when used

to treat small ICA aneurysms. Procedure-related morbidity and mortality are higher in the treatment of posterior circulation and giant aneurysms.

Kalpathy-Cramer, J., de Herrera, A. G. S., Demner-Fushman, D., Antani, S., Bedrick, S., & Müller, H. (2015). Evaluating performance of biomedical image retrieval systems-an overview of the medical image retrieval task at ImageCLEF 2004-2013. *Computerized Medical Imaging and Graphics, 39*, 55-61.

Medical image retrieval and classification have been extremely active research topics over the past 15 years. Within the ImageCLEF benchmark in medical image retrieval and classification, a standard test bed was created that allows researchers to compare their approaches and ideas on increasingly large and varied data sets including generated ground truth. This article describes the lessons learned in ten evaluation campaigns. A detailed analysis of the data also highlights the value of the resources created.

Kamimae-Lanning, A. N., Krasnow, S. M., Goloviznina, N. A., Zhu, X., Roth-Carter, Q. R., Levasseur, P. R., et al. (2015). Maternal high-fat diet and obesity compromise fetal hematopoiesis. *Molecular Metabolism, 4*(1), 25-38.

Objective: Recent evidence indicates that the adult hematopoietic system is susceptible to diet-induced lineage skewing. It is not known whether the developing hematopoietic system is subject to metabolic programming via in utero high-fat diet (HFD) exposure, an established mechanism of adult disease in several organ systems. We previously reported substantial losses in offspring liver size with prenatal HFD. As the liver is the main hematopoietic organ in the fetus, we asked whether the developmental expansion of the hematopoietic stem and progenitor cell (HSPC) pool is compromised by prenatal HFD and/or maternal obesity. Methods: We used quantitative assays, progenitor colony formation, flow cytometry, transplantation, and gene expression assays with a series of dietary manipulations to test the effects of gestational high-fat diet and maternal obesity on the day 14.5 fetal liver hematopoietic system. Results: Maternal obesity, particularly when paired with gestational HFD, restricts physiological expansion of fetal HSPCs while promoting the opposing cell fate of differentiation. Importantly, these effects are only partially ameliorated by gestational dietary adjustments for obese dams. Competitive transplantation

reveals compromised repopulation and myeloid-biased differentiation of HFD-programmed HSPCs to be a niche-dependent defect, apparent in HFD-conditioned male recipients. Fetal HSPC deficiencies coincide with perturbations in genes regulating metabolism, immune and inflammatory processes, and stress response, along with downregulation of genes critical for hematopoietic stem cell self-renewal and activation of pathways regulating cell migration. Conclusions: Our data reveal a previously unrecognized susceptibility to nutritional and metabolic developmental programming in the fetal HSPC compartment, which is a partially reversible and microenvironment-dependent defect perturbing stem and progenitor cell expansion and hematopoietic lineage commitment.

Kaseda, R., Jabs, K., Hunley, T. E., Jones, D., Bian, A., Allen, R. M., et al. (2015). Dysfunctional high-density lipoproteins in children with chronic kidney disease. *Metabolism: Clinical and Experimental*, 64(2), 263-273.

Objectives. Our aim was to determine if chronic kidney disease (CKD) occurring in childhood impairs the normally vasoprotective functions of high-density lipoproteins (HDLs). Materials and methods. HDLs were isolated from children with end-stage renal disease on dialysis (ESRD), children with moderate CKD and controls with normal kidney function. Macrophage response to HDLs was studied as expression of inflammatory markers (MCP-1, TNF- $\alpha$ , IL-1 $\beta$ ) and chemotaxis. Human umbilical vein endothelial cells were used for expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and adhesion. Cellular proliferation, apoptosis, and necrosis of endothelial cells were measured by MTS/PMS reagent-based assay, flow cytometry, and ELISA. Cholesterol efflux was assessed by gas chromatographic measurements of cholesterol in macrophages exposed to HDLs. Results. Compared with HDLControl, HDLCKD and HDLESRD heightened the cytokine response and disrupted macrophage chemotaxis. HDLControl reduced endothelial expression of ICAM-1, VCAM-1, E-selectin, whereas HDLCKD and HDLESRD were less effective and showed reduced capacity to protect endothelial cells against monocyte adhesion. Compared with a dramatically enhanced endothelial proliferation following injurious stimulus by HDLControl, neither HDLCKD nor HDLESRD caused proliferative effects. HDLs of all three groups were equally protective against apoptosis assessed by flow cytometry and cleaved caspase-3 activity. Compared to HDLControl, HDLCKD and HDLESRD trended toward reduced capacity as cholesterol

acceptors. Conclusion. CKD in children impairs HDL function. Even in the absence of long-standing and concomitant risk factors, CKD alters specific HDL functions linked to control of inflammation and endothelial responses.

Kaul, S. (2014). Is it time to replace physical examination with a hand-held ultrasound device? *Journal of Cardiovascular Echography*, 24(4), 97-102.

Attempts at using physical examination (PE) go back centuries, with inspection, palpation, and percussion being the mainstay of this approach until 2 centuries ago when the stethoscope was invented and auscultation became probably the most important element of PE for patients with known or suspected cardiovascular disease (CVD). Despite its several limitations, PE is still used, sometimes as the only means, of evaluating and following patients with CVD. In this paper I shall argue for the substitution of this inaccurate and archaic approach by direct visualization of the heart using a hand-held ultrasound (HHU) device. I am not in any way suggesting the substitution of a comprehensive echocardiographic examination by an expert sonographer/echocardiographer by HHU in patients with significant CVD. Instead, I am arguing for the replacement of PE for evaluation of the heart at the point of care as well as at the bedside, simply because HHU is more accurate and provides more meaningful information.

Kaye, J. (2010). *Imaging cognitive decline in aging: Predicting decline with structural imaging* Oxford University Press.

The focus of this chapter is predicting cognitive decline or dementia in normal older people using structural imaging. Key questions addressed include the following: What are the major methods, both clinical and imaging, that may help us to predict decline? What underlying pathologies do structural changes preceding decline suggest are developing in the brain? What is the evidence from structural studies that anatomical changes are present before behavioral ones or precede the diagnosis of mild cognitive impairment or dementia? Does imaging provide information about the pace of future decline? What are the limitations of these studies? Finally, what are the implications of structural imaging outcomes for application to the conduct of treatment studies and future research?

Kerns, E., Patel, S., & Cohen, D. M. (2014). Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia. *Clinical Nephrology*, 82(6), 397-401.

Hypertonic NaCl is first-line therapy for acute, severe and symptomatic hyponatremia; however, its use is often restricted to the intensive care unit (ICU). A 35-year-old female inpatient with an optic chiasm glioma and ventriculoperitoneal shunt for hydrocephalus developed acute hyponatremia (sodium 122 mEq/L) perhaps coinciding with haloperidol treatment. The sum of her urinary sodium and potassium concentrations was markedly hypertonic vis-à-vis plasma; it was inferred that serum sodium concentration would continue to fall even in the complete absence of fluid intake. Intravenous (IV) 3% NaCl was recommended; however, a city-wide public health emergency precluded her transfer to the ICU. She was treated with hourly oral NaCl tablets in a dose calculated to deliver the equivalent of 0.5 mL/kg/h of 3% NaCl with an objective of increasing the serum sodium concentration by 6 mEq/L. She experienced a graded and predictable increase in serum sodium concentration. A slight overshoot to 129 mEq/L was rapidly corrected with 0.25 l of D5W, and she stabilized at 127 mEq/L. We conclude that hourly oral NaCl, in conjunction with careful monitoring of the serum sodium concentration, may provide an attractive alternative to IV 3% NaCl for selected patients with severe hyponatremia.

Kim, E., & Thomas, C. R., Jr. (2015). Conditional survival of malignant thymoma using national population-based surveillance epidemiology and end results (SEER) registry (1973-2011). *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*,

INTRODUCTION: : Thymoma is a rare and unique tumor with a long natural history that makes it difficult to study. Consequently, there is a dearth of prospective diagnostic or therapeutic clinical trials. To our knowledge there has not been an analysis of conditional survival of thymoma in the literature. The specific aim of this study was to study the 5-year conditional survivals of a large population of thymoma patients. METHODS: : Cases of thymoma were extracted from the Surveillance, Epidemiology, and End Results (SEER) registry (1973-2011) and categorized into Masaoka-Koga stage groupings. The primary outcomes compared overall survival (OS), cause specific survival (CSS), and 5-year conditional OS and CSS, by stage. OS and CSS were calculated using the Kaplan-Meier method with the log-rank test for significance using SAS v9.3.

Conditional survival was the probability of surviving an additional 5 years at any point in follow-up, and used ANOVA to test significance. RESULTS: A total of 2,182 patients met inclusion criteria, and were categorized as Masaoka-Koga stage groupings of I-IIA ("localized", 24%), IIB ("regional", 16%), III-IV ("distant", 50%), and unknown (10%). Median age was 56 (18-91), and 53% were male. Earlier stages had better OS ( $p < 0.0001$ ) and CSS ( $p < 0.0001$ ). Twenty-year OS for local, regional, and distant stages were 42%, 30%, and 18%. Conditional survivals remained largely unchanged throughout follow-up. CONCLUSIONS: Conditional survival provides more relevant survival estimates for patients during follow-up. Further studies should investigate the possibility that thymoma should be considered a chronic disease.

Kim, E. Y., Chapman, T. R., Ryu, S., Chang, E. L., Galanopoulos, N., Jones, J., et al. (2014). ACR appropriateness criteria® non-spine bone metastases. *Journal of Palliative Medicine*, 18(1), 11-17.

Bone metastases are a common clinical problem, affecting many types of cancer patients. The presence of tumor in bone can cause significant morbidity including pain, neurological dysfunction, hypercalcemia, and pathological fracture leading to functional loss. The optimal treatment of a patient with bone metastases depends on many factors, including evaluation of the patient's goals of care, performance status, mechanical stability of the affected bone, life expectancy, and overall extent of disease. Treatment options may include radiotherapy, systemic therapies, surgical stabilization, medical pain management, and radiopharmaceuticals. Ideal management of bone metastases requires a coordinated multidisciplinary approach among diagnostic radiologists, radiation oncologists, medical oncologists, orthopedic surgeons, pain specialists, physiatrists, and palliative care specialists. The American College of Radiology Appropriateness Criteria® are evidence-based guidelines for specific clinical conditions that are reviewed every 3 years by a multidisciplinary expert panel. The guidelines development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

King, V. J., Fontaine, P. L., Atwood, L. A., Powers, E., Leeman, L., Ecker, J. L., et al. (2015). Clinical practice guideline executive summary: Labor after cesarean/planned vaginal birth after cesarean. *Annals of Family Medicine*, 13(1), 80-81.

Kirkpatrick, J. N., Hauptman, P. J., & Goodlin, S. J. (2015). Bundling informed consent and advance care planning in chronic cardiovascular disease: We need to talk. *JAMA Internal Medicine*, 175(1), 5-6.

Klaassen, Z., Singh, A. A., Howard, L. E., Feng, Z., Trock, B., Terris, M. K., et al. (2015). Is clinical stage T2c prostate cancer an intermediate- or high-risk disease? *Cancer*,

BACKGROUND: Clinical stage T2c (cT2c) is an indeterminate factor in prostate cancer (PC) risk stratification. According to the D'Amico grouping and American Urological Association guidelines, cT2c is a high risk, whereas the National Comprehensive Cancer Network and the European Urological Association classify cT2c as an intermediate risk. This study assessed whether cT2c tumors without other high-risk factors (clinical stage T2c, not otherwise specified [cT2c-NOS]) behaved as an intermediate or high risk through an analysis of biochemical recurrence (BCR) after radical prostatectomy. METHODS: Two thousand seven hundred fifty-nine men from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database and 12,900 men from Johns Hopkins Hospital (JHH) from 1988-2011 and 1982-2012, respectively, were analyzed. Patients were grouped into low-risk (prostate-specific antigen [PSA] 20 ng/mL, Gleason sum = 8-10, or cT3). Men with cT2c tumors who were not otherwise at high risk (ie, PSA < 20 ng/mL and Gleason sum < 8) were placed into a separate category termed cT2c-NOS. Associations between cT2c-NOS and intermediate- and high-risk patients and BCR were tested with the log-rank test and Cox proportional analysis models. RESULTS: Ninety-nine men (4%) from SEARCH and 202 men (2%) from JHH had tumors classified as cT2c-NOS. The cT2c-NOS patients had a BCR risk similar to that of the intermediate-risk patients (SEARCH, P = .27; JHH, P = .23) but a significantly lower BCR risk in comparison with the high-risk patients (SEARCH, P < .001; JHH, P < .001). When they were specifically compared with intermediate- and high-risk patients, after adjustments for year and center, cT2c-NOS patients had outcomes comparable to those of intermediate-risk patients (SEARCH, P = .53; JHH, P = .54) but significantly better than those of

high-risk patients (SEARCH,  $P = .003$ ; JHH,  $P < .001$ ). CONCLUSIONS: Patients with cT2c disease without other high-risk features had outcomes similar to the outcomes of patients with intermediate-risk PC and significantly better than the outcomes of patients with high-risk PC. These findings suggest that men with cT2c disease should be considered to be at intermediate risk.

Klein, R. F. (2005). *Murine models of osteoporosis* Humana Press Inc.

Osteoporosis is a disease characterized by an inadequate amount and/or faulty structure of bone, which increases the susceptibility to fracture with minimal trauma. Osteoporotic fractures are most commonly observed among the elderly. Yet, the pathogenesis of osteoporosis starts early in life, leading some researchers to view osteoporosis as a pediatric disease (1). Considerable past research has centered on the influence of reproductive, nutritional, and/or life-style factors on the development of osteoporosis. With the advent of new molecular genetic approaches, the focus of research has recently shifted toward genetic factors. Genetic epidemiological studies provide convincing descriptive data including population and ethnic differences, studies of familial aggregation, familial transmission patterns, and comparisons of twin concordance rates that tell a significant part of how the vulnerability to developing osteoporosis is inherited (2,3). Almost certainly, the development of osteoporosis will be found to involve a complex interplay between both genetic and environmental factors that are difficult to control in complex populations.

Kmoch, S., Majewski, J., Ramamurthy, V., Cao, S., Fahiminiya, S., Ren, H., et al. (2015). Mutations in PNPLA6 are linked to photoreceptor degeneration and various forms of childhood blindness. *Nature Communications*, 6, 5614.

Blindness due to retinal degeneration affects millions of people worldwide, but many disease-causing mutations remain unknown. PNPLA6 encodes the patatin-like phospholipase domain containing protein 6, also known as neuropathy target esterase (NTE), which is the target of toxic organophosphates that induce human paralysis due to severe axonopathy of large neurons. Mutations in PNPLA6 also cause human spastic paraplegia characterized by motor neuron degeneration. Here we identify PNPLA6 mutations in childhood blindness in seven families with retinal degeneration, including Leber congenital amaurosis and Oliver McFarlane syndrome.

PNPLA6 localizes mostly at the inner segment plasma membrane in photoreceptors and mutations in *Drosophila* PNPLA6 lead to photoreceptor cell death. We also report that lysophosphatidylcholine and lysophosphatidic acid levels are elevated in mutant *Drosophila*. These findings show a role for PNPLA6 in photoreceptor survival and identify phospholipid metabolism as a potential therapeutic target for some forms of blindness.

Konrad-Martin, D., Reavis, K. M., Austin, D., Reed, N., Gordon, J., McDermott, D., et al. (2015).

Hearing impairment in relation to severity of diabetes in a veteran cohort. *Ear and Hearing*,  
OBJECTIVE: Type 2 diabetes is epidemic among veterans, approaching three times the prevalence of the general population. Diabetes leads to devastating complications of vascular and neurologic malfunction and appears to impair auditory function. Hearing loss prevention is a major health-related initiative in the Veterans Health Administration. Thus, this research sought to identify, and quantify with effect sizes, differences in hearing, speech recognition, and hearing-related quality of life (QOL) measures associated with diabetes and to determine whether well-controlled diabetes diminishes the differences. DESIGN: The authors examined selected cross-sectional data from the baseline (initial) visit of a longitudinal study of Veterans with and without type 2 diabetes designed to assess the possible differences in age-related trajectories of peripheral and central auditory function between the two groups. In addition, the diabetes group was divided into subgroups on the basis of medical diagnosis of diabetes and current glycated hemoglobin (HbA1c) as a metric of disease severity and control. Outcome measures were pure-tone thresholds, word recognition using sentences presented in noise or time-compressed, and an inventory assessing the self-perceived impact of hearing loss on QOL. Data were analyzed from 130 Veterans ages 24 to 73 (mean 48) years with well-controlled (controlled) diabetes, poorly controlled (uncontrolled) diabetes, prediabetes, and no diabetes. Regression was used to identify any group differences in age, noise exposure history, and other sociodemographic factors, and multiple regression was used to model each outcome variable, adjusting for potential confounders. Results were evaluated in relation to diabetes duration, use of insulin (yes, no), and presence of selected diabetes complications (neuropathy and retinopathy). RESULTS: Compared with nondiabetics, Veterans with uncontrolled diabetes had significant differences in hearing at speech frequencies, including poorer hearing by 3 to 3.5 dB for thresholds at 250 Hz and in a

clinical pure-tone average, respectively. Compared with nondiabetic controls, individuals with uncontrolled diabetes also significantly more frequently reported that their hearing adversely impacted QOL on one of the three subscales (ability to adapt). Despite this, although they also had slightly poorer mean scores on both word recognition tasks performed, these differences did not reach statistical significance and all subjects performed well on these tasks. Compared with Veterans with controlled diabetes, those with uncontrolled disease tended to have had diabetes longer, be insulin-dependent, and have a greater prevalence of diabetic retinopathy. Results are generally comparable with the literature with regard to the magnitude of threshold differences and the prevalence of hearing impairment but extend prior work by providing threshold difference and hearing loss prevalence effect sizes by category of diabetes control and by including additional functional measures. CONCLUSIONS: In a cohort of Veterans with type 2 diabetes and relatively good hearing, significant effects of disease severity were found for hearing thresholds at a subset of frequencies and for one of the three QOL subscales. Significant differences were concentrated among those with poorly controlled diabetes based on current HbA1c. Results provide evidence that the observed hearing dysfunction in type 2 diabetes might be prevented or delayed through tight metabolic control. Findings need to be corroborated using longitudinal assessments.

Kuchenbaecker, K. B., Ramus, S. J., Tyrer, J., Lee, A., Shen, H. C., Beesley, J., et al. (2015).

Identification of six new susceptibility loci for invasive epithelial ovarian cancer. *Nature Genetics*, 47(2), 164-171.

Genome-wide association studies (GWAS) have identified 12 epithelial ovarian cancer (EOC) susceptibility alleles. The pattern of association at these loci is consistent in BRCA1 and BRCA2 mutation carriers who are at high risk of EOC. After imputation to 1000 Genomes Project data, we assessed associations of 11 million genetic variants with EOC risk from 15,437 cases unselected for family history and 30,845 controls and from 15,252 BRCA1 mutation carriers and 8,211 BRCA2 mutation carriers (3,096 with ovarian cancer), and we combined the results in a meta-analysis. This new study design yielded increased statistical power, leading to the discovery of six new EOC susceptibility loci. Variants at 1p36 (nearest gene, WNT4), 4q26 (SYNPO2), 9q34.2 (ABO) and 17q11.2 (ATAD5) were associated with EOC risk, and at 1p34.3 (RSP01) and

6p22.1 (GPX6) variants were specifically associated with the serous EOC subtype, all with  $P < 5 \times 10^{-8}$ . Incorporating these variants into risk assessment tools will improve clinical risk predictions for BRCA1 and BRCA2 mutation carriers.

Lassetter, J. H., Ray, G., Driessnack, M., & Williams, M. (2015). Consulting with children in the development of self-efficacy and recall tools related to nutrition and physical activity. *Journal for Specialists in Pediatric Nursing, 20*(1), 21-28.

Purpose: This article chronicles our efforts to develop an instrument with and for children-complete with insights, multiple iterations, and missteps along the way. The instruments we developed assess children's self-efficacy and recall related to healthy eating and physical activity.

Design and Methods: Five focus groups were held with 39 children to discuss the evolving instrument. Results: A nine-item self-efficacy instrument and a 10-item recall instrument were developed with Flesch-Kincaid grade levels of 1.8 and 4.0, respectively, which fifth graders can complete in less than 5min. Practice Implications: When assessing children in clinical practice or research, we should use instruments that have been developed with children's feedback and are child-centered. Without that assurance, assessment results can be questionable.

Lauer, A. K. (2014). Intravitreal anti-VEGF in retinopathy of prematurity: Several years on. *Asia-Pacific Journal of Ophthalmology (Philadelphia, Pa.), 3*(6), 329-330.

Lee, C. I., Gold, L. S., Nelson, H. D., Chou, R., Ramsey, S. D., & Sullivan, S. D. (2015). Comparative effectiveness of imaging modalities to determine metastatic breast cancer treatment response. *Breast, 24*(1), 3-11.

We performed a systematic review to address the comparative effectiveness of different imaging modalities in evaluating treatment response among metastatic breast cancer patients. We searched seven multidisciplinary electronic databases for relevant publications (January 2003-December 2013) and performed dual abstraction of details and results for all clinical studies that involved stage IV breast cancer patients and evaluated imaging for detecting treatment response. Among 159 citations reviewed, 17 single-institution, non-randomized, observational studies met our inclusion criteria. Several studies demonstrate that changes in PET/CT standard uptake values are associated with changes in tumor volume as determined by bone scan, MRI, and/or

CT. However, no studies evaluated comparative test performance between modalities or determined relationships between imaging findings and subsequent clinical decisions. Evidence for imaging's effectiveness in determining treatment response among metastatic breast cancer patients is limited. More rigorous research is needed to address imaging's value in this patient population.

Lee, C. S., Vellone, E., Lyons, K. S., Cocchieri, A., Bidwell, J. T., D'Agostino, F., et al. (2015). Patterns and predictors of patient and caregiver engagement in heart failure care: A multi-level dyadic study. *International Journal of Nursing Studies*, 52(2), 588-597.

Background: Heart failure is a burdensome clinical syndrome, and patients and their caregivers are responsible for the vast majority of heart failure care. Objectives: This study aimed to characterize naturally occurring archetypes of patient-caregiver dyads with respect to patient and caregiver contributions to heart failure self-care, and to identify patient-, caregiver- and dyadic-level determinants thereof. Design: Dyadic analysis of cross-sectional data on patients and their caregivers. Setting: Outpatient heart failure clinics in 28 Italian provinces. Participants: 509 Italian heart failure patients and their primary caregivers. Methods: Multilevel and mixture modeling were used to generate dyadic averages and incongruence in patient and caregiver contributions to heart failure self-care and identify common dyadic archetypes, respectively. Results: Three distinct archetypes were observed. 22.4% of dyads were labeled as novice and complementary because patients and caregivers contributed to different aspects of heart failure self-care that was generally poor; these dyads were predominantly older adults with less severe heart failure and their adult child caregivers. 56.4% of dyads were labeled as inconsistent and compensatory because caregivers reported greater contributions to the areas of self-care most insufficient on the part of the patients; patients in these dyads had the highest prevalence of hospitalizations for heart failure in the past year and the fewest limitations to performing activities of daily living independently. Finally, 21.2% of dyads were labeled as expert and collaborative because of high contributions to all aspects of heart failure self-care, the best relationship quality and lowest caregiver strain compared with the other archetypes; patients in this archetype were likely the sickest because they also had the worst heart failure-related quality of life. Conclusion: Three distinct archetypes of dyadic contributions to heart failure care

were observed that represent a gradient in the level of contributions to self-care, in addition to different approaches to working together to manage heart failure. Interventions and clinical programs that involve heart failure dyads should tailor strategies to take into consideration these distinct archetypes and their attributes.

