

References

- Abu-Hassan, D. W., Li, X., Ryan, E. I., Acott, T. S., & Kelley, M. J. (2014). Induced pluripotent stem cells restore function in a human cell loss model of open-angle glaucoma. *Stem Cells (Dayton, Ohio)*,
- Normally, trabecular meshwork (TM) and Schlemm's canal inner wall endothelial cells within the aqueous humor outflow pathway maintain intraocular pressure within a narrow safe range. Elevation in intraocular pressure, because of the loss of homeostatic regulation by these outflow pathway cells, is the primary risk factor for vision loss due to glaucomatous optic neuropathy. A notable feature associated with glaucoma is outflow pathway cell loss. Using controlled cell loss in ex vivo perfused human outflow pathway organ culture, we developed compelling experimental evidence that this level of cell loss compromises intraocular pressure homeostatic function. This function was restored by repopulation of the model with fresh trabecular meshwork cells. We then differentiated induced pluripotent stem cells (iPSCs) and used them to repopulate this cell depletion model. These differentiated cells (TM-like iPSCs) became similar to trabecular meshwork cells in both morphology and expression patterns. When transplanted, they were able to fully restore intraocular pressure homeostatic function. This successful transplantation of TM-like iPSCs establishes the conceptual feasibility of using autologous stem cells to restore intraocular pressure regulatory function in open-angle glaucoma patients, providing a novel alternative treatment option. *Stem Cells* 2014.
- Ahn, J., & Gish, R. G. (2014). Hepatitis D virus: A call to screening. *Gastroenterology and Hepatology*, *10*(10), 647-686.
- Hepatitis D virus causes an aggressive viral hepatitis with a virulent course of progression to cirrhosis and hepatic decompensation. It relies on hepatitis B coinfection for its pathogenesis and propagation. Hepatitis D virus had become the forgotten virus, with reduced public awareness, medical interest, and research support. Recently, there has been a resurgence of awareness and interest in hepatitis D, with improvements in diagnostic testing and establishment of international collaborative efforts to improve therapy. This article provides a framework to understand the impetus for increased screening as well as to identify key issues toward which collaborative efforts can be directed.

Alt, J. A., Smith, T. L., Schlosser, R. J., Mace, J. C., & Soler, Z. M. Sleep and quality of life

improvements after endoscopic sinus surgery in patients with chronic rhinosinusitis. *International Forum of Allergy and Rhinology*, 4(9), 693-701.

Background: Recent investigation has demonstrated that approximately 75% of patients with medically refractory chronic rhinosinusitis (CRS) report abnormal sleep quality, with strong correlation between worse sleep quality and more severe CRS disease severity. It remains unknown whether the treatment effect of endoscopic sinus surgery (ESS) for CRS results in appreciable sleep quality improvements. Methods: Adult patients (aged ≥ 18 years) with a current diagnosis of recalcitrant chronic rhinosinusitis (CRS), who voluntarily elected ESS as the next treatment modality (n = 301), were prospectively evaluated within 4 academic, tertiary care centers using treatment outcome instruments: the Rhinosinusitis Disability Index, the 22-item Sinonasal Outcome Test, the 2-item Patient Health Questionnaire, and the Pittsburgh Sleep Quality Index (PSQI) both before and after ESS. Results: Seventy-two percent (72%) of patients with CRS were found to have poor sleep (PSQI > 5) at baseline with a mean (standard deviation) global PSQI score of 9.4 (4.6). Surgery improved overall mean global PSQI scores (by 2.2 points), and all 7 subdomain scores of the PSQI. Similarly, the odds of good sleep quality (PSQI ≤ 5) in patients treated with sinus surgery increased significantly (odds ratio [OR] 5.94; 95% confidence interval [CI], 3.06 to 11.53; $p < 0.001$). Stepwise multivariate linear regression found that acetylsalicylic acid (ASA) intolerance (β [standard error], -1.94 [0.93]; 95% CI, -3.77 to -0.11; $p = 0.038$), history of prior sinus surgery (β [standard error], 1.10 (0.54); 95% CI, 0.03 to 2.16; $p = 0.044$), and frontal sinusotomy (β [standard error], -1.03 [0.62]; 95% CI, -2.26 to 0.20; $p = 0.099$) were found to significantly associate with improvement in PSQI sleep scores. Conclusion: Among patients with CRS, reduced sleep quality, poor disease-specific quality of life, and greater disease severity were improved following ESS. 2014 ARS-AAOA, LLC.

Anderson, V. C., Obayashi, J. T., Kaye, J. A., Quinn, J. F., Berryhill, P., Riccelli, L. P., et al. (2014).

Longitudinal relaxographic imaging of white matter hyperintensities in the elderly. *Fluids and Barriers of the CNS*, 11, 24-8118-11-24. eCollection 2014.

BACKGROUND: Incidental white matter hyperintensities (WMHs) are common findings on T2-weighted magnetic resonance images of the aged brain and have been associated with cognitive

decline. While a variety of pathogenic mechanisms have been proposed, the origin of WMHs and the extent to which lesions in the deep and periventricular white matter reflect distinct etiologies remains unclear. Our aim was to quantify the fractional blood volume (v_b) of small WMHs in vivo using a novel magnetic resonance imaging (MRI) approach and examine the contribution of blood-brain barrier disturbances to WMH formation in the deep and periventricular white matter.

METHODS: Twenty-three elderly volunteers (aged 59-82 years) underwent 7 Tesla relaxographic imaging and fluid-attenuated inversion recovery (FLAIR) MRI. Maps of longitudinal relaxation rate constant (R_1) were prepared before contrast reagent (CR) injection and throughout CR washout. Voxelwise estimates of v_b were determined by fitting temporal changes in R_1 values to a two-site model that incorporates the effects of transendothelial water exchange. Average v_b values in deep and periventricular WMHs were determined after semi-automated segmentation of FLAIR images. Ventricular permeability was estimated from the change in CSF R_1 values during CR washout.

RESULTS: In the absence of CR, the total water fraction in both deep and periventricular WMHs was increased compared to normal appearing white matter (NAWM). The v_b of deep WMHs was 1.8 ± 0.6 mL/100 g and was significantly reduced compared to NAWM (2.4 ± 0.8 mL/100 g). In contrast, the v_b of periventricular WMHs was unchanged compared to NAWM, decreased with ventricular volume and showed a positive association with ventricular permeability.

CONCLUSIONS: Hyperintensities in the deep WM appear to be driven by vascular compromise, while those in the periventricular WM are most likely the result of a compromised ependyma in which the small vessels remain relatively intact. These findings support varying contributions of blood-brain barrier and brain-CSF interface disturbances in the pathophysiology of deep and periventricular WMHs in the aged human brain.

Angier, H., Likumahuwa, S., Finnegan, S., Vakarcis, T., Nelson, C., Bazemore, A., et al. (2014). Using geographic information systems (GIS) to identify communities in need of health insurance outreach: An OCHIN practice-based research network (PBRN) report. *Journal of the American Board of Family Medicine : JABFM*, 27(6), 804-810.

BACKGROUND: Our(.) practice-based research network (PBRN) is conducting an outreach intervention to increase health insurance coverage for patients seen in the network. To assist with outreach site selection, we sought an understandable way to use electronic health record

(EHR) data to locate uninsured patients. METHODS: Health insurance information was displayed within a web-based mapping platform to demonstrate the feasibility of using geographic information systems (GIS) to visualize EHR data. This study used EHR data from 52 clinics in the OCHIN PBRN. We included cross-sectional coverage data for patients aged 0 to 64 years with at least 1 visit to a study clinic during 2011 (n = 228,284). RESULTS: Our PBRN was successful in using GIS to identify intervention sites. Through use of the maps, we found geographic variation in insurance rates of patients seeking care in OCHIN PBRN clinics. Insurance rates also varied by age: The percentage of adults without insurance ranged from 13.2% to 86.8%; rates of children lacking insurance ranged from 1.1% to 71.7%. GIS also showed some areas of households with median incomes that had low insurance rates. DISCUSSION: EHR data can be imported into a web-based GIS mapping tool to visualize patient information. Using EHR data, we were able to observe smaller areas than could be seen using only publicly available data. Using this information, we identified appropriate OCHIN PBRN clinics for dissemination of an EHR-based insurance outreach intervention. GIS could also be used by clinics to visualize other patient-level characteristics to target clinic outreach efforts or interventions.

Aylor, M., Anderson, J. M., Vanderford, P., Halsey, M., Lai, S., & Braner, D. A. (2014). Videos in clinical medicine. reduction of pulled elbow. *The New England Journal of Medicine*, 371(21), e32.

Bansal, M., Yang, J., Karan, C., Menden, M. P., Costello, J. C., Tang, H., et al. (2014). A community computational challenge to predict the activity of pairs of compounds. *Nature Biotechnology*, Recent therapeutic successes have renewed interest in drug combinations, but experimental screening approaches are costly and often identify only small numbers of synergistic combinations. The DREAM consortium launched an open challenge to foster the development of in silico methods to computationally rank 91 compound pairs, from the most synergistic to the most antagonistic, based on gene-expression profiles of human B cells treated with individual compounds at multiple time points and concentrations. Using scoring metrics based on experimental dose-response curves, we assessed 32 methods (31 community-generated approaches and SynGen), four of which performed significantly better than random guessing. We highlight similarities between the methods. Although the accuracy of predictions was not optimal,

we find that computational prediction of compound-pair activity is possible, and that community challenges can be useful to advance the field of in silico compound-synergy prediction.

Barbaranelli, C., Lee, C. S., Vellone, E., & Riegel, B. Dimensionality and reliability of the self-care of heart failure index scales: Further evidence from confirmatory factor analysis. *Research in Nursing and Health*, 37(6), 524-537.

The Self-Care of Heart Failure Index (SCHFI) is used widely, but issues with reliability have been evident. Cronbach alpha coefficient is usually used to assess reliability, but this approach assumes a unidimensional scale. The purpose of this article is to address the dimensionality and internal consistency reliability of the SCHFI. This was a secondary analysis of data from 629 adults with heart failure enrolled in three separate studies conducted in the northeastern and northwestern United States. Following testing for scale dimensionality using confirmatory factor analysis, reliability was tested using coefficient alpha and alternative options. Confirmatory factor analysis demonstrated that: (a) the Self-Care Maintenance Scale has a multidimensional four-factor structure; (b) the Self-Care Management Scale has a two-factor structure, but the primary factors loaded on a common higher-order factor; and (c) the Self-Care Confidence Scale is unidimensional. Reliability estimates for the three scales, obtained with methods compatible with each scale's dimensionality, were adequate or high. The results of the analysis demonstrate that issues of dimensionality and reliability cannot be separated. Appropriate estimates of reliability that are consistent with the dimensionality of the scale must be used. In the case of the SCHFI, coefficient alpha should not be used to assess reliability of the self-care maintenance and the self-care management scales, due to their multidimensionality. When performing psychometric evaluations, we recommend testing dimensionality before assessing reliability, as well using multiple indices of reliability, such as model-based internal consistency, composite reliability, and omega and maximal reliability coefficients.

Bayestehtashk, A., Asgari, M., Shafran, I., & McNames, J. (2015). Fully automated assessment of the severity of parkinson's disease from speech. *Computer Speech & Language*, 29(1), 172-185.

For several decades now, there has been sporadic interest in automatically characterizing the speech impairment due to Parkinson's disease (PD). Most early studies were confined to

quantifying a few speech features that were easy to compute. More recent studies have adopted a machine learning approach where a large number of potential features are extracted and the models are learned automatically from the data. In the same vein, here we characterize the disease using a relatively large cohort of 168 subjects, collected from multiple (three) clinics. We elicited speech using three tasks - the sustained phonation task, the diadochokinetic task and a reading task, all within a time budget of 4 minutes, prompted by a portable device. From these recordings, we extracted 1582 features for each subject using openSMILE, a standard feature extraction tool. We compared the effectiveness of three strategies for learning a regularized regression and find that ridge regression performs better than lasso and support vector regression for our task. We refine the feature extraction to capture pitch-related cues, including jitter and shimmer, more accurately using a time-varying harmonic model of speech. Our results show that the severity of the disease can be inferred from speech with a mean absolute error of about 5.5, explaining 61% of the variance and consistently well-above chance across all clinics. Of the three speech elicitation tasks, we find that the reading task is significantly better at capturing cues than diadochokinetic or sustained phonation task. In all, we have demonstrated that the data collection and inference can be fully automated, and the results show that speech-based assessment has promising practical application in PD. The techniques reported here are more widely applicable to other paralinguistic tasks in clinical domain.

Bee, Y. S., Alonzo, B., & Ng, J. D. (2014). Review of AlloDerm acellular human dermis regenerative tissue matrix in multiple types of oculofacial plastic and reconstructive surgery. *Ophthalmic Plastic and Reconstructive Surgery*,

PURPOSE:: AlloDerm acellular human dermis is used for repair or replacement of damaged or inadequate skin tissue. It has been used successfully in multiple types of surgeries, including abdominal wall reconstruction, breast reconstruction, and head and neck reconstruction. Its application to ophthalmic plastic and reconstructive surgery is less well described. This study seeks to evaluate the efficacy and factors influencing surgical outcomes using Alloderm in multiple types of oculofacial plastic surgery. METHODS:: Institutional Review Board-approved retrospective review of 84 patients who underwent surgical procedures using Alloderm.

Preoperative demographic data, comorbidities, smoking, clinical etiology, surgical methods,

Alloderm type, and outcome (cosmetic and functional) were evaluated. RESULTS: This study included 84 patients, accounting for a total of 98 procedures. Mean age was 52.5 years (3-93 years). Etiologies necessitating surgery included malignancy in 26 patients (31.0%), trauma in 19 patients (22.6%), congenital lesions in 15 patients (17.9%), and senile change in 11 patients (13.1%). Surgical procedures included lower eyelid posterior lamella elongation, socket and fornix reconstruction, scar repair, patch grafts, and filler. Mean duration of follow up was 530 days. Overall, 92.8% of patients had favorable outcomes. Factors associated with significantly worse outcomes included smoking, congenital anomaly etiologies, and previous graft/flaps in the same area ($p = 0.03$, $p = 0.029$, and $p = 0.007$, respectively). CONCLUSIONS: This study suggests that Alloderm acellular human dermis can be used safely and effectively in multiple types of oculofacial procedures. Smoking, congenital anomaly etiologies, and previous graft/flap were associated with poor cosmetic and functional outcomes.

Beer, P. A., Knapp, D. J., Miller, P. H., Kannan, N., Sloma, I., Heel, K., et al. (2014). Disruption of IKAROS activity in primitive chronic phase CML cells mimics myeloid disease progression. *Blood*, Without effective therapy, chronic phase chronic myeloid leukemia (CP-CML) evolves into an acute leukemia (blast crisis; BC) that displays either myeloid or B-lymphoid characteristics. This transition is often preceded by a clinically recognized, but biologically poorly characterized, accelerated phase (AP). Here we report that IKAROS protein is absent or reduced in bone marrow blasts from most CML patients with advanced myeloid disease (AP or BC). This contrasts with primitive CP-CML cells and BCR-ABL1-negative acute myeloid leukemia blasts which express readily detectable IKAROS. To investigate whether loss of IKAROS contributes to myeloid disease progression in CP-CML, we examined the effects of forced expression of a dominant-negative isoform of IKAROS (IK6) in CP-CML patients' CD34+ cells. We confirmed that IK6 disrupts IKAROS activity in transduced CP-CML cells and showed that it confers on them features of AP-CML, including a prolonged increased output in vitro and in xenografted mice of primitive cells with an enhanced ability to differentiate into basophils. Expression of IK6 in CD34+ CP-CML cells also led to activation of STAT5 and transcriptional repression of its negative regulators. These findings implicate loss of IKAROS as a frequent step and potential diagnostic harbinger of progressive myeloid disease in CML patients.

Beer, T. M., & Tombal, B. (2014). The authors reply. *New England Journal of Medicine*, 371(18), 1755-1756.

Benninger, B. (2014). Google glass, ultrasound and palpation: The anatomy teacher of the future?

Clinical Anatomy (New York, N.Y.),

Traditional palpation techniques are used less often in today's modern medical arena.

Technological advances in imaging, for example, often supplant the need for such types of tactility. Herein, we discuss our recent experience using Google Glass in the teaching of anatomy to medical students, a method that melds traditional medical palpation with cutting edge technology. Based on our study, teachers of the new millennium might use Google Glass coupled with ultrasound and palpation in the teaching of human anatomy to medical students. Such a technology combines palpation, diagnosis, visualization, and learning of anatomy. Glass has provided a platform to position a live ultrasound image for us to view while examining the patient. This technology will allow the physicians of the future to embrace placing ones hand on the body while receiving both palpation and visual stimulation. *Clin. Anat.*, 2014. (c) 2014 Wiley Periodicals, Inc.

Bleyer, A., Asselin, B. L., Koontz, S. E., & Hunger, S. P. (2014). Clinical application of asparaginase activity levels following treatment with pegaspargase. *Pediatric Blood & Cancer*,

Asparaginase, an enzyme used to treat acute lymphoblastic leukemia and related forms of nonHodgkin lymphoma, depletes asparagine, which leads to lymphoblast cell death. Unlike most chemotherapeutic agents, asparaginase is a foreign protein that can result in clinical allergy and/or silent hypersensitivity with production of neutralizing antibodies that inactivate asparaginase. In North America, asparaginase activity levels can now be obtained via a commercially available assay, for therapeutic drug monitoring and investigation of potential allergic reactions. Herein, we provide recommendations and a corresponding algorithm for the clinical application of this assay after treatment with pegaspargase to evaluate suspected hypersensitivity reactions and/or silent inactivation. *Pediatr Blood Cancer* (c) 2014 Wiley Periodicals, Inc.

Boardman, C. R., & Sonnenberg, A. (2014). Magical thinking. *Clinical and Translational Gastroenterology*, 5, e63.

Broberg, C., McLarry, J., Mitchell, J., Winter, C., Doberne, J., Woods, P., et al. (2014). Accuracy of administrative data for detection and categorization of adult congenital heart disease patients from an electronic medical record. *Pediatric Cardiology*,

Diagnostic codes used in healthcare administration have been employed extensively in clinical research to identify target patient populations, including demonstration of important clinical outcomes among adults with congenital heart disease. However, little is known about the reliability of code-derived data in this context. We sought to determine the accuracy of International Classification of Disease-9th Revision (ICD-9) diagnoses and the reliability of retrieval algorithms in adults with congenital heart disease (ACHD). Pilot testing of a hierarchical algorithm to identify ACHD patients and determine their principle congenital diagnosis was performed. A revised algorithm was then applied retrospectively to a sample of all outpatients seen by providers who see general cardiology and ACHD patients. Using all ICD-9 codes available from any encounter, accuracy for detection and categorization of sub-types were compared to physician chart review. After initial testing on 334 patients, the revised algorithm was applied to 740 patients. The sensitivity and specificity for ACHD patient identification from this specialty clinic population were 99 and 88 %, respectively. Of 411 (56 %) non-ACHD patients, 49 were incorrectly categorized as ACHD by the algorithm. Of ACHD patients, 326 of 329 were correctly identified by diagnostic codes and categorization of ACHD defect sub-type was correct in 263 (80 %). Administrative data can be used for identification of ACHD patients based on ICD-9 codes with excellent sensitivity and reasonable specificity. Accurate categorization that would be utilized for quality indicators by ACHD defect type is less robust. Additional testing should be done using non-referral populations.

Burdick, D. J., Cholerton, B., Watson, G. S., Siderowf, A., Trojanowski, J. Q., Weintraub, D., et al. (2014). People with parkinson's disease and normal MMSE score have a broad range of cognitive performance. *Movement Disorders*, 29(10), 1258-1264.