Lee, D. S., & Goeres, L. M. (2015). Higher antihypertensive dose increases risk of falls in older people. *Evidence-Based Nursing,*

Lee-Lin, F., Nguyen, T., Pedhiwala, N., Dieckmann, N., & Menon, U. (2015). A breast health educational program for chinese-american women: 3- to 12-month postintervention effect. *American Journal of Health Promotion, 29*(3), 173-181.

Purpose. To test the efficacy of a culturally targeted breast cancer screening educational program in increasing mammogram completion in Chinese-American immigrant women. Design.

Randomized controlled study Setting. Chinese communities, Portland, Oregon. Subjects. From April 2010 to September 2011, 300 women were randomized to receive a theory-based, culturally targeted breast cancer screening educational intervention (n = 147) or a mammography screening brochure published by the National Cancer Institute (n = 153).

Intervention. The two-part intervention consisted of group teaching with targeted, theory-based messages followed by individual counseling sessions. Measures. Mammography completion, perceived susceptibility, perceived benefits, perceived barriers, perceived cultural barriers, and demographic variables. Analysis. A 2×3 mixed logistic model was applied to determine odds ratio of mammogram completion. Results. Behavior changed in both groups, with a total of 170 participants (56.7%) reporting a mammogram at 12 months. The logistic model indicated increased odds of mammogram completion in the intervention compared to the control group at 3, 6, and 12 months. When controlling for marital status, age, and age moved to the United States, the intervention group was nine times more likely to complete mammograms than the control group. Conclusion. The culturally targeted educational program significantly increased mammogram use among Chinese immigrant women. Further testing of effectiveness in larger community settings is needed. The intervention may also serve as a foundation from which to develop education to increase cancer screening among other minority subgroups.

LeMond, L., Camacho, S. A., & Goodlin, S. J. (2015). Palliative care and decision making in advanced heart failure. *Current Treatment Options in Cardiovascular Medicine*, 17(2), 359.

OPINION STATEMENT: The diagnosis of advanced heart failure (HF) is established in patients for whom symptoms are refractory to guideline-directed therapies. Palliative care (PC) is based on symptom management and support of the patient and family, making its integration into the care of those with advanced HF essential. Comorbidities including frailty, cognitive dysfunction, and depression are often under-recognized in patients with advanced HF and may correlate with outcomes. Decisions should be based on the patient's values, goals agreed upon by the clinician with the patient, and what is medically reasonable. Palliative Care should be integrated to help with both palliation of symptoms and support for families and patients.

Leshem, Y. A., Hajar, T., Hanifin, J. M., & Simpson, E. L. (2015). What the EASI score tells us about the severity of atopic dermatitis - an interpretability study. *The British Journal of Dermatology*,

BACKGROUND: The EASI (Eczema Area and Severity Index) is an investigator-assessed instrument measuring the severity of clinical signs in atopic dermatitis (AD). The EASI was identified as one of the best validated outcome measures for AD; however, no previous studies address how to interpret the EASI score for clinical use. OBJECTIVES: To evaluate the interpretability and the ease of use of the EASI. METHODS: A retrospective analysis of pediatric and adult patients with AD was performed. Interpretability was evaluated by stratifying the EASI scores according to the Investigator's Global Assessment. The severity strata displaying the highest kappa coefficient of agreement were then selected as the recommended EASI band. The time to administer the EASI was recorded in a subgroup of patients. RESULTS: The suggested severity strata for the EASI are: 0=clear; 0.1-1=almost clear; 1.1-7=mild; 7.1-21=moderate; 21.1-50=severe; 50.1-72=very severe, kappa = 0.75. The EASI was also found to be acceptable in terms of ease of use, with assessments by trained investigators taking approximately six minutes. CONCLUSIONS: Our study provides the first guide for interpreting the EASI score. It enables translation of the EASI numerical output into an AD global severity state that should be more meaningful to providers and patients. Along with a short administration time, the EASI demonstrates adequate feasibility, further supporting its use in clinical trials. This article is protected by copyright. All rights reserved.

Li, M. H., Suchland, K. L., & Ingram, S. L. (2015). GABAergic transmission and enhanced modulation by opioids and endocannabinoids in adult rat rostral ventromedial medulla. *The Journal of Physiology*, 593(1), 217-230.

KEY POINTS: Electrical stimulation of the rostral ventromedial medulla (RVM) facilitates pain behaviours in neonates but inhibits these behaviours in adults. The cellular mechanisms underlying these changes in RVM modulation of pain behaviours are not known. We optimized whole-cell patch-clamp recordings for RVM neurons in animals older than postnatal day 30 and compared the results to postnatal day 10-21 animals. Our results demonstrate that the gamma-aminobutyric acid (GABA) release is lower and opioid effects are more evident in adult rats compared to early postnatal rats. A cannabinoid receptor antagonist significantly increased GABA release in mature but not in immature RVM neurons suggesting the presence of local endocannabinoid tone in mature RVM. ABSTRACT: Neurons in the rostral ventromedial medulla (RVM) play critical and complex roles in pain modulation. Recent studies have shown that electrical stimulation of the RVM produces pain facilitation in young animals (postnatal (PN) day < 21) but predominantly inhibits pain behaviours in adults. The cellular mechanisms underlying these changes in RVM modulation of pain behaviours are not known. This is in part because whole-cell patch-clamp studies in RVM to date have been in young (PN day < 18) animals because the organization and abundance of myelinated fibres in this region make the RVM a challenging area for whole-cell patch-clamp recording in adults. Several neurotransmitter systems, including GABAergic neurotransmission, undergo developmental changes that mature by PN day 21. Thus, we focused on optimizing whole-cell patch-clamp recordings for RVM neurons in animals older than PN day 30 and compared the results to animals at PN day 10-21. Our results demonstrate that the probability of GABA release is lower and that opioid and endocannabinoid effects are more evident in adult rats (mature) compared to early postnatal (immature) rats. Differences in these properties of RVM neurons may contribute to the developmental changes in descending control of pain from the RVM to the spinal cord.

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Neurons in the rostral ventromedial medulla (RVM) play critical and complex roles in pain modulation. Recent studies have shown that electrical stimulation of the RVM produces pain facilitation in young animals (postnatal (PN) day < 21) but predominantly inhibits pain behaviours in adults. The cellular mechanisms underlying these changes in RVM modulation of pain behaviours are not known. This is in part because whole-cell patch-clamp studies in RVM to date have been in young (PN day < 18) animals because the organization and abundance of myelinated fibres in this region make the RVM a challenging area for whole-cell patch-clamp recording in adults. Several neurotransmitter systems, including GABAergic neurotransmission, undergo developmental changes that mature by PN day 21. Thus, we focused on optimizing whole-cell patch-clamp recordings for RVM neurons in animals older than PN day 30 and compared the results to animals at PN day 10-21. Our results demonstrate that the probability of GABA release is lower and that opioid and endocannabinoid effects are more evident in adult rats (mature) compared to early postnatal (immature) rats. Differences in these properties of RVM neurons may contribute to the developmental changes in descending control of pain from the RVM to the spinal cord.

Liebling, M. R. (2015). Treg cell function in rheumatoid arthritis is compromised by CTLA-4 promoter methylation resulting in failure to activate the IDO pathway. *Arthritis & Rheumatology (Hoboken, N.J.)*,

Lin, S., Sabbah, W., Sedgley, C. M., & Whitten, B. (2015). A survey for endodontists in today's economy: Exploring the current state of endodontics as a profession and the relationship between endodontists and their referral base. *Journal of Endodontics*,

INTRODUCTION: The purpose of this study was to assess the perceptions, referral trends, and practice patterns of practicing endodontists in the United States and any effect the recent economy may have had on these. METHODS: A 24-question survey was formulated and sent via [www.surveymonkey.com](http://www.surveymonkey.com) to 3255 active members of the American Association of Endodontists. Overall, 875 participants completed the survey, a response rate of 26.9%. RESULTS: The average number of treatment cases per day was 5.7. Average work hours per week were 34.3 for

men and 30.7 for women (P 20 years), practice in urban settings, and practice in a solo environment are most significantly affected.

Linfante, I., Starosciak, A. K., Walker, G. R., Dabus, G., Castonguay, A. C., Gupta, R., et al. (2015).

Predictors of poor outcome despite recanalization: A multiple regression analysis of the NASA registry. *Journal of Neurointerventional Surgery*,

BACKGROUND: Mechanical thrombectomy with stent-retrievers results in higher recanalization rates compared with previous devices. Despite successful recanalization rates (Thrombolysis in Cerebral Infarction (TICI) score  $\geq 2b$ ) of 70-83%, good outcomes by 90-day modified Rankin Scale (mRS) score 2) despite successful recanalization (TICI  $\geq 2b$ ) in the North American Solitaire Stent Retriever Acute Stroke (NASA) registry. METHODS: Logistic regression was used to evaluate baseline characteristics and recanalization outcomes for association with 90-day mRS score of 0-2 (good outcome) vs 3-6 (poor outcome). Univariate tests were carried out for all factors. A multivariable model was developed based on backwards selection from the factors with at least marginal significance ( $p \leq 0.1$ ) despite successful recanalization (TICI  $\geq 2b$ ) in the North American Solitaire Stent Retriever Acute Stroke (NASA) registry. METHODS: Logistic regression was used to evaluate baseline characteristics and recanalization outcomes for association with 90-day mRS score of 0-2 (good outcome) vs 3-6 (poor outcome). Univariate tests were carried out for all factors. A multivariable model was developed based on backwards selection from the factors with at least marginal significance ( $p \leq 0.1$ ) despite successful recanalization (TICI  $\geq 2b$ ) in the North American Solitaire Stent Retriever Acute Stroke (NASA) registry. RESULTS: Age  $\geq 80$  years, occlusion site of internal carotid artery (ICA)/basilar artery, National Institute of Health Stroke Scale (NIHSS) score  $\geq 18$ , history of diabetes mellitus, TICI 2b, use of rescue therapy, not using a balloon-guided catheter or intravenous tissue plasminogen activator (IV t-PA), and  $>30$  min to recanalization ( $p \leq 0.05$ ). Age  $\geq 80$  years, occlusion site ICA/basilar, initial NIHSS score  $\geq 18$ , diabetes, absence of IV t-PA,  $\geq 3$  passes, and use of rescue therapy were significant independent predictors of poor 90-day outcome in a model with good predictive power (c-index=0.80). CONCLUSIONS: Age, occlusion site, high NIHSS, diabetes, no IV t-PA,  $\geq 3$  passes, and use of rescue therapy are associated with poor 90-day outcome despite successful recanalization.

Liu, F., Zhang, Z. -, Zhang, X. -, & Xu, J. -. (2014). 2-D honeycomb MI wave communication system. *Tongxin Xuebao/Journal on Communications*, 35(12), 190-195.

To realize the high reliable communication and the wireless power transmission in the wireless underground sensor network, a new type of 2D honeycomb magneto-inductive network was put forward at VLF band. The system model was established, and bandwidth, group velocity and beam forming technologies were researched based on the current dispersion equations. Simulation with Runge-Kutta method was carried out to verify the efficiency of the network. The result show that the omnidirectional propagation can be realized in the proposed honeycomb network with more balanced bandwidth and group velocity in every direction compared with the square lattice structure. Directional communication can also be realized based on the cooperative multi-antenna technology. The proposed honeycomb magneto-inductive network is very suitable to build wireless sensor networks with high connectivity and power efficiency in the underground environments.

Liu, N., Niu, G., Xie, Z., Chen, Z., Itzek, A., Kreth, J., et al. (2015). The streptococcus mutans irvA gene encodes a trans-acting riboregulatory mRNA. *Molecular Cell*, 57(1), 179-190.

In both prokaryotes and eukaryotes, insight into gene function is typically obtained by insilico homology searches and/or phenotypic analyses of strains bearing mutations within open reading frames. However, the studies herein illustrate how mRNA function is not limited to the expression of a cognate protein. We demonstrate that a stress-induced protein-encoding mRNA (irvA) from the dental caries pathogen *Streptococcus mutans* directly modulates target mRNA (gbpC) stability through seed pairing interactions. The 5' untranslated region of irvA mRNA is a trans riboregulator of gbpC and a critical activator of the DDAG stress response, whereas IrvA functions independently in the regulation of natural competence. The irvA riboregulatory domain controls GbpC production by forming irvA-gbpC hybrid mRNA duplexes that prevent gbpC degradation by an RNase J2-mediated pathway. These studies implicate a potentially ubiquitous role for typical protein-encoding mRNAs as riboregulators, which could alter current concepts in gene regulation.

Lo, J. O., Feist, C. D., Hashima, J., & Shaffer, B. L. (2015). Jacobsen syndrome detected by noninvasive prenatal testing. *Obstetrics and Gynecology*, 125(2), 387-389.

**BACKGROUND:** Noninvasive prenatal testing has a high detection rate of common fetal chromosomal aneuploidies. However, detection of additional chromosome abnormalities has not been well described or validated. **CASE:** We report a case of Jacobsen syndrome, a congenital disorder involving deletion of chromosome 11q, detected by noninvasive prenatal testing at 14 weeks of gestation and confirmed on neonatal testing with array chromosomal genomic hybridization. **CONCLUSION:** Noninvasive prenatal testing should be considered when multiple fetal anomalies are present and invasive testing is declined. As the clinical application of noninvasive prenatal testing continues to evolve, additional submicroscopic chromosomal information may be clinically helpful and should be confirmed with diagnostic testing until larger studies help further define the screening characteristics of noninvasive prenatal testing.

Lombardi, A. J., Hoskins, E. E., Foglesong, G. D., Wikenheiser-Brokamp, K. A., Wiesmueller, L., Hanenberg, H., et al. (2015). Acquisition of relative interstrand crosslinker resistance and PARP inhibitor sensitivity in fanconi anemia head and neck cancers. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

**Purpose:** Fanconi anemia (FA) is an inherited disorder associated with a constitutional defect in the FA DNA repair machinery that is essential for resolution of DNA interstrand crosslinks.

Individuals with FA are predisposed to formation of head and neck squamous cell carcinomas (HNSCCs) at a young age. Prognosis is poor, partly due to patient intolerance of chemotherapy and radiation requiring dose reduction, which may lead to early recurrence of disease.

**Experimental Design:** Using HNSCC cell lines derived from the tumors of FA patients, and murine HNSCC cell lines derived from the tumors of wild type and Fancc<sup>-/-</sup> mice, we sought to define FA-dependent chemosensitivity and DNA repair characteristics. We utilized DNA repair reporter assays to explore the preference of FA HNSCC cells for non-homologous end joining (NHEJ).

**Results:** Surprisingly, interstrand crosslinker (ICL) sensitivity was not necessarily FA-dependent in human or murine cell systems. Our results suggest that the increased Ku-dependent NHEJ that is expected in FA cells did not mediate relative ICL resistance. ICL exposure resulted in increased DNA damage sensing and repair by poly(ADP-ribose) polymerase (PARP) in FA-deficient cells.

Moreover, human and murine FA HNSCC cells were sensitive to PARP inhibition, and sensitivity of human cells was attenuated by FA gene complementation. **Conclusions:** The observed reliance

upon PARP-mediated mechanisms reveals a means by which FA HNSCCs can acquire relative resistance to the ICL-based chemotherapy that is a foundation of HNSCC treatment, as well as a potential target for overcoming chemoresistance in the chemosensitive individual.

Lou, S. M., Montgomery, P. A., Larkin, K. L., Winthrop, K., Zierhut, M., Rosenbaum, J. T., et al.

(2015). Diagnosis and treatment for ocular tuberculosis among uveitis specialists: The international perspective. *Ocular Immunology and Inflammation*, 23(1), 32-39.

Abstract Purpose: To assess the approach of international specialists, who primarily practice in tuberculosis-endemic areas, to ocular tuberculosis (TB). METHODS: International experts from India, Brazil, Taiwan, and more than 10 other countries were surveyed using two clinical cases and general questions. RESULTS: A total of 244 experts were sent a survey about the treatment and diagnosis of ocular tuberculosis; 65 responded (27%), of whom 34 were affiliated with practices in India, while 31 primarily practice at international sites outside of India and North America. The data from this survey were compared with the results of a similar survey sent to members of the American Uveitis Society. The survey provided normative data on how physicians evaluate patients with uveitis as well as opinions about ocular TB. Responses varied widely on topics such as tests to include in the workup of undifferentiated uveitis, initial therapy, and duration of treatment. Physicians from developing countries relied more on chest CT scans and tuberculin skin testing (TST) than their counterparts in developed countries. CONCLUSIONS: The approach to diagnosis and management of TB is heterogeneous worldwide. However, there are substantial differences in the clinical approach to uveitis depending on the clinician's location of practice.

Lovejoy, J., Riffe, D., & Lovejoy, T. I. (2015). An examination of direct and indirect effects of exposure and attention to health media on intentions to avoid unprotected sun exposure. *Health Communication*, 30(3), 261-270.

Skin cancer is the most commonly diagnosed cancer in the United States, accounting for more than 2 million diagnoses and more than 9,000 deaths annually. A regional online survey of students enrolled at institutions of higher education (N = 1,251) examined (a) associations between health media use and intentions to avoid unprotected sun exposure and (b) theoretically

derived health behavior constructs that may mediate the relationship between media use and individuals' decisions to avoid unprotected sun exposure. Individuals with greater exposure and attention to health information in television, magazines, and newspapers had higher intentions to avoid unprotected sun exposure. Multiple mediation models indicated that health behavior constructs collectively mediated the relationship between television use and sun-protective behavioral intentions. Both cumulative and specific indirect mediating effects were observed for the relationship between magazine use and sun-protective behavioral intentions. However, the direction of effects was opposite to the hypothesized direction, due primarily to the association of magazine use with less favorable attitudes about sun protection and reduced behavioral control to avoid unprotected sun exposure. This study provides preliminary evidence for the interrelationships among media use, internal psychological states and cognitions, and health behavior decision making. Future studies should further explicate the mediating processes that account for the relationships between media and health behavior.

Lovering, A. T., Elliott, J. E., Laurie, S. S., Beasley, K. M., Gust, C. E., Mangum, T. S., et al. (2014).

Ventilatory and sensory responses in adult survivors of preterm birth and bronchopulmonary dysplasia with reduced exercise capacity. *Annals of the American Thoracic Society*, 11(10), 1528-1537.

Objectives: To test the hypothesis that adult survivors of preterm birth (<32 wk gestational age) with (n = 20) and without BPD (n = 15) with reduced exercise capacity demonstrate clinically important respiratory limitations at near-maximal exercise compared with full-term control subjects (n = 20). Methods: Detailed ventilatory and sensory measurements were made before and during exercise on all patients in the three study groups. Measurements and Main Results: During exercise at 90% of peak  $\dot{V}O_2$  ( $\dot{V}O_{2peak}$ ), inspiratory reserve volume decreased to  $\approx 0.5$  L in all groups, but this occurred at significantly lower absolute workloads and  $\dot{V}E$  in ex-preterm subjects with and without BPD compared with full-term control subjects. Severe dyspnea was present and similar at comparable  $\dot{V}E$  between all groups, but leg discomfort at comparable workloads was greater in ex-preterm subjects with and without BPD compared with control subjects. At 50 to 90% of  $\dot{V}O_{2peak}$ , exercise-induced expiratory flow limitation was significantly greater in ex-preterm subjects with BPD compared with ex-preterm subjects without BPD and

control subjects. The degree of expiratory flow limitation in ex-preterm subjects with and without BPD was significantly related to neonatal O<sub>2</sub> therapy duration. Conclusions: Severe dyspnea and leg discomfort associated with critical constraints on VT expansion may lead to reduced exercise tolerance in adults born very or extremely preterm, whether or not their birth was complicated by BPD and despite differences in expiratory flow limitation. In this regard, adults born very or extremely preterm have respiratory limitations to exercise similar to patients with chronic obstructive pulmonary disease. Rationale: Adults born very to extremely preterm, with or without bronchopulmonary dysplasia (BPD), have obstructive lung disease, but it is unknown whether this results in respiratory limitations, such as mechanical constraints to VT expansion during exercise leading to intolerable dyspnea and reduced exercise tolerance, as it does in patients with chronic obstructive pulmonary disease.

Lutsep, H. L., Barnwell, S. L., Larsen, D. T., Lynn, M. J., Hong, M., Turan, T. N., et al. (2015).

Outcome in patients previously on antithrombotic therapy in the SAMMPRIS trial: Subgroup analysis. *Stroke; a Journal of Cerebral Circulation*,

BACKGROUND AND PURPOSE: Stenting has been used as a rescue therapy in patients with intracranial arterial stenosis and a transient ischemic attack or stroke when on antithrombotic therapy (AT). We determined whether the stenting versus aggressive medical therapy for intracranial arterial stenosis (SAMMPRIS) trial supported this approach by comparing the treatments within subgroups of patients whose qualifying event (QE) occurred on versus off of AT. METHODS: The primary outcome, 30-day stroke and death and later strokes in the territory of the qualifying artery, was compared between (1) percutaneous transluminal angioplasty and stenting plus aggressive medical therapy (PTAS) versus aggressive medical management therapy alone (AMM) for patients whose QE occurred on versus off AT and between (2) patients whose QE occurred on versus off AT separately for the treatment groups. RESULTS: Among the 284/451 (63%) patients who had their QE on AT, the 2-year primary end point rates were 15.6% for those randomized to AMM (n=140) and 21.6% for PTAS (n=144; P=0.043, log-rank test). In the 167 patients not on AT, the 2-year primary end point rates were 11.6% for AMM (n=87) and 18.8% for PTAS (n=80; P=0.31, log-rank test). Within both treatment groups, there was no difference in the time to the primary end point between patients who were on or off AT (AMM,

P=0.96; PTAS, P=0.52; log-rank test). CONCLUSIONS: SAMMPRIS results indicate that the benefit of AMM over PTAS is similar in patients on versus off AT at the QE and that failure of AT is not a predictor of increased risk of a primary end point. CLINICAL TRIAL REGISTRATION: URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00576693.

Lyon, E., Cockerill, F. R., Bale, S. J., Beadling, C., Bry, L., Hagenkord, J., et al. (2015). Next generation sequencing in clinical diagnostics: Experiences of early adopters. *Clinical Chemistry*, 61(1), 41-49.

Macey, T. A., Bobeck, E. N., Suchland, K. L., Morgan, M. M., & Ingram, S. L. (2015). Change in functional selectivity of morphine with the development of antinociceptive tolerance. *British Journal of Pharmacology*, 172(2), 549-561.

Background and Purpose Opioids, such as morphine, are the most effective treatment for pain but their efficacy is diminished with the development of tolerance following repeated administration. Recently, we found that morphine activated ERK in opioid-tolerant but not in naïve rats, suggesting that morphine activation of  $\mu$ -opioid receptors is altered following repeated morphine administration. Here, we have tested the hypothesis that  $\mu$ -opioid receptor activation of ERK in the ventrolateral periaqueductal gray (vlPAG) is dependent on dynamin, a protein implicated in receptor endocytosis. Experimental Approach Rats were made tolerant to repeated microinjections of morphine into the vlPAG. The effects of dynamin on ERK activation and antinociception were assessed by microinjecting myristoylated dominant-negative dynamin peptide (Dyn-DN) or a scrambled control peptide into the vlPAG. Microinjection of a fluorescent dermorphin analogue (DERM-A594) into the vlPAG was used to monitor  $\mu$ -opioid receptor internalization. Key Results Morphine did not activate ERK and Dyn-DN administration had no effect on morphine-induced antinociception in saline-pretreated rats. In contrast, morphine-induced ERK activation in morphine-pretreated rats that was blocked by Dyn-DN administration. Dyn-DN also inhibited morphine antinociception. Finally, morphine reduced DERM-A594 internalization only in morphine-tolerant rats indicating that  $\mu$ -opioid receptors were internalized and unavailable to bind DERM-A594. Conclusions and Implications Repeated morphine administration increased  $\mu$ -opioid receptor activation of ERK signalling via a dynamin-dependent

mechanism. These results demonstrate that the balance of agonist signalling to G-protein and dynamin-dependent pathways is altered, effectively changing the functional selectivity of the agonist-receptor complex. **Linked Articles** This article is part of a themed section on Opioids: New Pathways to Functional Selectivity.

Mackey, R. H., Mora, S., Bertoni, A. G., Wassel, C. L., Carnethon, M. R., Sibley, C. T., et al. (2015).

Lipoprotein particles and incident type 2 diabetes in the multi-ethnic study of atherosclerosis.

*Diabetes Care,*

**OBJECTIVE:** In the Multi-Ethnic Study of Atherosclerosis (MESA), we evaluated associations of baseline levels of a lipoprotein-based insulin resistance (IR) index (LP-IR), IR-related lipoprotein particles, mean particle sizes, and lipids, with incident type 2 diabetes, independent of confounders, glucose, insulin, and the HOMA-IR. **RESEARCH DESIGN AND METHODS:** Among 5,314 adults aged 45-84 years without baseline diabetes or cardiovascular disease, 656 cases of diabetes were identified during a mean follow-up of 7.7 years. Lipoprotein particle concentrations, size, and LP-IR were determined by nuclear magnetic resonance spectroscopy of stored baseline plasma. Potential effect modification, by race/ethnicity, sex, baseline use of lipid-lowering medications or hormone therapy, or glucose strata ( $\geq 100$  mg/dL), was also evaluated. **RESULTS:** Higher levels of LP-IR, large VLDL particles (VLDL-Ps), small LDL particles, triglycerides (TG), and TG-to-HDL cholesterol (HDL-C) and lower levels of large HDL particles, smaller HDL and LDL size, and larger VLDL size were significantly associated with incident diabetes adjusted for confounders and glucose or insulin. These also were similar by race/ethnicity, sex, and treatment group. Associations were similar for LP-IR, large VLDL-P, mean VLDL size, TG, and TG/HDL-C; they persisted for LP-IR, large VLDL-Ps, or mean VLDL size adjusted for HOMA-IR or TG/HDL-C and glucose but not for the TG-to-HDL-C ratio adjusted for LP-IR or for HOMA-IR or insulin if adjusted for LP-IR and glucose. **CONCLUSIONS:** Among ethnically diverse men and women, LP-IR, large VLDL-Ps, large VLDL size, TG, and TG/HDL-C were associated with incident diabetes independent of established risk factors, glucose, insulin, or HOMA-IR, as well as the use of lipid-lowering medications or hormone therapy.

Mansoor, A. M., & Karlapudi, S. P. (2015). Images in clinical medicine. kussmaul's sign. *The New England Journal of Medicine*, 372(2), e3.

Mansoor, A. M., & Karlapudi, S. P. (2015). Kussmaul's sign. *New England Journal of Medicine*, 372(2), e3.

Mao, Y., Jin, X., Dutta, G. G., Scholz, J. P., & Agrawal, S. K. (2015). Human movement training with a cable driven ARm EXoskeleton (CAREX). *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 23(1), 84-92.

In recent years, the authors have proposed lightweight exoskeleton designs for upper arm rehabilitation using multi-stage cable-driven parallel mechanism. Previously, the authors have demonstrated via experiments that it is possible to apply "assist-as-needed" forces in all directions at the end-effector with such an exoskeleton acting on an anthropomorphic machine arm. A human-exoskeleton interface was also presented to show the feasibility of CAREX on human subjects. The goals of this paper are to 1) further address issues when CAREX is mounted on human subjects, e.g., generation of continuous cable tension trajectories 2) demonstrate the feasibility and effectiveness of CAREX on movement training of healthy human subjects and a stroke patient. In this research, CAREX is rigidly attached to an arm orthosis worn by human subjects. The cable routing points are optimized to achieve a relatively large "tensioned" static workspace. A new cable tension planner based on quadratic programming is used to generate continuous cable tension trajectory for smooth motion. Experiments were carried out on eight healthy subjects. The experimental results show that CAREX can help the subjects move closer to a prescribed circular path using the force fields generated by the exoskeleton. The subjects also adapt to the path shortly after training. CAREX was also evaluated on a stroke patient to test the feasibility of its use on patients with neural impairment. The results show that the patient was able to move closer to a prescribed straight line path with the "assist-as-needed" force field.

Marx, P., Meiers, M., & Brückner, R. (2014). Activity of the response regulator CiaR in mutants of streptococcus pneumoniae R6 altered in acetyl phosphate production. *Frontiers in Microbiology*, 5(DEC)

The two-component regulatory system CiaRH of *Streptococcus pneumoniae* is implicated in

competence,  $\beta$ -lactam resistance, maintenance of cell integrity, bacteriocin production, host colonization, and virulence. Depending on the growth conditions, CiaR can be highly active in the absence of its cognate kinase CiaH, although phosphorylation of CiaR is required for DNA binding and gene regulation. To test the possibility that acetyl phosphate (AcP) could be the alternative phosphodonor, genes involved in pyruvate metabolism were disrupted to alter cellular levels of acetyl phosphate. Inactivating the genes of pyruvate oxidase SpxB, phosphotransacetylase Pta, and acetate kinase AckA, resulted in very low AcP levels and in strongly reduced CiaR-mediated gene expression in CiaH-deficient strains. Therefore, alternative phosphorylation of CiaR appears to proceed via AcP. The AcP effect on CiaR is not detected in strains with CiaH. Attempts to obtain elevated AcP by preventing its degradation by acetate kinase AckA, were not successful in CiaH-deficient strains with a functional SpxB, the most important enzyme for AcP production in *S. pneumoniae*. The *ciaH-spxB-ackA* mutant producing intermediate amounts of AcP could be constructed and showed a promoter activation, which was much higher than expected. Since activation was dependent on AcP, it can apparently be used more efficiently for CiaR phosphorylation in the absence of AckA. Therefore, high AcP levels in the absence of CiaH and AckA may cause extreme overexpression of the CiaR regulon leading to synthetic lethality. AckA is also involved in a regulatory response, which is mediated by CiaH. Addition of acetate to the growth medium switch CiaH from kinase to phosphatase. This switch is lost in the absence of AckA indicating metabolism of acetate is required, which starts with the production of AcP by AckA. Therefore, AckA plays a special regulatory role in the control of the CiaRH two-component regulatory system.

Maziarz, R. T., Devos, T., Bachier, C. R., Goldstein, S. C., Leis, J. F., Devine, S. M., et al. (2014).

Single and multiple dose MultiStem (multipotent adult progenitor cell) therapy prophylaxis of acute graft-versus-host disease in myeloablative allogeneic hematopoietic cell transplantation: A phase 1 trial. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

We conducted a multicenter, phase 1 dose escalation study evaluating the safety of the allogeneic multipotent adult progenitor cell (MAPC, MultiStem, Athersys, Inc., Cleveland, OH) stromal product administered as an adjunct therapy to 36 patients after myeloablative allogeneic

hematopoietic cell transplantation (HCT). Patients received increasing doses of MAPC (1, 5, or 10 million cells per kilogram recipient weight) as a single i.v. dose on day +2 after HCT (n = 18), or once weekly for up to 5 doses (1 or 5 million cells per kilogram; n = 18). Infusional and regimen-related toxicities were assessed for 30 days after the last MAPC dose. Of 36 allogeneic HCT donors (17 related and 19 unrelated), 35 were 6/6 HLA matched. MAPC infusions were well tolerated without associated infusional toxicity, graft failure, or increased incidence of infection. Median times to neutrophil (n = 36) and platelet (n = 31) engraftment were 15 (range, 11 to 25) and 16 (range, 11 to 41) days, respectively. The overall cumulative incidences of grades II to IV and III and IV acute graft-versus-host disease (GVHD) at day 100 were 37% and 14%, respectively (n = 36). In the group that received the highest single MAPC dose (10 million cells/kg), day 100 incidence of grade II to IV GVHD was 11.1% (1 of 9) with no observed cases of grade III and IV GVHD. We found no evidence for MHC class II allogeneic antibody induction, although some patients showed an increase in serum anticlass I titers compared with baseline. MAPC contribution to blood chimerism was negligible. These phase I data support the safety of stromal stem cell therapy and suggest that MAPC should be tested prospectively as a novel therapeutic option for GVHD prophylaxis after HCT.

McCormick, J. A., & Ellison, D. H. (2015). Distal convoluted tubule. *Comprehensive Physiology*, 5(1), 45-98.

The distal convoluted tubule (DCT) is a short nephron segment, interposed between the macula densa and collecting duct. Even though it is short, it plays a key role in regulating extracellular fluid volume and electrolyte homeostasis. DCT cells are rich in mitochondria, and possess the highest density of Na(+)/K(+)-ATPase along the nephron, where it is expressed on the highly amplified basolateral membranes. DCT cells are largely water impermeable, and reabsorb sodium and chloride across the apical membrane via electroneutral pathways. Prominent among this is the thiazide-sensitive sodium chloride cotransporter, target of widely used diuretic drugs. These cells also play a key role in magnesium reabsorption, which occurs predominantly, via a transient receptor potential channel (TRPM6). Human genetic diseases in which DCT function is perturbed have provided critical insights into the physiological role of the DCT, and how transport is regulated. These include Familial Hyperkalemic Hypertension, the salt-wasting diseases Gitelman

syndrome and EAST syndrome, and hereditary hypomagnesemias. The DCT is also established as an important target for the hormones angiotensin II and aldosterone; it also appears to respond to sympathetic-nerve stimulation and changes in plasma potassium. Here, we discuss what is currently known about DCT physiology. Early studies that determined transport rates of ions by the DCT are described, as are the channels and transporters expressed along the DCT with the advent of molecular cloning. Regulation of expression and activity of these channels and transporters is also described; particular emphasis is placed on the contribution of genetic forms of DCT dysregulation to our understanding. (c) 2015 American Physiological Society. *Compr Physiol* 5: 45-98, 2015.

Mello, C. V., & Pinaud, R. (2006). *Immediate early gene regulation in the auditory system* Springer US.

Immediate early genes (IEGs) are genes whose expression in the brain is sensitive to the activation state of neuronal cells (see other chapters in this book and the reviews in Kaczmarek and Robertson, 2002). Although the exact relationship between neuronal activation and IEG expression is not entirely understood, the analysis of induced expression of IEGs has been extremely useful in the identification and study of brain regions activated by specific sensory stimuli or behavioral conditions. This is the case because IEG studies are non-invasive, allowing the mapping of brain activation without interfering with the animal's ability to behave or respond to the stimulus being presented. In addition, although IEG expression studies generally lack temporal resolution (but see the chapter by Guzowski in this volume), this type of analysis allows for the mapping of global patterns of activation with cellular resolution. Furthermore, some IEGs have been linked to neuronal plasticity (Guzowski et al., 1999; Jones et al., 2001) and their activation may indicate sites where experience-dependent changes take place in the brain. The present chapter discusses the use of IEG expression analysis to study brain regions and pathways involved in the processing of auditory stimuli in vertebrates (for previous reviews on related topics, see Chaudhuri, 1997; Clayton, 2000; Chaudhuri and Zangenehpour, 2002; Mello, 2002a, 2004; Mello et al., 2004).

Merchan, L. M., Hassan, H. E., Terrin, M. L., Waites, K. B., Kaufman, D. A., Ambalavanan, N., et al.

(2015). Pharmacokinetics, microbial response, and pulmonary outcomes of multidose intravenous azithromycin in preterm infants at risk for ureaplasma respiratory colonization. *Antimicrobial Agents and Chemotherapy*, 59(1), 570-578.

The study objectives were to refine the population pharmacokinetics (PK) model, determine microbial clearance, and assess short-term pulmonary outcomes of multiple-dose azithromycin treatment in preterm infants at risk for Ureaplasma respiratory colonization. Fifteen subjects (7 of whom were Ureaplasma positive) received intravenous azithromycin at 20 mg/kg of body weight every 24 h for 3 doses. Azithromycin concentrations were determined in plasma samples obtained up to 168 h post-first dose by using a validated liquid chromatography-tandem mass spectrometry method. Respiratory samples were obtained predose and at three time points post-last dose for Ureaplasma culture, PCR, antibiotic susceptibility testing, and cytokine concentration determinations. Pharmacokinetic data from these 15 subjects as well as 25 additional subjects (who received either a single 10-mg/kg dose [n = 12] or a single 20-mg/kg dose [n = 13]) were analyzed by using a nonlinear mixed-effect population modeling (NONMEM) approach. Pulmonary outcomes were assessed at 36 weeks post-menstrual age and 6 months adjusted age. A 2-compartment model with all PK parameters allometrically scaled on body weight best described the azithromycin pharmacokinetics in preterm neonates. The population pharmacokinetics parameter estimates for clearance, central volume of distribution, intercompartmental clearance, and peripheral volume of distribution were  $0.15 \text{ liters/h} \cdot \text{kg}^{0.75}$ ,  $1.88 \text{ liters} \cdot \text{kg}$ ,  $1.79 \text{ liters/h} \cdot \text{kg}^{0.75}$ , and  $13 \text{ liters} \cdot \text{kg}$ , respectively. The estimated area under the concentration-time curve over 24 h (AUC<sub>24</sub>)/MIC<sub>90</sub> value was 4 h. All posttreatment cultures were negative, and there were no drug-related adverse events. One Ureaplasma-positive infant died at 4 months of age, but no survivors were hospitalized for respiratory etiologies during the first 6 months (adjusted age). Thus, a 3-day course of 20 mg/kg/day intravenous azithromycin shows preliminary efficacy in eradicating Ureaplasma spp. from the preterm respiratory tract.

Messaoudi, I., Damania, B., & Wong, S. W. (2009). *Primate models for gammaherpesvirus-associated malignancies* Springer US.

Non-human primates (NHP) represent an invaluable resource for elucidating and understanding

disease processes in humans, as humans and NHP share close developmental, physiological and evolutionary relationships (Hendrickx and Binkerd 1990). For infectious disease research, NHP have historically played an important role as they are either susceptible to infectious agents that cause disease in humans (Kirschstein et al. 1960) or harbor infectious agents that are closely related to those that infect and cause disease in humans (Wenner et al. 1975). For example, NHP harbor herpesviruses that have coevolved with their hosts and are genetically more closely related to human herpesviruses than other mammalian herpesviruses. More importantly, these simian herpesvirus homologues, which include alpha ( $\alpha$ ), beta ( $\beta$ ) and gamma ( $\gamma$ ) herpesviruses, are capable of causing similar, if not identical, disease manifestations in their natural host, which makes them excellent models to dissect the complicated host-pathogen interactions that lead to disease. NHP can be divided into two groups, Old World and New World, both of which harbor  $\gamma$ -herpesviruses that can be divided into two classes: lymphocryptovirus ( $\gamma$ -1) and rhadinovirus ( $\gamma$ -2). The phylogenetic relationship of the simian  $\gamma$ -herpesviruses with human  $\gamma$ -herpesviruses is shown in Fig. 27.1, and demonstrates their close evolutionary relationships. The remainder of this chapter will discuss representative simian  $\gamma$ -herpesviruses from Old World and New World monkeys and their utility as models of human disease. Table 27.1 lists the  $\gamma$ -herpesviruses identified to date. Some of these viruses have not been isolated and cultured, but have been so named on the basis of limited DNA sequence analysis.

Messaoudi, I., Young, J. E., Colman, R. J., Handy, A. M., Roth, G. S., Ingram, D. K., et al. (2010).

*Aging and the effect of calorie restriction in rhesus monkeys* Springer Netherlands.

Calorie restriction (CR), defined as the consumption of fewer calories in the absence of malnutrition, has been shown to decelerate the rate of aging and result in several health benefits in many short-lived species. Beginning about 20 years ago, well-controlled long-term studies initiated at both the National Institute on Aging and the Wisconsin National Primate Research Center have been investigating the effect of CR in long-lived rhesus monkeys, an animal model that closely recapitulates human biology. The studies were uniquely designed but share a common hypothesis that 30% CR will delay age-related diseases and increase lifespan in a long-lived mammal. Results from both studies have established a beneficial effect of CR in terms of body weight, body composition, insulin sensitivity, oxidative stress, and several hormone profiles

or no detrimental effect on reproduction and sensory systems. More recently, work has focused on both behavioral and immune function alterations and thus this review emphasizes some of these findings and provides an update on female reproductive studies and sarcopenia.

Metten, P., Iancu, O. D., Spence, S. E., Walter, N. A., Oberbeck, D., Harrington, C. A., et al. (2014).

Dual-trait selection for ethanol consumption and withdrawal: Genetic and transcriptional network effects. *Alcoholism, Clinical and Experimental Research*, 38(12), 2915-2924.

BACKGROUND: Data from C57BL/6J (B6) x DBA/2J (D2) F2 intercrosses (B6xD2 F2), standard and recombinant inbred strains, and heterogeneous stock mice indicate that a reciprocal (or inverse) genetic relationship exists between alcohol consumption and withdrawal severity. Furthermore, some genetic studies have detected reciprocal quantitative trait loci (QTLs) for these traits. We used a novel mouse model developed by simultaneous selection for both high alcohol consumption/low withdrawal and low alcohol consumption/high withdrawal and analyzed the gene expression and genome-wide genotypic differences. METHODS: Randomly chosen third selected generation (S3) mice (N = 24/sex/line), bred from a B6xD2 F2, were genotyped using the Mouse Universal Genotyping Array, which provided 2,760 informative markers. QTL analysis used a marker-by-marker strategy with the threshold for a significant log of the odds (LOD) set at 10. Gene expression in the ventral striatum was measured using the Illumina Mouse 8.2 array. Differential gene expression and the weighted gene co-expression network analysis (WGCNA) were implemented. RESULTS: Significant QTLs for consumption/withdrawal were detected on chromosomes (Chr) 2, 4, 9, and 12. A suggestive QTL mapped to Chr 6. Some of the QTLs overlapped with known QTLs mapped for 1 of the traits individually. One thousand seven hundred and forty-five transcripts were detected as being differentially expressed between the lines; there was some overlap with known withdrawal genes (e.g., *Mpdz*) located within QTL regions. WGCNA revealed several modules of co-expressed genes showing significant effects in both differential expression and intramodular connectivity; a module richly annotated with kinase-related annotations was most affected. CONCLUSIONS: Marked effects of selection on expression and network structure were detected. QTLs overlapping with differentially expressed genes on Chr 2 (distal) and 4 suggest that these are cis-eQTLs (Chr 2: *Kif3b*, *Kcnq2*; Chr 4: *Mpdz*, *Snpc3*). Other QTLs identified were on Chr 2 (proximal), 9, and 12. Network results point to involvement

of kinase-related mechanisms and outline the need for further efforts such as interrogation of noncoding RNAs.

Milas, M. (2015). The genomic medicine paradigm shift. *Journal of Surgical Oncology*, 111(1), 1-2.

Nabozny, M. J., Kruser, J. M., Steffens, N. M., Brasel, K. J., Campbell, T. C., Gaines, M. E., et al.

(2015). Constructing high-stakes surgical decisions: It is better to die trying. *Annals of Surgery*,

OBJECTIVES:: To explore high-stakes surgical decision making from the perspective of seniors and surgeons. BACKGROUND:: A majority of older chronically ill patients would decline a low-risk procedure if the outcome was severe functional impairment. However, 25% of Medicare beneficiaries have surgery in their last 3 months of life, which may be inconsistent with their preferences. How patients make decisions to have surgery may contribute to this problem of unwanted care. METHODS:: We convened 4 focus groups at senior centers and 2 groups of surgeons in Madison and Milwaukee, Wisconsin, where we showed a video about a decision regarding a choice between surgery and palliative care. We used qualitative content analysis to identify themes about communication and explanatory models for end-of-life treatment decisions. RESULTS:: Seniors (N = 37) and surgeons (N = 17) agreed that maximizing quality of life should guide treatment decisions for older patients. However, when faced with an acute choice between surgery and palliative care, seniors viewed this either as a choice between life and death or a decision about how to die. Although surgeons agreed that very frail patients should not have surgery, they held conflicting views about presenting treatment options. CONCLUSIONS:: Seniors and surgeons highly value quality of life, but this notion is difficult to incorporate in acute surgical decisions. Some seniors use values to consider a choice between surgery and palliative care, whereas others view this as a simple choice between life and death. Surgeons acknowledge challenges framing decisions and describe a clinical momentum that promotes surgical intervention.

Nagalla, S. R., Snyder, C. K., Michaels, J. E., Laughlin, M. J., Roberts, C. T., Balaji, M., et al. (2015).

Maternal serum biomarkers for risk assessment in gestational diabetes. A potential universal screening test to predict GDM status. *Indian Journal of Endocrinology and Metabolism*, 19(1), 155-159.

The prevalence of gestational diabetes mellitus (GDM) is increasing because of the worldwide obesity/diabetes epidemic. The complications of untreated GDM affect both the mother and baby and include complications during pregnancy as well as increased risk of subsequent type-2 diabetes in mothers and offspring. Standard tests for hyperglycemia in diabetes, such as fasting glucose and hemoglobin (HbA1c), are currently not recommended for GDM screening. Instead, an oral glucose tolerance test is specified, which is invasive, time-consuming, and not easily accessible to many at-risk populations. In this study, we describe a multi-analyte maternal serum profile test that incorporates novel glycoprotein biomarkers and previously described GDM-associated markers. In screening for GDM by multi-analyte panel, the detection rate was 87% at a false-positive rate of 1%.

Nass, S. J., Beaupin, L. K., Demark-Wahnefried, W., Fasciano, K., Ganz, P. A., Hayes-Lattin, B., et al. (2015). Identifying and addressing the needs of adolescents and young adults with cancer: Summary of an institute of medicine workshop. *The Oncologist*,  
Cancer is the leading disease-related cause of death in adolescents and young adults (AYAs). This population faces many short- and long-term health and psychosocial consequences of cancer diagnosis and treatment, but many programs for cancer treatment, survivorship care, and psychosocial support do not focus on the specific needs of AYA cancer patients. Recognizing this health care disparity, the National Cancer Policy Forum of the Institute of Medicine convened a public workshop to examine the needs of AYA patients with cancer. Workshop participants identified many gaps and challenges in the care of AYA cancer patients and discussed potential strategies to address these needs. Suggestions included ways to improve access to care for AYAs, to deliver cancer care that better meets the medical and psychosocial needs of AYAs, to develop educational programs for providers who care for AYA cancer survivors, and to enhance the evidence base for AYAs with cancer by facilitating participation in research.