Cognitive impairment, including dementia, is common in Parkinson's disease (PD). TheMini-

Mental State Examination (MMSE) has been recommended as a screening tool for Parkinson's disease dementia (PDD), with values below 26 indicative of possible dementia. Using a detailed neuropsychological battery, we examined the range of cognitive impairment in PD patients with an MMSE score of 26 or higher. In this multicenter, cross-sectional, observational study, we performed neuropsychological testing in a sample of 788 PD patients with MMSE scores of 26 or higher. Evaluation included tests of global cognition, executive function, language, memory, and visuospatial skills. A consensus panel reviewed results for 342 subjects and assigned a diagnosis of no cognitive impairment, mild cognitive impairment, or dementia. Sixty-seven percent of the 788 subjects performed 1.5 standard deviations below the normative mean on at least one test. On eight of the 15 tests, more than 20% of subjects scored 1.5 standard deviations or more below the normative mean. Greatest impairments were found on Hopkins Verbal Learning and Digit Symbol Coding tests. The sensitivity of the MMSE to detect dementia was 45% in a subset of participants who underwent clinical diagnostic procedures. A remarkably wide range of cognitive impairment can be found in PD patients with a relatively high score on the MMSE, including a level of cognitive impairment consistent with dementia. Given these findings, clinicians must be aware of the limitations of the MMSE in detecting cognitive impairment, including dementia, in PD.

Caverzagie, K. J., Cooney, T. G., Hemmer, P. A., & Berkowitz, L. (2014). The development of entrustable professional activities for internal medicine residency training: A report from the education redesign committee of the alliance for academic internal medicine. *Academic Medicine : Journal of the Association of American Medical Colleges*,

PURPOSE: The Alliance for Academic Internal Medicine charged its Education Redesign Committee with the task of assisting internal medicine residency program directors in meeting the challenges of competency-based assessment that were part of the Accreditation Council for Graduate Medical Education's (ACGME's) Next Accreditation System. METHOD: Recognizing the limitations of the ACGME general competencies as an organizing framework for assessment and the inability of the milestones to provide the needed context for faculty to assess residents' competence, the Education Redesign Committee in 2011 adopted the work-based assessment framework of entrustable professional activities (EPAs). The committee selected the EPA framework after

reviewing the literature on competency-based education and EPAs and consulting with experts in evaluation and assessment. The committee used an iterative approach with broad-based feedback from multiple sources, including program directors, training institutions, medical organizations, and specialty societies, to develop a set of EPAs that together define the core of the internal medicine profession. RESULTS: The resulting 16 EPAs are those activities expected of a resident who is ready to enter unsupervised practice, and they provide a starting point from which training programs could develop assessments and curricula. The committee also provided a strategy for the use of these EPAs in competency-based evaluation. CONCLUSIONS: These EPAs are intended to serve as a starting point or guide for program directors to begin developing meaningful, work-based assessments that inform the evaluation of residents' competence.

Cetas, J. S., McFarlane, R., Kronfeld, K., Smitasin, P., Liu, J. J., & Raskin, J. S. (2014). Brainstem opioidergic system is involved in early response to experimental SAH. *Translational Stroke Research*,

Subarachnoid hemorrhage (SAH) is a form of stroke with high rates of mortality and permanent disability for patients who survive the initial event. Previous research has focused on delayed cerebral vasospasm of large conduit arteries as the cause of poor long-term outcomes after SAH. New evidence suggests that acute failure to restore cerebral blood flow (CBF) after SAH may be setting the stage for delayed ischemic neurological deficits. Our lab previously demonstrated that the rostral ventromedial medulla (RVM), an autonomic and sensorimotor integration center, is important for maintaining CBF after experimental SAH. In this study, we have demonstrated that ablation of mu-opioid receptor containing cells with dexamorphin conjugates in the RVM results in a high mortality rate after experimental SAH and, in survivors, causes a dramatic decrease in CBF. Further, locally blocking the mu-opioid receptor with the antagonist naltrexone attenuated the reduction in CBF secondary to experimental SAH. Saturating mu-opioid receptors with the agonist [D-Ala(2),NMe-Phe(4),Gly-ol(5)]-encephalin (DAMGO) had no effect. Taken together, these results suggest that SAH activates opioidergic signaling in the RVM with a resultant reduction in CBF. Further, cells in the RVM that contain mu-opioid receptors are important for survival after acute SAH. We propose that failure of the RVM mu-opioid receptor cells to initiate

the compensatory CBF response sets the stage for acute and delayed ischemic injury following SAH.

Chang, S., Ren, G., Steiner, R. D., Merkens, L., Rouillet, J. B., Korade, Z., et al. (2014). Elevated autophagy and mitochondrial dysfunction in the smith-lemli-opitz syndrome. *Molecular Genetics and Metabolism Reports*, 1, 431-442.

Smith-Lemli-Opitz syndrome (SLOS) is a congenital, autosomal recessive metabolic and developmental disorder caused by mutations in the enzyme which catalyzes the reduction of 7-dehydrocholesterol (7DHC) to cholesterol. Herein we show that dermal fibroblasts obtained from SLOS children display increased basal levels of LC3B-II, the hallmark protein signifying increased autophagy. The elevated LC3B-II is accompanied by increased beclin-1 and cellular autophagosome content. We also show that the LC3B-II concentration in SLOS cells is directly proportional to the cellular concentration of 7DHC, suggesting that the increased autophagy is caused by 7DHC accumulation secondary to defective DHCR7. Further, the increased basal LC3B-II levels were decreased significantly by pretreating the cells with antioxidants implicating a role for oxidative stress in elevating autophagy in SLOS cells. Considering the possible source of oxidative stress, we examined mitochondrial function in the SLOS cells using JC-1 assay and found significant mitochondrial dysfunction compared to mitochondria in control cells. In addition, the levels of PINK1 which targets dysfunctional mitochondria for removal by the autophagic pathway are elevated in SLOS cells, consistent with mitochondrial dysfunction as a stimulant of mitophagy in SLOS. This suggests the increase in autophagic activity may be protective, i.e., to remove dysfunctional mitochondria. Taken together, these studies are consistent with a role for mitochondrial dysfunction leading to increased autophagy in SLOS pathophysiology.

Childers, R. (2014). Disconnect. *Journal of General Internal Medicine*,

Chiovaro, J. (2014). Capsule commentary on turner et al., chronic opioid therapy urine drug testing in primary care: Prevalence and predictors of aberrant results. *Journal of General Internal Medicine*,

Cho, S., & von Gersdorff, H. (2014). Proton-mediated block of Ca²⁺ channels during multivesicular release regulates short-term plasticity at an auditory hair cell synapse. *The Journal of*

Neuroscience : The Official Journal of the Society for Neuroscience, 34(48), 15877-15887.

Synaptic vesicles release both neurotransmitter and protons during exocytosis, which may result in a transient acidification of the synaptic cleft that can block Ca^{2+} channels located close to the sites of exocytosis. Evidence for this effect has been reported for retinal ribbon-type synapses, but not for hair cell ribbon synapses. Here, we report evidence for proton release from bullfrog auditory hair cells when they are held at more physiological, in vivo-like holding potentials ($V_h = -60$ mV) that facilitate multivesicular release. During paired recordings of hair cells and afferent fibers, L-type voltage-gated Ca^{2+} currents showed a transient block, which was highly correlated with the EPSC amplitude (or the amount of glutamate release). This effect was masked at $V_h = -90$ mV due to the presence of a T-type Ca^{2+} current and blocked by strong pH buffering with HEPES or TABS. Increasing vesicular pH with internal methylamine in hair cells also abolished the transient block. High concentrations of intracellular Ca^{2+} buffer (10 mM BAPTA) greatly reduced exocytosis and abolished the transient block of the Ca^{2+} current. We estimate that this transient block is due to the rapid multivesicular release of approximately 600-1300 H^{+} ions per synaptic ribbon. Finally, during a train of depolarizing pulses, paired pulse plasticity was significantly changed by using 40 mM HEPES in addition to bicarbonate buffer. We propose that this transient block of Ca^{2+} current leads to more efficient exocytosis per Ca^{2+} ion influx and it may contribute to spike adaptation at the auditory nerve.

Chowdhury, S., Haehnel, B. M., & Chanda, B. (2014). Interfacial gating triad is crucial for electromechanical transduction in voltage-activated potassium channels. *Journal of General Physiology, 144(5), 457-467.*

Voltage-dependent potassium channels play a crucial role in electrical excitability and cellular signaling by regulating potassium ion flux across membranes. Movement of charged residues in the voltage-sensing domain leads to a series of conformational changes that culminate in channel opening in response to changes in membrane potential. However, the molecular machinery that relays these conformational changes from voltage sensor to the pore is not well understood. Here we use generalized interaction-energy analysis (GIA) to estimate the strength of sitespecific interactions between amino acid residues putatively involved in the electromechanical coupling of the voltage sensor and pore in the outwardly rectifying KV channel. We identified candidate

interactors at the interface between the S4-S5 linker and the pore domain using a structure-guided graph theoretical approach that revealed clusters of conserved and closely packed residues. One such cluster, located at the intracellular intersubunit interface, comprises three residues (arginine 394, glutamate 395, and tyrosine 485) that interact with each other. The calculated interaction energies were 3-5 kcal, which is especially notable given that the net free-energy change during activation of the Shaker KV channel is ~14 kcal. We find that this triad is delicately maintained by balance of interactions that are responsible for structural integrity of the intersubunit interface while maintaining sufficient flexibility at a critical gating hinge for optimal transmission of force to the pore gate.

Chowdhury, S., Haehnel, B. M., & Chanda, B. (2014). A self-consistent approach for determining pairwise interactions that underlie channel activation. *Journal of General Physiology*, 144(5), 441-455.

Signaling proteins such as ion channels largely exist in two functional forms, corresponding to the active and resting states, connected by multiple intermediates. Multiparametric kinetic models based on sophisticated electrophysiological experiments have been devised to identify molecular interactions of these conformational transitions. However, this approach is arduous and is not suitable for large-scale perturbation analysis of interaction pathways. Recently, we described a model-free method to obtain the net free energy of activation in voltage- and ligand-activated ion channels. Here we extend this approach to estimate pairwise interaction energies of side chains that contribute to gating transitions. Our approach, which we call generalized interaction-energy analysis (GIA), combines median voltage estimates obtained from charge-voltage curves with mutant cycle analysis to ascertain the strengths of pairwise interactions. We show that, for a system with an arbitrary gating scheme, the nonadditive contributions of amino acid pairs to the net free energy of activation can be computed in a self-consistent manner. Numerical analyses of sequential and allosteric models of channel activation also show that this approach can measure energetic nonadditivities even when perturbations affect multiple transitions. To demonstrate the experimental application of this method, we reevaluated the interaction energies of six previously described long-range interactors in the Shaker potassium channel. Our approach offers the ability

to generate detailed interaction energy maps in voltage and ligand-activated ion channels and can be extended to any force-driven system as long as associated "displacement" can be measured.

Claxton, A., Baker, L. D., Hanson, A., Trittschuh, E. H., Cholerton, B., Morgan, A., et al. (2014). Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. *Journal of Alzheimer's Disease : JAD*,
Previous trials have shown promising effects of intranasally administered insulin for adults with Alzheimer's disease dementia (AD) or amnesic mild cognitive impairment (MCI). These trials used regular insulin, which has a shorter half-life compared to long-lasting insulin analogues such as insulin detemir. The current trial examined whether intranasal insulin detemir improves cognition or daily functioning for adults with MCI or AD. Sixty adults diagnosed with MCI or mild to moderate AD received placebo (n = 20), 20 IU of insulin detemir (n = 21), or 40 IU of insulin detemir (n = 19) for 21 days, administered with a nasal drug delivery device. Results revealed a treatment effect for the memory composite for the 40 IU group compared with placebo ($p < 0.05$). This effect was moderated by APOE status ($p < 0.05$), reflecting improvement for APOE-epsilon4 carriers ($p < 0.02$), and worsening for non-carriers ($p < 0.02$). Higher insulin resistance at baseline predicted greater improvement with the 40 IU dose ($r = 0.54$, $p < 0.02$). Significant treatment effects were also apparent for verbal working memory ($p < 0.03$) and visuospatial working memory ($p < 0.04$), reflecting improvement for subjects who received the high dose of intranasal insulin detemir. No significant differences were found for daily functioning or executive functioning. In conclusion, daily treatment with 40 IU insulin detemir modulated cognition for adults with AD or MCI, with APOE-related differences in treatment response for the primary memory composite. Future research is needed to examine the mechanistic basis of APOE-related treatment differences, and to further assess the efficacy and safety of insulin detemir.

Cloyes, K. G., Rosenkranz, S. J., Wold, D., Berry, P. H., & Supiano, K. P. (2014). To be truly alive: Motivation among prison inmate hospice volunteers and the transformative process of end-of-life peer care service. *American Journal of Hospice and Palliative Medicine*, 31(7), 735-748.
Some US prisons are meeting the growing need for end-of-life care through inmate volunteer programs, yet knowledge of the motivations of inmate caregivers is underdeveloped. This study

explored the motivations of inmate hospice volunteers from across Louisiana State (n = 75) through an open-ended survey, a grounded theory approach to analysis, and comparison of responses by experience level and gender. Participants expressed complex motivations; Inter-related themes on personal growth, social responsibility and ethical service to vulnerable peers suggested that inmate caregivers experience an underlying process of personal and social transformation, from hospice as a source of positive self-identity to peer-caregiving as a foundation for community. Better understanding of inmate caregiver motivations and processes will help prisons devise effective and sustainable end of life peer-care programs.

Coffin, S. E., Klieger, S. B., Duggan, C., Charles Huskins, W., Milstone, A. M., Potter-Bynoe, G., et al. (2014). Central line–associated bloodstream infections in neonates with gastrointestinal conditions: Developing a candidate definition for mucosal barrier injury bloodstream infections. *Infection Control and Hospital Epidemiology*, 35(11), 1391-1399.

Objective: To develop a candidate definition for central line–associated bloodstream infection (CLABSI) in neonates with presumed mucosal barrier injury due to gastrointestinal (MBI-GI) conditions and to evaluate epidemiology and microbiology of MBI-GI CLABSI in infants. Design: Multi center retrospective cohort study. Setting: Neonatal intensive care units from 14 US children's hospitals and pediatric facilities. Methods: A multidisciplinary focus group developed a candidate MBI-GI CLABSI definition based on presence of an MBI-GI condition, parenteral nutrition (PN) exposure, and an eligible enteric organism. CLABSI surveillance data from participating hospitals were supplemented by chart review to identify MBI-GI conditions and PN exposure. Results: During 2009–2012, 410 CLABSIs occurred in 376 infants. MBI-GI conditions and PN exposure occurred in 149 (40%) and 324 (86%) of these 376 neonates, respectively. The distribution of pathogens was similar among neonates with versus without MBI-GI conditions and PN exposure. Fifty-nine (16%) of the 376 initial CLABSI episodes met the candidate MBI-GI CLABSI definition. Subsequent versus initial CLABSIs were more likely to be caused by an enteric organism (22 of 34 [65%] vs 151 of 376 [40%]; $P = .009$) and to meet the candidate MBI-GI CLABSI definition (19 of 34 [56%] vs 59 of 376 [16%]; $P < .01$). Conclusions: While MBI-GI conditions and PN exposure were common, only 16% of initial CLABSIs met the candidate definition of MBI-GI CLABSI. The high proportion of MBI-GI CLABSIs among subsequent

infections suggests that infants with MBI-GI CLABSI should be a population targeted for further surveillance and interventional research.

Crary, J. F., Trojanowski, J. Q., Schneider, J. A., Abisambra, J. F., Abner, E. L., Alafuzoff, I., et al.

(2014). Primary age-related tauopathy (PART): A common pathology associated with human aging. *Acta Neuropathologica*,

We recommend a new term, "primary age-related tauopathy" (PART), to describe a pathology that is commonly observed in the brains of aged individuals. Many autopsy studies have reported brains with neurofibrillary tangles (NFTs) that are indistinguishable from those of Alzheimer's disease (AD), in the absence of amyloid (A β) plaques. For these "NFT+/A β -" brains, for which formal criteria for AD neuropathologic changes are not met, the NFTs are mostly restricted to structures in the medial temporal lobe, basal forebrain, brainstem, and olfactory areas (bulb and cortex). Symptoms in persons with PART usually range from normal to amnesic cognitive changes, with only a minority exhibiting profound impairment. Because cognitive impairment is often mild, existing clinicopathologic designations, such as "tangle-only dementia" and "tangle-predominant senile dementia", are imprecise and not appropriate for most subjects. PART is almost universally detectable at autopsy among elderly individuals, yet this pathological process cannot be specifically identified pre-mortem at the present time. Improved biomarkers and tau imaging may enable diagnosis of PART in clinical settings in the future. Indeed, recent studies have identified a common biomarker profile consisting of temporal lobe atrophy and tauopathy without evidence of A β accumulation. For both researchers and clinicians, a revised nomenclature will raise awareness of this extremely common pathologic change while providing a conceptual foundation for future studies. Prior reports that have elucidated features of the pathologic entity we refer to as PART are discussed, and working neuropathological diagnostic criteria are proposed.

Danve, A., Reddy, A., Vakil-Gilani, K., Garg, N., Dinno, A., & Deodhar, A. (2014). Routine assessment of patient index data 3 score (RAPID3) correlates well with bath ankylosing spondylitis disease activity index (BASDAI) in the assessment of disease activity and monitoring progression of axial spondyloarthritis. *Clinical Rheumatology*,

Routine Assessment of Patient Index Data 3 (RAPID3) is a composite index, very useful for assessment of disease activity of various rheumatic diseases including RA. If RAPID3 can also reliably measure disease activity in axial spondyloarthritis (axSpA), it may prove to be a practical and effective quantitative assessment tool in busy practices. We studied the association of RAPID3 with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Patients with Ankylosing Spondylitis (AS) seen from 2007 to 2012 were classified as having AS or non-radiographic axial spondyloarthritis (nr-axSpA) using modified New York criteria and Assessment of SpondyloArthritis International Society criteria, respectively. Patients with simultaneous BASDAI and RAPID3 scores were enrolled (N = 112; 105 with AS, seven with nr-axSpA). Multiple regression and nonparametric receiver operating characteristics were used. Baseline mean (SD) BASDAI and RAPID3 were 4.2 (2.5) and 3.8 (2.3), respectively. Multiple linear regressions modeled a quadratic relationship between BASDAI and RAPID3 for 321 observations in 112 patients with axSpA (1) cross-sectionally: BASDAI predicted by RAPID3 (beta = 1.171; s.e. = 0.113, p < 0.001) and RAPID3 (beta = -0.037; s.e. = 0.014, p = 0.011) with an adjusted R² of 0.676; and (2) longitudinally: BASDAI predicted by RAPID3 (beta = 1.196; s.e. = 0.111, p < 0.001), RAPID3 (beta = -0.042; s.e. = 0.014, p = 0.004), and visit number (beta = -0.142; s.e. = 0.038, p < 0.001) with an adjusted R² of 0.689. RAPID3 (correctly classified) corresponded to BASDAI scores of 2, 4, and 6: 1.40 (85.8 %), 3.33 (81.9 %), and 5.43 (87.1 %), respectively. RAPID3 correlates well with BASDAI in monitoring axSpA patients (including AS) in cross-sectional and longitudinal follow-up. Since it also correlates with measures of disease activity of other rheumatic diseases including RA, RAPID3 could be an attractive measure for assessing and monitoring disease activity of several conditions seen in busy rheumatology practices.

Deconde, A. S., Mace, J. C., Alt, J. A., Schlosser, R. J., Smith, T. L., & Soler, Z. M. Comparative effectiveness of medical and surgical therapy on olfaction in chronic rhinosinusitis: A prospective, multi-institutional study. *International Forum of Allergy and Rhinology*, 4(9), 725-733.

Background: Evidence comparing the impact of medical and surgical management of chronic rhinosinusitis on olfactory function is limited. This study evaluates olfactory outcomes in patients who failed initial medical management and elect either continued medical management or endoscopic sinus surgery (ESS) followed by medical management. Methods: Adult subjects were

prospectively enrolled into a nonrandomized, multi-institutional cohort. Baseline characteristics, quality-of-life and objective clinical findings were collected along with 2 quality-of-life disease-specific measures, the Rhinosinusitis Disability Index (RSDI) and Sinonasal Outcome Test (SNOT-22). The primary outcome measure was the posttreatment change (≥ 6 months) in the Brief Smell Identification Test (B-SIT). Bivariate and multivariate analyses compared B-SIT changes by treatment type while controlling for baseline cofactors. Results: Subjects ($n = 280$) were enrolled between March 2011 and May 2013. Baseline B-SIT scores (mean \pm standard deviation) were comparable between medical and surgical treatment groups (8.8 ± 3.2 vs 9.0 ± 3.2 ; $p = 0.703$). Subjects with baseline impaired olfaction ($n = 83$; 29.6%) experienced B-SIT improvement in both the medical ($n = 17$; 2.3 ± 2.8 ; $p = 0.005$) and surgical ($n = 66$; 2.1 ± 3.0 ; $p = 0.050$). Conclusion: Subjects electing ESS experienced gains in olfaction comparable to subjects electing continued medical management. Further study with larger sample size and more sensitive measures of olfaction are needed to determine differences between treatment groups.