Newgard, C. D., Meier, E. N., Bulger, E. M., Buick, J., Sheehan, K., Lin, S., et al. (2015). Revisiting the "golden hour": An evaluation of out-of-hospital time in shock and traumatic brain injury. *Annals of Emergency Medicine*,

STUDY OBJECTIVE: We evaluate patients with shock and traumatic brain injury who were

previously enrolled in an out-of-hospital clinical trial to test the association between out-of-hospital time and outcome. METHODS: This was a secondary analysis of patients with shock and traumatic brain injury who were aged 15 years or older and enrolled in a Resuscitation Outcomes Consortium out-of-hospital clinical trial by 81 emergency medical services agencies transporting to 46 Level I and II trauma centers in 11 sites (May 2006 through May 2009). Inclusion criteria were systolic blood pressure less than or equal to 70 mm Hg or systolic blood pressure 71 to 90 mm Hg with pulse rate greater than or equal to 108 beats/min (shock cohort) and Glasgow Coma Scale score less than or equal to 8 (traumatic brain injury cohort); patients meeting both criteria were placed in the shock cohort. Primary outcomes were 28-day mortality (shock cohort) and 6-month Glasgow Outcome Scale-Extended score less than or equal to 4 (traumatic brain injury cohort). RESULTS: There were 778 patients in the shock cohort (26% 28-day mortality) and 1,239 patients in the traumatic brain injury cohort (53% 6-month Glasgow Outcome Scale-Extended score  $\leq 4$ ). Out-of-hospital time greater than 60 minutes was not associated with worse outcomes after accounting for important confounders in the shock cohort (adjusted odds ratio [aOR] 1.42; 95% confidence interval [CI] 0.77 to 2.62) or traumatic brain injury cohort (aOR 0.77; 95% CI 0.51 to 1.15). However, shock patients requiring early critical hospital resources and arriving after 60 minutes had higher 28-day mortality (aOR 2.37; 95% CI 1.05 to 5.37); this finding was not observed among a similar traumatic brain injury subgroup. CONCLUSION: Among out-of-hospital trauma patients meeting physiologic criteria for shock and traumatic brain injury, there was no association between time and outcome. However, the subgroup of shock patients requiring early critical resources and arriving after 60 minutes had higher mortality.

Nolz, J. C. (2015). Molecular mechanisms of CD8 T cell trafficking and localization. *Cellular and Molecular Life Sciences* : CMLS,

Cytotoxic CD8<sup>+</sup> T cells are potent mediators of host protection against disease due to their ability to directly kill cells infected with intracellular pathogens and produce inflammatory cytokines at the site of infection. To fully achieve this objective, naive CD8<sup>+</sup> T cells must be able to survey the entire body for the presence of foreign or "non-self" antigen that is delivered to draining lymph nodes following infection or tissue injury. Once activated, CD8<sup>+</sup> T cells undergo many rounds of

cell division, acquire effector functions, and are no longer restricted to the circulation and lymphoid compartments like their naive counterparts, but rather are drawn to inflamed tissues to combat infection. As CD8<sup>+</sup> T cells transition from naive to effector to memory populations, this is accompanied by dynamic changes in the expression of adhesion molecules and chemokine receptors that ultimately dictate their localization in vivo. Thus, an understanding of the molecular mechanisms regulating CD8<sup>+</sup> T cell trafficking and localization is critical for vaccine design, control of infectious diseases, treatment of autoimmune disorders, and cancer immunotherapy.

Olson, C. R., Owen, D. C., Ryabinin, A. E., Mello, C. V., & White, S. A. (2014). Drinking songs: Alcohol effects on learned song of zebra finches. *Plos One*, 9(12)

Speech impairment is one of the most intriguing and least understood effects of alcohol on cognitive function, largely due to the lack of data on alcohol effects on vocalizations in the context of an appropriate experimental model organism. Zebra finches, a representative songbird and a premier model for understanding the neurobiology of vocal production and learning, learn song in a manner analogous to how humans learn speech. Here we show that when allowed access, finches readily drink alcohol, increase their blood ethanol concentrations (BEC) significantly, and sing a song with altered acoustic structure. The most pronounced effects were decreased amplitude and increased entropy, the latter likely reflecting a disruption in the birds' ability to maintain the spectral structure of song under alcohol. Furthermore, specific syllables, which have distinct acoustic structures, were differentially influenced by alcohol, likely reflecting a diversity in the neural mechanisms required for their production. Remarkably, these effects on vocalizations occurred without overt effects on general behavioral measures, and importantly, they occurred within a range of BEC that can be considered risky for humans. Our results suggest that the variable effects of alcohol on finch song reflect differential alcohol sensitivity of the brain circuitry elements that control different aspects of song production. They also point to finches as an informative model for understanding how alcohol affects the neuronal circuits that control the production of learned motor behaviors.

Orloff, S. L. (2015). An alternative technique for harvesting marginal liver grafts with a replaced or accessory right hepatic artery. *World Journal of Surgery*,

Oster, N. V., Geller, B. M., Carney, P. A., Reisch, L. M., Onega, T., Weaver, D. L., et al. (2014).

Demographic and practice characteristics of pathologists who enjoy breast tissue interpretation. *Breast (Edinburgh, Scotland)*,

Physician attributes, job satisfaction and confidence in clinical skills are associated with enhanced performance and better patient outcomes. We surveyed 252 pathologists to evaluate associations between enjoyment of breast pathology, demographic/clinical characteristics and diagnostic performance. Diagnostic performance was determined by comparing pathologist assessments of a set of 60 cases with consensus assessments of the same cases made by a panel of experienced pathologists. Eighty-three percent of study participants reported enjoying breast pathology. Pathologists who enjoy breast interpretation were more likely to review  $\geq 10$  cases/week ( $p = 0.003$ ), report breast interpretation expertise ( $p = 0.013$ ) and have high levels of confidence interpreting breast pathology ( $p < 0.001$ ). These pathologists were less likely to report that the field was challenging ( $p < 0.001$ ) and that breast cases make them more nervous than other types of pathology ( $p < 0.001$ ). Enjoyment was not associated with diagnostic performance. Millions of women undergo breast biopsy annually, thus it is reassuring that although nearly a fifth of practicing pathologists who interpret breast tissue report not enjoying the field, precision is not impacted.

Ostrowski, K. A., Polackwich, A. S., Conlin, M. J., Hedges, J. C., & Fuchs, E. F. (2015). Impact of gross

and microscopic vasal fluid during vasectomy reversal on pregnancy. *The Journal of Urology*,

PURPOSE: To compare fertility outcomes with gross and microscopic fluid findings at the time of vasectomy reversal at a high volume vasectomy reversal center. MATERIALS & METHODS: A retrospective study of a prospective database was performed. All vasectomy reversals were performed by a single surgeon (EFF) between 1978-2011. Clinical pregnancy rate was either self-reported or via patient mailers. Patient and operative findings were determined through database review. We classified vasal fluid as opalescent, creamy, pasty, or clear. Intraoperative light microscopy was used to determine if sperm or sperm parts were present and if they motile.

Multivariate analysis was performed evaluating patient age, partner age, years after vasectomy, type of surgery, gross and microscopic fluid analysis. RESULTS: A total of 2,947 microsurgical vasectomy reversals were reviewed after we excluded reversals done for post-vasectomy pain. We determined the pregnancy status of 902 (31%). On univariate analysis with respect to pregnancy, motile sperm found at the time of vasovasostomy (VV) neared statistical significance ( $p=0.075$ ) and there was no difference between bilateral versus unilateral motile sperm. Gross fluid appearance was not statistically significant but we found the following order of pregnancy success: opalescent, creamy, clear, and pasty fluid. Using multivariate analysis, only female partner age and sperm heads only or no sperm seen on light microscopy had statistical significance ( $p<0.05$ ). CONCLUSIONS: Motile sperm at the time of vasectomy reversal approaches statistical significance on univariate analysis as factors that affect clinical pregnancy rates. In multivariate analysis, female partner age and microscopic findings of either sperm heads only or no sperm are inversely related to pregnancy rates. This data will help counsel couples after reversal and reinforces the importance of female partner age.

Palejwala, N. V., & Lauer, A. K. (2014). Aflibercept: An update on recent milestones achieved. *Drugs of Today (Barcelona, Spain : 1998)*, 50(12), 779-790.

In the last decade, intravitreal medications targeted to vascular endothelial growth factor (VEGF) such as pegaptanib, ranibizumab and bevacizumab have revolutionized the treatment and significantly improved visual acuity outcomes in patients with retinal vascular diseases such as age-related macular degeneration (AMD), diabetic macula edema (DME) and retinal vein occlusion (RVO). In recent years, aflibercept, an anti-VEGF drug that targets all isoforms of VEGF as well as placenta growth factor, has shown similar effectiveness in recent clinical trials. Aflibercept has firmly joined ranibizumab and bevacizumab as an important therapeutic option in the management of neovascular AMD. More recently, aflibercept appears to be contending with ranibizumab and bevacizumab as an important therapeutic option in the management of DME and RVO.

Pan, C., Korff, A., Galasko, D., Gingham, C., Peskind, E., Li, G., et al. (2015). Diagnostic values of cerebrospinal fluid T-tau and Abeta42 using meso scale discovery assays for alzheimer's disease.

*Journal of Alzheimer's Disease : JAD,*

Background: Meso Scale Discovery (MSD) recently established electrochemiluminescence-based assays to measure cerebrospinal fluid (CSF) levels of total tau (t-tau) and amyloid-beta 1-42 peptide (Abeta42) that can aid in the diagnosis of Alzheimer's disease (AD). The goal of this investigation is to independently evaluate this platform and establish cut-off values of these biomarkers for AD diagnosis. Objective: To validate the analytical and clinical performance of the MSD t-tau and Abeta42 kits and propose diagnostic cut-off values for the field. Methods: The analytical performance of the CSF t-tau and Abeta42 assays was determined, followed by assessment of diagnostic performance of CSF t-tau, Abeta42, and t-tau/Abeta42 in three clinically characterized cohorts. Results: Both MSD assays demonstrated consistent and stable analytical performance, as well as resistance to several important pre-analytic variables. Diagnostically, t-tau/Abeta42 performed the best. Conclusions: Our results independently confirm the analytical and clinical performance of the MSD CSF t-tau and Abeta42 assays. Based on a large, multi-center, clinically-diagnosed cohort, we propose for the first time candidate diagnostic cut-offs for MSD measured CSF t-tau, Abeta42, and t-tau/Abeta42. However, these values need to be refined as more subjects are included and the assays are tested by other laboratories.

Patil, E., & Thurmond, A. (2015). The history and current status of fallopian tube pressures - developing alternate methods for confirmation of tubal occlusion. *Contraception*, Permanent contraception with hysteroscopic tubal ligation is an increasingly popular choice for women around the world. However, inconveniences associated with the required confirmation test for tubal occlusion can be prohibitive. As new methods of permanent contraception are being investigated, ways of making all aspects of the procedure more accessible and comfortable for women should be considered. Means of examining tubal patency in the infertility population, such as tubal perfusion pressures measured at the time of hysterosalpingogram (HSG), provide inspiration for alternative methods of tubal occlusion confirmation after contraception. Evaluation of intrauterine pressures measured by a manometer attached to an intrauterine balloon catheter could serve as a preliminary tool for verification of tubal occlusion; higher pressures would indicate tubal occlusion and lower pressures would indicate the need for confirmatory HSG. The

development and validation of this technique is ongoing and could reduce overall costs and patient burdens associated with the current tubal occlusion confirmation procedure.

Petersen, C., & DeMuro, P. (2015). Legal and regulatory considerations associated with use of patient-generated health data from social media and mobile health (mHealth) devices. *Applied Clinical Informatics*, 6(1), 16-26.

Patient-generated health data are coming into broader use across the health care spectrum and hold great promise as a means to improve care and health outcomes. At the same time, rapid evolution in the social media and mobile health (mHealth) market has promoted an environment in which creation and transmission of personal health information is easy, quick, and appealing to patients. However, adoption of social media and mHealth by providers is hampered by legal and regulatory concerns with regard to data ownership and data use. This article defines common forms of patient-generated health data (PGHD) and describes how PGHD is used in clinical settings. It explores issues related to protection of personal health information, including that of children and adolescents, data security, and other potential barriers such as physician licensure. It also discusses regulatory and legal considerations providers and patients should consider before using social media and mobile health apps.

Petraglia, A. L., Plog, B. A., Dayawansa, S., Dashnaw, M. L., Czerniecka, K., Walker, C. T., et al. (2014). The pathophysiology underlying repetitive mild traumatic brain injury in a novel mouse model of chronic traumatic encephalopathy. *Surgical Neurology International*, 5, 184-7806.147566. eCollection 2014.

**BACKGROUND:** An animal model of chronic traumatic encephalopathy (CTE) is essential for further understanding the pathophysiological link between repetitive head injury and the development of chronic neurodegenerative disease. We previously described a model of repetitive mild traumatic brain injury (mTBI) in mice that encapsulates the neurobehavioral spectrum characteristic of patients with CTE. We aimed to study the pathophysiological mechanisms underlying this animal model. **METHODS:** Our previously described model allows for controlled, closed head impacts to unanesthetized mice. Briefly, 12-week-old mice were divided into three groups: Control, single, and repetitive mTBI. Repetitive mTBI mice received six concussive

impacts daily, for 7 days. Mice were then subsequently sacrificed for macro- and micro-histopathologic analysis at 7 days, 1 month, and 6 months after the last TBI received. Brain sections were immunostained for glial fibrillary acidic protein (GFAP) for astrocytes, CD68 for activated microglia, and AT8 for phosphorylated tau protein. RESULTS: Brains from single and repetitive mTBI mice lacked macroscopic tissue damage at all time-points. Single mTBI resulted in an acute reactive astrocytosis at 7 days and increased phospho-tau immunoreactivity that was present acutely and at 1 month, but was not persistent at 6 months. Repetitive mTBI resulted in a more marked neuroinflammatory response, with persistent and widespread astrogliosis and microglial activation, as well as significantly elevated phospho-tau immunoreactivity to 6-months. CONCLUSIONS: The neuropathological findings in this new model of repetitive mTBI resemble some of the histopathological hallmarks of CTE, including increased astrogliosis, microglial activation, and hyperphosphorylated tau protein accumulation.

Phillips, T. J., Reed, C., & Pastor, R. (2015). Preclinical evidence implicating corticotropin-releasing factor signaling in ethanol consumption and neuroadaptation. *Genes, Brain, and Behavior*, 14(1), 98-135.

The results of many studies support the influence of the corticotropin-releasing factor (CRF) system on ethanol (EtOH) consumption and EtOH-induced neuroadaptations that are critical in the addiction process. This review summarizes the preclinical data in this area after first providing an overview of the components of the CRF system. This complex system involves hypothalamic and extra-hypothalamic mechanisms that play a role in the central and peripheral consequences of stressors, including EtOH and other drugs of abuse. In addition, several endogenous ligands and targets make up this system and show differences in their involvement in EtOH drinking and in the effects of chronic or repeated EtOH treatment. In general, genetic and pharmacological approaches paint a consistent picture of the importance of CRF signaling via type 1 CRF receptors (CRF1) in EtOH-induced neuroadaptations that result in higher levels of intake, encourage alcohol seeking during abstinence and alter EtOH sensitivity. Furthermore, genetic findings in rodents, non-human primates and humans have provided some evidence of associations of genetic polymorphisms in CRF-related genes with EtOH drinking, although additional data are needed. These results suggest that CRF1 antagonists have potential as pharmacotherapeutics for

alcohol use disorders. However, given the broad and important role of these receptors in adaptation to environmental and other challenges, full antagonist effects may be too profound and consideration should be given to treatments with modulatory effects.

Pizzimenti, C. L., & Lattal, K. M. (2015). Epigenetics and memory: Causes, consequences and treatments for post-traumatic stress disorder and addiction. *Genes, Brain, and Behavior*, 14(1), 73-84.

Understanding the interaction between fear and reward at the circuit and molecular levels has implications for basic scientific approaches to memory and for understanding the etiology of psychiatric disorders. Both stress and exposure to drugs of abuse induce epigenetic changes that result in persistent behavioral changes, some of which may contribute to the formation of a drug addiction or a stress-related psychiatric disorder. Converging evidence suggests that similar behavioral, neurobiological and molecular mechanisms control the extinction of learned fear and drug-seeking responses. This may, in part, account for the fact that individuals with post-traumatic stress disorder have a significantly elevated risk of developing a substance use disorder and have high rates of relapse to drugs of abuse, even after long periods of abstinence. At the behavioral level, a major challenge in treatments is that extinguished behavior is often not persistent, returning with changes in context, the passage of time or exposure to mild stressors. A common goal of treatments is therefore to weaken the ability of stressors to induce relapse. With the discovery of epigenetic mechanisms that create persistent molecular signals, recent work on extinction has focused on how modulating these epigenetic targets can create lasting extinction of fear or drug-seeking behavior. Here, we review recent evidence pointing to common behavioral, systems and epigenetic mechanisms in the regulation of fear and drug seeking. We suggest that targeting these mechanisms in combination with behavioral therapy may promote treatment and weaken stress-induced relapse.

Probst, M. A., & Sun, B. C. (2014). How can we improve management of syncope in the emergency department? *Cardiology Journal*, 21(6), 643-650.

Syncope is a common and challenging presenting complaint to the Emergency Department (ED). Despite substantial research efforts, there is still considerable uncertainty about the optimal ED

management of syncope. There is continued interest among clinicians and researchers in improving diagnostic algorithms and optimizing resource utilization. In this paper, we discuss 4 strategies to improve the emergency care of syncope patients: (1) Development of accurate and consistent risk-stratification, (2) Increased use of syncope observation protocols, (3) Evaluation of a discharge with ambulatory monitoring pathway, (4) Use of shared decision-making for disposition decisions. Since current risk-stratification tools have fallen short with regard to subsequent validation and implementation into clinical practice, we outline key factors for future risk-stratification research. We propose that observation units have the potential to safely decrease length-of-stay and hospital costs for hemodynamically stable, intermediate risk patients without adversely affecting clinical outcomes. For appropriate patients with a negative ED evaluation, we recommend consideration of direct discharge, with ambulatory monitoring and expedited follow-up, as a means of decreasing costs and reducing iatrogenic harms. Finally, we advocate for the use of shared decision-making regarding the ultimate disposition of select, intermediate risk patients who have not had a serious condition revealed in the ED. If properly implemented, these four strategies could significantly improve the care of ED syncope patients by helping clinicians identify truly high-risk patients, decreasing unnecessary hospitalizations, and increasing patient satisfaction.

Puy, C., Tucker, E. I., Matafonov, A., Cheng, Q., Zientek, K. D., Gailani, D., et al. (2015). Activated factor XI increases the procoagulant activity of the extrinsic pathway by inactivating tissue factor pathway inhibitor. *Blood*,

Activation of coagulation factor XI (FXI) may play a role in hemostasis. The primary substrate of activated FXI (FXIa) is FIX, leading to FX activation (FXa) and thrombin generation. However, recent studies suggest the hemostatic role of FXI may not be restricted to the activation of FIX. We explored whether FXI could interact with and inhibit the activity of tissue factor pathway inhibitor (TFPI). TFPI is an essential reversible inhibitor of activated factor X (FXa), and also inhibits the FVIIa-TF complex. We found that FXIa neutralized both endothelium- and platelet-derived TFPI by cleaving the protein between the Kunitz (K) 1 and K2 domains (Lys86/Thr87) and at the active sites of the K2 (Arg107/Gly108) and K3 (Arg199/Ala200) domains. Addition of FXIa to plasma was able to reverse the ability of TFPI to prolong TF-initiated clotting times in FXI-

or FIX-deficient plasma, and FXa-initiated clotting times in FX-deficient plasma. Treatment of cultured endothelial cells with FXIa increased the generation of FXa and promoted TF-dependent fibrin formation in recalcified plasma. Together, these results suggest that the hemostatic role of FXIa may be attributed not only to activation of FIX but also to promoting the extrinsic pathway of thrombin generation through inactivation of TFPI.

Quittner, A. L., O'Donnell, A. E., Salathe, M. A., Lewis, S. A., Li, X., Montgomery, A. B., et al. (2015).

Quality of life questionnaire-bronchiectasis: Final psychometric analyses and determination of minimal important difference scores. *Thorax*, 70(1), 12-20.

Background: The Quality of Life-Bronchiectasis (QOL-B), a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for patients with non-cystic fibrosis (CF) bronchiectasis, contains 37 items on 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden). Methods: Psychometric analyses of QOL-B V.3.0 used data from two double-blind, multicentre, randomised, placebo-controlled, phase III trials of aztreonam for inhalation solution (AZLI) in 542 patients with non-CF bronchiectasis and Gram-negative endobronchial infection. Results: Excellent internal consistency (Cronbach's  $\alpha \geq 0.70$ ) and 2-week test-retest reliability (intraclass correlation coefficients  $\geq 0.72$ ) were demonstrated for each scale. Convergent validity with 6 min walk test was observed for Physical and Role Functioning scores. No floor or ceiling effects (baseline scores of 0 or 100) were found for the Respiratory Symptoms scale (primary endpoint of trials). Baseline Respiratory Symptoms scores discriminated between patients based on baseline FEV<sub>1</sub>% predicted in only one trial. The minimal important difference score for the Respiratory Symptoms scale was 8.0 points. AZLI did not show efficacy in the two phase III trials. QOL-B responsivity to treatment was assessed by examining changes from baseline QOL-B scores at study visits at which protocol-defined pulmonary exacerbations were reported. Mean Respiratory Symptoms scores decreased 14.0 and 14.2 points from baseline for placebo-treated and AZLI-treated patients with exacerbations, indicating that worsening respiratory symptoms were reflected in clinically meaningful changes in QOL-B scores. Conclusions: Previously established content validity, reliability and responsivity of the QOL-B are

confirmed by this final validation study. The QOL-B is available for use in clinical trials and routine clinical practice.

Rackham, D. M., C Herink, M., Stevens, I. G., Cardoza, N. M., & Singh, H. (2014). Evidence behind FDA alerts for drugs with adverse cardiovascular effects: Implications for clinical practice. *Pharmacotherapy*, 34(4), 358-372.

The U.S. Food and Drug Administration (FDA) periodically publishes Drug Safety Communications and Drug Alerts notifying health care practitioners and the general public of important information regarding drug therapies following FDA approval. These alerts can result in both positive and negative effects on patient care. Most clinical trials are not designed to detect long-term safety end points, and postmarketing surveillance along with patient reported events are often instrumental in signaling the potential harmful effect of a drug. Recently, many cardiovascular (CV) safety announcements have been released for FDA-approved drugs. Because a premature warning could discourage a much needed treatment or prompt a sudden discontinuation, it is essential to evaluate the evidence supporting these FDA alerts to provide effective patient care and to avoid unwarranted changes in therapy. Conversely, paying attention to these warnings in cases involving high-risk patients can prevent adverse effects and litigation. This article reviews the evidence behind recent FDA alerts for drugs with adverse CV effects and discusses the clinical practice implications.

Riddle, M. C. (2015). Welcome reassurance about GLP-1 drugs-but they are still young and not fully grown. *Diabetes Care*, 38(2), 183-185.