DeLoughery, T. G., & Beer, T. M. (2014). Bevacizumab and thrombosis: Some answers but questions remain. *Cancer*,

Denneson, L. M., Teo, A. R., Ganzini, L., Helmer, D. A., Bair, M. J., & Dobscha, S. K. (2014). Military veterans' experiences with suicidal ideation: Implications for intervention and prevention. *Suicide & Life-Threatening Behavior*,

We sought to understand Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) veterans' experiences with suicidal ideation. Semi-structured interviews with 34 OEF/OIF veterans addressed circumstances leading up to disclosure of suicidal ideation during brief clinical assessments. We used an iterative, inductive and deductive thematic analysis approach. Results revealed three pervasive, persistent domains that reinforce the uniqueness of veteran suicidal thoughts: military culture, difficult deployment experiences, and postdeployment adjustment challenges. Within postdeployment, we identified four themes that serve as intervention targets: adjusting to civilian culture, changes to sense of self, feeling overwhelmed by stressors, and lacking life purpose or meaning.

Deodhar, A., Braun, J., Inman, R. D., van der Heijde, D., Zhou, Y., Xu, S., et al. (2014). Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. *Annals of the Rheumatic Diseases*,

OBJECTIVE: Assess golimumab efficacy/safety through 5 years in patients with active ankylosing spondylitis (AS). METHODS: 356 patients with AS were randomly assigned to placebo, golimumab 50 mg or 100 mg every 4 weeks. At week 16, patients with inadequate response early escaped with blinded dose adjustments (placebo to 50 mg, 50 mg to 100 mg). At week 24, all patients receiving placebo crossed over to 50 mg. Blinded active therapy continued through week 104; from week 104 to week 252, the golimumab dose could be adjusted. Intent-to-treat and observed efficacy data were assessed by randomised treatment groups. RESULTS: At week 256, and with >4.5 years of golimumab, overall intent-to-treat Assessment in SpondyloArthritis international Society criteria for 20% improvement (ASAS20) and ASAS40 response rates were 66.0% (235/356) and 57.0% (203/356), respectively; Bath AS Disease Activity Index 50% improvement response was 55.9% (199/356). Observed response rates among the 255 (72%) patients who continued golimumab through week 252 were consistent, albeit somewhat higher. Among patients who increased golimumab from 50 to 100 mg, 60.6% (20/33) and 44.7% (17/38) achieved ASAS20/ASAS40 responses, respectively, following ≥ 2 consecutive doses of golimumab 100 mg. Golimumab safety through week 268 was similar to that through week 24 regardless of dose. CONCLUSIONS: Clinical improvements observed in patients treated with golimumab through week 24 were sustained through week 256 (5 years). Long-term golimumab safety is consistent with that of other established tumour-necrosis-factor-antagonists. TRIAL REGISTRATION NUMBER: ClinicalTrials.gov: NCT00265083.

DeVoe, J. E., Angier, H., Burdick, T., & Gold, R. (2014). Health information technology: An untapped resource to help keep patients insured. *Annals of Family Medicine*, 12(6), 568-572.

The recent confluence of: (1) changing state and national insurance-related policies, and (2) the rapid growth in electronic health record (EHR) use, yields an unprecedented opportunity for patient-centered medical homes (PCMHs) and other primary care practices or care settings to use health information technology (HIT) and health information exchange (HIE) in novel ways to impact patient health. We propose that HIT is an untapped resource for supporting clinic-based

efforts to help eligible patients obtain and maintain insurance coverage. This commentary presents a conceptual model and guiding principles for this idea. Additionally, it describes insurance support tools that could be used to conduct 'inreach' and 'outreach' with patients around health insurance, similar to how HIT is used to manage chronic disease and panels of patients, and to improve population health outcomes.

Deyo, R. A., Irvine, J. M., Hallvik, S. E., Hildebran, C., Beran, T., Millet, L. M., et al. (2014). Leading a horse to water: Facilitating registration and use of a prescription drug monitoring program. *The Clinical Journal of Pain*,

OBJECTIVES: Prescription Drug Monitoring Programs (PDMPs) can help inform patient management, coordinate care, and identify drug safety risks, abuse, or diversion. However, many clinicians are not registered to use these systems, and use may be suboptimal. We sought to describe outreach efforts in one state (Oregon); quantify uptake of system use; identify barriers; and identify potential system improvements. **METHODS:** Program reports of outreach efforts and operational metrics provided rates of registration and use. A statewide survey identified perceived barriers and potential improvements from users and non-users of the system.

RESULTS: Even with extensive registration efforts, less than 25 percent of clinicians and pharmacists acquired PDMP accounts over 2 years of operation. Rapid increases in registration and use in 2013 corresponded to new requirements among large pharmacy chains that pharmacists register for and use the PDMP. Among surveyed PDMP non-users, nearly half were unaware they could register. Among users and non-users, over two-thirds indicated that time constraints were a major barrier and over half thought inability to delegate access was a major barrier. Desired improvements included linking state systems, faster entry of pharmacy data, and use of unique patient identifiers. Users also wanted better insurance coverage for mental health and addiction referrals. **DISCUSSION:** Increasing registration and use of PDMPs remains important. Clinician feedback indicates that program enhancements and healthcare system changes would facilitate using and responding to PDMP information. It appears premature to judge the efficacy of PDMPs until best practices for their use are identified and impacts are assessed.

Deyo, R. A., Jarvik, J. G., & Chou, R. (2014). In process citation. [Kreuzschmerzen in der Primarversorgung] *Praxis*, 103(23), 1401-1407.

Dobbertin, K., Horner-Johnson, W., Lee, J. C., & Andresen, E. M. (2014). Subgroup differences in having a usual source of health care among working-age adults with and without disabilities. *Disability and Health Journal*,

Background: Having a usual source of health care is positively associated with regular health maintenance visits and receipt of preventive services. People with disabilities are, overall, more likely than those without disabilities to have a usual source of care (USC). However, the population of people with disabilities is quite heterogenous, and some segments of the population may have less access to a USC than others. Objective: To determine whether there are significant subgroup differences in having a USC within the U.S. population of working-age adults with disabilities, and to compare adults with and without disabilities while controlling for other subgroup differences. Methods: We analyzed Medical Expenditure Panel Survey annual data files from 2002 to 2008. We performed both bivariate and multivariate logistic regression analyses to examine the relationship of sociodemographic and disability subgroup variables with having a USC. Results: Within the disability population, individuals who were younger; male; Black, Hispanic, or other (non-White) race; less educated; of lower income; or uninsured for part or all of the year were significantly less likely to have a USC. These differences mirrored those among adults without disabilities. When controlling for these differences, people with physical, hearing, or multiple disabilities had greater odds of having a USC than people without disabilities, but those with vision or cognitive limitations did not differ significantly from the non-disabled referent group. Conclusions: Disparities among people with and without disabilities are similar, underscoring the need for attention to disparities within the disability population.

Dobscha, S. K., Denneson, L. M., Kovas, A. E., Teo, A., Forsberg, C. W., Kaplan, M. S., et al. (2014). Correlates of suicide among veterans treated in primary care: Case–Control study of a nationally representative sample. *Journal of General Internal Medicine*,

BACKGROUND: Veterans receiving Veterans Affairs (VA) healthcare have increased suicide risk compared to the general population. Many patients see primary care clinicians prior to suicide.

Yet little is known about the correlates of suicide among patients who receive primary care treatment prior to death. OBJECTIVE: Our aim was to describe characteristics of veterans who received VA primary care in the 6 months prior to suicide; and to compare these to characteristics of control patients who also received VA primary care. DESIGN: This was a retrospective case-control study. SUBJECTS: The investigators partnered with VA operations leaders to obtain death certificate data from 11 states for veterans who died by suicide in 2009. Cases were matched 1:2 to controls based on age, sex, and clinician. MAIN MEASURES: Demographic, diagnosis, and utilization data were obtained from VA's Corporate Data Warehouse. Additional clinical and psychosocial context data were collected using manual medical record review. Multivariate conditional logistic regression was used to examine associations between potential predictor variables and suicide. KEY RESULTS: Two hundred and sixty-nine veteran cases were matched to 538 controls. Average subject age was 63 years; 97 % were male. Rates of mental health conditions, functional decline, sleep disturbance, suicidal ideation, and psychosocial stressors were all significantly greater in cases compared to controls. In the final model describing men in the sample, non-white race (OR = 0.51; 95 % CI = 0.27–0.98) and VA service-connected disability (OR = 0.54; 95 % CI = 0.36–0.80) were associated with decreased odds of suicide, while anxiety disorder (OR = 3.52; 95 % CI = 1.79–6.92), functional decline (OR = 2.52; 95 % CI = 1.55–4.10), depression (OR = 1.82; 95 % CI = 1.07–3.10), and endorsement of suicidal ideation (OR = 2.27; 95 % CI = 1.07–4.83) were associated with greater odds of suicide. CONCLUSIONS: Assessment for anxiety disorders and functional decline in addition to suicidal ideation and depression may be especially important for determining suicide risk in this population. Continued development of interventions that support identifying and addressing these conditions in primary care is indicated.

Donaldson, M., & Touger-Decker, R. (2014). Vitamin and mineral supplements: Friend or foe when combined with medications? *Journal of the American Dental Association (1939)*, 145(11), 1153-1158.

BACKGROUND: Given the prevalence of vitamin and mineral supplement use among consumers and the potential for vitamin- and mineral-drug interactions, as well as oral and systemic adverse effects of excess consumption, oral health care providers (OHCPs) should ask all patients about

their use. The challenges for OHCPs are how to recognize oral and systemic manifestations of these interactions and how to safely manage the care of these patients while avoiding potential interactions. **METHODS:** The authors reviewed the literature regarding interactions between popular vitamin and mineral supplements and medications used commonly in dentistry. They used clinical databases and decision support tools to classify interactions according to their level of patient risk. They address interactions of greatest clinical concern with a high-quality evidence-based foundation in either randomized controlled clinical trials or meta-analyses. **CONCLUSION:** Most medications used commonly in dentistry can be prescribed safely without regard to vitamin- and mineral-drug interactions. However, patients taking anticoagulants or cytochrome P450 3A4 substrates (such as clarithromycin, erythromycin, ketoconazole, itraconazole, midazolam and triazolam) in addition to specific vitamin or mineral supplements (vitamins D, E, K, calcium, fluoride, iron, magnesium, selenium or zinc) may face additional challenges. OHCPs need to recognize these potential interactions and know how to manage the care of patients who may be receiving treatment with these combination therapies. **PRACTICAL IMPLICATIONS:** Recognition and avoidance of potential vitamin- and mineral-drug interactions will help clinicians optimize patient treatment while emphasizing patient safety.

Doohan, N. C., Endres, J., Koehn, N., Miller, J., Scherger, J. E., Martin, J., et al. (2014). Back to the future: Reflections on the history of the future of family medicine. *Journal of the American Board of Family Medicine : JABFM*, 27(6), 839-845.

These are historic times for family medicine. The profession is moving beyond the visionary blueprint of the Future of Family Medicine (FFM) report while working to harness the momentum created by the FFM movement. Preparing for, and leading through, the next transformative wave of change (FFM version 2.0) will require the engagement of multigenerational and multidisciplinary visionaries who bring wisdom from diverse experiences. Active group reflection on the past will potentiate the collective work being done to best chart the future. Historical competency is critically important for family medicine's future. This article describes the historical context of the development and launch of the FFM report, emphasizing the professional activism that preceded and followed it. This article is intended to spark intergenerational dialog by providing a multigenerational reflection on the history of FFM and the evolution that has occurred

in family medicine over the past decade. Such intergenerational conversations enable our elders to share wisdom with our youth, while allowing our discipline to visualize history through the eyes of future generations.

Dugan, J., Griffiths, E., Snow, P., Rosenzweig, H., Lee, E., Brown, B., et al. (2014). Blau syndrome-associated Nod2 mutation alters expression of full-length NOD2 and limits responses to muramyl dipeptide in knock-in mice. *Journal of Immunology (Baltimore, Md.: 1950)*,

The biochemical mechanism by which mutations in nucleotide-binding oligomerization domain containing 2 (NOD2) cause Blau syndrome is unknown. Several studies have examined the effect of mutations associated with Blau syndrome in vitro, but none has looked at the implication of the mutations in vivo. To test the hypothesis that mutated NOD2 causes alterations in signaling pathways downstream of NOD2, we created a Nod2 knock-in mouse carrying the most common mutation seen in Blau syndrome, R314Q (corresponding to R334Q in humans). The endogenous regulatory elements of mouse Nod2 were unaltered. R314Q mice showed reduced cytokine production in response to i.p. and intravitreal muramyl dipeptide (MDP). Macrophages from R314Q mice showed reduced NF-kappaB and IL-6 responses, blunted phosphorylation of MAPKs, and deficient ubiquitination of receptor-interacting protein 2 in response to MDP. R314Q mice expressed a truncated 80-kDa form of NOD2 that was most likely generated by a posttranslational event because there was no evidence for a stop codon or alternative splicing event. Human macrophages from two patients with Blau syndrome also showed a reduction of both cytokine production and phosphorylation of p38 in response to MDP, indicating that both R314Q mice and cells from patients with Blau syndrome show reduced responses to MDP. These data indicate that the R314Q mutation when studied with the Nod2 endogenous regulatory elements left intact is associated with marked structural and biochemical changes that are significantly different from those observed from studies of the mutation using overexpression, transient transfection systems.

Duke, D. C., Raymond, J. K., & Harris, M. A. (2014). The diabetes related executive functioning scale (DREFS): Pilot results. *Children's Health Care, 43(4)*, 327-344.

The assessment of youth executive functioning (EF) associated with diabetes management has

been difficult to accomplish, yet is important to optimizing adherence. To improve EF assessment, we developed the Diabetes Related Executive Functioning Scale (DREFS) and piloted its administration to 50 youth with type 1 diabetes and their caregivers. Youth/caregiver dyads completed analogous versions of the DREFS, Behavioral Rating Inventory of Executive Functioning (BRIEF), and the Self-Administered Diabetes Self-Management Profile (SA-DSMP). HbA1c assays were used as an index of glycemic control. Caregiver and youth DREFS scores were associated with BRIEF, SA-DSMP totals, and HbA1c.

Eilers, J., Harris, D., Henry, K., & Johnson, L. A. (2014). Evidence-based interventions for cancer treatment-related mucositis: Putting evidence into practice. *Clinical Journal of Oncology Nursing*, 18(0), 80-96.

Mucositis is an inflammatory process that can involve the mucosal epithelial cells from the mouth to the rectum. Historically, mucositis and stomatitis were used interchangeably, but momentum has increased toward more specific terminology since the 2000s. Stomatitis refers to inflammatory diseases of the mouth, including the mucosa, dentition, periapices, and periodontium, whereas mucositis refers more globally to an inflammatory process involving the mucous membranes of the oral cavity and the gastrointestinal tract. In addition, differentiation is needed regarding mucositis involving the oral cavity and the remainder of the gastrointestinal tract that require use of a scope-type device for close examination. As a result, oral cavity mucositis has been the focus of the majority of the studies reported to date. The mucous membranes beyond the oral cavity are more challenging to view, so the mouth has been presented as revealing potential changes in the gastrointestinal tract. However, because of the variation in morphology, function of different locations, and risks associated with procedures to validate that speculation, evidence is limited. The purpose of this article is to review evidence-based interventions for mucositis, particularly in the oral cavity, and provide clinicians with guidelines for nursing interventions.

Ellison, D. H., & Ingelfinger, J. (2014). A quest - halting the progression of autosomal dominant polycystic kidney disease. *The New England Journal of Medicine*, Progression to end-stage kidney disease in autosomal dominant polycystic kidney disease

(ADPKD) ultimately occurs in most patients, even with the best available therapy. Clinical trials that test strategies to prevent or at least forestall progression are emblematic of the current era, yet none, to date, have greatly affected outcome. Because elevated blood pressure in patients with this disease is associated with greater total kidney volume as well as activation of the renin-angiotensin-aldosterone system (RAAS) and the progression of kidney disease, trials of blood-pressure control and medications that might work are crucial. It has been suggested that treatment with multiple agents . . .

Elman, M. J., Ayala, A., Bressler, N. M., Browning, D., Flaxel, C. J., Glassman, A. R., et al. (2014).

Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology*,

Objective: To report 5-year results from a previously reported trial evaluating intravitreal 0.5 mg ranibizumab with prompt versus deferred (for =24 weeks) focal/grid laser treatment for diabetic macular edema (DME). Design: Multicenter, randomized clinical trial. Participants: Among participants from the trial with 3 years of follow-up who subsequently consented to a 2-year extension and survived through 5 years, 124 (97%) and 111 (92%) completed the 5-year visit in the prompt and deferred groups, respectively. Methods: Random assignment to ranibizumab every 4 weeks until no longer improving (with resumption if worsening) and prompt or deferred (=24 weeks) focal/grid laser treatment. Main Outcome Measures: Best-corrected visual acuity at the 5-year visit. Results: The mean change in visual acuity letter score from baseline to the 5-year visit was +7.2 letters in the prompt laser group compared with +9.8 letters in the deferred laser group (mean difference, -2.6 letters; 95% confidence interval, -5.5 to +0.4 letters; . P = 0.09). At the 5-year visit in the prompt versus deferred laser groups, there was vision loss of =10 letters in 9% versus 8%, an improvement of =10 letters in 46% versus 58%, and an improvement of =15 letters in 27% versus 38% of participants, respectively. From baseline to 5 years, 56% of participants in the deferred group did not receive laser. The median number of injections was 13 versus 17 in the prompt and deferral groups, including 54% and 45% receiving no injections during year 4 and 62% and 52% receiving no injections during year 5, respectively. Conclusions: Five-year results suggest focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better than deferring laser treatment for =24 weeks in eyes with DME involving

the central macula with vision impairment. Although more than half of eyes in which laser treatment is deferred may avoid laser for at least 5 years, such eyes may require more injections to achieve these results when following this protocol. Most eyes treated with ranibizumab and either prompt or deferred laser maintain vision gains obtained by the first year through 5 years with little additional treatment after 3 years.

Elsa, C. R., Kneiss, J. A., & Wood, L. J. (2014). Induction of IL-6 by cytotoxic chemotherapy is associated with loss of lean body and fat mass in tumor-free female mice. *Biological Research for Nursing*,

Cancer patients treated with cytotoxic chemotherapy experience fatigue and changes in body composition that can impact physical functioning and quality of life during and after treatment. Interleukin-6 (IL-6) is associated with fatigue in cancer survivors and plays an important role in the regulation of body composition. The purpose of the present study was to determine the specific role of IL-6 in cyclophosphamide-doxorubicin-5-fluorouracil (CAF)-induced changes in fatigue, food intake, and body composition using mice lacking IL-6. Female wild-type (WT) and IL-6 $-/-$ mice were injected with four cycles of CAF or normal saline (NS) administered at 21-day intervals. Daily voluntary wheel-running activity (VWRA), used as a proxy for fatigue, and food intake were monitored daily up to 21 days after the fourth dose. Dual-energy X-ray absorptiometry (DEXA) was used to assess treatment-related changes in lean body mass (LBM), fat mass (FM), and bone mineral content (BMC). Patterns of change in fatigue and food intake did not differ between CAF-treated WT and IL-6 $-/-$ mice. However, a Genotype x Drug interaction was observed for LBM ($p = 0.047$) and FM ($p = 0.035$) but not BMC ($p = .569$). Whereas WT mice lost LBM and FM during CAF treatment, IL-6-deficient mice did not. Treatment-related decreases in levels of the anabolic hormone insulin-like growth factor-1 (IGF-1) may contribute to LBM and FM loss since CAF decreased IGF-1 levels in an IL-6-dependent manner. These findings implicate IL-6 and possibly IGF-1 in the regulation of body composition in breast cancer patients exposed to cytotoxic chemotherapy.

Engelmann, F., Josset, L., Girke, T., Park, B., Barron, A., Dewane, J., et al. (2014). Pathophysiologic and transcriptomic analyses of viscerotropic yellow fever in a rhesus macaque model. *PLoS*

Neglected Tropical Diseases, 8(11), e3295.