Riddle, M. C., Gerstein, H. C., Jung, H., Mellbin, L. G., Rydén, L., Rosenstock, J., et al. (2015). Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. *Diabetes Care*, 38(1), 22-28.

OBJECTIVE : Hypoglycemia is a leading risk of glucose-lowering therapy. Treatment with insulin glargine compared with standard care early in the course of dysglycemia in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial provides information on the frequency and predictors of hypoglycemia in this setting. RESEARCH DESIGN AND METHODS : A total of 12,537 people with high cardiovascular risk and dysglycemia treated with one or no oral

glucose-lowering agents were randomized to add glargine titrated to a fasting glucose level of  $\leq 5.3$  mmol/L ( $\leq 95$  mg/dL) or to use standard therapies. Independent associations of both nonsevere hypoglycemia (symptomatic and confirmed with a glucose level of  $\leq 3$  mmol/L [ $\leq 54$  mg/dL]) and severe hypoglycemia with characteristics at baseline, treatment allocation, and average HbA1c were assessed by Cox proportional hazards models. RESULTS : During a median follow-up period of 6.2 years, 28% of participants reported nonsevere hypoglycemia, and 3.8% reported severe hypoglycemia. Prior use of a sulfonylurea and allocation to glargine independently predicted a higher risk for both categories of participants. Nonsevere events were independently associated with younger age, lower BMI, the presence of diabetes, and higher baseline HbA1c level. Severe events were associated with older age, hypertension, higher serum creatinine level, and lower cognitive function, but not baseline glycemic status. Progressively higher on-treatment HbA1c level was associated with a lower risk of nonsevere events in both treatment groups; a lower risk of severe events in the glargine group, and a higher risk of severe events with standard care. CONCLUSIONS : Hypoglycemia was relatively uncommon in the ORIGIN trial, but was more frequent with sulfonylurea use at baseline and allocation to glargine. Nonsevere and severe events were associated with different clinical characteristics, awareness of which may guide individualized therapy. © 2015 by the American Diabetes Association.

Ritchie, C., Cylinder, I., Platt, E. J., & Barklis, E. (2015). Analysis of hiv-1 gag protein interactions via biotin ligase tagging. *Journal of Virology*,

We have examined the interactions of wild type (WT) and matrix protein-deleted (DeltaMA) HIV-1 precursor Gag (PrGag) proteins in virus-producing cells using a biotin ligase tagging approach. To do so, WT and DeltaMA PrGag proteins were tagged with the *E. coli* promiscuous biotin ligase (BirA\*), expressed in cells, and examined. Localization patterns of PrGag proteins and biotinylated proteins overlapped, consistent with observations that BirA\*-tagged proteins biotinylate neighbor proteins that are in close proximity. Results indicate that BirA\*-tagged PrGag proteins biotinylated themselves, as well as WT PrGag proteins in trans. Previous data have shown that the HIV-1 Envelope (Env) protein requires an interaction with MA for assembly into virions. Unexpectedly, DeltaMA proteins biotinylated Env, whereas WT BirA\*-tagged proteins did not, suggesting the presence of MA made Env inaccessible to biotinylation. We also identified

over fifty cellular proteins that were biotinylated by BirA\*-tagged PrGag proteins. These included membrane proteins, cytoskeleton-associated proteins, nuclear transport factors, lipid metabolism regulators, translation factors, and RNA processing proteins. The identification of these biotinylated proteins offers new insights as to HIV-1 Gag protein trafficking and activities, and provide new potential targets for antiviral interference. IMPORTANCE: We have employed a novel strategy to analyze the interactions of the HIV-1 structural Gag proteins, which involved tagging wild type and mutant Gag proteins with a biotin ligase. Expression of the tagged proteins in cells allowed us to analyze proteins that came in close proximity to the Gag proteins as they were synthesized, transported, assembled and released from cells. The tagged proteins biotinylated proteins encoded by the HIV-1 pol gene and neighbor Gag proteins, but surprisingly, only the mutant Gag protein biotinylated the HIV-1 Envelope protein. We also identified over fifty cellular proteins that were biotinylated, including membrane and cytoskeletal proteins, and proteins involved in lipid metabolism, nuclear import, translation and RNA processing. Our results offer new insights as to HIV-1 Gag protein trafficking and activities, and provide new potential targets for antiviral interference.

Robinson, P. C., Claushuis, T. A. M., Cortes, A., Martin, T. M., Evans, D. M., Leo, P., et al. (2015).

Genetic dissection of acute anterior uveitis reveals similarities and differences in associations observed with ankylosing spondylitis. *Arthritis and Rheumatology*, 67(1), 140-151.

Conclusion These findings of both novel AAU-specific associations and associations shared with AS demonstrate overlapping but also distinct genetic susceptibility loci for AAU and AS. The associations in IL10 and IL18R1 are shared with inflammatory bowel disease, suggesting common etiologic pathways. Objective To use high-density genotyping to investigate the genetic associations of acute anterior uveitis (AAU) in patients with and those without ankylosing spondylitis (AS) Methods We genotyped samples from 1,711 patients with AAU (either primary or combined with AS), 2,339 AS patients without AAU, and 10,000 control subjects on an Illumina ImmunoChip Infinium microarray. We also used data for AS patients from previous genome-wide association studies to investigate the AS risk locus ANTXR2 for its putative effect in AAU. ANTXR2 expression in mouse eyes was investigated by real-time quantitative reverse transcription-polymerase chain reaction. Results A comparison between all patients with AAU and healthy

control subjects showed strong association over HLA-B, corresponding to the HLA-B27 tag single-nucleotide polymorphism rs116488202. The association of 3 non-major histocompatibility complex loci, IL23R, the intergenic region 2p15, and ERAP1, reached genome-wide significance ( $P < 5 \times 10^{-8}$ ). Five loci harboring the immune-related genes IL10-IL19, IL18R1-IL1R1, IL6R, the chromosome 1q32 locus harboring KIF21B, as well as the eye-related gene EYS, were also associated, reaching a suggestive level of significance ( $P < 5 \times 10^{-6}$ ). Several previously confirmed AS associations demonstrated significant differences in effect size between AS patients with AAU and AS patients without AAU. ANTXR2 expression varied across eye compartments.

Rodrigues, J. K., Navarro, P. A., Zelinski, M. B., Stouffer, R. L., & Xu, J. (2015). Direct actions of androgens on the survival, growth and secretion of steroids and anti-mullerian hormone by individual macaque follicles during three-dimensional culture. *Human Reproduction (Oxford, England)*,

STUDY QUESTION: What are the direct effects of androgens on primate follicular development and function at specific stages of folliculogenesis? SUMMARY ANSWER: Androgen addition altered primate follicle survival, growth, steroid and anti-Mullerian hormone (AMH) production, and oocyte quality in vitro, in a dose- and stage-dependent manner. WHAT IS KNOWN ALREADY: Androgens have local actions in the ovary, particularly in the developing follicles. It is hypothesized that androgen promotes early follicular growth, but becomes detrimental to the antral follicles in primates. STUDY DESIGN, SIZE, DURATION: In vitro follicle maturation was performed using rhesus macaques. Secondary (125-225 microm) follicles were mechanically isolated from 14 pairs of ovaries, encapsulated into alginate (0.25% w/v), and cultured for 40 days. PARTICIPANTS/MATERIALS, SETTING, METHODS: Individual follicles were cultured in a 5% O<sub>2</sub> environment, in alpha minimum essential medium supplemented with recombinant human FSH. Follicles were randomly assigned to experiments of steroid ablation by trilostane (TRL), testosterone (T) replacement and dihydrotestosterone (DHT) replacement. Follicle survival and growth were assessed. Follicles with diameters  $\geq 500$   $\mu\text{m}$  at Week 5 were categorized as fast-grow follicles. Pregnenolone (P5), progesterone (P4), estradiol (E2) and AMH concentrations in media were measured. Meiotic maturation and fertilization of oocytes from recombinant human chorionic gonadotrophin-treated follicles were assessed at the end of culture. MAIN RESULTS AND

THE ROLE OF CHANCE: Compared with controls, TRL exposure reduced ( $P < 0.05$ ) follicle survival, antrum formation rate and follicle diameters at Week 5. While P5 concentrations increased ( $P < 0.05$ ) following TRL treatment, P4 levels decreased ( $P < 0.05$ ) in fast-grow follicles at Week 5. Few healthy oocytes were retrieved from antral follicles developed in the presence of TRL. T replacement with TRL increased ( $P < 0.05$ ) follicle survival and antrum formation at Week 5, compared with TRL alone, to levels comparable to controls. However, high-dose T with TRL decreased ( $P < 0.05$ ) diameters of fast-grow follicles. Although P4 concentrations produced by fast-grow follicles were not altered by T in the presence of TRL, there was a dose-dependent increase ( $P < 0.05$ ) in E2 levels at Week 5. High-dose T with TRL decreased ( $P < 0.05$ ) AMH production by fast-grow follicles at Week 3. More healthy oocytes were retrieved from antral follicles developed in TRL+T compared with TRL alone. DHT had the similar effects to those of high-dose T, except that DHT replacement decreased ( $P < 0.05$ ) E2 concentrations produced by fast-grow follicles at Week 5 regardless of TRL treatment.

LIMITATION, REASONS FOR CAUTION: This study reports T and DHT actions on in vitro-developed individual primate (macaque) follicles, which are limited to the interval from the secondary to small antral stage.

WIDER IMPLICATION OF THE FINDINGS: The above findings provide novel information on the role(s) of androgens in primate follicular development and oocyte maturation. We hypothesize that androgens promote pre-antral follicle development, but inhibit antral follicle growth and function in primates. While androgens can act positively, excess levels of androgens may have negative impacts on primate folliculogenesis.

STUDY FUNDING/COMPETING INTERESTS: NIH U54 RR024347/RL1HD058294/PL1EB008542 (Oncofertility Consortium), NIH U54 HD071836 (SCCPIR), NIH ORWH/NICHD 2K12HD043488 (BIRCWH), NIH FIC TW/HD-00668, ONPRC 8P51OD011092. There are no conflicts of interest.

Rodriguez, M. I., Darney, B. G., Elman, E., Linz, R., Caughey, A. B., & McConnell, K. J. (2015). Examining quality of contraceptive services for adolescents in Oregon's family planning program. *Contraception*.

Objective: To assess the quality of care provided to adolescents (10-19 years old) compared to women (aged 20-25 years) who accessed services in Oregon's Contraceptive Care (CCare) program. Study Design: We analyzed data routinely collected using the Clinic Visit Record form

from women aged 25 years and younger who visited CCare clinics between January 1, 2004, and October 31, 2010. Modern methods were characterized into three tiers: Tier 1 is the intrauterine device, implant and sterilization; Tier 2, hormonal methods; and Tier 3, all barrier methods. Nonmodern methods included no method, withdrawal and natural family planning. We used multivariable logistic regression models to examine the effect of age on three indicators of quality of contraceptive care: transitioning from a nonmodern to a modern method, transitioning from Tier 3 methods to Tier 1 or Tier 2 methods, and initiation of long-acting reversible contraception (LARC). We then produced predicted probabilities to facilitate data interpretation. Results: Adolescents accounted for 344,856 (41%) of the 848,221 clinic visits occurring in CCare among women under age 25. Compared with women (ages 20-25 years), young and older adolescents had decreased odds of LARC initiation [odds ratio (OR) 0.24 (95% confidence interval [CI] 0.16-0.35) and OR 0.44 (95% CI 0.38-0.52), respectively]. However, compared with women, both young and older adolescents had increased odds of leaving with any contraceptive method [OR 1.8 95% (CI 1.26-2.59) and OR 1.42 (95% CI 1.21-1.66)]. Among clients presenting with no method of contraception at the beginning of the visit, 78.7% of young adolescents (95% CI 73.84-83.03) compared with 81.44% (95% CI 77.02-85.52) of older adolescents, and 76.63% (95% CI 69.90-80.75) of young women left with a modern method, controlling for other covariates. Conclusion: Although adolescents served by CCare are more likely to initiate contraception, they are less likely to receive LARC than women aged 20-25 years. Implication: Efforts are needed to ensure that adolescents have access to highly effective reversible contraception.

Ronnekleiv, O. K., Zhang, C., Bosch, M. A., & Kelly, M. J. (2014). Kisspeptin and gonadotropin-releasing hormone neuronal excitability: Molecular mechanisms driven by 17beta-estradiol. *Neuroendocrinology*,

Kisspeptin is a neuropeptide that signals via a G $\alpha$ q-coupled receptor, GPR54, in gonadotropin-releasing hormone (GnRH) neurons and is essential for pubertal maturation and fertility. Kisspeptin depolarizes and excites GnRH neurons primarily through the activation of canonical transient receptor potential (TRPC) channels and the inhibition of K<sup>+</sup> channels. The gonadal steroid 17beta-estradiol (E2) upregulates not only kisspeptin (Kiss1) mRNA but also

increases the excitability of the rostral forebrain Kiss1 neurons. In addition, a primary postsynaptic action of E2 on GnRH neurons is to upregulate the expression of channel transcripts that orchestrate the downstream signaling of kisspeptin in GnRH neurons. These include not only TRPC4 channels but also low-voltage-activated T-type calcium channels and high-voltage-activated L-, N- and R-type calcium channel transcripts. Moreover, E2 has direct membrane-initiated actions to alter the excitability of GnRH neurons by enhancing ATP-sensitive potassium channel activity, which is critical for maintaining GnRH neurons in a hyperpolarized state for the recruitment of T-type calcium channels that are important for burst firing. Therefore, E2 modulates the excitability of GnRH neurons as well as of Kiss1 neurons by altering the expression and/or function of ion channels; moreover, kisspeptin provides critical excitatory input to GnRH neurons to facilitate burst firing activity and peptide release. (c) 2015 S. Karger AG, Basel.

Roselli, C. E. (2013). *The distribution and regulation of aromatase in the mammalian brain: From mice to monkeys* Oxford University Press.

The mammalian brain produces low levels of estrogens relative to the ovary and placenta, but by restricting synthesis to the site of estrogen action is able to exert powerful effects on neural development and function. The final step in estrogen production is the conversion of androgens to estrogens by cytochrome P450 aromatase. Recent evidence that hippocampus is capable of synthesizing estrogen de novo from cholesterol suggests a new paradigm for mammals in which sex steroids act independently of the gonads to regulate brain functions. In general, aromatase exhibits a dynamic and complex regulation that varies regionally, as well as with an animal's age, sex, and physiologic status. This chapter summarizes our current understanding of the distribution and regulation of aromatase in the mammalian brain and describes classic as well as novel functions for local estrogen synthesis in the brain.

Rosenbaum, J. T., Choi, D., Wilson, D. J., Grossniklaus, H. E., Sibley, C. H., Harrington, C. A., et al. (2015). Molecular diagnosis of orbital inflammatory disease. *Experimental and Molecular Pathology*,

Orbital inflammatory diseases include thyroid eye disease (TED), granulomatosis with polyangiitis (GPA), sarcoidosis, and nonspecific orbital inflammation (NSOI). Histopathological diagnosis

usually relies on the clinical context and is not always definitive. Gene expression profiling provides diagnostic and therapeutic information in several malignancies, but its role in evaluating nonmalignant disease is relatively untested. We hypothesized that gene expression profiling could provide diagnostic information for NSOI. We collected formalin-fixed, paraffin-embedded orbital biopsies from 10 institutions and 83 subjects including 25 with thyroid eye disease, 25 nonspecific orbital inflammation, 20 healthy controls, 6 with granulomatosis with polyangiitis, and 7 with sarcoidosis. Tissues were divided into discovery and validation sets. Gene expression was quantified using Affymetrix U133 Plus 2.0 microarrays. A random forest statistical algorithm based on data from 39 probe sets identified controls, GPA, or TED with an average accuracy of 76% ( $p=0.02$ ). Random forest analysis indicated that 52% of tissues from patients with nonspecific inflammation were consistent with a diagnosis of GPA. Molecular diagnosis by gene expression profiling will augment clinical data and histopathology in differentiating forms of orbital inflammatory disease.

Saitz, T. R., & Serefoglu, E. C. (2015). Sexual dysfunction in 2014: Men enjoy a year of significant progress. *Nature Reviews.Urology*,

Sakoulas, G., Nonejuie, P., Kullar, R., Pogliano, J., Rybak, M. J., & Nizet, V. (2015). Examining the use of ceftaroline in the treatment of streptococcus pneumoniae meningitis with reference to human cathelicidin LL-37. *Antimicrobial Agents and Chemotherapy*,

Five cases of bacterial meningitis treated with ceftaroline (4 *S. pneumoniae*; 1 *S. aureus*) are summarized. The pharmacodynamics between cathelicidin LL-37 and ceftaroline are evaluated against *S. pneumoniae*. Patients who received ceftaroline 600 mg q8hr (1 *S. aureus*; 3 *S. pneumoniae*) were successfully treated; 1 patient with *S. pneumoniae* who received 600 mg q12hr failed. Ceftaroline increased negative surface charge and sensitized *S. pneumoniae* to killing by LL-37, a peptide implicated in blood-brain barrier defense.

Salehi, S., Gwinner, F., Mitchell, J. C., Pfeifer, C., & Ferracane, J. L. (2015). Cytotoxicity of resin composites containing bioactive glass fillers. *Dental Materials : Official Publication of the Academy of Dental Materials*, 31(2), 195-203.

OBJECTIVE: To determine the in vitro cytotoxicity of dental composites containing bioactive glass

fillers. METHODS: Dental composites (50:50 Bis-GMA/TEGDMA resin: 72.5wt% filler, 67.5% Sr-glass and 5% OX50) containing different concentrations (0, 5, 10 and 15wt%) of two sol-gel bioactive glasses, BAG65 (65mole% SiO<sub>2</sub>, 31mole% CaO, 4mole% P<sub>2</sub>O<sub>5</sub>) and BAG61 (3mole% F added) were evaluated for cytotoxicity using Alamar Blue assay. First, composite extracts were obtained from 7 day incubations of composites in cell culture medium at 37 degrees C. Undifferentiated pulp cells (OD-21) were exposed to dilutions of the original extracts for 3, 5, and 7 days. Then freshly cured composite disks were incubated with OD-21 cells (n=5) for 2 days. Subsequently, fresh composite disks were incubated in culture medium at 37 degrees C for 7 days, and then the extracted disks were incubated with OD-21 cells for 2 days. Finally, fresh composites disks were light cured for 3, 5, and 20s and incubated with OD-21 cells (n=5) for 1, 3, 5, and 7 days. To verify that the three different curing modes produced different levels of degree of conversion (DC), the DC of each composite was determined by FTIR. Groups (n=5) were compared with ANOVA/Tukey's ( $\alpha \leq 0.05$ ). RESULTS: Extracts from all composites significantly reduced cell viability until a dilution of 1:8 or lower, where the extract became equal to the control. All freshly-cured composites showed significantly reduced cell viability at two days. However, no reduction in cell viability was observed for any composite that had been previously soaked in media before exposure to the cells. Composites with reduced DC (3s vs. 20s cure), as verified by FTIR, showed significantly reduced cell viability. SIGNIFICANCE: The results show that the composites, independent of composition, had equivalent potency in terms of reducing the viability of the cells in culture. Soaking the composites for 7 days before exposing them to the cells suggested that the "toxic" components had been extracted and the materials were no longer cytotoxic. The results demonstrate that the cytotoxicity of composites with and without BAG must predominantly be attributed to the release of residual monomers, and not to the presence of the BAG.

Sangvanich, T., Ngamcherdtrakul, W., Lee, R., Morry, J., Castro, D., Fryxell, G. E., et al. (2014).

Nanoporous sorbent material as an oral phosphate binder and for aqueous phosphate, chromate, and arsenate removal. *Journal of Nanomedicine & Nanotechnology*, 5, 1000222.

Phosphate removal is both biologically and environmentally important. Biologically, hyperphosphatemia is a critical condition in end-stage chronic kidney disease patients. Patients

with hyperphosphatemia are treated long-term with oral phosphate binders to prevent phosphate absorption to the body by capturing phosphate in the gastrointestinal (GI) tract followed by fecal excretion. Environmentally, phosphate levels in natural water resources must be regulated according to limits set forth by the US Environmental Protection Agency. By utilizing nanotechnology and ligand design, we developed a new material to overcome limitations of traditional sorbent materials such as low phosphate binding capacity, slow binding kinetics, and negative interference by other anions. A phosphate binder based on iron-ethylenediamine on nanoporous silica (Fe-EDA-SAMMS) has been optimized for substrates and Fe(III) deposition methods. The Fe-EDA-SAMMS material had a 4-fold increase in phosphate binding capacity and a broader operating pH window compared to other reports. The material had a faster phosphate binding rate and was significantly less affected by other anions than Sevelamer HCl, the gold standard oral phosphate binder, and AG(R) 1-X8, a commercially available anion exchanger. It had less cytotoxicity to Caco-2 cells than lanthanum carbonate, another prescribed oral phosphate binder. The Fe-EDA-SAMMS also had high capacity for arsenate and chromate, two of the most toxic anions in natural water.

Sansoni, E. R., Sautter, N. B., Mace, J. C., Smith, T. L., Yawn, J. R., Lawrence, L. A., et al. (2015).

Vitamin D as a novel regulator of basic fibroblast growth factor in chronic rhinosinusitis with nasal polyposis. *International Forum of Allergy & Rhinology*,

BACKGROUND: The immunopathogenesis of chronic rhinosinusitis (CRS) is largely unknown, but it is thought that different inflammatory profiles are responsible for the different CRS subtypes. 25-Hydroxyvitamin-D (25-VD3) has been shown to alter inflammatory mediators in other disease processes and 25-VD3 deficiency is associated with CRS with nasal polyps (CRSwNP), but it is unknown if 25-VD3 levels impact local inflammation in CRS. This study investigated the correlation between plasma 25-VD3 and sinonasal mucus monocyte chemoattractant protein-1 (MCP-1), regulated upon activation normal T cell expressed and secreted (RANTES), and basic fibroblast growth factor (bFGF) levels in patients with CRS. METHODS: Study subjects undergoing endoscopic sinus surgery (ESS) for CRS were prospectively enrolled from January 2012 to August 2014. Control subjects included patients undergoing ESS for noninflammatory pathology. Blood and sinonasal mucus were collected at the time of ESS. Plasma 25-VD3 was measured by

enzyme-linked immunosorbent assay (ELISA) and mucus levels of MCP-1, RANTES, and bFGF by cytometric bead array (CBA). RESULTS: A total of 57 patients were enrolled and categorized as CRS without nasal polyps (CRSsNP) (n = 31), CRSwNP (n = 14), and controls (n = 12). No significant correlation was found between MCP-1 and 25-VD3. There was a significant negative correlation between 25-VD3 and RANTES (r = -0.612; p = 0.026) and bFGF (r = -0.578; p = 0.039) in CRSwNP patients; however, there was no significant correlation in CRSsNP patients. CONCLUSION: This data suggests that 25-VD3 may play a role in regulation of RANTES and bFGF expression in CRSwNP. This may occur through regulation of NP fibroblasts or other immune cells. Further investigation is warranted to better elucidate the role of RANTES, bFGF, and 25-VD3 in CRSwNP.

Sauer, S. W., Opp, S., Komatsuzaki, S., Blank, A. E., Mittelbronn, M., Burgard, P., et al. (2015).