Infection with yellow fever virus (YFV), an explosively replicating flavivirus, results in viral hemorrhagic disease characterized by cardiovascular shock and multi-organ failure. Unvaccinated populations experience 20 to 50% fatality. Few studies have examined the pathophysiological changes that occur in humans during YFV infection due to the sporadic nature and remote locations of outbreaks. Rhesus macaques are highly susceptible to YFV infection, providing a robust animal model to investigate host-pathogen interactions. In this study, we characterized disease progression as well as alterations in immune system homeostasis, cytokine production and gene expression in rhesus macaques infected with the virulent YFV strain DakH1279 (YFV-DakH1279). Following infection, YFV-DakH1279 replicated to high titers resulting in viscerotropic disease with approximately 72% mortality. Data presented in this manuscript demonstrate for the first time that lethal YFV infection results in profound lymphopenia that precedes the hallmark changes in liver enzymes and that although tissue damage was noted in liver, kidneys, and lymphoid tissues, viral antigen was only detected in the liver. These observations suggest that additional tissue damage could be due to indirect effects of viral replication. Indeed, circulating levels of several cytokines peaked shortly before euthanasia. Our study also includes the first description of YFV-DakH1279-induced changes in gene expression within peripheral blood mononuclear cells 3 days post-infection prior to any clinical signs. These data show that infection with wild type YFV-DakH1279 or live-attenuated vaccine strain YFV-17D, resulted in 765 and 46 differentially expressed genes (DEGs), respectively. DEGs detected after YFV-17D infection were mostly associated with innate immunity, whereas YFV-DakH1279 infection resulted in dysregulation of genes associated with the development of immune response, ion metabolism, and apoptosis. Therefore, WT-YFV infection is associated with significant changes in gene expression that are detectable before the onset of clinical symptoms and may influence disease progression and outcome of infection.

Fairchild, B., Webb, T. P., Xiang, Q., Tarima, S., & Brasel, K. J. (2014). Sarcopenia and frailty in elderly trauma patients. *Presentations from the 9th Annual Electric Utilities Environmental Conference*,

Background: Sarcopenia describes a loss of muscle mass and resultant decrease in strength,

mobility, and function that can be quantified by CT. We hypothesized that sarcopenia and related frailty characteristics are related to discharge disposition after blunt traumatic injury in the elderly. Methods: We reviewed charts of 252 elderly blunt trauma patients who underwent abdominal CT prior to hospital admission. Data for thirteen frailty characteristics were abstracted. Sarcopenia was measured by obtaining skeletal muscle cross-sectional area (CSA) from each patient's psoas major muscle using Slice-O-Matic® software. Dispositions were grouped as dependent and independent based on discharge location. χ^2 , Fisher's exact, and logistic regression were used to determine factors associated with discharge dependence. Results: Mean age 76 years, 49 % male, median ISS 9.0 (IQR = 8.0–17.0). Discharge destination was independent in 61.5 %, dependent in 29 %, and 9.5 % of patients died. Each 1 cm² increase in psoas muscle CSA was associated with a 20 % decrease in dependent living ($p < 0.0001$). Gender, weakness, hospital complication, and cognitive impairment were also associated with disposition; ISS was not ($p = 0.4754$). Conclusions: Lower psoas major muscle CSA is related to discharge destination in elderly trauma patients and can be obtained from the admission CT. Lower psoas muscle CSA is related to loss of independence upon discharge in the elderly. The early availability of this variable during the hospitalization of elderly trauma patients may aid in discharge planning and the transition to dependent living.

Ferracane, J. L., & Giannobile, W. V. (2014). Novel biomaterials and technologies for the dental, oral, and craniofacial structures. *Journal of Dental Research*, 93(12), 1185-1186.

Ford, M. M., Nickel, J. D., Kaufman, M. N., & Finn, D. A. (2014). Null mutation of 5alpha-reductase type I gene alters ethanol consumption patterns in a sex-dependent manner. *Behavior Genetics*, The neuroactive steroid allopregnanolone (ALLO) is a positive modulator of GABAA receptors, and manipulation of neuroactive steroid levels via injection of ALLO or the 5alpha-reductase inhibitor finasteride alters ethanol self-administration patterns in male, but not female, mice. The *Srd5a1* gene encodes the enzyme 5alpha-reductase-1, which is required for the synthesis of ALLO. The current studies investigated the influence of *Srd5a1* deletion on voluntary ethanol consumption in male and female wildtype (WT) and knockout (KO) mice. Under a continuous access condition, 6 and 10 % ethanol intake was significantly greater in KO versus WT females, but significantly

lower in KO versus WT males. In 2-h limited access sessions, Srd5a1 deletion retarded acquisition of 10 % ethanol intake in female mice, but facilitated it in males, versus respective WT mice. The present findings demonstrate that the Srd5a1 gene modulates ethanol consumption in a sex-dependent manner that is also contingent upon ethanol access condition and concentration.

Fromme, E. K. (2014). Clarification requested on potential conflicts of interest in narayanan et al. *Journal of Palliative Medicine,*

Fu, Y., Rope, R., Fargue, S., Cohen, H. T., Holmes, R. P., & Cohen, D. M. (2014). A mutation creating a highly active out-of-frame alternative translation initiation site within the 5' UTR of the GRHPR gene 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 premature termination (p.Gln232Argfs*3). Two 5' 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 1.3 kb 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.

Geller, M. D., Pei, Y., Spurgeon, S. E., Durum, C., & Leeborg, N. J. (2014). Chronic lymphocytic leukemia with a FGFR3 translocation: Case report and literature review of an uncommon cytogenetic event. *Cancer Genetics,*
The t(4;14) (p16; q32) with fusion of the IGH (immunoglobulin heavy chain) and FGFR3 (fibroblast growth factor receptor 3) genes are rarely present in patients with chronic lymphocytic leukemia (CLL), with only two previously reported cases. We herein describe a unique case of CLL

with the occurrence of a t(4;14) (p16;q32), trisomy 12, and deletion of 11q13-q23 in the same clonal cells. In contrast to myeloma, in which FGFR3 translocations are a common early cytogenetic hit, FGFR3 rearrangement in CLL appears to occur later in the disease course.

Geltzeller, C. B., Lu, K. C., Diggs, B. S., Deveney, K. E., Keyashian, K., Herzig, D. O., et al. (2014).

Initial surgical management of ulcerative colitis in the biologic era. *Diseases of the Colon and Rectum*, 57(12), 1358-1363.

BACKGROUND: The initial minimum operation for ulcerative colitis is a total abdominal colectomy. Healthy patients may undergo proctectomy at the same time; however, for ill patients, proctectomy is delayed. Since the introduction of biologic medications in 2005, ulcerative colitis medical management has changed dramatically. **OBJECTIVE:** We examined how operative management for ulcerative colitis has changed from the prebiologic to biologic eras. **DESIGN:** We conducted a retrospective review of data on patients with ulcerative colitis who were included in the Nationwide Inpatient Sample database. **SETTINGS:** This study was conducted at a single university. **PATIENTS:** A total of 1,547,852 patients with ulcerative colitis who were admitted to a US hospital from 1991 to 2011 were included in the study. **MAIN OUTCOME MEASURES:** We examined patients whose initial operation consisted of total abdominal colectomy without proctectomy versus a total proctocolectomy with or without a pouch. We also examined which operation was done at the time of the construction of an ileoanal pouch. Patients who underwent colectomy and pouch construction in the same hospitalization were compared with those who received pouch formation at a subsequent hospitalization. **RESULTS:** Ulcerative colitis-related admissions rose by 170% during the years examined, and the number of patients who required total abdominal colectomy increased by 44%. Total abdominal colectomy increased by 15%, as opposed to total proctocolectomy ($p < 0.001$). Pouch construction at a subsequent operation increased by 16% ($p = 0.002$). Since 2008, total abdominal colectomy has surpassed total proctocolectomy as the most common initial surgical intervention for ulcerative colitis.

LIMITATIONS: The Nationwide Inpatient Sample is a retrospective database, and we were limited to examining the variables within it. **CONCLUSIONS:** Total abdominal colectomy is currently the most common initial operation for patients with ulcerative colitis, and an ileoanal pouch is more frequently constructed at a subsequent hospitalization. These trends coincide with the initiation of

biologic treatments and may imply that patients are acutely ill at the time of initial operation.

Alternately, there may be surgeon-perceived bias of increased surgical risk or a shift in care to specialized surgeons for pouch construction.

Gerrah, R., Sunstrom Pa-C, R. E., & Hohimer, A. R. (2014). Pretreatment of synthetic vascular grafts with heparin before implantation, a simple technique to reduce the risk of thrombosis. *Vascular*, Thrombosis of synthetic grafts commonly used in cardiovascular surgery is a major complication. We examined whether pretreatment of the graft with heparin reduces the risk of early thrombosis. A circuit was assembled to compare two pairs of shunts simultaneously in the same animal. The study shunts were pretreated with heparin. After 2 hours of circulation, clot formation was evaluated by image analysis techniques. The pretreated grafts had fewer blood clots adhered to the surface by direct visual inspection. The image analysis showed 5 vs. 39 clots, 0.01% vs. 1.8% clotted area, and 62 vs. 5630 clot pixel area between the treated and non-treated grafts respectively, $p < 0.05$. Pretreatment of the synthetic graft with heparin prior to implantation reduces the risk of early clot formation. This simple practice might be helpful to prevent initial thrombosis of the graft and later occlusion.

Ghetie, D., Mehraban, N., & Sibley, C. H. (2015). Cold hard facts of cryoglobulinemia: Updates on clinical features and treatment advances. *Rheumatic Diseases Clinics of North America*, 41(1), 93-108.

Cryoglobulins are immunoglobulins that precipitate at temperatures less than 37 degrees C. They occur secondary to infectious, autoimmune, and malignant processes. In the Brouet classification, type I cryoglobulinemia is caused by hyperviscosity, whereas type II and III manifestations are caused by vasculitis in target organs (primarily skin, peripheral nerves, and kidney). New classification criteria were recently proposed that may help with study and treatment of cryoglobulinemic vasculitis (CryoVas). Hepatitis C virus is the most common cause of CryoVas and treatment with antivirals can be curative in mild cases, whereas rituximab is highly effective in treating active vasculitis in more severe cases.

Gievers, L., Kim, D. H., & Garcia, A. M. (2014). Newborn with hypotonia, congenital heart disease, hypoglycemia, and enlarged corneas. *Neoreviews*, 15(11), e510-e513.

Gilbert, K., Joseph, R., Vo, A., Patel, T., Chaudhry, S., Nguyen, U., et al. (2014). Children with severe early childhood caries: Streptococci genetic strains within carious and white spot lesions. *Journal of Oral Microbiology*, 6, 10.3402/jom.v6.25805. eCollection 2014.

BACKGROUND AND OBJECTIVES: Mutans streptococci (MS) are one of the major microbiological determinants of dental caries. The objectives of this study are to identify distinct MS and non-MS streptococci strains that are located at carious sites and non-carious enamel surfaces in children with severe early childhood caries (S-ECC), and assess if cariogenic MS and non-cariogenic streptococci might independently exist as primary bacterial strains on distinct sites within the dentition of individual children. **DESIGN:** Dental plaque from children (N=20; aged 3-6) with S-ECC was collected from carious lesions (CLs), white spot lesions (WSLs) and non-carious enamel surfaces. Streptococcal isolates (N=10-20) from each site were subjected to polymerase chain reaction (PCR) to identify MS, and arbitrarily primed-PCR for assignment of genetic strains. Primary strains were identified as $\geq 50\%$ of the total isolates surveyed at any site. In several cases, strains were characterized for aciduricity using ATP-driven bioluminescence and subjected to PCR-determination of potential MS virulence products. Identification of non-MS was determined by 16S rRNA gene sequencing. **RESULTS:** Sixty-four independent MS or non-MS streptococcal strains were identified. All children contained 1-6 strains. In many patients (N=11), single primary MS strains were identified throughout the dentition. In other patients (N=4), primary MS strains were identified within CLs that were distinct from primary strains found on enamel. *Streptococcus gordonii* strains were identified as primary strains on enamel or WSLs in four children, and in general were less aciduric than MS strains. **CONCLUSIONS:** Many children with S-ECC contained only a single primary MS strain that was present in both carious and non-carious sites. In some cases, MS and non-cariogenic *S. gordonii* strains were found to independently exist as dominant strains at different locations within the dentition of individual children, and the aciduric potential of these strains may influence susceptibility in the development of CLs.

Grzybowski, A., Ascaso, F. J., Kupidura-Majewski, K., & Packer, M. (2014). Continuation of anticoagulant and antiplatelet therapy during phacoemulsification cataract surgery. *Current Opinion in Ophthalmology*,

PURPOSE OF REVIEW: The objective of this review is to evaluate the result of cataract surgery in

patients continuing antiplatelet and/or anticoagulant treatment. RECENT FINDINGS: The number of elderly patients using anticoagulant and antiplatelet treatment in prevention of venous thromboembolism has significantly increased in recent years. It was believed for many years that those patients might be at higher risk for complications during ocular surgery. Thus, different strategies were proposed to prevent these complications, including discontinuation of anticoagulants, dose reduction, or low-molecular-weight heparin replacement. We performed a PubMed search over a period of 7 years (2007-2013) about possible intraoperative and postoperative complications in patients receiving anticoagulant and/or antiplatelet therapy at the time of cataract surgery. No significant increase in intraoperative or postoperative complications has been identified. SUMMARY: Phacoemulsification of uncomplicated cataracts with intraocular lens implantation can be performed safely in high-risk patients, taking both anticoagulants and antiplatelet drugs when topical anesthesia is administered and cataract surgery is performed through a clear corneal incision by a skilled surgeon.

Hagen, M. W., Riddle, A., McClendon, E., Gong, X., Shaver, D., Srivastava, T., et al. (2014). Role of recurrent hypoxia-ischemia in preterm white matter injury severity. *PLoS One*, 9(11), e112800.

OBJECTIVE: Although the spectrum of white matter injury (WMI) in preterm infants is shifting from cystic necrotic lesions to milder forms, the factors that contribute to this changing spectrum are unclear. We hypothesized that recurrent hypoxia-ischemia (rHI) will exacerbate the spectrum of WMI defined by markers of inflammation and molecules related to the extracellular matrix (hyaluronan (HA) and the PH20 hyaluronidase) that regulate maturation of the oligodendrocyte (OL) lineage after WMI. METHODS: We employed a preterm fetal sheep model of in utero moderate hypoxemia and global severe but not complete cerebral ischemia that reproduces the spectrum of human WMI. The response to rHI was compared against corresponding early or later single episodes of HI. An ordinal rating scale of WMI was compared against an unbiased quantitative image analysis protocol that provided continuous histo-pathological outcome measures for astrogliosis and microglial activation. Late oligodendrocyte progenitors (preOLs) were quantified by stereology. Analysis of hyaluronan and the hyaluronidase PH20 defined the progressive response of the extracellular matrix to WMI. RESULTS: rHI resulted in a more severe spectrum of WMI with a greater burden of necrosis, but an expanded population of preOLs that

displayed reduced susceptibility to cell death. WMI from single episodes of HI or rHI was accompanied by elevated HA levels and increased labeling for PH20. Expression of PH20 in fetal ovine WMI was confirmed by RT-PCR and RNA-sequencing. CONCLUSIONS: rHI is associated with an increased risk for more severe WMI with necrosis, but reduced risk for preOL degeneration compared to single episodes of HI. Expansion of the preOL pool may be linked to elevated hyaluronan and PH20.

Hampton, D. A., Fabricant, L. J., & Schreiber, M. A. (2014). Response: The need for a definitive clinical trial of cryopreserved red blood cells. *The Journal of Trauma and Acute Care Surgery*, 77(6), 1004-1005.

Hansen, K. F., Sakamoto, K., Pelz, C., Impey, S., & Obrietan, K. (2014). Profiling status epilepticus-induced changes in hippocampal RNA expression using high-throughput RNA sequencing. *Scientific Reports*, 4, 6930.

Status epilepticus (SE) is a life-threatening condition that can give rise to a number of neurological disorders, including learning deficits, depression, and epilepsy. Many of the effects of SE appear to be mediated by alterations in gene expression. To gain deeper insight into how SE affects the transcriptome, we employed the pilocarpine SE model in mice and Illumina-based high-throughput sequencing to characterize alterations in gene expression from the induction of SE, to the development of spontaneous seizure activity. While some genes were upregulated over the entire course of the pathological progression, each of the three sequenced time points (12-hour, 10-days and 6-weeks post-SE) had a largely unique transcriptional profile. Hence, genes that regulate synaptic physiology and transcription were most prominently altered at 12-hours post-SE; at 10-days post-SE, marked changes in metabolic and homeostatic gene expression were detected; at 6-weeks, substantial changes in the expression of cell excitability and morphogenesis genes were detected. At the level of cell signaling, KEGG analysis revealed dynamic changes within the MAPK pathways, as well as in CREB-associated gene expression. Notably, the inducible expression of several noncoding transcripts was also detected. These findings offer potential new insights into the cellular events that shape SE-evoked pathology.

Hansen, L. (2014). Liver transplantation in older adults. *Journal of Gerontological Nursing, 40*(9), 8-13.

Liver transplantation is the only definitive treatment therapy for end-stage liver disease. In the United States, approximately 15% of annual liver transplant recipients are 65 or older. The most common postoperative complications are infection, acute graft rejection, and acute renal failure. To prevent complications, recipients are treated with immunosuppressive medications and anti-infective agents. The long-term complications of liver transplantation are a consequence of long-term use of immunosuppressive medications and recurrence of the original disease in the liver. Nurses play a critical role in supporting and educating recipients and their primary support persons about post-transplant follow-up care, including laboratory test schedules, medication management, and infection prevention. Strict compliance with follow-up care provides the greatest possibility of avoiding complications or organ rejection.

Hansen, L., Yan, Y., & Rosenkranz, S. J. (2014). The power of the liver transplant waiting list: A case presentation. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses, 23*(6), 510-515.

End-stage liver disease (ESLD), the final stage of chronic liver disease, is treated with liver transplant. Many patients have serious ESLD-related complications and are admitted to the intensive care unit for treatment. Such patients are temporarily unsuitable to undergo transplant surgery and are placed into a temporarily inactive category, "status 7," on the transplant waiting list. Status 7 patients account for about 15% of all patients on the list. To describe the experience of a status 7 patient on the liver transplant waiting list from the perspectives of family members, 38 hours of bedside observation of participants, 9 semistructured interviews with 6 family members, and 9 semistructured interviews with 8 health care professionals from nursing, medicine, and other health care disciplines were done. Data were analyzed via conventional content analysis. Family members' perspectives fit into 3 phases that correspond to the progression of the patient's clinical condition: dealing with crisis, confusion and frustration, and back on the road to transplant. All 3 phases related to 1 goal: getting the patient's status reactivated on the liver transplant waiting list. This case exposes the struggles that patients with

ESLD and their families may go through during the status 7 period and could serve as a starting point for further examination of this period.

Hartmann, E. E., Stout, A. U., Lynn, M. J., Yen, K. G., Kruger, S. J., & Lambert, S. R. (2014).

Stereopsis results at 4.5 years of age in the infant aphakia treatment study. *American Journal of Ophthalmology*,

Purpose: To determine whether stereopsis of infants treated for monocular cataracts varies with the type of optical correction used. Design: Randomized prospective clinical trial. Methods: The Infant Aphakia Treatment Study randomized 114 patients with unilateral cataracts at age 1-7 months to either primary intraocular lens (IOL) or contact lens correction. At 4.5 years of age a masked examiner assessed stereopsis on these patients using 3 different tests: (1) Frisby; (2) Randot Preschool; and (3) Titmus Fly. Results: Twenty-eight patients (25%) had a positive response to at least 1 of the stereopsis tests. There was no statistically significant difference in stereopsis between the 2 treatment groups: Frisby (contact lens, 6 [11%]; IOL, 7 [13%]; $P = .99$), Randot (contact lens, 3 [6%]; IOL, 1 [2%]; $P = .62$), or Titmus (contact lens, 8 [15%]; IOL, 13 [23%]; $P = .34$). The median age at surgery for patients with stereopsis was younger than for those without stereopsis (1.2 vs 2.4 months; $P = .002$). The median visual acuity for patients with stereopsis was better than for those without stereopsis (20/40 vs 20/252; $P = .0003$). Conclusion: The type of optical correction did not influence stereopsis outcomes. However, 2 other factors did: age at surgery and visual acuity in the treated eye at age 4.5 years. Early surgery for unilateral congenital cataract and the presence of visual acuity better than or equal to 20/40 appear to be more important than the type of initial optical correction used for the development of stereopsis.

Hassan, S., Petrella, T. M., Zhang, T., Kamel-Reid, S., Nordio, F., Baccarelli, A., et al. (2014).

Pathologic complete response to intralesional interleukin-2 therapy associated with improved survival in melanoma patients with in-transit disease. *Annals of Surgical Oncology*,

Results: Ten patients (10/31, 32 %) achieved a pathologic complete response (pCR), 17/21 (55 %) had a partial response, and 4/21 (19 %) had progressive disease on treatment. pCR to IL-2 therapy was associated with overall survival (log-rank $p = 0.004$) and improved progression-free

survival (PFS) [adjusted hazard ratio (HR) 0.11; 95 % CI 0.02–0.47; $p = 0.003$]. A higher CD8+ T cell infiltrate was identified in in-transit lesions with a pCR compared with the other lesions (mean IHC score 3.78 vs. 2.61; $p = 0.01$). Patients with an elevated CD8+ infiltrate demonstrated an improved PFS (unadjusted HR 0.08; 95 % CI 0.01–0.52; $p = 0.008$).

Conclusions: Thirty-two percent of patients achieved pCR with intralesional IL-2 therapy and had a significantly improved PFS compared with the rest of the cohort, which may be explained by a systemic CD8+ T-cell response. Purpose: Melanoma patients with in-transit disease have a high mortality rate despite various treatment strategies. The aim of this study was to validate the role of intralesional interleukin (IL)-2, to understand its mechanism of action, and to better understand factors that may influence its response. Methods: We retrospectively collected the clinicopathological data of 31 consecutive patients who presented to a tertiary care cancer center for treatment of in-transit melanoma with intralesional IL-2. Kaplan–Meier survival curves and multivariable Cox regression analysis were performed. Immunohistochemistry (IHC) was used to better understand the immune response to localized IL-2 therapy. Targeted next-generation sequencing was performed to genomically characterize the tumors.

Heintzman, J., Gold, R., Krist, A., Crosson, J., Likumahuwa, S., & DeVoe, J. E. (2014). Practice-based research networks (PBRNs) are promising laboratories for conducting dissemination and implementation research. *Journal of the American Board of Family Medicine : JABFM*, 27(6), 759-762.

Dissemination and implementation science addresses the application of research findings in varied health care settings. Despite the potential benefit of dissemination and implementation work to primary care, ideal laboratories for this science have been elusive. Practice-based research networks (PBRNs) have a long history of conducting research in community clinical settings, demonstrating an approach that could be used to execute multiple research projects over time in broad and varied settings. PBRNs also are uniquely structured and increasingly involved in pragmatic trials, a research design central to dissemination and implementation science. We argue that PBRNs and dissemination and implementation scientists are ideally suited to work together and that the collaboration of these 2 groups will yield great value for the future of primary care and the delivery of evidence-based health care.

Hettmer, S., Li, Z., Billin, A. N., Barr, F. G., Cornelison, D. D. W., Ehrlich, A. R., et al. (2014).

Rhabdomyosarcoma: Current challenges and their implications for developing therapies. *Cold Spring Harbor Perspectives in Biology*, 6(11)

Rhabdomyosarcoma (RMS) represents a rare, heterogeneous group of mesodermal malignancies with skeletal muscle differentiation. One major subgroup of RMS tumors (so-called "fusion-positive" tumors) carries exclusive chromosomal translocations that join the DNA-binding domain of the PAX3 or PAX7 gene to the transactivation domain of the FOXO1 (previously known as FKHR) gene. Fusion-negative RMS represents a heterogeneous spectrum of tumors with frequent RAS pathway activation. Overtly metastatic disease at diagnosis is more frequently found in individuals with fusion-positive than in those with fusion-negative tumors. RMS is the most common pediatric soft-tissue sarcoma, and approximately 60% of all children and adolescents diagnosed with RMS are cured by currently available multimodal therapies. However, a curative outcome is achieved in ~30% of high-risk individuals with RMS, including all those diagnosed as adults, those diagnosed with fusion-positive tumors during childhood (including metastatic and nonmetastatic tumors), and those diagnosed with metastatic disease during childhood (including fusion-positive and fusion-negative tumors). This white paper outlines current challenges in RMS research and their implications for developing more effective therapies. Urgent clinical problems include local control, systemic disease, need for improved risk stratification, and characterization of differences in disease course in children and adults. Biological challenges include definition of the cellular functions of PAX-FOXO1 fusion proteins, clarification of disease heterogeneity, elucidation of the cellular origins of RMS, delineation of the tumor microenvironment, and identification of means for rational selection and testing of new combination therapies. To streamline future therapeutic developments, it will be critical to improve access to fresh tumor tissue for research purposes, consider alternative trial designs to optimize early clinical testing of candidate drugs, coalesce advocacy efforts to garner public and industry support, and facilitate collaborative efforts between academia and industry.

Hitchcock, L. N., & Lattal, K. M. (2014). Histone-mediated epigenetics in addiction. *Progress in Molecular Biology and Translational Science*, 128, 51-87.

Many of the brain regions, neurotransmitter systems, and behavioral changes that occur after

occasional drug use in healthy subjects and after chronic drug abuse in addicted patients are well characterized. An emerging literature suggests that epigenetic processes, those processes that regulate the accessibility of DNA to regulatory proteins within the nucleus, are keys to how addiction develops and how it may be treated. Investigations of the regulation of chromatin, the organizational system of DNA, by histone modification are leading to a new understanding of the cellular and behavioral alterations that occur after drug use. We will describe how, when, and where histone tails are modified and how some of the most recognized histone regulation patterns are involved in the cycle of addiction, including initial and chronic drug intake, withdrawal, abstinence, and relapse. Finally, we consider how an approach that targets histone modifications may promote successful treatment.

Huang, H., & Trussell, L. O. (2014). Presynaptic HCN channels regulate vesicular glutamate transport. *Neuron*, *84*(2), 340-346.

The amount of neurotransmitter stored in synaptic vesicles determines postsynaptic quantal size and thus the strength of synaptic transmission. However, little is known about regulation of vesicular neurotransmitter uptake. In recordings from the calyx of Held, a giant mammalian glutamatergic synapse, we found that changes in presynaptic Na⁺ concentration above and below a resting value of 13mM regulated vesicular glutamate uptake, consistent with activation of a vesicular monovalent cation Na⁺(K⁺)/H⁺ exchanger. Na⁺ flux through presynaptic plasma membrane hyperpolarization-activated cyclic nucleotide-gated (HCN) channels enhanced presynaptic Na⁺ concentration and thus controlled postsynaptic quantal size. Our results indicate that a plasma membrane ion channel controls synaptic strength by modulating vesicular neurotransmitter uptake through a Na⁺-dependent process.

Ianchulev, T., Minckler, D. S., Hoskins, H. D., Packer, M., Stamper, R., Pamnani, R. D., et al. (2014). Wearable technology with head-mounted displays and visual function. *Jama*, *312*(17), 1799-1801.

Jones, B. L., & Smith, S. M. (2014). Choice of crystalloid and mortality in sepsis-all in the timing? *Critical Care Medicine*, *42*(12), e796.

Karmy-Jones, R., Namias, N., Coimbra, R., Moore, E. E., Schreiber, M., McIntyre, R., Jr, et al. (2014).

Western trauma association critical decisions in trauma: Penetrating chest trauma. *The Journal of Trauma and Acute Care Surgery*, 77(6), 994-1002.

Kim, C. C., Swetter, S. M., Curiel-Lewandrowski, C., Grichnik, J. M., Grossman, D., Halpern, A. C., et al. (2014). Addressing the knowledge gap in clinical recommendations for management and complete excision of clinically atypical Nevi/Dysplastic nevi: Pigmented lesion subcommittee consensus statement. *JAMA Dermatology*,

Importance: The management of clinically atypical nevi/dysplastic nevi (CAN/DN) is controversial, with few data to guide the process. Management recommendations for DN with positive histologic margins were developed by the Delphi method to achieve consensus among members of the Pigmented Lesion Subcommittee (PLS) of the Melanoma Prevention Working Group (MPWG) after reviewing the current evidence. Objectives: To outline key issues related to the management of CAN/DN: (1) biopsies of CAN and how positive margins arise, (2) whether incompletely excised DN evolve into melanoma, (3) current data on the outcomes of DN with positive histologic margins, (4) consensus recommendations, and (5) a proposal for future studies, including a large-scale study to help guide the management of DN with positive margins. Evidence Review: The literature, including recent studies examining management and outcomes of DN with positive margins between 2009 to 2014, was reviewed. Findings: A consensus statement by the PLS of the MPWG following review of the literature, group discussions, and a structured Delphi method consensus. Conclusions and Relevance: This consensus statement reviews the complexities of management of CAN/DN. A review of the literature and 2 rounds of a structured Delphi consensus resulted in the following recommendations: (1) mildly and moderately DN with clear margins do not need to be reexcised, (2) mildly DN biopsied with positive histologic margins without clinical residual pigmentation may be safely observed rather than reexcised, and (3) observation may be a reasonable option for management of moderately DN with positive histologic margins without clinically apparent residual pigmentation; however, more data are needed to make definitive recommendations in this clinical scenario.

Kirkpatrick, J. N., Hauptman, P. J., & Goodlin, S. J. (2014). Bundling informed consent and advance care planning in chronic cardiovascular disease: We need to talk. *JAMA Internal Medicine*,

Kissell, N., Mudd, J. O., Gelow, J. M., Chong, L. E., & Yuen, K. C. (2014). Cardiogenic shock due to non-ischemic cardiomyopathy induced by severe anterior hypopituitarism. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, , 1-17.

Objective: To review a case of life-threatening cardiogenic shock due to non-ischemic cardiomyopathy associated with anterior hypopituitarism, and to compare this case with previous reported cases in the literature. Methods: We report the clinical presentation, biochemistry, imaging, treatment, and outcome of a patient with cardiogenic shock. We conducted an English language literature search of non-ischemic cardiomyopathy associated with hypopituitarism secondary to Sheehan syndrome. Results: Cardiogenic shock due to non-ischemic cardiomyopathy associated with anterior hypopituitarism is rare, and has been attributed to TSH, cortisol and GH deficiencies. A 40-year-old woman with no previous cardiac history, presented with cardiogenic shock due to non-ischemic cardiomyopathy. Echocardiography revealed global hypokinesia with severely decreased left ventricular ejection fraction. She was treated with inotropes and an intra-aortic balloon pump. Patient volunteered a history of severe postpartum hemorrhage 20 years ago during childbirth with subsequent failure to lactate. Further workup confirmed central hypothyroidism, hypoadrenalism, hypogonadism, and GH deficiency, and MRI of her pituitary demonstrated an empty sella. She was treated with levothyroxine and hydrocortisone replacement therapy. After 18 months, echocardiography revealed partial, but not complete reversal, of her ejection fraction. Conclusion: We report an unusual case of persistent non-ischemic cardiomyopathy, and highlight the importance of considering hypopituitarism secondary to Sheehan syndrome as an etiology of cardiomyopathy in young women presenting with cardiogenic shock. The continued presence of persistent non-ischemic cardiomyopathy is likely to be due to the effects of prolonged untreated anterior hypopituitarism. Instituting appropriate hormone replacement therapy may improve the overall cardiac function of these patients.

Kruer, R. M., Barton, C. A., Roberti, G., Gilbert, B., & McMillian, W. D. (2014). Antimicrobial

prophylaxis during *hirudo medicinalis* therapy: A multicenter study. *Journal of Reconstructive Microsurgery*,

Background Medicinal leeches (*Hirudo medicinalis*) are indicated for salvage of tissue flaps, grafts, or replants when venous congestion threatens tissue viability. The purpose of this study was to evaluate the efficacy of prophylactic antimicrobial agents in patients who received medicinal leech therapy. Materials and Methods A multicenter retrospective cohort study of all adult patients between January 1, 2010, and February 28, 2013, who received medicinal leech therapy was conducted. Results Antimicrobial prophylaxis was documented in 54 (91.5%) of the included patients, ciprofloxacin, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, and ceftriaxone in 33 (61.1%), 18 (33.3%), 2 (3.7%), and 2 (3.7%) patients, respectively. Surgical site infection (SSI) was found in seven (11.9%) patients, all of whom received antimicrobial prophylaxis. *Aeromonas* spp. was isolated in four infections, and all isolates were resistant to the chosen prophylactic agent. The SSI incidence was similar between antimicrobial prophylaxis agents. Conclusion Trimethoprim-sulfamethoxazole and ciprofloxacin appear equally effective at preventing leech-associated infections.

Landis, J. L., Palmer, V. S., & Spencer, P. S. (2014). Nodding syndrome in kitgum district, uganda:

Association with conflict and internal displacement. *BMJ Open*, 4(11), e006195-2014-006195.

OBJECTIVES: To test for any temporal association of Nodding syndrome with wartime conflict, casualties and household displacement in Kitgum District, northern Uganda. METHODS: Data were obtained from publicly available information reported by the Ugandan Ministry of Health (MOH), the Armed Conflict Location & Event Data (ACLED) Project of the University of Sussex in the UK, peer-reviewed publications in professional journals and other sources. RESULTS: Reports of Nodding syndrome began to appear in 1997, with the first recorded cases in Kitgum District in 1998. Cases rapidly increased annually beginning in 2001, with peaks in 2003-2005 and 2008, 5-6 years after peaks in the number of wartime conflicts and deaths. Additionally, peaks of Nodding syndrome cases followed peak influxes 5-7 years earlier of households into internal displacement camps. CONCLUSIONS: Peaks of Nodding syndrome reported by the MOH are associated with,

but temporally displaced from, peaks of wartime conflicts, deaths and household internment, where infectious disease was rampant and food insecurity rife.

Lee, S., Amici, S., Tavori, H., Zeng, W. M., Freeland, S., Fazio, S., et al. (2014). PMP22 is critical for actin-mediated cellular functions and for establishing lipid rafts. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 34(48), 16140-16152.

Haploinsufficiency of peripheral myelin protein 22 (PMP22) causes hereditary neuropathy with liability to pressure palsies, a peripheral nerve lesion induced by minimal trauma or compression. As PMP22 is localized to cholesterol-enriched membrane domains that are closely linked with the underlying actin network, we asked whether the myelin instability associated with PMP22 deficiency could be mediated by involvement of the protein in actin-dependent cellular functions and/or lipid raft integrity. In peripheral nerves and cells from mice with PMP22 deletion, we assessed the organization of filamentous actin (F-actin), and actin-dependent cellular functions. Using in vitro models, we discovered that, in the absence of PMP22, the migration and adhesion capacity of Schwann cells and fibroblasts are similarly impaired. Furthermore, PMP22-deficient Schwann cells produce shortened myelin internodes, and display compressed axial cell length and collapsed lamellipodia. During early postnatal development, F-actin-enriched Schmidt-Lanterman incisures do not form properly in nerves from PMP22(-/-) mice, and the expression and localization of molecules associated with uncompacted myelin domains and lipid rafts, including flotillin-1, cholesterol, and GM1 ganglioside, are altered. In addition, we identified changes in the levels and distribution of cholesterol and ApoE when PMP22 is absent. Significantly, cholesterol supplementation of the culture medium corrects the elongation and migration deficits of PMP22(-/-) Schwann cells, suggesting that the observed functional impairments are directly linked with cholesterol deficiency of the plasma membrane. Our findings support a novel role for PMP22 in the linkage of the actin cytoskeleton with the plasma membrane, likely through regulating the cholesterol content of lipid rafts.

Lewis, M. S., McMillan, G. P., Hutter, M., Folmer, R. L., Wilmington, D., Casiana, L., et al. (2014).

Does interferon beta-1a impact pure-tone hearing sensitivity among individuals with multiple sclerosis? *The Journal of Neuroscience Nursing : Journal of the American Association of*

Neuroscience Nurses, 46(6), 351-360.

BACKGROUND: Previous studies reported that particular types of interferon medications might contribute to hearing loss in some patients. The package insert included in the original Food and Drug Administration application for intramuscular interferon beta-1a (Avonex) stated that some patients in the treatment group reported decreased hearing sensitivity. **OBJECTIVE:** The purpose of the present investigation was to assess if individuals with multiple sclerosis (MS) taking intramuscular interferon beta-1a have significantly poorer hearing thresholds than those not currently using any disease-modifying therapies. **METHODS:** This was a secondary analysis of data collected as part of two larger studies evaluating auditory function in patients with MS. The goal of this analysis was to determine if users of interferon beta-1a do not have significantly worse hearing thresholds than nonusers of disease-modifying therapies, after adjusting for potential confounders. A linear mixed model was fit to the audiometric thresholds of our subjects. This model included interferon beta-1a use, MS disease subtype, gender, test frequency, age, disease duration (number of years), and the Expanded Disability Status Scale score. **RESULTS AND CONCLUSIONS:** With all subjects included, there is insufficient evidence to say that intramuscular interferon-beta 1a is not ototoxic (in relation to nonuse of a disease-modifying therapy) at all frequencies tested except 3000 and 6000 Hz. After removing two influential subjects, the results indicated that there is statistical support for no ototoxic effect of intramuscular interferon beta-1a at test frequencies from 250 to 6000 Hz. There is insufficient evidence, however, to rule out an ototoxic effect at 8000 Hz. Future studies should further evaluate the effect of interferon on auditory function in patients with MS. Neuroscience nurses should monitor their patients' hearing throughout the course of treatment.

Lewis, M. S., Wilson, R. A., Walker, K., Stegeman-Olsen, J., Norman, D. J., Barry, J. M., et al. (2014). Factors in cardiac risk stratification of candidates for renal transplant. *European Journal of Preventive Cardiology, 6(4), 251-255.*

Background Renal transplant candidates are at high risk of fatal and nonfatal cardiac events. **Methods** This study evaluated five clinical risk factors age at least 50 years, insulin-requiring diabetes mellitus, angina, congestive heart failure and an abnormal electrocardiogram (ECG) (excluding left ventricular hypertrophy) - that had been Used in the first tier of a two-tiered

prospectively applied risk stratification algorithm. ReSULTs Using multiple logistic regression analysis, age at least 50 years, abnormal ECG, and diabetes mellitus were independently predictive of cardiac death. Of the two remaining clinical risk factors, the presence of angina had independent predictive value for nonfatal cardiac events (myocardial infarction, coronary angioplasty, bypass surgery, and unstable angina). The independent predictive value of congestive heart failure approached statistical significance. Conclusion Clinical risk-factor analysis is helpful in identifying renal transplant candidates at high risk for fatal or nonfatal cardiac events.

Linden, A., & Butterworth, S. W. (2014). A comprehensive hospital-based intervention to reduce readmissions for chronically ill patients: A randomized controlled trial. *American Journal of Managed Care*, 20(10), 783-792.

Objectives Medicare penalizes hospitals with 30-day readmissions above their expected rates. Hospitals have responded by implementing transitional care interventions; however, there is limited evidence to inform the development of a successful intervention. Study Design Parallel-group, stratified, randomized controlled trial. Methods A total of 512 patients hospitalized at 2 community hospitals, with congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD), were randomly assigned to the intervention (n = 253) or usual care (n = 259). The intervention encompassed a 90-day hospital-based transitional care program. The primary end points were 30- and 90-day all-cause readmissions. Secondary measures included all-cause emergency department (ED) visits and mortality. Results On average, study participants were 67 years of age, 57% female, and 70% insured by Medicare. There was no statistical difference between treatment groups on 30-day readmission incidence rates (difference, 0.040; 95% CI, -0.047 to 0.127; P = .36), or 90-day readmission incidence rates (difference of 0.035; 95% CI -0.122 to 0.192; P = .66). Groups also did not differ in ED visit incidence rates at 30 or 90 days. The mortality rate among patients with CHF showed no difference between groups (risk ratio = 0.90; 95% CI, 0.40-2.05). However, for COPD, mortality at 90 days was lower in the intervention group than in the usual care group (risk ratio = 0.28; 95% CI, 0.10-0.83). Conclusions Stand-alone community hospitals may be unable to prevent readmissions despite the use of comprehensive, evidence-based intervention components that are within their control. Better

collaboration between hospitals and community-based providers is needed to ensure continuity of care for discharged patients.