Multifactorial modulation of susceptibility to l-lysine in an animal model of glutaric aciduria type I. *Biochimica Et Biophysica Acta*,

Glutaric aciduria type I is an inherited defect in l-lysine, l-hydroxylysine and l-tryptophan degradation caused by deficiency of glutaryl-CoA dehydrogenase (GCDH). The majority of untreated patients presents with accumulation of neurotoxic metabolites - glutaric acid (GA) and 3-hydroxyglutaric acid (3-OHGA) - and striatal injury. *Gcdh*<sup>-/-</sup> mice display elevated levels of GA and 3-OH-GA but do not spontaneously develop striatal lesions. l-lysine-enriched diets (appr. 235mg/d) were suggested to induce a neurological phenotype similar to affected patients. In our hands 93% of mice stressed according to the published protocol remained asymptomatic. To understand the underlying mechanism, we modified their genetic background (F1 C57BL6/Jx129/SvCrl) and increased the daily oral l-lysine supply (235-433mg). We identified three modulating factors, (1) gender, (2) genetic background, and (3) amount of l-lysine. Male mice displayed higher vulnerability and inbreeding for more than two generations as well as elevating l-lysine supply increased the diet-induced mortality rate (up to 89%). Onset of first symptoms leads to strongly reduced intake of food and, thus, l-lysine suggesting a threshold for toxic metabolite production to induce neurological disease. GA and 3-OH-GA tissue concentrations did not correlate with dietary l-lysine supply but differed between symptomatic and asymptomatic mice. Cerebral activities of glyceraldehyde 3-phosphate dehydrogenase, 2-

oxoglutarate dehydrogenase complex, and aconitase were decreased. Symptomatic mice did not develop striatal lesions or intracerebral hemorrhages. We found severe spongiosis in the hippocampus of Gcdh<sup>-/-</sup> mice which was independent of dietary l-lysine supply. In conclusion, the l-lysine-induced pathology in Gcdh<sup>-/-</sup> mice depends on genetic and dietary parameters.

Schaefer, C., Mann, R., Sadosky, A., Daniel, S., Parsons, B., Nieshoff, E., et al. (2014). Burden of illness associated with peripheral and central neuropathic pain among adults seeking treatment in the united states: A patient-centered evaluation. *Pain Medicine (United States)*, 15(12), 2105-2119.

Objective: The aim of this study was to evaluate patient-reported burden associated with peripheral and central neuropathic pain (NeP) by pain severity and NeP condition. Design: Six hundred twenty-four subjects with one of six NeP conditions were recruited during routine office visits. Subjects consented to retrospective chart review and completed a one-time questionnaire (including EuroQol-5 dimensions, 12-item Short-Form Health Survey, Brief Pain Inventory-Short Form, Medical Outcomes Study Sleep Scale, Hospital Anxiety and Depression Scale, and demographic and clinical characteristics). Pain severity scores were used to stratify subjects by mild, moderate, and severe pain. Summary statistics and frequency distributions were calculated. Differences by severity level were compared using Kruskal-Wallis (continuous variables) and chi-square or Fisher's exact test (categorical variables). Effect size was computed with Cohen's d (mild vs severe). Results: Subjects' mean age was 55.5. The majority (80.8%) had moderate or severe pain. Patient-reported outcomes (health status, physical and mental health, pain interference with function, sleep, anxiety, and depression) were significantly worse among subjects with greater pain severity (all  $P < 0.05$ ) for all others. The observed burden was most substantial among chronic low back pain-NeP, although the pattern of disease burden was similar across the six NeP conditions. Conclusions: Subjects across NeP conditions exhibited high pain levels, which were significantly associated with poor function, compromised health status and sleep, and increased anxiety and depression. Results indicate substantial patient burden across broad NeP, particularly among subjects with severe pain.

Schlueter, R. K., Azarow, K. S., Hines, A. G., Varman, M., Abdessalam, S. F., Raynor, S. C., et al.

(2015). Identifying strategies to decrease infectious complications of gastroschisis repair. *Journal of Pediatric Surgery*, 50(1), 98-101.

PURPOSE: We describe the infectious complications of gastroschisis in order to identify modifiable factors to decrease these complications. METHODS: Data from 155 gastroschisis patients (2001-2013) were reviewed. Complicated gastroschisis (intestinal atresia, necrotic bowel, or perforation) were excluded, leaving 129 patients for review. Patient demographics, surgical details, postoperative infections and complications, and length of stay were reviewed. We used CDC definitions of infectious complications. RESULTS: The average gestational age of patients was 35.97weeks. Silos were used in 46% of patients (n=59) for an average of 7.4days. Thirty-one patients (24%) acquired an infection within the first 60days of life. Patients who developed an infection were born earlier in gestation (P=0.02), weighed less (P=0.01), required silos more often (P=0.01), and received a sutured repair (P=0.04). Length of stay of patients with an infection was longer than in patients without infection (P=0.01). CONCLUSIONS: Infectious complications following gastroschisis repair are common. Subsets of gastroschisis patients at increased risk of infection include patients with silos, preterm delivery, low birth weight, and sutured repair. Based on our findings, our recommendation would be to carry gastroschisis patients to term and advocate against the routine use of silos, reserving their use for those cases when primary closure is not possible.

Schousboe, J. T., Rosen, H. R., Vokes, T. J., Cauley, J. A., Cummings, S. R., Nevitt, M. C., et al.

(2014). Prediction models of prevalent radiographic vertebral fractures among older men. *Journal of Clinical Densitometry : The Official Journal of the International Society for Clinical Densitometry*, 17(4), 449-457.

No studies have compared how well different prediction models discriminate older men who have a radiographic prevalent vertebral fracture (PVFx) from those who do not. We used area under receiver operating characteristic curves and a net reclassification index to compare how well regression-derived prediction models and nonregression prediction tools identify PVFx among men age  $\geq 65$  yr with femoral neck T-score of -1.0 or less enrolled in the Osteoporotic Fractures in Men Study. The area under receiver operating characteristic for a model with age,

bone mineral density, and historical height loss (HHL) was 0.682 compared with 0.692 for a complex model with age, bone mineral density, HHL, prior non-spine fracture, body mass index, back pain, grip strength, smoking, and glucocorticoid use (p values for difference in 5 bootstrapped samples 0.14-0.92). This complex model, using a cutpoint prevalence of 5%, correctly reclassified only a net 5.7% (p = 0.13) of men as having or not having a PVFx compared with a simple criteria list (age  $\geq$  80 yr, HHL  $>$ 4 cm, or glucocorticoid use). In conclusion, simple criteria identify older men with PVFx and regression-based models. Future research to identify additional risk factors that more accurately identify older men with PVFx is needed.

Selden, N. R. (2015). Commentary to: "development, organisation and implementation of a surgical skills 'boot camp': SIMweek". *World Journal of Surgery*,

Selden, N. R., Haglund, M. M., Selden, N. R., & Haglund, M. M. (2015). Duty-hour exceptions for neurosurgery residency programs. *The Virtual Mentor : VM*, 17(1), 23-32.

Shen, J., Nielson, C. M., Marshall, L. M., Lee, D. C., Keaveny, T. M., Orwoll, E. S., et al. (2015). The association between BMI and QCT-derived proximal hip structure and strength in older men: A cross-sectional study. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*,

Although higher body mass index (BMI) is associated with higher bone mineral density, recent evidence indicates that increased BMI may not be consistently associated with reduced hip fracture risk. Moreover, substantial proportions of hip fractures occur among overweight and obese men and women. The role of increased BMI and obesity on bone density, structure, and strength at the hip is not well understood. We conducted cross-sectional analyses between BMI and various density and structure measures derived from quantitative computed tomography (QCT)-scans of the proximal femur, in 3067 men (mean age: 73 y) from the Osteoporotic Fractures in Men Study (MrOS). Finite element (FE) analysis of hip QCT scans was performed for a subcohort of 672 men to provide a measure of femoral strength for a simulated sideways fall. The impact force was estimated using patient-specific weight and height information.

Multivariable general linear models were used to examine the associations between BMI and hip

QCT measures. The relationship of BMI with hip QCT measures was significantly different between men categorized as non-obese and obese (P for interaction 30), increasing BMI was not associated with any of those parameters. In addition, compared to non-obese men, obese men had a higher hip strength, but also a higher ratio of impact force to strength ( $P < 0.0001$ ), in theory increasing their risk of hip fracture despite their increased strength. These results provide a better understanding of hip fracture risk in obese men. This article is protected by copyright. All rights reserved.

Shi, M., Movius, J., Dator, R., Aro, P., Zhao, Y., Pan, C., et al. (2015). Cerebrospinal fluid peptides as potential parkinson disease biomarkers: A staged pipeline for discovery and validation. *Molecular & Cellular Proteomics : MCP*,

Finding robust biomarkers for Parkinson disease (PD) is currently hampered by inherent technical limitations associated with imaging or antibody-based protein assays. To circumvent the challenges, we adapted a staged pipeline, starting from our previous proteomic profiling followed by high-throughput targeted mass spectrometry (MS), to identify peptides in human cerebrospinal fluid (CSF) for PD diagnosis and disease severity correlation. In this multicenter study consisting of training and validation sets, a total of 178 subjects were randomly selected from a retrospective cohort, matching age and sex between PD patients, healthy controls, and neurological controls with Alzheimer disease (AD). From ~14,000 unique peptides displaying differences between PD and healthy control in proteomic investigations, 126 peptides were selected based on relevance and observability in CSF using bioinformatic analysis and MS screening, and then quantified by highly accurate and sensitive selected reaction monitoring (SRM) in the CSF of 30 PD patients vs 30 healthy controls (training set), followed by diagnostic (receiver operating characteristics) and disease severity correlation analyses. The most promising candidates were further tested in an independent cohort of 40 PD patients, 38 AD patients, and 40 healthy controls (validation set). A panel of 5 peptides (derived from SPP1, LRP1, CSF1R, EPHA4, and TIMP1) was identified to provide an area under curve (AUC) of 0.873 (sensitivity=76.7%, specificity=80.0%) for PD versus healthy controls in the training set. The performance was essentially confirmed in the validation set (AUC=0.853, sensitivity=82.5%, specificity=82.5%). Additionally, this panel could also differentiate the PD and AD groups

(AUC=0.990, sensitivity=95.0%, specificity=97.4%). Furthermore, a combination of two peptides belonging to proteins TIMP1 and APLP1 significantly correlated with disease severity as determined by the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores in both the training ( $r=0.381$ ,  $p=0.038$ ) and the validation ( $r=0.339$ ,  $p=0.032$ ) sets. The novel panel of CSF peptides, if validated in independent cohorts, could be used to assist in clinical diagnosis of PD and has the potential to help monitoring or predicting disease progression.

Skoog, S. J. (2015). Editorial comment. *Journal of Urology*, 193(2), 661.

Smith, M. D., Adeniji, A., Wahed, A. S., Patterson, E., Chapman, W., Courcoulas, A. P., et al. (2014).

Technical factors associated with anastomotic leak after roux-en-Y gastric bypass. *Surgery for Obesity and Related Diseases : Official Journal of the American Society for Bariatric Surgery*,

BACKGROUND: Anastomotic leak is one of the most serious complications after Roux-en-Y gastric bypass (RYGB). Our objective was to examine the relationship between technical factors and incidence of clinically relevant anastomotic leak after RYGB in longitudinal assessment of bariatric surgery (LABS). The setting of the study was 11 bariatric centers in the United States, university, and private practice. METHODS: Patient characteristics, technical factors of surgery, and postoperative outcomes were assessed by trained researchers using standardized protocols. Correlation of surgical factors of patients undergoing RYGB ( $n = 4444$ ) with the incidence of postoperative anastomotic leak was assessed by univariate chi2 analysis. RESULTS: Forty-four participants (1.0%, 95% CI .7%-1.3%) experienced a clinically relevant anastomotic leak. Of these, 39 (89%) underwent abdominal reoperation and 3 (7%) died. Technical factors associated with anastomotic leak were open surgery ( $P<.0001$ ), revision surgery ( $P<.0001$ ), and use of an abdominal drain ( $P = .02$ ). Provocative leak testing, method of gastrojejunostomy, and use of fibrin sealant were not associated with anastomotic leak. CONCLUSIONS: Anastomotic leak after RYGB was rare (1.0%). Most cases required reintervention; however, the majority (93%) recovered from this event. Open surgery, revision surgery, and routine drain placement were associated with increased leak rate. Some of these findings may be due to differences in preoperative patient risk.

Smith, M. D., Adeniji, A., Wahed, A. S., Patterson, E., Chapman, W., Courcoulas, A. P., et al. (2015).

Technical factors associated with anastomotic leak after roux-en-Y gastric bypass. *Surgery for Obesity and Related Diseases*,

Background: Anastomotic leak is one of the most serious complications after Roux-en-Y gastric bypass (RYGB). Our objective was to examine the relationship between technical factors and incidence of clinically relevant anastomotic leak after RYGB in longitudinal assessment of bariatric surgery (LABS). The setting of the study was 11 bariatric centers in the United States, university, and private practice. Methods: Patient characteristics, technical factors of surgery, and postoperative outcomes were assessed by trained researchers using standardized protocols. Correlation of surgical factors of patients undergoing RYGB (n = 4444) with the incidence of postoperative anastomotic leak was assessed by univariate  $\chi^2$  analysis. Results: Forty-four participants (1.0%, 95% CI .7%-1.3%) experienced a clinically relevant anastomotic leak. Of these, 39 (89%) underwent abdominal reoperation and 3 (7%) died. Technical factors associated with anastomotic leak were open surgery (P<.0001), revision surgery (P<.0001), and use of an abdominal drain (P = .02). Provocative leak testing, method of gastrojejunostomy, and use of fibrin sealant were not associated with anastomotic leak. Conclusions: Anastomotic leak after RYGB was rare (1.0%). Most cases required reintervention; however, the majority (93%) recovered from this event. Open surgery, revision surgery, and routine drain placement were associated with increased leak rate. Some of these findings may be due to differences in preoperative patient risk.

Sparkenbaugh, E. M., Chantrathammachart, P., Wang, S., Jonas, W., Kirchhofer, D., Gailani, D., et al.

(2015). Excess of heme induces tissue factor-dependent activation of coagulation in mice.

*Haematologica*,

An excess of free heme is present in the blood during many types of hemolytic anemia. This has been linked to organ damage caused by heme-mediated oxidative stress and vascular inflammation. We investigated the mechanism of heme-induced coagulation activation in vivo. Heme caused coagulation activation in wild type mice that was attenuated by an anti-tissue factor antibody and in mice expressing low levels of tissue factor. In contrast, neither factor XI deletion nor inhibition of factor XIIa-mediated factor XI activation reduced heme-induced

coagulation activation, suggesting that the intrinsic coagulation pathway is not involved. We investigated the source of tissue factor in heme-induced coagulation activation. Heme increased the procoagulant activity of mouse macrophages and human PBMCs. Tissue factor-positive staining was observed on leukocytes isolated from the blood of heme-treated mice but not on endothelial cells in the lungs. Furthermore, heme increased vascular permeability in the mouse lungs, kidney and heart. Deletion of tissue factor from either myeloid cells, hematopoietic and endothelial cells, or inhibition of tissue factor expressed by non-hematopoietic cells did not reduce heme-induced coagulation activation. However, heme-induced activation of coagulation was abolished when both non-hematopoietic and hematopoietic cell tissue factor was inhibited. Finally, we demonstrated that coagulation activation was partially attenuated in sickle cell mice treated with recombinant hemopexin to neutralize free heme. Our results indicate that heme promotes tissue factor-dependent coagulation activation and induces tissue factor expression on leukocytes in vivo. We also demonstrated that free heme may contribute to thrombin generation in a mouse model of sickle cell disease.

Stephenson, D., Perry, D., Bens, C., Bain, L. J., Berry, D., Krams, M., et al. (2014). Charting a path toward combination therapy for alzheimer's disease. *Expert Review of Neurotherapeutics*, 15(1), 107-113.

It is acknowledged that progress in combined therapeutic approaches for Alzheimer's disease (AD) will require an unprecedented level of collaboration. At a meeting co-hosted by the Accelerate Cure/Treatments for Alzheimer's Disease Coalition and the Critical Path Institute, investigators from industry, academia and regulatory agencies agreed on the need for combinatorial approaches to treating AD. The need for advancing multiple targets includes recognition for novel adaptive trial designs that incorporate existing and new biomarkers to evaluate drug effects independently and in combination. A combination trial now being planned may test drugs targeting different pathogenic pathways or multiple targets along a common pathway. Collaborations and consortia-based strategies are pivotal for success and a regulatory framework is recommended for success.

Stickles, A. M., Justino de Almeida, M., Morrissey, J. M., Sheridan, K. A., Forquer, I. P., Nilsen, A., et al. (2015). Subtle changes in endochin-like quinolone (ELQ) structure alter site of inhibition within the cytochrome bc1 complex of *Plasmodium falciparum*. *Antimicrobial Agents and Chemotherapy*, The cytochrome bc1 complex (cyt bc1) is the third component of the mitochondrial electron transport chain and is the target of several potent antimalarial compounds, including the naphthoquinone atovaquone (ATV) and the 4(1H)-quinolone ELQ-300. Mechanistically, cyt bc1 facilitates the transfer of electrons from ubiquinol to cytochrome c and contains both oxidative (Qo) and reductive (Qi) catalytic sites that are amenable to small molecule inhibition. Although many antimalarial compounds, including ATV, effectively target the Qo site, it has been challenging to design selective Qi site inhibitors with the ability to circumvent clinical ATV resistance, and little is known about how chemical structure contributes to site selectivity within cyt bc1. Here, we used the proposed Qi site inhibitor ELQ-300 to generate a drug-resistant *P. falciparum* clone containing an I22L mutation at the Qi region of cyt b. Using this "D1" clone and the Y268S Qo mutant strain, Tm90-C2B, we created a structure activity map of Qi vs. Qo site selectivity for a series of endochin-like, 4(1H)-quinolones (ELQs). We found that Qi site inhibition was associated with compounds containing 6-position halogens or aryl 3-position side chains, while Qo site inhibition was favored by 5,7-dihalogen groups or 7-position substituents. In addition to identifying ELQ-300 as a preferential Qi site inhibitor, our data suggest that the 4(1H)-quinolone scaffold is compatible with binding to either site of cyt bc1 and that minor chemical changes can influence Qo or Qi site inhibition by the ELQs.

Strong, M. J., Thompson, E. M., Roundy, N., & Selden, N. R. (2015). Use of lumbar laminoplasty vs. laminotomy for transection of the filum terminale does not affect early complication rates or postoperative course. *Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery*,

INTRODUCTION: Various techniques are used for spinal cord untethering. The purpose of this study was to compare patient characteristics, postoperative course, and early complications after laminotomy vs. laminoplasty for transection of the filum terminale for tethered cord release.

METHODS: Retrospective analysis of clinical and magnetic resonance imaging data was undertaken for all patients (<18 years) who underwent tethered cord release by transection of

the filum terminale at Oregon Health & Science University, Doernbecher Children's Hospital, from 2000 to 2011. RESULTS: Data from two hundred and forty-eight patients were analyzed. Mean age was 5.2 years (range 0.3 to 16.8 years). Access to the thecal space during surgery was achieved using laminotomy or laminoplasty in 82 (33.1 %) and 166 (66.9 %) patients, respectively. Laminoplasty patients were significantly younger than laminotomy patients (3.2 vs. 9.3 years,  $p < 0.0001$ ); other clinical and radiographic characteristics were similar between the groups. Nine patients (3.6 %) experienced early complications, including cerebrospinal fluid leak ( $n = 2$ ), suprafascial infection requiring surgical management and intravenous (IV) antibiotics ( $n = 3$ ) or IV antibiotics alone ( $n = 1$ ), a small area of peri-incisional cutaneous necrosis ( $n = 1$ ), perioperative seizures ( $n = 1$ ), and mild, transient malignant hyperthermia ( $n = 1$ ). There was no difference in the number of early complications between the two groups. Univariate and multivariate analyses revealed no significant risk factor for postoperative complication associated with technique. As judged by caregivers, independent of surgical technique, 97 % of patients improved after surgery. CONCLUSION: There was no difference in complication risk when performing transection of the filum terminale for tethered cord release using laminotomy or laminoplasty.

Szatmari, P., Georgiades, S., Duku, E., Bennett, T. A., Bryson, S., Fombonne, E., et al. (2015).

Developmental trajectories of symptom severity and adaptive functioning in an inception cohort of preschool children with autism spectrum disorder. *JAMA Psychiatry*,

Importance: Symptom severity and adaptive functioning are fundamental domains of the autism spectrum disorder (ASD) phenotype. To date, the longitudinal association between these 2 domains has not been examined. Objective: To describe the developmental trajectories of autistic symptom severity and adaptive functioning in a large inception cohort of preschool children with ASD. Design, Setting, and Participants: The sample consisted of 421 newly diagnosed preschool children with ASD 2 to 4 years old (355 boys; mean age at study enrollment, 39.87 months) participating in a large Canadian multisite longitudinal study (Pathways in ASD Study).

Prospective data collected at 4 points from time of diagnosis to age 6 years were used to track the developmental trajectories of children. Main Outcomes and Measures: Autistic symptom severity was indexed using the Autism Diagnostic Observation Schedule. Adaptive functioning

was indexed using the Vineland Adaptive Behavior Scales, Second Edition. Results: Two distinct trajectory groups provided the best fit to the autistic symptom severity data. Group 1 (11.4% of the sample) had less severe symptoms and an improving trajectory ( $P < .05$ ), whereas group 2 (88.6% of the sample) had more severe symptoms and a stable trajectory. Three distinct trajectory groups provided the best fit to the adaptive functioning data. Group 1 (29.2% of the sample) showed lower functioning and a worsening trajectory, group 2 (49.9% of the sample) had moderate functioning and a stable trajectory, and group 3 (20.9% of the sample) had higher functioning and an improving trajectory ( $P < .05$ ). Cross-trajectory overlap between the autistic symptom severity and adaptive functioning groups was low ( $\phi = 0.13$ ,  $P < .05$ ). Sex was a significant predictor of autistic symptom severity group membership and age at diagnosis, and language and cognitive scores at baseline predicted membership in adaptive functioning trajectories. Trajectories of both symptom severity and adaptive functioning predicted several different outcomes at age 6 years. Conclusions and Relevance: Findings confirm the heterogeneous nature of developmental trajectories in ASD. Change in adaptive functioning suggests that improvement is possible in roughly 20% of the sample. Autistic symptom severity appears to be more stable, with roughly 11% of the sample showing a marked decrease in symptom severity. During the preschool years, there appears to be only a small amount of "yoking" of developmental trajectories in autistic symptom severity and adaptive functioning. It is imperative that a flexible suite of interventions that target both autistic symptom severity and adaptive functioning should be implemented and tailored to each child's strengths and difficulties.

Tavori, H., Rashid, S., & Fazio, S. (2015). On the function and homeostasis of PCSK9: Reciprocal interaction with LDLR and additional lipid effects. *Atherosclerosis*, 238(2), 264-270.