Lo, J. O., Shaffer, B. L., Allen, A. J., Little, S. E., Cheng, Y. W., & Caughey, A. B. (2014). Intrahepatic cholestasis of pregnancy and timing of delivery. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, , 1-5.

Abstract Objective: We examined the morbidities from delivery at earlier gestational ages versus intrauterine fetal demise (IUFD) for women with intrahepatic cholestasis of pregnancy (ICP) to determine the optimal gestational age for delivery. Methods: A decision-analytic model was created to compare delivery at 35 through 38 weeks gestation for different delivery strategies: (1) empiric steroids; (2) steroids if fetal lung maturity (FLM) negative; (3) wait a week and retest if FLM negative; or (4) deliver immediately. Literature review identified 18 studies that estimated IUFD in ICP; we used the mean rate, 1.74%, and assumed a uniform distribution from 34 to 40 weeks gestation. Large cohort data was used to calculate neonatal morbidity rates at each gestational age. Maternal and neonatal quality-adjusted life years (QALYs) were combined. Univariate sensitivity and Monte Carlo analyses were performed to test for robustness. Results: Immediate delivery at 36 weeks without FLM testing and steroid administration was the optimal strategy as compared to delivery at 36 weeks with steroids (+47 QALYs) and as compared to immediate delivery at 35 weeks (+210 QALYs). Our results were robust up to a 30% increase in the rate of IUFD. Conclusion: Immediate delivery at 36 weeks in women with ICP is the optimal delivery strategy.

Longstreet, B., Balakrishnan, K., Saltzman, B., Perkins, J. A., & Dighe, M. (2014). Prognostic value of a simplified anatomically based nomenclature for fetal nuchal lymphatic anomalies. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*,

OBJECTIVE: To propose an anatomic classification for fetal nuchal lymphatic anomalies that will be clinically useful and to evaluate the classification's value in predicting chromosomal abnormalities, pregnancy outcomes, other associated fetal anomalies, and spontaneous

resolution of these lesions. STUDY DESIGN: Retrospective cohort study. SETTING: Tertiary academic hospital and affiliated tertiary children's hospital. SUBJECTS AND METHODS: Mother-baby pairs diagnosed with fetal nuchal lymphatic anomalies in a prenatal ultrasound database. Anomalies were classified as nuchal thickening, dorsal lymphatic malformation, or ventral lymphatic malformation. Pregnancy outcomes, prevalence of chromosomal and anatomic abnormalities, and rates of spontaneous lesion resolution were determined for each group. RESULTS: The study included 189 patients: 58 with nuchal thickening, 120 with dorsal lymphatic malformation, and 11 with ventral lymphatic malformation. In fetuses for whom chromosomal analysis was available, chromosomal abnormalities were strongly associated with dorsal lymphatic malformations (83%), less associated with nuchal thickening (29%), and not associated with ventral lymphatic malformations. Dorsal lymphatic malformation predicted high rates of elective (43%) and spontaneous (20%) termination of pregnancy and showed the strongest association with cardiac, renal, and skeletal anomalies. Nuchal thickening was more likely to resolve in utero than dorsal lymphatic malformations, while no ventral lymphatic malformation resolved spontaneously. CONCLUSIONS: Fetal nuchal anomalies demonstrate significant and clinically important prognostic differences depending on their anatomic location. The simple classification system proposed here therefore provides useful information to clinicians involved in the pre- and postnatal management of children with these anomalies.

Lyon, E., Cockerill, F. R., 3rd, Bale, S. J., Beadling, C., Bry, L., Hagenkord, J., et al. (2014). Next generation sequencing in clinical diagnostics: Experiences of early adopters. *Clinical Chemistry*,

Maier, M. A., & Peterson, T. D. (2014). Observations of a diatom chytrid parasite in the lower columbia river. *Northwest Science*, 88(3), 234-245.

Often overlooked, zoosporic fungal parasites of phytoplankton ('chytrids') are present in aquatic systems worldwide. Although extensive studies in lakes give insight into potential impacts of chytrid epidemics on phytoplankton blooms and organic matter cycling, the ecological significance of chytrid infections of phytoplankton is still poorly understood in lotic systems. Here, we report the first observations of chytrid parasites attached to multiple diatom species in the lower Columbia River. We isolated a chytrid parasite of the dominant spring bloom diatom, *Asterionella*

formosa, and sequenced DNA from several regions within the ribosomal RNA gene. We also investigated the specificity of the *A. formosa* chytrid to host and non-host diatoms with isolated cultures and found no cross infection at the species level. In the Columbia River, alterations in the hydrograph following the installation of hydroelectric dams may have opened a niche for chytrid parasites. Greater retention times may allow diatoms to bloom and provide a prolonged interaction period whereby chytrid parasites are able to infect hosts. Future research is needed to assess the seasonality and severity of chytrid infections on diatoms in the lower Columbia River and to evaluate the potential role of zoospore fungi in influencing the food web structure and biogeochemical cycling in river systems.

Martin, E., Haney, E., Shannon, J., Cauley, J., Ensrud, K., Keaveny, T., et al. (2014). Femoral volumetric bone density, geometry, and strength in relation to 25-hydroxy vitamin D in older men. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*,

Low serum 25-hydroxy vitamin D (25(OH)D) concentrations are associated with increased hip fracture risk and decreased femoral areal bone mineral density (BMD) among elderly men. Structural dimensions of the proximal femur and volumetric BMD in cortical and trabecular compartments are also associated with hip fracture risk. However, associations of volumetric BMD or structural dimensions with serum 25(OH)D concentrations among older men remain unclear. In a random sample of 1608 men aged ≥ 65 years from the Osteoporotic Fractures in Men Study (MrOS), baseline serum 25(OH)D concentrations were measured by liquid chromatography/mass spectrometry assays. Femoral neck geometry and volumetric BMD derived from quantitative computed tomography included integral, cortical, and trabecular volumetric BMD; cross-sectional area; integral and cortical volume; and cortical volume as a percent of integral volume. We studied 888 men with vitamin D, parathyroid hormone (PTH), femoral neck geometry, and BMD measures. Whole-bone femoral strength and load-strength ratio from finite element (FE) analysis were also available for 356 men from this sample. Multivariable linear regression was used to estimate least square means of each femoral measure within quartiles of 25(OH)D adjusted for age, race, body mass index, height, latitude, and season of blood draw. Tests of linear trend in the means were performed across increasing quartile of serum 25(OH)D

levels. Mean cortical volume (p trend = 0.006) and cortical volume as a percent of integral volume (p trend < 0.001) increased across increasing quartile of 25(OH)D level. However, overall femoral neck size (area and integral volume) did not vary by 25(OH)D level. Femoral neck volumetric BMD measures increased in a graded manner with higher 25(OH)D levels (p trend < 0.001). Femoral strength, but not load-strength ratio, increased with increasing 25(OH)D. Adjustment for PTH did not materially change these associations. We conclude that in older men, higher levels of endogenous 25(OH)D may increase whole-bone strength by increasing femoral volumetric BMD and cortical volume. This article is protected by copyright. All rights reserved.

McCarthy, M. S., Morgan, B. B., Heineman, J. T., & Martindale, R. G. (2014). Nutritional armor for the injured warfighter: Omega-3 fatty acids in surgery, trauma, and intensive care. *Military Medicine*, 179(11 Suppl), 88-94.

Nutrients have traditionally been viewed as a means to provide basic energy for cellular homeostasis and amino acids for protein synthesis in all humans. Young, healthy men and women in the military today are presumed to be well nourished and mentally and physically fit to perform their duties in austere environments. Exposure to high-intensity projectiles, blast injuries, and other wounds of war, however, is an everyday occurrence during deployment that potentially challenges all homeostatic mechanisms. After sustaining such devastating injuries, critically ill, surgical, and trauma patients are in a constant dynamic state between the systemic inflammatory response syndrome (and compensatory anti-inflammatory response syndrome). Compelling evidence supports both immune and metabolic response modulation by specific nutrients, including omega-3 fatty acids, primarily eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The concept of providing nutrients as therapeutic rather than supportive agents to meet the basic cellular caloric and metabolic demands requires a major paradigm shift. Although the exact route and dose of these metabolically active lipids has yet to be determined, data from large clinical studies of cellular ex-vivo experiments in patients support the liberal use of eicosapentaenoic acid and docosahexaenoic acid in the setting of trauma, surgery, and intensive care.

McCormick, J. A., Yang, C. -, Zhang, C., Davidge, B., Blankenstein, K. I., Terker, A. S., et al. (2014).

Hyperkalemic hypertension-associated cullin 3 promotes WNK signaling by degrading KLHL3.

Journal of Clinical Investigation, 124(11), 4723-4736.

Familial hyperkalemic hypertension (FHHT) is a monogenic disease resulting from mutations in genes encoding WNK kinases, the ubiquitin scaffold protein cullin 3 (CUL3), or the substrate adaptor kelch-like 3 (KLHL3). Disease-associated CUL3 mutations abrogate WNK kinase degradation in cells, but it is not clear how mutant forms of CUL3 promote WNK stability. Here, we demonstrated that an FHHT-causing CUL3 mutant (CUL3 Δ 403-459) not only retains the ability to bind and ubiquitylate WNK kinases and KLHL3 in cells, but is also more heavily neddylated and activated than WT CUL3. In cells, activated CUL3 Δ 403-459 depleted KLHL3, preventing WNK degradation, despite increased CUL3-mediated WNK ubiquitylation; therefore, CUL3 loss in kidney should phenocopy FHHT in murine models. As predicted, nephron-specific deletion of Cul3 in mice did increase WNK kinase levels and the abundance of phosphorylated Na-Cl cotransporter (NCC). Over time, however, Cul3 deletion caused renal dysfunction, including hypochloremic alkalosis, diabetes insipidus, and salt-sensitive hypotension, with depletion of sodium potassium chloride cotransporter 2 and aquaporin 2. Moreover, these animals exhibited renal inflammation, fibrosis, and increased cyclin E. These results indicate that FHHT-associated CUL3 Δ 403-459 targets KLHL3 for degradation, thereby preventing WNK degradation, whereas general loss of CUL3 activity - while also impairing WNK degradation - has widespread toxic effects in the kidney.

McCully, B. H., Dean, R. K., McCully, S. P., & Schreiber, M. A. (2014). Diet-induced obesity prevents

the development of acute traumatic coagulopathy. *The Journal of Trauma and Acute Care*

Surgery, 77(6), 873-878.

BACKGROUND: Obesity and hemorrhagic shock following trauma are predictors of mortality but have conflicting effects on coagulation. Following hemorrhage, tissue injury and hypoperfusion lead to acute traumatic coagulopathy (ATC), producing a hypocoagulable state. Inversely, obesity promotes clotting and impairs fibrinolysis to yield a hypercoagulable state. High rates of venous thromboembolism, organ failure, and early mortality may be caused by hypercoagulability in obese patients. We hypothesize that obesity prevents the development of ATC following injury-

induced hemorrhagic shock. METHODS: Male Sprague-Dawley rats (250-275 g) were fed a high-fat diet (32% kcal from fat) for 4 weeks to 6 weeks and diverged into obesity-resistant (OR, n = 9) and obesity-prone (OP, n = 9) groups. Age-matched control (CON) rats were fed normal diet (10% kcal from fat, n = 9). Anesthetized rats were subjected to an uncontrolled hemorrhage by a Grade V splenic injury to a mean arterial pressure (MAP) of 40 mm Hg. Hypotension (MAP, 30-40 mm Hg) was maintained for 30 minutes to induce shock. MAP, heart rate, lactate, base excess, cytokines, blood loss, and thrombelastography (TEG) parameters were measured before and after hemorrhagic shock. RESULTS: At baseline, OP rats exhibited a shorter time to 20-mm clot (K), and higher rate of clot formation (alpha angle), clot strength (maximal amplitude), and coagulation index, compared with the CON rats ($p < 0.05$), indicating enhanced coagulation. Physiologic parameters following shock were similar between groups. In the CON and OR rats, shock prolonged the time to clot initiation (R) and K and decreased alpha angle and coagulation index (all $p < 0.05$ vs. baseline). In contrast, shock had no effect on these TEG parameters in the OP rats. Maximal amplitude was the only TEG parameter affected by shock in the OP rats, which was decreased in all groups. CONCLUSION: Obesity prevents the development of ATC following hemorrhage shock. Complications associated with obesity following hemorrhagic shock may be attributed to the preserved hypercoagulable state.

Melmed, S., Kleinberg, D. L., Bonert, V., & Fliseriu, M. (2014). Acromegaly: Assessing the disorder and navigating therapeutic options for treatment. *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, 20(0), 7-17.

Merchan, L. M., Hassan, H. E., Terrin, M. L., Waites, K. B., Kaufman, D. A., Ambalavanan, N., et al. (2014). Pharmacokinetics, microbial response, and pulmonary outcomes of multi-dose intravenous azithromycin in preterm infants at risk for ureaplasma respiratory colonization. *Antimicrobial Agents and Chemotherapy*, The study objective was to refine the population pharmacokinetics model, determine microbial clearance, and assess short-term pulmonary outcomes of multiple dose azithromycin treatment in preterm infants at risk for Ureaplasma respiratory colon-ization. Fifteen subjects (Ureaplasma-

positive=7) received intravenous azithromycin 20 mg/kg every 24h for 3 doses. Azithromycin concentrations were determined in plasma samples obtained up to 168h post-first dose, by a validated LC/MS/MS method. Respiratory samples were obtained pre-dose and at three time points post-last dose for *Ureaplasma* culture, PCR, antibiotic susceptibility testing, and cytokine concentrations. Pharmacokinetic data from these 15 subjects as well as 25 additional subjects [single 10 mg/kg dose (N=12), single 20 mg/kg dose (N=13)] were analyzed using a non-linear mixed-effect population modeling (NONMEM) approach. Pulmonary outcomes were assessed at 36 wk 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 pharmacokinetic parameters' estimates for clearance, central volume of distribution, inter-compartmental clearance, and peripheral volume of distribution were $0.15 \text{ L/h} \times \text{WT}(\text{kg})^{0.75}$, $1.88 \text{ L} \times \text{WT}(\text{kg})$, $1.79 \text{ L/h} \times \text{WT}(\text{kg})^{0.75}$ and $13 \text{ L} \times \text{WT}(\text{kg})$, respectively. The estimated AUC₂₄/MIC₉₀ was approximately 4 hr. All post-treatment 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. A 3 day course of 20 mg/kg/day intravenous azithromycin shows preliminary efficacy in eradicating *Ureaplasma* spp. from the preterm respiratory tract.

Meyer, C., Engelmann, F., Arnold, N., Krah, D. L., Meulen, J. T., Haberthur, K., et al. (2014). Abortive intrabronchial infection of rhesus macaques with varicella zoster virus provides partial protection against simian varicella virus challenge. *Journal of Virology*,

Varicella zoster virus (VZV) is a human neurotropic alphaherpesvirus and the etiological agent of varicella (chickenpox) and herpes zoster (HZ, shingles). Previously, inoculation of monkeys via the subcutaneous, intratracheal, intravenous or oral-nasal-conjunctival routes did not recapitulate all the hallmarks of VZV infection including varicella, immunity, latency and reactivation.

Intrabronchial inoculation of rhesus macaques (RMs) with simian varicella virus (SVV), a homolog of VZV, recapitulates virologic and immunologic hallmarks of VZV infection in humans. Given that VZV is acquired primarily via the respiratory route, we investigated whether intrabronchial inoculation of RMs with VZV would result in a robust model. Despite the lack of varicella and viral

replication in either the lungs or whole blood, all four RMs generated an immune response characterized by generation of VZV-specific antibodies and T cells. Two of 4 VZV inoculated RMs were challenged with SVV to determine cross-protection. VZV-immune RMs displayed no varicella rash, decreased SVV viral loads as well as earlier and stronger humoral and cellular immune responses compared to controls. In contrast to SVV, no VZV DNA was detected in sensory ganglia at necropsy. In summary, following an abortive VZV infection, RMs developed an adaptive immune response that confers partial protection against SVV challenge. These data suggest that a replication incompetent VZV vaccine that does not establish latency may provide sufficient protection against VZV disease and that VZV vaccination of RMs followed by SVV challenge provides a model to evaluate new vaccines and therapeutics against VZV. **IMPORTANCE:** Although VZV vaccine strain Oka is attenuated, it can cause mild varicella, establish latency, and in rare cases reactivate to cause herpes zoster (HZ). Moreover, studies suggest that the HZ vaccine (Zostavax) only confers short-lived immunity. Development of more efficacious vaccines would be facilitated by a robust animal model of VZV infection. Data presented in this manuscript show that intrabronchial inoculation of rhesus macaques (RMs) with VZV resulted in an abortive VZV infection. Nevertheless, all animals generated a humoral and cellular immune response that conferred partial cross-protection against simian varicella virus (SVV) challenge. Additionally, VZV DNA was not detected in the sensory ganglia suggesting that viremia might be required for the establishment of latency. Therefore, VZV vaccination of RMs followed by SVV challenge is a model that will support the development of vaccines that boost protective T cell responses against VZV.

Michalowicz, B. S., Hyman, L., Hou, W., Oates, T. W., Jr, Reddy, M., Paquette, D. W., et al. (2014).

Factors associated with the clinical response to nonsurgical periodontal therapy in people with type 2 diabetes mellitus. *Journal of the American Dental Association* (1939), 145(12), 1227-1239.

BACKGROUND: Type 2 diabetes mellitus (T2DM) is a growing health problem worldwide. People with T2DM are at risk of experiencing periodontitis and likely require treatment. Using data from the national multicenter Diabetes and Periodontal Therapy Trial (DPTT), the authors assessed patient-based characteristics associated with the clinical response to nonsurgical therapy.

METHODS: The DPTT investigators randomly assigned adults with T2DM (hemoglobin A1c

[HbA1c] \geq 7 percent and 30 kilograms per square meter) experienced greater reductions in PD and BOP than did participants who were not obese (P .1). CONCLUSIONS: In patients with T2DM, baseline disease severity was associated with the clinical response to nonsurgical periodontal therapy. Body mass index and Hispanic ethnicity-but not glycemic control, diabetes duration or smoking-also may be useful in predicting clinical changes in this population. PRACTICAL IMPLICATIONS: These findings could help clinicians identify patients with T2DM who may or may not respond well to initial periodontal treatment.

Miller, L. M., Whitlatch, C. J., & Lyons, K. S. (2014). Shared decision-making in dementia: A review of patient and family carer involvement. *Dementia (London, England)*,

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

Miranda-Dominguez, O., Mills, B. D., Carpenter, S. D., Grant, K. A., Kroenke, C. D., Nigg, J. T., et al. (2014). Connectotyping: Model based fingerprinting of the functional connectome. *PLoS One*, 9(11), e111048.

A better characterization of how an individual's brain is functionally organized will likely bring dramatic advances to many fields of study. Here we show a model-based approach toward characterizing resting state functional connectivity MRI (rs-fcMRI) that is capable of identifying a so-called "connectotype", or functional fingerprint in individual participants. The approach rests

on a simple linear model that proposes the activity of a given brain region can be described by the weighted sum of its functional neighboring regions. The resulting coefficients correspond to a personalized model-based connectivity matrix that is capable of predicting the timeseries of each subject. Importantly, the model itself is subject specific and has the ability to predict an individual at a later date using a limited number of non-sequential frames. While we show that there is a significant amount of shared variance between models across subjects, the model's ability to discriminate an individual is driven by unique connections in higher order control regions in frontal and parietal cortices. Furthermore, we show that the connectotype is present in non-human primates as well, highlighting the translational potential of the approach.

Morrison, S. F., & Madden, C. J. (2014). Central nervous system regulation of brown adipose tissue. *Comprehensive Physiology*, 4(4), 1677-1713.