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a circulatory ligand that terminates the lifecycle of the low-density lipoprotein (LDL) receptor (LDLR) thus affecting plasma LDL-cholesterol (LDL-C) levels. Recent evidence shows that in addition to the straightforward mechanism of action, there are more complex interactions between PCSK9, LDLR and plasma lipoprotein levels, including: (a) the presence of both parallel and reciprocal regulation of surface LDLR and plasma PCSK9; (b) a correlation between PCSK9 and LDL-C levels dependent not only on the fact that PCSK9 removes hepatic LDLR, but also due to the fact that up to 40% of plasma

PCSK9 is physically associated with LDL; and (c) an association between plasma PCSK9 production and the assembly and secretion of triglyceride-rich lipoproteins. The effect of PCSK9 on LDLR is being successfully utilized toward the development of anti-PCSK9 therapies to reduce plasma LDL-C levels. Current biochemical research has uncovered additional mechanisms of action and interacting partners for PCSK9, and this opens the way for a more thorough understanding of the regulation, metabolism, and effects of this interesting protein.

Tavori, H., Su, Y. R., Yancey, P. G., Giunzioni, I., Wilhelm, A. J., Blakemore, J. L., et al. (2015).

Macrophage apoAI protects against dyslipidemia-induced dermatitis and atherosclerosis without affecting HDL. *Journal of Lipid Research*,

Tissue cholesterol accumulation, macrophage infiltration, and inflammation are features of some forms of dermatitis and atherosclerosis. High-density lipoprotein (HDL) and its main protein apoAI are acceptors of excess cholesterol from macrophages; this process inhibits tissue inflammation. Recent epidemiologic and clinical trial evidence questions the role of HDL and its manipulation in cardiovascular disease. We investigated the effect of ectopic macrophage apoAI expression on atherosclerosis and dermatitis induced by the combination of hypercholesterolemia and absence of HDL in mice. Hematopoietic progenitor cells were transduced to express human apoAI and transplanted into lethally irradiated LDLR<sup>-/-</sup>/apoAI<sup>-/-</sup> mice, which were then placed on a high-fat diet for 16 weeks. Macrophage apoAI expression reduced aortic CD4<sup>+</sup> T-cell levels (-39.8%), lesion size (-25%), and necrotic core area (-31.6%), without affecting serum HDL or aortic macrophage levels. Macrophage apoAI reduced skin cholesterol by 39.8%, restored skin morphology and reduced skin CD4<sup>+</sup> T-cell levels. Macrophage apoAI also reduced CD4<sup>+</sup> T-cell levels (-32.9%) in skin-draining lymph nodes, but had no effect on other T-cells, B-cells, dendritic cells, or macrophages compared to control transplanted mice. Thus, macrophage apoAI expression protects against atherosclerosis and dermatitis by reducing cholesterol accumulation and regulating CD4<sup>+</sup> T-cell levels, without affecting serum HDL or tissue macrophage levels.

Tehrani, S., Johnson, E. C., Cepurna, W. O., & Morrison, J. C. (2014). Astrocyte processes label for filamentous actin and reorient early within the optic nerve head in a rat glaucoma model.

*Investigative Ophthalmology & Visual Science*, 55(10), 6945-6952.

PURPOSE: To determine if astrocyte processes label for actin and to quantify the orientation of astrocytic processes within the optic nerve head (ONH) in a rat glaucoma model. METHODS: Chronic intraocular pressure (IOP) elevation was produced by episcleral hypertonic saline injection and tissues were collected after 5 weeks. For comparison, eyes with optic nerve transection were collected at 2 weeks. Fellow eyes served as controls. Axonal degeneration in retrobulbar optic nerves was graded on a scale of 1 to 5. Optic nerve head sections (n  $\geq$  4 eyes per group) were colabeled with phalloidin (actin marker) and antibodies to astrocytic glial fibrillary acidic protein and aquaporin 4, or axonal tubulin betaIII. Confocal microscopy and FIJI software were used to quantify the orientation of actin bundles. RESULTS: Control ONHs showed stereotypically arranged actin bundles within astrocyte processes. Optic nerve head actin bundle orientation was nearly perpendicular to axons (82.9 degrees  $\pm$  6.3 degrees relative to axonal axis), unlike the retrobulbar optic nerve (45.4 degrees  $\pm$  28.7 degrees,  $P < 0.05$ ). With IOP elevation, ONH actin bundle orientation became less perpendicular to axons, even in eyes with no perceivable axonal injury (i.e., 38.8 degrees  $\pm$  15.1 degrees in grade 1,  $P < 0.05$  in comparison to control ONHs). With severe injury, ONH actin bundle orientation became more parallel to the axonal axis (24.1 degrees  $\pm$  28.4 degrees,  $P < 0.05$  in comparison to control ONHs). Optic nerve head actin bundle orientation in transected optic nerves was unchanged. CONCLUSIONS: Actin labeling identifies fine astrocyte processes within the ONH. Optic nerve head astrocyte process reorientation occurs early in response to elevated IOP.

Terker, A. S., Zhang, C., McCormick, J. A., Lazelle, R. A., Zhang, C., Meermeier, N. P., et al. (2015).

Potassium modulates electrolyte balance and blood pressure through effects on distal cell voltage and chloride. *Cell Metabolism*, 21(1), 39-50.

Dietary potassium deficiency, common in modern diets, raises blood pressure and enhances salt sensitivity. Potassium homeostasis requires a molecular switch in the distal convoluted tubule (DCT), which fails in familial hyperkalemic hypertension (pseudohypoaldosteronism type 2), activating the thiazide-sensitive NaCl cotransporter, NCC. Here, we show that dietary potassium deficiency activates NCC, even in the setting of high salt intake, thereby causing sodium retention and a rise in blood pressure. The effect is dependent on plasma potassium, which modulates DCT cell membrane voltage and, in turn, intracellular chloride. Low intracellular chloride stimulates

WNK kinases to activate NCC, limiting potassium losses, even at the expense of increased blood pressure. These data show that DCT cells, like adrenal cells, sense potassium via membrane voltage. In the DCT, hyperpolarization activates NCC via WNK kinases, whereas in the adrenal gland, it inhibits aldosterone secretion. These effects work in concert to maintain potassium homeostasis.

Thielke, S., Corson, K., & Dobscha, S. K. (2014). Collaborative care for pain results in both symptom improvement and sustained reduction of pain and depression. *General Hospital Psychiatry*,  
OBJECTIVE: Traditional analytic approaches may oversimplify the mechanisms by which interventions effect change. Transition probability models can quantify both symptom improvement and sustained reduction in symptoms. We sought to quantify transition probabilities between higher and lower states for four outcome variables and to compare two treatment arms with respect to these transitions. METHOD: Secondary analysis of a year-long collaborative care intervention for chronic musculoskeletal pain in veterans. Forty-two clinicians were randomized to intervention or treatment as usual (TAU), with 401 patients nested within clinician. The outcome variables, pain intensity, pain interference, depression and disability scores were dichotomized (lower/higher). Probabilities of symptom improvement (transitioning from higher to lower) or sustained reduction (remaining lower) were compared between intervention and TAU groups at 0- to 3-, 3- to 6- and 6- to 12-month intervals. General estimating equations quantified the effect of the intervention on transitions. RESULTS: In adjusted models, the intervention group showed about 1.5 times greater odds of both symptom improvement and sustained reduction compared to TAU, for all the outcomes except disability. CONCLUSIONS: Despite no formal relapse prevention program, intervention patients were more likely than TAU patients to experience continued relief from depression and pain. Collaborative care interventions may provide benefits beyond just symptom reduction.

Tilki, D., Hu, B., Nguyen, H. G., Dall'Era, M. A., Bertini, R., Carballido, J. A., et al. (2015). Impact of synchronous metastasis distribution on cancer specific survival in renal cell carcinoma after radical nephrectomy with tumor thrombectomy. *Journal of Urology*, 193(2), 436-442.  
Purpose Metastatic renal cell carcinoma can be clinically diverse in terms of the pattern of

metastatic disease and response to treatment. We studied the impact of metastasis and location on cancer specific survival. Materials and Methods The records of 2,017 patients with renal cell cancer and tumor thrombus who underwent radical nephrectomy and tumor thrombectomy from 1971 to 2012 at 22 centers in the United States and Europe were analyzed. Number and location of synchronous metastases were compared with respect to patient cancer specific survival. Multivariable Cox regression models were used to quantify the impact of covariates. Results Lymph node metastasis (155) or distant metastasis (725) was present in 880 (44%) patients. Of the patients with distant disease 385 (53%) had an isolated metastasis. The 5-year cancer specific survival was 51.3% (95% CI 48.6-53.9) for the entire group. On univariable analysis patients with isolated lymph node metastasis had a significantly worse cancer specific survival than those with a solitary distant metastasis. The location of distant metastasis did not have any significant effect on cancer specific survival. On multivariable analysis the presence of lymph node metastasis, isolated distant metastasis and multiple distant metastases were independently associated with cancer specific survival. Moreover higher tumor thrombus level, papillary histology and the use of postoperative systemic therapy were independently associated with worse cancer specific survival. Conclusions In our multi-institutional series of patients with renal cell cancer who underwent radical nephrectomy and tumor thrombectomy, almost half of the patients had synchronous lymph node or distant organ metastasis. Survival was superior in patients with solitary distant metastasis compared to isolated lymph node disease.

Tuck, K. K., Brod, L., Nutt, J., & Fromme, E. K. (2015). Preferences of patients with Parkinson's disease for communication about advanced care planning. *American Journal of Hospice and Palliative Medicine*, 32(1), 68-77.

Tully, M., Trujillo, J., Hou, V., & Kirsch, J. (2014). Caring for a patient with unexpected pheochromocytoma complicated by medical fraud. *A & A Case Reports*, 2(5), 53-54.

We report a case of a patient who used multiple aliases as part of a medical fraud scheme. As a consequence, the surgical team was unaware of a left-sided adrenal mass that had been documented for this patient under another name. In the operating room, severe hypertension from the undiagnosed pheochromocytoma led to a ventricular fibrillation cardiac arrest. This case

demonstrates the importance of physician awareness of medical identity fraud and its potential consequences.

Varlamov, O., Chu, M., Cornea, A., Sampath, H., & Roberts, C. T. (2015). Cell-autonomous heterogeneity of nutrient uptake in white adipose tissue of rhesus macaques. *Endocrinology*, 156(1), 80-89.

Phenotypic diversity may play an adaptive role by providing graded biological responses to fluctuations in environmental stimuli. We used single-cell imaging of the metabolizable fluorescent fatty acid analog 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY)-C12 and fluorescent 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl) amino]-2-deoxy-D-glucose (2-NBDG) to explore cellular heterogeneity in nutrient uptake in white adipose tissue (WAT) explants of rhesus macaques. Surprisingly, WAT displayed a striking cell size-independent mosaic pattern, in that adjacent adipocytes varied with respect to insulin-stimulated BODIPY-C12 and 2-NBDG uptake. Relative free fatty acid (FFA) transport activity correlated with the cellular levels of FFA transporter protein-1 and the scavenger receptor CD36 in individual adipocytes. In vitro incubation of WAT explants for 24 hours caused partial desynchronization of cellular responses, suggesting that adipocytes may slowly alter their differential nutrient uptake activity. In vitro differentiated human adipocytes also exhibited a mosaic pattern of BODIPY-C12 uptake. WAT from animals containing a homogeneous population of large adipocytes was non-mosaic, in that every adipocyte exhibited a similar level of BODIPY-C12 fluorescence, suggesting that the development of obesity is associated with the loss of heterogeneity in WAT. Hence, for the first time, we demonstrate an intrinsic heterogeneity in FFA and glucose transport activity in WAT.

Varlamov, O., Kievit, P., Phu, K., Reddy, A. P., Roberts, C. T., Jr, & Bethea, C. L. (2014). Preliminary examination of olanzapine and diet interactions on metabolism in a female macaque. *Journal of Endocrinology and Diabetes*, 1(2), 9.

Clinical data suggest that atypical antipsychotics such as olanzapine (OLZ) induce significant metabolic changes that are serious side effects of their primary use. Since controlled human studies are problematic and rodent data may be poorly translatable, we have initiated

development of a macaque model of OLZ-induced metabolic disease. In this preliminary feasibility study, we examined some metabolic effects of OLZ in a female macaque in the context of a standard low-calorie/fat monkey chow diet followed by a high-fat/sugar Western-style diet (WSD). A female Japanese macaque was administered OLZ (1.25 mg/day) for 6 months, with dietary changes at 2-month intervals as follows: OLZ+Restricted chow, OLZ+Unrestricted chow, OLZ+WSD, and placebo+WSD. Weight was assessed weekly. Glucose tolerance tests (GTT) and Dexascans were performed at baseline and every 2 months. Omental (OM) and subcutaneous (SQ) adipose tissue biopsies were obtained at baseline, after OLZ+Unrestricted chow and after OLZ+WSD to evaluate adipocyte size, lipolysis and insulin-stimulated free fatty acid uptake (FFA). A separate trial was conducted on 2 monkeys with 5 days of OLZ- or no-treatment followed by RT-PCR on rostral and medial basal hypothalamus. Weight increased on OLZ+Restricted chow and stabilized on OLZ+Unrestricted chow. OLZ+WSD did not significantly change the weight plateau. Weight declined upon withdrawal of OLZ with continued WSD. Body fat increased from 14% at baseline to 22%, 30%, 28% and 19% at 2, 4, 6 and 8 mo, respectively, indicating that body fat was elevated on OLZ regardless of diet and declined upon OLZ removal. Glucose tolerance and the insulin response during GTT were normal with OLZ+Restricted chow or OLZ+Unrestricted chow. Addition of WSD with OLZ impaired glucose clearance during GTT. Insulin remained in the normal range, but first phase insulin secretion was reduced. After removal of OLZ, but continued WSD, glucose clearance returned to normal, but this was associated with hyperinsulinemia. Adipocyte diameter was increased in OM and SQ fat by OLZ+chow and OLZ+WSD to a similar extent. ( $p < 0.01$ , 2-way ANOVA). In OM, isoproterenol-stimulated lipolysis occurred at baseline. In both depots, isoproterenol-stimulated lipolysis occurred with OLZ+chow, but it was significantly blunted by addition of WSD (ANOVA  $p < 0.0001$ ; posthoc  $p < 0.05$ ). Insulin increased FFA uptake at baseline. OLZ +chow or OLZ+WSD increased basal FFA uptake and insulin-induced FFA uptake was blunted in both depots (posthoc  $p < 0.05$ ). There was a marked decrease in POMC gene expression, and increased AgRP and NPY expression in the hypothalamus. There was also a clear increase in serotonin (5HT) 2C, melanocortin (MCR4), and Leptin (LepR) receptor gene expression. These data support the hypotheses that OLZ acts on peripheral tissues as well as in the CNS; that changes in hypothalamic gene expression occur very rapidly and precede increased fat accumulation; that adipose tissue

exhibits insulin resistance prior to alterations in GTT; that addition of WSD to OLZ precipitates hyperglycemia without an obvious insulin response; and that removal of OLZ and continued WSD resulted in normalized glucose clearance and elevated insulin. These data suggest complex and early responses to OLZ that may be exacerbated by WSD.

Vellone, E., Barbaranelli, C., Lee, C. S., & Riegel, B. (2015). Measures of self-care in heart failure: Issues with factorial structure and reliability. *Heart and Lung: Journal of Acute and Critical Care*, 44(1), 82e86.

Verhoef, C., Singla, N., Moneta, G., Muir, W., Rijken, A., Lockstadt, H., et al. (2014). Fibrocaps for surgical hemostasis: Two randomized, controlled phase II trials. *The Journal of Surgical Research*,

BACKGROUND: Fibrocaps, a ready-to-use, dry-powder fibrin sealant containing human plasma-derived thrombin and fibrinogen, is being developed as an adjunct for surgical hemostasis.

MATERIALS AND METHODS: Safety and efficacy of Fibrocaps applied directly or by spray device, in combination with gelatin sponge, was compared with that of gelatin sponge-alone in two randomized, single-blind controlled trials: FC-002 US (United States) and FC-002 NL (the Netherlands). A total of 126 adult patients were randomized (Fibrocaps: n = 47 [FC-002 US], n = 39 [FC-002 NL]; gelatin sponge alone: n = 23 [FC-002 US], n = 17 [FC-002 NL]). One bleeding site was treated during a surgical procedure (n = 125). Time to hemostasis (primary end point) was measured, with a 28-d safety follow-up. Four surgical indications included hepatic resection (n = 58), spinal procedures (n = 37), peripheral vascular procedures (n = 30), and soft tissue dissection (n = 1). RESULTS: Mean (standard deviation) time to hemostasis was significantly shorter after Fibrocaps treatment than after gelatin sponge alone (FC-002 US: 1.9 [1.3] versus 4.8 min [3.1], P < 0.001; FC-002 NL: 2.2 [1.3] versus 4.4 min [3.1], P = 0.004). The incidence of hemostasis was greater after Fibrocaps compared with that of gelatin sponge alone within 3 min (FC-002 US: 83% versus 35%, P < 0.001; FC-002 NL: 77% versus 53%, P = 0.11), 5 min (94% versus 61%, P = 0.001; 95% versus 71%, P = 0.022), and 10 min (100% versus 78%, P = 0.003; 100% versus 82%, P = 0.025). Adverse events were consistent with surgical procedures performed and patients' underlying diseases and generally similar between treatment

arms; most were mild or moderate in severity. Non-neutralizing antithrombin antibodies were detected in 5% of Fibrocaps-treated patients on day 29. CONCLUSIONS: Fibrocaps had good safety and efficacy profiles, supporting continuing clinical development as a novel fibrin sealant.

Verhoef, C., Singla, N., Moneta, G., Muir, W., Rijken, A., Lockstadt, H., et al. (2015). Fibrocaps for surgical hemostasis: Two randomized, controlled phase II trials. *Journal of Surgical Research*,

Background: Fibrocaps, a ready-to-use, dry-powder fibrin sealant containing human plasma-derived thrombin and fibrinogen, is being developed as an adjunct for surgical hemostasis.

Materials and methods: Safety and efficacy of Fibrocaps applied directly or by spray device, in combination with gelatin sponge, was compared with that of gelatin sponge-alone in two randomized, single-blind controlled trials: FC-002 US (United States) and FC-002 NL (the Netherlands). A total of 126 adult patients were randomized (Fibrocaps: n=47 [FC-002 US], n=39 [FC-002 NL]; gelatin sponge alone: n=23 [FC-002 US], n=17 [FC-002 NL]). One bleeding site was treated during a surgical procedure (n=125). Time to hemostasis (primary end point) was measured, with a 28-d safety follow-up. Four surgical indications included hepatic resection (n=58), spinal procedures (n=37), peripheral vascular procedures (n=30), and soft tissue dissection (n=1). Results: Mean (standard deviation) time to hemostasis was significantly shorter after Fibrocaps treatment than after gelatin sponge alone (FC-002 US: 1.9 [1.3] versus 4.8 min [3.1],  $P<0.001$ ; FC-002 NL: 2.2 [1.3] versus 4.4 min [3.1],  $P=0.004$ ). The incidence of hemostasis was greater after Fibrocaps compared with that of gelatin sponge alone within 3min (FC-002 US: 83% versus 35%,  $P<0.001$ ; FC-002 NL: 77% versus 53%,  $P=0.11$ ), 5min (94% versus 61%,  $P=0.001$ ; 95% versus 71%,  $P=0.022$ ), and 10min (100% versus 78%,  $P=0.003$ ; 100% versus 82%,  $P=0.025$ ). Adverse events were consistent with surgical procedures performed and patients' underlying diseases and generally similar between treatment arms; most were mild or moderate in severity. Non-neutralizing antithrombin antibodies were detected in 5% of Fibrocaps-treated patients on day29. Conclusions: Fibrocaps had good safety and efficacy profiles, supporting continuing clinical development as a novel fibrin sealant.

Verstovsek, S., Mesa, R. A., Gotlib, J., Levy, R. S., Gupta, V., DiPersio, J. F., et al. (2015). Three-year efficacy, overall survival, and safety of ruxolitinib therapy in patients with myelofibrosis from the

COMFORT-I study. *Haematologica*,

In the phase III COMFORT-I study, the Janus kinase 1 (JAK1)/JAK2 inhibitor ruxolitinib provided significant improvements in splenomegaly, key symptoms, and quality-of-life measures and was associated with an overall survival benefit relative to placebo in patients with intermediate-2 or high-risk myelofibrosis. This planned analysis assessed the long-term efficacy and safety of ruxolitinib at a median follow-up of 149 weeks. At data cutoff, approximately 50% of patients originally randomized to ruxolitinib remained on treatment whereas all patients originally assigned to placebo had discontinued or crossed over to ruxolitinib. At week 144, mean spleen volume reduction was 34% with ruxolitinib. Previously observed improvements in quality-of-life measures were sustained with longer-term ruxolitinib therapy. Overall survival continued to favor ruxolitinib despite the majority of placebo patients crossing over to ruxolitinib (hazard ratio 0.69 [95% confidence interval: 0.46-1.03]; P=0.067). Exploratory analyses suggest that crossover may have contributed to an underestimation of the true survival difference between the treatment groups. Ruxolitinib continued to be generally well tolerated; there was no pattern of worsening of grade  $\geq 3$  anemia or thrombocytopenia with longer-term ruxolitinib exposure. These longer-term data continue to support the efficacy and safety of ruxolitinib in patients with myelofibrosis. The study is registered at [clinicaltrials.gov](https://clinicaltrials.gov): NCT00952289.

Von Gersdorff, H. (2008). *Synaptic transmission* Humana Press Inc.

Vu, T. Q., Lam, W. Y., Hatch, E. W., & Lidke, D. S. (2015). Quantum dots for quantitative imaging:

From single molecules to tissue. *Cell and Tissue Research*,

Since their introduction to biological imaging, quantum dots (QDs) have progressed from a little known, but attractive, technology to one that has gained broad application in many areas of biology. The versatile properties of these fluorescent nanoparticles have allowed investigators to conduct biological studies with extended spatiotemporal capabilities that were previously not possible. In this review, we focus on QD applications that provide enhanced quantitative information concerning protein dynamics and localization, including single particle tracking and immunohistochemistry, and finish by examining the prospects of upcoming applications, such as correlative light and electron microscopy and super-resolution. Advances in single molecule

imaging, including multi-color and three-dimensional QD tracking, have provided new insights into the mechanisms of cell signaling and protein trafficking. New forms of QD tracking in vivo have allowed the observation of biological processes at molecular level resolution in the physiological context of the whole animal. Further methodological development of multiplexed QD-based immunohistochemistry assays should enable more quantitative analysis of key proteins in tissue samples. These advances highlight the unique quantitative data sets that QDs can provide to further our understanding of biological and disease processes.

Waks, J. W., Soliman, E. Z., Henrikson, C. A., Sotoodehnia, N., Han, L., Agarwal, S. K., et al. (2015).

Beat-to-beat spatiotemporal variability in the T vector is associated with sudden cardiac death in participants without left ventricular hypertrophy: The atherosclerosis risk in communities (ARIC) study. *Journal of the American Heart Association*, 4(1), 10.1161/JAHA.114.001357.

BACKGROUND: Despite advances in prevention and treatment of cardiovascular disease, sudden cardiac death (SCD) remains a clinical challenge. Risk stratification in the general population is needed. METHODS AND RESULTS: Beat-to-beat spatiotemporal variability in the T vector was measured as the mean angle between consecutive T-wave vectors (mean TT' angle) on standard 12-lead ECGs in 14 024 participants in the Atherosclerosis Risk in Communities (ARIC) study. Subjects with left ventricular hypertrophy, atrial arrhythmias, frequent ectopy, ventricular pacing, or QRS duration  $\geq 120$  ms were excluded. The mean spatial TT' angle was  $5.21 \pm 3.55$  degrees. During a median of 14 years of follow-up, 235 SCDs occurred (1.24 per 1000 person-years). After adjustment for demographics, coronary heart disease risk factors, and known ECG markers for SCD, mean TT' angle was independently associated with SCD (hazard ratio 1.089; 95% CI 1.044 to 1.137; P90th percentile ( $>9.57$  degrees) was associated with a 2-fold increase in the hazard for SCD (hazard ratio 2.01; 95% CI 1.28 to 3.16; P=0.002). In a subgroup of patients with T-vector amplitude  $\geq 0.2$  mV, the association with SCD was almost twice as strong (hazard ratio 3.92; 95% CI 1.91 to 8.05; P90th percentile ( $>9.57$  degrees) was associated with a 2-fold increase in the hazard for SCD (hazard ratio 2.01; 95% CI 1.28 to 3.16; P=0.002). In a subgroup of patients with T-vector amplitude  $\geq 0.2$  mV, the association with SCD was almost twice as strong (hazard ratio 3.92; 95% CI 1.91 to 8.05; P90th percentile ( $>9.57$  degrees) was associated with a 2-fold increase in the hazard for SCD (hazard ratio 2.01; 95% CI 1.28 to 3.16;

P=0.002). In a subgroup of patients with T-vector amplitude  $\geq 0.2$  mV, the association with SCD was almost twice as strong (hazard ratio 3.92; 95% CI 1.91 to 8.05; P=55 years (Pinteraction=0.009). CONCLUSIONS: In a large, prospective, community-based cohort of left ventricular hypertrophy-free participants, increased beat-to-beat spatiotemporal variability in the T vector, as assessed by increasing TT' angle, was associated with SCD.

Wang, Y. X., Choi, Y., Chen, Z., Laurent, S., & Gibbs, S. L. (2014). Molecular imaging: From bench to clinic. *BioMed Research International*, 2014, 357258.

Wáng, Y. -. J., Choi, Y., Chen, Z., Laurent, S., & Gibbs, S. L. (2015). Molecular imaging: From bench to clinic. *BioMed Research International*, 2014

Warshaw, E. M., Maibach, H. I., Taylor, J. S., Sasseville, D., DeKoven, J. G., Zirwas, M. J., et al.

(2015). North american contact dermatitis group patch test results: 2011-2012. *Dermatitis : Contact, Atopic, Occupational, Drug*, 26(1), 49-59.

BACKGROUND: Patch testing is an important diagnostic tool for assessment of allergic contact dermatitis (ACD). OBJECTIVE: This study documents the North American Contact Dermatitis Group (NACDG) patch-testing results from January 1, 2011, to December 31, 2012. METHODS: At 12 centers in North America, patients were tested in a standardized manner with a series of 70 allergens. Data were manually verified and entered into a central database. Descriptive frequencies were calculated, and trends analyzed using chi statistics. RESULTS: Four thousand two hundred thirty-eight patients were tested; of these, 2705 patients (63.8%) had at least 1 positive reaction, and 2029 (48.0%) were ultimately determined to have a primary diagnosis of ACD. Four hundred eight patients (9.6%) had occupationally related skin disease. There were 7532 positive allergic reactions. As compared with previous reporting periods (2009-2010 and 2000-2010), positive reaction rates statistically increased for 6 allergens: methylchloroisothiazolinone/methylisothiazolinone (5.0%; risk ratios [RRs]: 2.01 [1.60-2.52], 1.87 [1.61-2.18]), lanolin alcohol (4.6%; RRs 1.83 [1.45-2.30], 2.10 [1.79-2.47]), cinnamic aldehyde (3.9%; 1.69 [1.32-2.15], 1.53 [1.28-1.82]), glutaral (1.5%; 1.67 [1.13-2.48], 1.31 [1.00-1.71]), paraben mix (1.4%; 1.77 [1.16-2.69], 1.44 [1.09-1.92]), and fragrance mix I (12.1%; RRs 1.42 [1.25-1.61], 1.24 [1.14-1.36]). Compared with the previous decade, positivity

rates for all formaldehyde-releasing preservatives significantly decreased (formaldehyde 6.6%; RR, 0.82 [0.73, 0.93]; quaternium-15 6.4% RR 0.75 [0.66, 0.85]; diazolidinyl urea 2.1%; RR, 0.67 [0.54, 0.84]; imidazolidinyl urea 1.6%, 0.60 [0.47, 0.77]; bronopol 1.6%; RR, 0.60 [0.46, 0.77]; DMDM hydantoin 1.6%; RR, 0.59 [0.54, 0.84]). Approximately a quarter of patients had at least 1 relevant allergic reaction to a non-NACDG allergen. In addition, approximately one-fourth to one-third of reactions detected by NACDG allergens would have been hypothetically missed by T.R.U.E. TEST (SmartPractice Denmark, Hillerod, Denmark). CONCLUSIONS: These data document the beginning of the epidemic of sensitivity to methylisothiazolinones in North America, which has been well documented in Europe. Patch testing with allergens beyond a standard screening tray is necessary for complete evaluation of occupational and nonoccupational ACD.

Wiegand, N., Geltzeiler, C. B., & Tsikitis, V. L. (2015). Trends in the surgical management of diverticulitis. *Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology*, 28(1), 25-30.

Sigmoid diverticulitis is an increasingly common Western disease associated with a high morbidity and cost of treatment. Improvement in the understanding of the disease process, along with advances in the diagnosis and medical management has led to recent changes in treatment recommendations. The natural history of diverticulitis is more benign than previously thought, and current trends favor more conservative, less invasive management. Despite current recommendations of more restrictive indications for surgery, practice trends indicate an increase in elective operations being performed for the treatment of diverticulitis. Due to diversity in disease presentation, in many cases, optimal surgical treatment of acute diverticulitis remains unclear with regard to patient selection, timing, and technical approach in both elective and urgent settings. As a result, data is limited to mostly retrospective and non-randomized studies. This review addresses the current treatment recommendations for surgical management of diverticulitis, highlighting technical aspects and patterns of care.

Wilhelm, C. J., Hashimoto, J. G., Roberts, M. L., Bloom, S. H., Beard, D. K., & Wiren, K. M. (2015). Females uniquely vulnerable to alcohol-induced neurotoxicity show altered glucocorticoid

signaling. *Brain Research*,

Women are more sensitive to the harmful effects of alcohol (EtOH) abuse than men, yet the underlying mechanisms remain poorly understood. Previous gene expression analysis of the medial prefrontal cortex (mPFC) following a chronic intoxication paradigm using continuous 72h vapor inhalation found that females, but not males, exhibit an inflammatory response at peak withdrawal that is associated with cell damage. Given that glucocorticoids can function as anti-inflammatories, are known to increase with EtOH exposure, and influence neurotoxicity, we hypothesized that males and females may exhibit an altered corticosterone (CORT) response following chronic intoxication. Analysis of serum CORT levels revealed the expected increase during withdrawal with no difference between males and females, while control males but not females exhibited higher CORT concentrations than naive animals. Glucocorticoid signaling characterized using focused qPCR arrays identified a sexually dimorphic response in the mPFC during withdrawal, particularly among astrocyte-enriched genes. These genes include aquaporin-1 (Aqp1), sphingosine kinase 1 (Sphk1) and connective tissue growth factor (Ctgf); genes associated with inflammatory signaling, and tissue damage and repair. Bioinformatic analysis also revealed activation of inflammatory signaling and cell death pathways in females. Confirmation studies showed that female mice exhibited significant neuronal degeneration within the anterior cingulate cortex (ACC). By contrast, EtOH exposure lead to a significant reduction in cell death in males. Thus, distinct glucocorticoid signaling pathways are associated with sexually dimorphic neurotoxicity, suggesting one mechanism by which EtOH-exposed females are particularly vulnerable to the damaging effects of alcohol in the CNS.

Win, T. T., Venkatesh, B. A., Volpe, G. J., Mewton, N., Rizzi, P., Sharma, R. K., et al. (2015).

Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI study. *Heart Rhythm*, 12(1), 155-162.

BACKGROUND: Abnormal P-terminal force in lead V1 (PTFV1) is associated with an increased risk of heart failure, stroke, atrial fibrillation, and death. OBJECTIVE: Our goal was to explore associations of left ventricular (LV) diffuse fibrosis with left atrial (LA) function and electrocardiographic (ECG) measures of LA electrical activity. METHODS: Patients without atrial

fibrillation (n = 91; mean age 59.5 years; 61.5% men; 65.9% white) with structural heart disease (spatial QRS-T angle  $\geq 105^\circ$  and/or Selvester QRS score  $\geq 5$  on ECG) but LV ejection fraction  $>35\%$  underwent clinical evaluation, cardiac magnetic resonance, and resting ECG. LA function indices were obtained by multimodality tissue tracking using 2- and 4-chamber long-axis images. T1 mapping and late gadolinium enhancement were used to assess diffuse LV fibrosis and presence of scar. P-prime in V1 amplitude (PPaV1) and duration (PPdV1), averaged P-wave-duration, PR interval, and P-wave axis were automatically measured using 12 SLTM algorithm. PTFV1 was calculated as a product of PPaV1 and PPdV1. RESULTS: In linear regression after adjustment for demographic characteristics, body mass index, maximum LA volume index, presence of scar, and LV mass index, each decile increase in LV interstitial fibrosis was associated with 0.76 mV\*ms increase in negative abnormal PTFV1 (95% confidence interval [CI] -1.42 to -0.09; P = .025), 15.3 ms prolongation of PPdV1 (95% CI 6.9 to 23.8; P = .001) and 5.4 ms prolongation of averaged P-duration (95% CI 0.9-10.0; P = .020). LV fibrosis did not affect LA function. PPaV1 and PTFV1 were associated with an increase in LA volumes and decrease in LA emptying fraction and LA reservoir function. CONCLUSION: LV interstitial fibrosis is associated with abnormal PTFV1, prolonged PPdV1, and P-duration, but does not affect LA function.

Winthrop, K. L., Ku, J. H., Marras, T. K., Griffith, D. E., Daley, C. L., Olivier, K. N., et al. (2015). The tolerability of linezolid in the treatment of nontuberculous mycobacterial disease. *The European Respiratory Journal*,

Wolf, D. P., Mitalipov, N., & Mitalipov, S. (2014). Mitochondrial replacement therapy in reproductive medicine. *Trends in Molecular Medicine*,

Mitochondrial dysfunction is implicated in disease and age-related infertility. Mitochondrial replacement therapies (MRT) in oocytes or zygotes, such as pronuclear (PNT), spindle (ST), or polar body (PBT) transfer, could prevent second-generation transmission of mitochondrial DNA (mtDNA) defects. PNT, associated with high levels of mtDNA carryover in mice but low levels in human embryos, carries ethical issues secondary to donor embryo destruction. ST, developed in primates, supports normal development to adults and low mtDNA carryover. PBT in mice, coupled with PN or ST, may increase the yield of reconstructed embryos with low mtDNA carryover. MRT

also offers replacement of the deficient cytoplasm in oocytes from older patients, with the expectation of high pregnancy rates following in vitro fertilization.

Wolf, D. P., Mitalipov, N., & Mitalipov, S. (2015). Mitochondrial replacement therapy in reproductive medicine. *Trends in Molecular Medicine,*

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Wolf, G. M. (2015). Letter-sound reading: Teaching preschool children print-to-sound processing. *Early Childhood Education Journal,*

This intervention study investigated the growth of letter sound reading and growth of consonant–vowel–consonant (CVC) word decoding abilities for a representative sample of 41 US children in preschool settings. Specifically, the study evaluated the effectiveness of a 3-step letter-sound teaching intervention in teaching preschool children to decode, or read, single letters. The study compared a control group, which received the preschool’s standard letter-sound instruction, to an intervention group which received a 3-step letter-sound instruction intervention. The children’s growth in letter-sound reading and CVC word decoding abilities were assessed at baseline and 2, 4, 6 and 8 weeks. When compared to the control group, the growth of letter-sound reading ability was slightly higher for the intervention group. The rate of increase in letter-sound reading was significantly faster for the intervention group. In both groups, too few children learned to decode any CVC words to allow for analysis. Results of this study support the use of the intervention strategy in preschools for teaching children print-to-sound processing.

Wong, T. E., Delaney, M., Gernsheimer, T., Matthews, D. C., Brogan, T. V., Mazor, R., et al. (2015).

Antithrombin concentrates use in children on extracorporeal membrane oxygenation: A retrospective cohort 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:: To investigate whether receipt of any antithrombin concentrate improves laboratory and clinical outcomes in children undergoing extracorporeal membrane oxygenation for respiratory failure during their hospitalization compared with those who did not receive antithrombin. DESIGN:: Retrospective cohort study. SETTING:: Single, tertiary-care pediatric hospital. PATIENTS:: Sixty-four neonatal and pediatric patients who underwent extracorporeal membrane oxygenation for respiratory failure between January 2007 and September 2011.

INTERVENTION:: Exposure to any antithrombin concentrate during their extracorporeal membrane oxygenation course compared with similar children who never received antithrombin concentrate. MEASUREMENTS AND MAIN RESULTS:: Thirty patients received at least one dose of antithrombin during their extracorporeal membrane oxygenation course and 34 patients did not receive any. The median age at admission was less than 1-month old. Age, duration of extracorporeal membrane oxygenation, or first antithrombin level did not differ significantly between the two cohorts. The mean plasma antithrombin level in those who never received antithrombin was 42.2% compared with 66% in those who received it. However, few levels reached the targeted antithrombin level of 120% and those who did fell back to deficient levels within an average of 6.8 hours. For those who received antithrombin concentrate, heparin infusion rates decreased by an average of 10.2 U/kg/hr for at least 12 hours following administration. No statistical differences were noted in the number of extracorporeal membrane oxygenation circuit changes, in vivo clots or hemorrhages, transfusion requirements, hospital or ICU length of stay, or in-hospital mortality. CONCLUSIONS:: Intermittent, on-demand dosing of antithrombin concentrate in pediatric patients on extracorporeal membrane oxygenation for respiratory failure increased antithrombin levels, but not typically to the targeted level. Patients who received antithrombin concentrate also had decreased heparin requirements for at least 12 hours after dosing. However, no differences were noted in the measured clinical endpoints. A prospective, randomized study of this intervention may require different dosing strategies; such a study is warranted given the unproven efficacy of this costly product.

Wood, D. C., Pelc, L. A., Pozzi, N., Wallisch, M., Verbout, N. G., Tucker, E. I., et al. (2015). WEDGE:

An anticoagulant thrombin mutant produced by autoactivation. *Journal of Thrombosis and Haemostasis*, 13(1), 111-114.

Summary: Background: The production of therapeutically relevant proteases typically involves activation of a zymogen precursor by external enzymes, which may raise regulatory issues about availability and purity. Recent studies of thrombin precursors have shown how to engineer constructs that spontaneously convert to the mature protease by autoactivation, without the need for external enzymes. Objectives: Autoactivation is an innovative strategy that promises to simplify the production of proteases of therapeutic relevance, but has not been tested in practical applications. The aim of this study was to provide a direct test of this strategy. Methods: An autoactivating version of the thrombin mutant W215A/E217A (WE), which is currently in preclinical development as an anticoagulant, was engineered. Results and Conclusions: The autoactivating version of WE can be produced in large quantities, like WE made in BHK cells or *Escherichia coli*, and retains all significant functional properties in vitro and in vivo. The results serve as proof of principle that autoactivation is an innovative and effective strategy for the production of trypsin-like proteases of therapeutic relevance.

Yang, O. O., Ali, A., Kasahara, N., Faure-Kumar, E., Bae, J. Y., Picker, L. J., et al. (2015). Short

conserved sequences of HIV-1 are highly immunogenic and shift immunodominance. *Journal of Virology*, 89(2), 1195-1204.

Cellular immunity is pivotal in HIV-1 pathogenesis but is hampered by viral sequence diversity. An approach to minimize this diversity is to focus immunity on conserved proteome sequences; therefore, we selected four relatively conserved regions (Gag amino acids 148 to 214 and 250 to 335, Env amino acids 521 to 606, and Nef amino acids 106 to 148), each created in three mosaics, to provide better coverage of M-group HIV-1 sequences. A conserved-region vaccine (CRV) delivering genes for these four regions as equal mixtures of three mosaics each (each region at a separate injection site) was compared to a whole-protein vaccine (WPV) delivering equimolar amounts of genes for whole Gag, Env, and Nef as clade B consensus sequences (separate injection sites). Three rhesus macaques were vaccinated via three DNA primes and a recombinant adenovirus type 5 boost (weeks 0, 4, 8, and 24, respectively). Although CRV inserts

were about one-fifth that of WPV, the CRV generated comparable-magnitude blood CD4+ and CD8+ T lymphocyte responses against Gag, Env, and Nef. WPV responses preferentially targeted proteome areas outside the selected conserved regions in direct proportion to sequence lengths, indicating similar immunogenicities for the conserved regions and the outside regions. The CRV yielded a conserved-region targeting density that was approximately 5-fold higher than that of the WPV. A similar pattern was seen for bronchoalveolar lymphocytes, but with quadruple the magnitudes seen in blood. Overall, these findings demonstrate that the selected conserved regions are highly immunogenic and that anatomically isolated vaccinations with these regions focus immunodominance compared to the case for full-length protein vaccination.

Young, A. T., Merkel, M. J., Heitner, S. B., & Schulman, P. M. (2015). Focused echocardiography during glucagon administration to diagnose beta-blocker-induced cardiomyopathy. *Journal of Cardiothoracic and Vascular Anesthesia*,

Young, J. M., Nelson, J. W., Cheng, J., Zhang, W., Mader, S., Davis, C. M., et al. (2015). Peroxisomal biogenesis in ischemic brain. *Antioxidants and Redox Signaling*, 22(2), 109-120.

Aims: Peroxisomes are highly adaptable and dynamic organelles, adjusting their size, number, and enzyme composition to changing environmental and metabolic demands. We determined whether peroxisomes respond to ischemia, and whether peroxisomal biogenesis is an adaptive response to cerebral ischemia. Results: Focal cerebral ischemia induced peroxisomal biogenesis in peri-infarct neurons, which was associated with a corresponding increase in peroxisomal antioxidant enzyme catalase. Peroxisomal biogenesis was also observed in primary cultured cortical neurons subjected to ischemic insult induced by oxygen-glucose deprivation (OGD). A catalase inhibitor increased OGD-induced neuronal death. Moreover, preventing peroxisomal proliferation by knocking down dynamin-related protein 1 (Drp1) exacerbated neuronal death induced by OGD, whereas enhancing peroxisomal biogenesis pharmacologically using a peroxisome proliferator-activated receptor-alpha agonist protected against neuronal death induced by OGD. Innovation: This is the first documentation of ischemia-induced peroxisomal biogenesis in mammalian brain using a combined in vivo and in vitro approach, electron microscopy, high-resolution laser-scanning confocal microscopy, and super-resolution structured

illumination microscopy. Conclusion: Our findings suggest that neurons respond to ischemic injury by increasing peroxisome biogenesis, which serves a protective function, likely mediated by enhanced antioxidant capacity of neurons. *Antioxid. Redox Signal.* 22, 109-120.

Zhang, Q. -, Benedetti, E., Deater, M., Schubert, K., Major, A., Pelz, C., et al. (2015). Oxymetholone therapy of fanconi anemia suppresses osteopontin transcription and induces hematopoietic stem cell cycling. *Stem Cell Reports*, 4(1), 90-102.

Androgens are widely used for treating Fanconi anemia (FA) and other human bone marrow failure syndromes, but their mode of action remains incompletely understood. Aged *Fancd2*<sup>-/-</sup> mice were used to assess the therapeutic efficacy of oxymetholone (OXM) and its mechanism of action. Eighteen-month-old *Fancd2*<sup>-/-</sup> mice recapitulated key human FA phenotypes, including reduced bone marrow cellularity, red cell macrocytosis, and peripheral pancytopenia. As in humans, chronic OXM treatment significantly improved these hematological parameters and stimulated the proliferation of hematopoietic stem and progenitor cells. RNA-Seq analysis implicated downregulation of osteopontin as an important potential mechanism for the drug's action. Consistent with the increased stem cell proliferation, competitive repopulation assays demonstrated that chronic OXM therapy eventually resulted in stem cell exhaustion. These results expand our knowledge of the regulation of hematopoietic stem cell proliferation and have direct clinical implications for the treatment of bone marrow failure.

Zhu, W., Dotson, A. L., Libal, N. L., Lapato, A. S., Bodhankar, S., Offner, H., et al. (2014).

Recombinant T-cell receptor ligand RTL1000 limits inflammation and decreases infarct size after experimental ischemic stroke in middle-aged mice. *Neuroscience*, 288C, 112-119.

We have previously demonstrated that recombinant T-cell receptor ligand 1000 (RTL1000) reduces infarct size and improves long-term functional recovery after experimental stroke in young transgenic mice expressing human leukocyte antigen DR2 (DR2-Tg). In this study, we determined the effect of RTL1000 on infarct size in 12-month-old middle-aged DR2-Tg mice, and investigated its mechanism of action. Twelve-month-old male DR2-Tg mice underwent 60min of intraluminal reversible middle cerebral artery occlusion (MCAO). Vehicle or RTL1000 was injected 4, 24, 48 and 72h after MCAO. Cortical, striatal and total hemispheric infarcts were measured

96h after stroke. Spleen and brain tissues were collected 96h after stroke for immunological analysis. Our data showed that RTL1000 significantly reduced infarct size 96h after MCAO in middle-aged male DR2-Tg mice. RTL1000 decreased the number of activated monocytes/microglia cells (CD11b+CD45hi) and CD3+ T cells in the ischemic hemisphere. RTL1000 also reduced the percentage of total T cells and inflammatory neutrophils in the spleen. These findings suggest that RTL1000 protects against ischemic stroke in middle-aged male mice by limiting post-ischemic inflammation.

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*Recombinant T-cell receptor ligand RTL1000 limits inflammation and decreases infarct size after experimental ischemic stroke in middle-aged mice* Elsevier Ltd.

We have previously demonstrated that recombinant T-cell receptor ligand 1000 (RTL1000) reduces infarct size and improves long-term functional recovery after experimental stroke in young transgenic mice expressing human leukocyte antigen DR2 (DR2-Tg). In this study, we determined the effect of RTL1000 on infarct size in 12-month-old middle-aged DR2-Tg mice, and investigated its mechanism of action. Twelve-month-old male DR2-Tg mice underwent 60min of intraluminal reversible middle cerebral artery occlusion (MCAO). Vehicle or RTL1000 was injected 4, 24, 48 and 72h after MCAO. Cortical, striatal and total hemispheric infarcts were measured 96h after stroke. Spleen and brain tissues were collected 96h after stroke for immunological analysis. Our data showed that RTL1000 significantly reduced infarct size 96h after MCAO in middle-aged male DR2-Tg mice. RTL1000 decreased the number of activated monocytes/microglia cells (CD11b+CD45hi) and CD3+ T cells in the ischemic hemisphere. RTL1000 also reduced the percentage of total T cells and inflammatory neutrophils in the spleen. These findings suggest that RTL1000 protects against ischemic stroke in middle-aged male mice by limiting post-ischemic inflammation.