Thermogenesis, the production of heat energy, in brown adipose tissue is a significant component of the homeostatic repertoire to maintain body temperature during the challenge of low environmental temperature in many species from mouse to man and plays a key role in elevating body temperature during the febrile response to infection. The sympathetic neural outflow determining brown adipose tissue (BAT) thermogenesis is regulated by neural networks in the CNS which increase BAT sympathetic nerve activity in response to cutaneous and deep body thermoreceptor signals. Many behavioral states, including wakefulness, immunologic responses, and stress, are characterized by elevations in core body temperature to which central command-driven BAT activation makes a significant contribution. Since energy consumption during BAT thermogenesis involves oxidation of lipid and glucose fuel molecules, the CNS network driving cold-defensive and behavioral state-related BAT activation is strongly influenced by signals reflecting the short- and long-term availability of the fuel molecules essential for BAT metabolism and, in turn, the regulation of BAT thermogenesis in response to metabolic signals can contribute to energy balance, regulation of body adipose stores and glucose utilization. This review summarizes our understanding of the functional organization and neurochemical influences within the CNS networks that modulate the level of BAT sympathetic nerve activity to produce the thermoregulatory and metabolic alterations in BAT thermogenesis and BAT energy expenditure

that contribute to overall energy homeostasis and the autonomic support of behavior. (c) 2014 American Physiological Society. *Compr Physiol* 4: 1677-1713, 2014.

Muldoon, L. L., Wu, Y. J., Pagel, M. A., & Neuwelt, E. A. (2014). N-acetylcysteine chemoprotection without decreased cisplatin antitumor efficacy in pediatric tumor models. *Journal of Neuro-Oncology*,

Decreasing oxidative damage with the antioxidant agent N-acetylcysteine (NAC) can block the side effects of chemotherapy, but may diminish anti-tumor efficacy. We tested the potential for interactions of high dose NAC against a minimally effective cisplatin chemotherapy regimen in rat models of human pediatric cancers. Athymic rats received subcutaneous implantation of human SK-N-AS neuroblastoma cells or intra-cerebellar implantation of human D283-MED medulloblastoma cells. Rats were untreated or treated with cisplatin (3 or 4 mg/kg IV) with or without NAC (1,000 mg/kg IV) 30 min before or 4 h after cisplatin treatment. Blood urea nitrogen (BUN) and tumor volumes were measured. Cisplatin decreased the growth of SK-N-AS neuroblastoma subcutaneous tumors from 17.7 +/- 4.9 to 6.4 +/- 2.5 fold over baseline 2 weeks after treatment ($P < 0.001$). Pretreatment with NAC decreased cisplatin efficacy, while 4 h delayed NAC did not significantly affect cisplatin anti-tumor effects (relative tumor volume 6.8 +/- 2.0 fold baseline, $P < 0.001$). In D283-MED medulloblastoma brain tumors, cisplatin decreased final tumor volume to 3.9 +/- 2.3 mm³ compared to untreated tumor volume of 45.9 +/- 38.7 ($P = 0.008$). Delayed NAC did not significantly alter cisplatin efficacy (tumor volume 6.8 +/- 8.1 mm³, $P = 0.014$ versus control). Cisplatin was minimally nephrotoxic in these models. NAC decreased cisplatin-induced elevations in BUN ($P < 0.02$). NAC chemoprotection did not alter cisplatin therapy, if delayed until 4 h after chemotherapy. These data support a Phase I/II clinical trial of delayed NAC to reduce ototoxicity in children with localized pediatric cancers.

Nelson, H. D. (2013). In response. *Annals of Internal Medicine*, 158(2), 141.

O'Connor, R. M., Fung, J. M., Sharp, K. H., Benner, J. S., McClung, C., Cushing, S., et al. (2014). Gill bacteria enable a novel digestive strategy in a wood-feeding mollusk. *Proceedings of the National Academy of Sciences of the United States of America*, 111(47), E5096-104.

Bacteria play many important roles in animal digestive systems, including the provision of

enzymes critical to digestion. Typically, complex communities of bacteria reside in the gut lumen in direct contact with the ingested materials they help to digest. Here, we demonstrate a previously undescribed digestive strategy in the wood-eating marine bivalve *Bankia setacea*, wherein digestive bacteria are housed in a location remote from the gut. These bivalves, commonly known as shipworms, lack a resident microbiota in the gut compartment where wood is digested but harbor endosymbiotic bacteria within specialized cells in their gills. We show that this comparatively simple bacterial community produces wood-degrading enzymes that are selectively translocated from gill to gut. These enzymes, which include just a small subset of the predicted wood-degrading enzymes encoded in the endosymbiont genomes, accumulate in the gut to the near exclusion of other endosymbiont-made proteins. This strategy of remote enzyme production provides the shipworm with a mechanism to capture liberated sugars from wood without competition from an endogenous gut microbiota. Because only those proteins required for wood digestion are translocated to the gut, this newly described system reveals which of many possible enzymes and enzyme combinations are minimally required for wood degradation. Thus, although it has historically had negative impacts on human welfare, the shipworm digestive process now has the potential to have a positive impact on industries that convert wood and other plant biomass to renewable fuels, fine chemicals, food, feeds, textiles, and paper products.

Pan, C., Zhou, Y., Dator, R., Ginghina, C., Zhao, Y., Movius, J., et al. (2014). Targeted discovery and validation of plasma biomarkers of parkinsons disease. *Journal of Proteome Research*, 13(11), 4535-4545.

Despite extensive research, an unmet need remains for protein biomarkers of Parkinsons disease (PD) in peripheral body fluids, especially blood, which is easily accessible clinically. The discovery of such biomarkers is challenging, however, due to the enormous complexity and huge dynamic range of human blood proteins, which are derived from nearly all organ systems, with those originating specifically from the central nervous system (CNS) being exceptionally low in abundance. In this investigation of a relatively large cohort (~300 subjects), selected reaction monitoring (SRM) assays (a targeted approach) were used to probe plasma peptides derived from glycoproteins previously found to be altered in the CNS based on PD diagnosis or severity. Next, the detected peptides were interrogated for their diagnostic sensitivity and specificity as

well as the correlation with PD severity, as determined by the Unified Parkinsons Disease Rating Scale (UPDRS). The results revealed that 12 of the 50 candidate glycopeptides were reliably and consistently identified in plasma samples, with three of them displaying significant differences among diagnostic groups. A combination of four peptides (derived from PRNP, HSPG2, MEGF8, and NCAM1) provided an overall area under curve (AUC) of 0.753 (sensitivity: 90.4%; specificity: 50.0%). Additionally, combining two peptides (derived from MEGF8 and ICAM1) yielded significant correlation with PD severity, that is, UPDRS ($r = 0.293$, $p = 0.004$). The significance of these results is at least two-fold: (1) it is possible to use a targeted approach to identify otherwise very difficult to detect CNS related biomarkers in peripheral blood and (2) the novel biomarkers, if validated in independent cohorts, can be employed to assist with clinical diagnosis of PD as well as monitoring disease progression.

Paul, A. S., Wan, E. A., Adenwala, F., Schafermeyer, E., Preiser, N., Kaye, J., et al. (2014). MobileRF: A robust device-free tracking system based on a hybrid neural network HMM classifier. *2014 ACM International Joint Conference on Pervasive and Ubiquitous Computing, UbiComp 2014*, pp. 159-170.

We present a device-free indoor tracking system that uses received signal strength (RSS) from radio frequency (RF) transceivers to estimate the location of a person. While many RSS-based tracking systems use a body-worn device or tag, this approach requires no such tag. The approach is based on the key principle that RF signals between wall-mounted transceivers reflect and absorb differently depending on a person's movement within their home. A hierarchical neural network hidden Markov model (NN-HMM) classifier estimates both movement patterns and stand vs. walk conditions to perform tracking accurately. The algorithm and features used are specifically robust to changes in RSS mean shifts in the environment over time allowing for greater than 90% region level classification accuracy over an extended testing period. In addition to tracking, the system also estimates the number of people in different regions. It is currently being developed to support independent living and long-term monitoring of seniors.

Phillips, K. G., Lee, A. M., Tormoen, G. W., Rigg, R. A., Kolatkar, A., Luttgen, M., et al. (2014). The thrombotic potential of circulating tumor microemboli: Computational modeling of circulating

tumor cell-induced coagulation. *American Journal of Physiology. Cell Physiology*, ,
ajpcell.00315.2014.

Thrombotic events can herald the diagnosis of cancer, preceding any cancer-related clinical symptoms. Patients with cancer are at a 4-7 fold increased risk of suffering from venous thromboembolism (VTE), with approximately 7,000 patients with lung cancer presenting from VTEs. However, the physical biology underlying cancer-associated VTE remains poorly understood. Several lines of evidence suggest that the shedding of tissue factor (TF)-positive circulating tumor cells (CTCs) and microparticles from primary tumors may serve as a trigger for cancer-associated thrombosis. To investigate the potential direct and indirect roles of CTCs in VTE, we characterized thrombin generation by CTCs in an interactive numerical model coupling blood flow with advection-diffusion kinetics. Geometric measurements of CTCs isolated from the peripheral blood of a lung cancer patient prior to undergoing lobectomy formed the basis of the simulations. Singlet, doublet, and aggregate circulating tumormicroemboli (CTM) were investigated in the model. Our numerical model demonstrated that CTM could potentiate occlusive events that drastically reduce blood flow and serve as a platform for the promotion of thrombin generation in flowing blood. These results provide a characterization of CTM dynamics in the vasculature and demonstrate an integrative framework combining clinical, biophysical, and mathematical approaches to enhance our understanding of CTCs and their potential direct and indirect roles in VTE formation.

Rissi, J. J., Gelmon, S., Saulino, E., Merrithew, N., Baker, R., & Hatcher, P. (2015). Building the foundation for health system transformation: Oregon's patient-centered primary care home program. *Journal of Public Health Management and Practice : JPHMP*, 21(1), 34-41.

OBJECTIVE: Health system reform is largely dependent upon the transformation of primary care in addition to the alignment of incentives that mediate the allocation of resources. The Patient-Centered Medical Home (PCMH) is a model of enhanced primary care that encourages coordination, patient-centered care, integration of public health services, and innovative methods for improving population health—all critical elements of health system reform. Because it changes the way primary care is organized and delivered, the PCMH model has been adopted as a foundational component of Oregon's health system transformation. This article presents insights

drawn from an evaluation of the implementation of Oregon's Patient-Centered Primary Care Home (PCPCH) program and the adoption of the model by primary care providers. DESIGN: We used a mixed-methods approach consisting of 2 surveys of recognized PCPCH practices, qualitative document analysis, and key informant interviews. Evaluation research findings were triangulated with findings from PCPCH clinic site visits conducted as part of a regulatory verification process. RESULTS: Survey results describe a broad range of strategies and practices adopted by recognized PCPCH clinics within 6 defined core attributes: (1) access to care; (2) accountability; (3) comprehensive whole-person care; (4) continuity; (5) coordination and integration; and (6) person- and family-centered care. We also identify 4 key factors that influenced the conceptualization, development, and implementation of the PCPCH program: (1) support and motivations; (2) administrative barriers and resource constraints; (3) alignment of short- and long-term financial incentives; and (4) leadership and interpersonal relationships. CONCLUSIONS: This evaluation provides insights into the factors that influence implementation of a primary care home program as public policy; the strategies and challenges associated with implementation of the model; and the implications of both for other states that are engaged in-or considering-similar system reform efforts.

Roeske, T. C., Scharff, C., Olson, C. R., Nshdejan, A., & Mello, C. V. (2014). Long-distance retinoid signaling in the zebra finch brain. *PLoS One*, 9(11), e111722.

All-trans retinoic acid (ATRA), the main active metabolite of vitamin A, is a powerful signaling molecule that regulates large-scale morphogenetic processes during vertebrate embryonic development, but is also involved post-natally in regulating neural plasticity and cognition. In songbirds, it plays an important role in the maturation of learned song. The distribution of the ATRA-synthesizing enzyme, zRaldH, and of ATRA receptors (RARs) have been described, but information on the distribution of other components of the retinoid signaling pathway is still lacking. To address this gap, we have determined the expression patterns of two obligatory RAR co-receptors, the retinoid X receptors (RXR) alpha and gamma, and of the three ATRA-degrading cytochromes CYP26A1, CYP26B1, and CYP26C1. We have also studied the distribution of zRaldH protein using immunohistochemistry, and generated a refined map of ATRA localization, using a modified reporter cell assay to examine entire brain sections. Our results show that (1) ATRA is

more broadly distributed in the brain than previously predicted by the spatially restricted distribution of zRa1DH transcripts. This could be due to long-range transport of zRa1DH enzyme between different nuclei of the song system: Experimental lesions of putative zRa1DH peptide source regions diminish ATRA-induced transcription in target regions. (2) Four telencephalic song nuclei express different and specific subsets of retinoid-related receptors and could be targets of retinoid regulation; in the case of the lateral magnocellular nucleus of the anterior nidopallium (IMAN), receptor expression is dynamically regulated in a circadian and age-dependent manner. (3) High-order auditory areas exhibit a complex distribution of transcripts representing ATRA synthesizing and degrading enzymes and could also be a target of retinoid signaling. Together, our survey across multiple connected song nuclei and auditory brain regions underscores the prominent role of retinoid signaling in modulating the circuitry that underlies the acquisition and production of learned vocalizations.

Rohlfing, J., Navarro, R., Maniya, O. Z., Hughes, B. D., & Rogalsky, D. K. (2014). Medical student debt and major life choices other than specialty. *Medical Education Online*, 19, 25603.

BACKGROUND: Median indebtedness at graduation is now more than \$170,000 for graduates of US Medical Schools. Debate still exists as to whether higher debt levels influence students to choose high paying non-primary care specialties. Notably, no previous research on the topic has taken into account cost of attendance when constructing a debt model, nor has any research examined the non-career major life decisions that medical students face. **METHODS:** Medical students were surveyed using an anonymous electronic instrument developed for this study. The survey was delivered through a link included in a study email and students were recruited from school wide listservs and through snowball sampling (students were encouraged to share a link to the survey with other medical students). No incentives were offered for survey completion.

RESULTS: Responses were recorded from 102 US Allopathic medical schools (n=3,032), with 22 institutions (11 public, 11 private) meeting inclusion criteria of 10% student body response proportion (n=1,846). Students with higher debt relative to their peers at their home institution reported higher frequencies of feeling callous towards others, were more likely to choose a specialty with a higher average annual income, were less likely to plan to practice in underserved locations, and were less likely to choose primary care specialties. Students with higher aggregate

amounts of medical student loan debt were more likely to report high levels of stress from their educational debt, to delay getting married and to report disagreement that they would choose to become a physician again, if given the opportunity to revisit that choice. Increases in both aggregate and relative debt were associated with delaying having children, delaying buying a house, concerns about managing and paying back educational debt, and worrying that educational debt will influence one's specialty choice. CONCLUSIONS: Medical student debt and particularly debt relative to peers at the same institution appears to influence the way that students approach major life choices like when to start a family, when to buy a home, and what specialty to choose. Future research should take into account cost of attendance when looking for the impact of medical student debt on major life choices.

Rowell, S. E., Barbosa, R. R., Lennox, T. C., Fair, K. A., Rao, A. J., Underwood, S. J., et al. (2014).

Moderate elevations in international normalized ratio should not lead to delays in neurosurgical intervention in patients with traumatic brain injury. *The Journal of Trauma and Acute Care Surgery*, 77(6), 846-851.

BACKGROUND: The management of severe traumatic brain injury (TBI) frequently involves invasive intracranial monitoring or cranial surgery. In our institution, intracranial procedures are often deferred until an international normalized ratio (INR) of less than 1.4 is achieved. There is no evidence that a moderately elevated INR is associated with increased risk of bleeding in patients undergoing neurosurgical intervention (NI). Thrombelastography (TEG) provides a functional assessment of clotting and has been shown to better predict clinically relevant coagulopathy compared with INR. We hypothesized that in patients with TBI, an elevated INR would result in increased time to NI and would not be associated with coagulation abnormalities based on TEG. METHODS: A secondary analysis of prospectively collected data was performed in trauma patients with intracranial hemorrhage that underwent NI (defined as cranial surgery or intracranial pressure monitoring) within 24 hours of arrival. Time from admission to NI was recorded. TEG and routine coagulation assays were obtained at admission. Patients were considered hypocoagulable based on INR if their admission INR was greater than 1.4 (high INR). Manufacturer-specified values were used to determine hypocoagulability for each TEG variable. RESULTS: Sixty-one patients (median head Abbreviated Injury Scale [AIS] score, 5) met entry

criteria, of whom 16% had high INR. Demographic, physiologic, and injury scoring data were similar between groups. The median time to NI was longer in patients with high INR (358 minutes vs. 184 minutes, $p = 0.027$). High-INR patients were transfused more plasma than patients with an INR of 1.4 or less (2 U vs. 0 U, $p = 0.01$). There was no association between an elevated INR and hypocoagulability based on TEG. CONCLUSION: TBI patients with an admission INR of greater than 1.4 had a longer time to NI. The use of plasma transfusion to decrease the INR may have contributed to this delay. A moderately elevated INR was not associated with coagulation abnormalities based on TEG. Routine plasma transfusion to correct a moderately elevated INR before NI should be reexamined. LEVEL OF EVIDENCE: Diagnostic study, level III.

Sadanandam, A., Gray, J., & Hanahan, D. (2014). Reply to colorectal cancer classification based on gene expression is not associated with FOLFIRI response. *Nature Medicine*, 20(11), 1231-1232.

Sakyi, K. S., Surkan, P. J., Fombonne, E., Chollet, A., & Melchior, M. (2014). Childhood friendships and psychological difficulties in young adulthood: An 18-year follow-up study. *European Child and Adolescent Psychiatry*,

Childhood friendships have been shown to impact mental health over the short term; however, it is unclear whether these effects are sustained into young adulthood. We studied the prospective association between childhood friendships and psychological difficulties in young adulthood. Data come from 1,103 French 22–35 year olds participating in the TEMPO study. Childhood friendships were ascertained in 1991 when participants were 4–16 years old. Psychological difficulties were measured in 2009 using the Adult Self-Report. Logistic regression models controlled for participants' age, sex, childhood psychological difficulties and parental characteristics. Young adults who had no childhood friends had higher odds of psychological difficulties than those with at least one friend: (adjusted ORs 2.45; 95 % CI 1.32–4.66, $p = 0.01$ for high internalizing symptoms; 1.81; 95 % CI 0.94–3.54, $p = 0.08$ for high externalizing symptoms). Social relations early in life may have consequences for adult psychological well-being.

Salati, J., & Caughey, A. B. (2014). Progesterone for the prevention of preterm birth. *Neoreviews*, 15(11), e484-e492.

Preterm birth is the leading cause of neonatal morbidity and mortality in the United States and is

one of the leading causes worldwide, with the highest rates of mortality occurring in those born at less than 32 weeks' gestation. A history of preterm birth is one of the strongest risk factors for recurrent preterm delivery; however, early cervical shortening and multiple gestations also confer an increased risk of preterm birth. The precise causal mechanisms underlying the preterm birth pathway are still under investigation; however, available evidence suggests a role of progesterone in preterm birth prevention in certain high-risk populations. Specifically, intramuscular 17-hydroxyprogesterone appears beneficial in women with a prior preterm birth at less than 37 weeks' gestation (relative risk, 0.55; 95% confidence interval, 0.42–74) and preterm birth at less than 34 weeks' gestation (relative risk, 0.31; 95% confidence interval, 0.14–0.69). Vaginal progesterone has been found to reduce preterm birth in women with a foreshortened cervix as measured by transvaginal ultrasonography. There is unfortunately no evidence whatsoever that progesterone reduces preterm birth among women with multiple gestations. Additional research into the mechanisms of preterm birth and the potential for progesterone and other preventive interventions is necessary.

Schaefer, C., Sadosky, A., Mann, R., Daniel, S., Parsons, B., Tuchman, M., et al. (2014). Pain severity and the economic burden of neuropathic pain in the United States: BEAT neuropathic pain observational study. *ClinicoEconomics and Outcomes Research : CEOR*, 6, 483-496.

BACKGROUND: As with many chronic conditions, patients with neuropathic pain (NeP) are high consumers of health care resources. However, limited literature exists on the economic burden of NeP, including its impact on productivity. The aim of this study was to characterize health care resource utilization, productivity, and costs associated with NeP by pain severity level in US adults. **METHODS:** Subjects (n=624) with painful diabetic peripheral neuropathy, human immunodeficiency virus-related peripheral NeP, post-trauma/post-surgical NeP, spinal cord injury with NeP, chronic low back pain with NeP, and small fiber neuropathy were recruited during routine office visits to US community-based general practitioners and specialists. Clinicians captured clinical characteristics, NeP-related medications, and health care resource utilization based on 6-month retrospective medical chart review. Subjects completed questionnaires on demographics, pain/symptoms, costs, and productivity. Brief Pain Inventory pain severity scores were used to classify subjects by mild, moderate, or severe pain. Annualized NeP-related costs

(adjusted for covariates) were estimated, and differences across pain severity groups were evaluated. RESULTS: In total, 624 subjects were recruited (mean age 55.5+/-13.7 years; 55.4% male), and 504/624 (80.8%) reported moderate or severe pain. Statistically significant differences were observed across pain severity levels for number of comorbidities, prescription medications, physician office visits, and lost productivity (all $P \leq 0.0001$). At all pain severity levels, indirect costs were the primary cost driver. After adjusting for demographic and clinical variables, total mean (95% confidence interval [CI]) annualized direct medical costs to payers, direct costs to subjects, and indirect costs per subject were US\$6,016 (95% CI 5,316-6,716), US\$2,219 (95% CI 1,919-2,519), and US\$19,000 (95% CI 17,197-20,802), respectively, with significant differences across pain severity levels. CONCLUSION: Subjects with NeP, mainly those showing moderate or severe pain, had significant associations between pain severity and NeP-related health care resource utilization, productivity, and costs. The economic burden, particularly indirect costs, was highest among those with severe pain and higher than previously reported in studies of specific NeP conditions.

Schlansky, B., & Braillon, A. (2014). Dietary modification to prevent hepatocellular carcinoma is not low-hanging fruit. *Gastroenterology*, 147(5), 954-956.

Seifer, D. B., Minkoff, H., & Merhi, Z. (2014). Putting 'family' back in family planning. *Human Reproduction (Oxford, England)*,

Family planning visits are designed to help women build families in a manner most compatible with their life goals. Women's knowledge regarding age-related fertility is suboptimal, and first wanted pregnancies are now occurring at older ages. Here we review the issue of diminishing chances of a pregnancy occurring in women over 30 years of age. A debate arises over whether to perform a standard fertility assessment at an age when, for example, oocyte freezing is still practical and feasible, knowing that the proven predictors in subfertile couples may be less informative, or even inappropriate, in women without complaints about fertility. Studies have demonstrated that if women knew that their fertility was diminishing, they might alter life plans, including having children sooner or considering oocyte preservation. Therefore, we argue that

physicians need to make an effort to evaluate a woman's childbearing priorities, though not necessarily their fertility, during the initial family planning visit.

Sheriff, F., Narayanan, N. S., Huttner, A. J., & Baehring, J. M. (2014). Vogt-koyanagi-harada syndrome: A novel case and brief review of focal neurologic presentations. *Neurology(R) Neuroimmunology & Neuroinflammation*, 1(4), e49.

Shi, Z., & Brooks, V. L. (2014). Leptin differentially increases sympathetic nerve activity and its baroreflex regulation in female rats: Role of estrogen. *The Journal of Physiology*, Obesity and hypertension are commonly associated, and activation of the sympathetic nervous system is considered to be a major contributor, at least in part due to the central actions of leptin. However, while leptin increases sympathetic nerve activity (SNA) in males, whether leptin is equally effective in females is unknown. Here, we show that intracerebroventricular (ICV) leptin increases lumbar (LSNA) and renal (RSNA) SNA and baroreflex control of LSNA and RSNA in alpha-chloralose anesthetized female rats, but only during proestrus. In contrast, ICV leptin increased basal and baroreflex control of splanchnic SNA (SSNA) and heart rate (HR) in rats in both the proestrus and diestrus states. The effects of leptin on basal LSNA, RSNA, SSNA, and HR were similar in males and proestrus females; however, ICV leptin increased mean arterial pressure (MAP) only in males. Leptin did not alter LSNA or HR in ovariectomized (OVX) rats, but its effects were normalized with 4 days of estrogen treatment. Bilateral nano-injection of SHU9119 into the paraventricular nucleus of the hypothalamus (PVN), to block alpha-melanocyte-stimulating hormone (alpha-MSH) type 3 and 4 receptors, decreased LSNA in leptin-treated proestrus but not diestrus rats. Unlike leptin, ICV insulin infusion increased basal and baroreflex control of LSNA and HR similarly in proestrus and diestrus rats; these responses did not differ from those in male rats. We conclude that, in female rats, leptin's stimulatory effects on SNA are differentially enhanced by estrogen, at least in part via an increase in alpha-MSH activity in the PVN. These data further suggest that the actions of leptin and insulin to increase the activity of various sympathetic nerves occur via different neuronal pathways or cellular mechanisms. These results may explain the poor correlation in females of SNA with adiposity, or of MAP with leptin.

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Shin, K., Lim, A., Zhao, C., Sahoo, D., Pan, Y., Spiekerkoetter, E., et al. (2014). Hedgehog signaling restrains bladder cancer progression by eliciting stromal production of urothelial differentiation factors. *Cancer Cell*, 26(4), 521-533.

Hedgehog (Hh) pathway inhibitors are clinically effective in treatment of basal cell carcinoma and medulloblastoma, but fail therapeutically or accelerate progression in treatment of endodermally derived colon and pancreatic cancers. In bladder, another organ of endodermal origin, we find that despite its initial presence in the cancer cell of origin Sonic hedgehog (Shh) expression is invariably lost during progression to invasive urothelial carcinoma. Genetic blockade of stromal response to Shh furthermore dramatically accelerates progression and decreases survival time. This cancer-restraining effect of Hh pathway activity is associated with stromal expression of BMP signals, which stimulate urothelial differentiation. Progression is dramatically reduced by pharmacological activation of BMP pathway activity with low-dose FK506, suggesting an approach to management of human bladder cancer.

Singh, H., McGregor, J. C., Nigro, S. J., Higginson, A., & Larsen, G. C. (2014). Evaluation of collaborative therapy review to improve care of heart failure patients. *The American Journal of Managed Care*, 20(10), e425-31.

Objectives As more demands are placed on primary care providers, new innovative models are required to optimize heart failure (HF) care. The purpose of this study was to evaluate a collaborative therapy review (CTR) program that was implemented to improve guideline-based therapy among HF outpatients. **Study Design and Methods** We screened patient lists of 18 PCPs at the Portland Veterans Affairs Medical Center to identify patients with an ICD-9 code for HF. The charts of patients with ejection fractions (EFs) < 40% were then abstracted in more detail. The CTR team reviewed each patient and provided specific guideline-based recommendations. The team then gave specific recommendations to providers through the electronic medical record system. We categorized recommendations relating to drug or device therapies, or need for laboratory testing, and calculated provider acceptance rates by recommendation type. **Results** Of the 641 patients reviewed, 156 patients had detailed chart reviews. We found opportunities for improvement in care in 70 (45%) patients who received 100 recommendations. Among the 100 recommendations, 62 (55%) were for guideline-based drugs, 12 (17%) were for consideration of

device therapy, and 26 (24%) were to update lab tests or echocardiograms. Eighty percent of the recommendations were acted on within 90 days. Conclusions The CTR program was able to facilitate guideline-based management for HF patients by identifying treatment gaps and making specific guideline-based recommendations to PCPs. While further evaluations are needed, this approach may serve as an efficient method of leveraging the expertise of specialty-trained clinicians to optimize patient care.

Singleton, J., Osborn, J. L., Lillis, L., Hawkins, K., Guelig, D., Price, W., et al. (2014). Electricity-free amplification and detection for molecular point-of-care diagnosis of HIV-1. *PLoS One*, 9(11), e113693.

In resource-limited settings, the lack of decentralized molecular diagnostic testing and sparse access to centralized medical facilities can present a critical barrier to timely diagnosis, treatment, and subsequent control and elimination of infectious diseases. Isothermal nucleic acid amplification methods, including reverse transcription loop-mediated isothermal amplification (RT-LAMP), are well-suited for decentralized point-of-care molecular testing in minimal infrastructure laboratories since they significantly reduce the complexity of equipment and power requirements. Despite reduced complexity, however, there is still a need for a constant heat source to enable isothermal nucleic acid amplification. This requirement poses significant challenges for laboratories in developing countries where electricity is often unreliable or unavailable. To address this need, we previously developed a low-cost, electricity-free heater using an exothermic reaction thermally coupled with a phase change material. This heater achieved acceptable performance, but exhibited considerable variability. Furthermore, as an enabling technology, the heater was an incomplete diagnostic solution. Here we describe a more precise, affordable, and robust heater design with thermal standard deviation <0.5 degrees C at operating temperature, a cost of approximately US\$.06 per test for heater reaction materials, and an ambient temperature operating range from 16 degrees C to 30 degrees C. We also pair the heater with nucleic acid lateral flow (NALF)-detection for a visual readout. To further illustrate the utility of the electricity-free heater and NALF-detection platform, we demonstrate sensitive and repeatable detection of HIV-1 with a ss-actin positive internal amplification control from processed sample to result in less than 80 minutes. Together, these elements are building blocks

for an electricity-free platform capable of isothermal amplification and detection of a variety of pathogens.

Smith, M. W., Ash, J. S., Sittig, D. F., & Singh, H. (2014). Resilient practices in maintaining safety of health information technologies. *Journal of Cognitive Engineering and Decision Making*, 8(3), 265-282.

Electronic health record systems (EHRs) can improve safety and reliability of health care, but they can also introduce new vulnerabilities by failing to accommodate changes within a dynamic EHR-enabled health care system. Continuous assessment and improvement is thus essential for achieving resilience in EHR-enabled health care systems. Given the rapid adoption of EHRs by many organizations that are still early in their experiences with EHR safety, it is important to understand practices for maintaining resilience used by organizations with a track record of success in EHR use. We conducted interviews about safety practices with 56 key informants (including information technology managers, chief medical information officers, physicians, and patient safety officers) at two large health care systems recognized as leaders in EHR use. We identified 156 references to resilience-related practices from 41 informants. Framework analysis generated five categories of resilient practices: (a) sensitivity to dynamics and interdependencies affecting risks, (b) basic monitoring and responding practices, (c) management of practices and resources for monitoring and responding, (d) sensitivity to risks beyond the horizon, and (e) reflecting on risks with the safety and quality control process itself. The categories reflect three functions that facilitate resilience: reflection, transcending boundaries, and involving sharp-end practitioners in safety management.

Sonnenberg, A. (2014). Therapy without diagnosis. *The American Journal of Gastroenterology*, 109(11), 1837-1838.

Sotirova-Kohli, M., Opwis, K., Roesler, C., Smith, S. M., Rosen, D. H., Vaid, J., et al. (2013).

Symbol/Meaning paired-associate recall: An "archetypal memory" advantage? *Behavioral Sciences (Basel, Switzerland)*, 3(4), 541-561.

The theory of the archetypes and the hypothesis of the collective unconscious are two of the central characteristics of analytical psychology. These provoke, however, varying reactions

among academic psychologists. Empirical studies which test these hypotheses are rare. Rosen, Smith, Huston and Gonzales proposed a cognitive psychological experimental paradigm to investigate the nature of archetypes and the collective unconscious as archetypal (evolutionary) memory. In this article we report the results of a cross-cultural replication of Rosen et al. conducted in the German-speaking part of Switzerland. In short, this experiment corroborated previous findings by Rosen et al., based on English speakers, and demonstrated a recall advantage for archetypal symbol meaning pairs vs. other symbol/meaning pairings. The fact that the same pattern of results was observed across two different cultures and languages makes it less likely that they are attributable to a specific cultural or linguistic context.

Sox, C. M., Dell, M., Phillipi, C. A., Cabral, H. J., Vargas, G., & Lewin, L. O. (2014). Feedback on oral presentations during pediatric clerkships: A randomized controlled trial. *Pediatrics*, 134(5), 965-971.

OBJECTIVE: To measure the effects of participating in structured oral presentation evaluation sessions early in pediatric clerkships on students' subsequent presentations. **METHODS:** We conducted a single-blind, 3-arm, cluster randomized controlled trial during pediatric clerkships at Boston University School of Medicine, University of Maryland School of Medicine, Oregon Health & Science University, and Case Western Reserve University School of Medicine. Blocks of students at each school were randomly assigned to experience either (1) no formal presentation feedback (control) or a small-group presentation feedback session early in pediatric clerkships in which students gave live presentations and received feedback from faculty who rated their presentations by using a (2) single-item (simple) or (3) 18-item (detailed) evaluation form. At the clerkship end, overall quality of subjects' presentations was rated by faculty blinded to randomization status, and subjects reported whether their presentations had improved. Analyses included multivariable linear and logistic regressions clustered on clerkship block that controlled for medical school. **RESULTS:** A total of 476 participants were evenly divided into the 3 arms, which had similar characteristics. Compared with controls, presentation quality was significantly associated with participating in detailed (coefficient: 0.38; 95% confidence interval [CI]: 0.07-0.69) but not simple (coefficient: 0.16; 95% CI: -0.12-0.43) feedback sessions. Similarly, student self-report of presentation improvement was significantly associated with participating in

detailed (odds ratio: 2.16; 95% CI: 1.11-4.18] but not simple (odds ratio: 1.89; 95% CI: 0.91-3.93) feedback sessions. CONCLUSIONS: Small-group presentation feedback sessions led by faculty using a detailed evaluation form resulted in clerkship students delivering oral presentations of higher quality compared with controls.

Spiros, A., Roberts, P., & Geerts, H. (2014). A computer-based quantitative systems pharmacology model of negative symptoms in schizophrenia: Exploring glycine modulation of excitation-inhibition balance. *Frontiers in Pharmacology*, 5, 229.

Although many antipsychotics can reasonably control positive symptoms in schizophrenia, patients' return to society is often hindered by negative symptoms and cognitive deficits. As an alternative to animal rodent models that are often not very predictive for the clinical situation, we developed a new computer-based mechanistic modeling approach. This Quantitative Systems Pharmacology approach combines preclinical basic neurophysiology of a biophysically realistic neuronal ventromedial cortical-ventral striatal network identified from human imaging studies that are associated with negative symptoms. Calibration of a few biological coupling parameters using a retrospective clinical database of 34 drug-dose combinations resulted in correlation coefficients greater than 0.60, while a robust quantitative prediction of a number of independent trials was observed. We then simulated the effect of glycine modulation on the anticipated clinical outcomes. The quantitative biochemistry of glycine interaction with the different NMDA-NR2 subunits, neurodevelopmental trajectory of the NMDA-NR2B in the human schizophrenia pathology, their specific localization on excitatory vs. inhibitory interneurons and the electrogenic nature of the glycine transporter resulted in an inverse U-shape dose-response with an optimum in the low micromolar glycine concentration. Quantitative systems pharmacology based computer modeling of complex humanized brain circuits is a powerful alternative approach to explain the non-monotonic dose-response observed in past clinical trial outcomes with sarcosine, D-cycloserine, glycine, or D-serine or with glycine transporter inhibitors. In general it can be helpful to better understand the human neurophysiology of negative symptoms, especially with targets that show non-monotonic dose-responses.

Starmer, A. J., Spector, N. D., Srivastava, R., West, D. C., Rosenbluth, G., Allen, A. D., et al. (2014).

Changes in medical errors after implementation of a handoff program. *The New England Journal of Medicine*, 371(19), 1803-1812.

BACKGROUND: Miscommunications are a leading cause of serious medical errors. Data from multicenter studies assessing programs designed to improve handoff of information about patient care are lacking. METHODS: We conducted a prospective intervention study of a resident handoff-improvement program in nine hospitals, measuring rates of medical errors, preventable adverse events, and miscommunications, as well as resident workflow. The intervention included a mnemonic to standardize oral and written handoffs, handoff and communication training, a faculty development and observation program, and a sustainability campaign. Error rates were measured through active surveillance. Handoffs were assessed by means of evaluation of printed handoff documents and audio recordings. Workflow was assessed through time-motion observations. The primary outcome had two components: medical errors and preventable adverse events. RESULTS: In 10,740 patient admissions, the medical-error rate decreased by 23% from the preintervention period to the postintervention period (24.5 vs. 18.8 per 100 admissions, $P < 0.001$), and the rate of preventable adverse events decreased by 30% (4.7 vs. 3.3 events per 100 admissions, $P < 0.001$). The rate of nonpreventable adverse events did not change significantly (3.0 and 2.8 events per 100 admissions, $P = 0.79$). Site-level analyses showed significant error reductions at six of nine sites. Across sites, significant increases were observed in the inclusion of all prespecified key elements in written documents and oral communication during handoff (nine written and five oral elements; $P < 0.001$ for all 14 comparisons). There were no significant changes from the preintervention period to the postintervention period in the duration of oral handoffs (2.4 and 2.5 minutes per patient, respectively; $P = 0.55$) or in resident workflow, including patient-family contact and computer time. CONCLUSIONS: Implementation of the handoff program was associated with reductions in medical errors and in preventable adverse events and with improvements in communication, without a negative effect on workflow. (Funded by the Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, and others.).

Stecker, E. C. (2014). Picturing inflammation in blood vessels. *Science Translational Medicine*, 6(255)

Stempel, A. J., Morgans, C. W., Timothy Stout, J., & Appukuttan, B. (2014). Simultaneous visualization and cell-specific confirmation of RNA and protein in the mouse retina. *Molecular Vision*, 20, 1366-1373.

Purpose: Simultaneous dual labeling to visualize specific RNA and protein content within the same formalin-fixed paraffin embedded (FFPE) section can be technically challenging and usually impossible, because of variables such as tissue fixation time and pretreatment methods to access the target RNA or protein. Within a specific experiment, ocular tissue sections can be a precious commodity. Thus, the ability to easily and consistently detect and localize cell-specific expression of RNA and protein within a single slide would be advantageous. In this study, we describe a simplified and reliable method for combined in situ hybridization (ISH) and immunohistochemistry (IHC) for detection of mRNA and protein, respectively, within the same FFPE ocular tissue.

Methods: Whole mouse eyes were prepared for 5 micron FFPE sections after fixation for 3, 24, 48 or 72 h. Customized probes from Advanced Cell Diagnostics to detect mRNA for vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1-alpha (HIF-1 α), and hypoxia-inducible factor 2-alpha (HIF-2 α) were used for ISH. Various parameters were tested using the novel RNAscope method for ISH and optimized for compatibility with subsequent IHC for glial fibrillary acidic protein (GFAP) or GS-lectin within the same tissue section. Dual fluorescent visualization of Fast Red ISH and Alexa Fluor 488 IHC signal was observed with confocal microscopy.

Results: A fixation time of 72 h was found to be optimal for ISH and subsequent IHC. The RNAscope probes for VEGF, HIF-1 α , and HIF-2 α mRNA all gave a strong Fast Red signal with both 48 h and 72 h fixed tissue, but the optimal IHC signal for either GFAP or GS-lectin within a retinal tissue section after ISH processing was observed with 72 h fixation. A pretreatment boiling time of 15 min and a dilution factor of 1:15 for the pretreatment protease solution were found to be optimal and necessary for successful ISH visualization with 72 h FFPE ocular tissue.

Conclusions: The protocol presented here provides a simple and reliable method to simultaneously detect mRNA and protein within the same paraffin-embedded ocular tissue section. The procedure, after preparation of FFPE sections, can be performed over a 2-day or 4-day period. We provide an optimization strategy that may be adapted for any RNAscope probe set and antibody for determining retinal or ocular cell-specific patterns of expression.

Swank, M. L., Marshall, N. E., Caughey, A. B., Main, E. K., Gilbert, W. M., Melsop, K. A., et al. (2014).

Pregnancy outcomes in the super obese, stratified by weight gain above and below institute of medicine guidelines. *Obstetrics and Gynecology*, 124(6), 1105-1110.

OBJECTIVE: To examine the association of antenatal weight gain above and below the 2009 Institute of Medicine (IOM) guidelines in the super-obese population (body mass index [BMI] of 50 or higher) on the maternal and neonatal morbidities of gestational hypertension or preeclampsia (pregnancy-induced hypertension), gestational diabetes mellitus, cesarean delivery, birth weight more than 4,000 g and more than 4,500 g, low birth weight, and preterm birth.

METHODS: The effect of gestational weight gain was assessed in this retrospective cohort study using California birth certificate and patient discharge diagnosis data. Unconditional logistic regression was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) as a function of antenatal weight gain. Weight gain within 2009 IOM guidelines (11-20 pounds) served as the reference group. RESULTS: The study population consisted of 1,034 women.

Women gaining below, within, and above IOM guidelines accounted for 38.3, 23.5, and 38.2%, respectively. Weight gain below IOM guidelines was not associated with a statistically increased odds of preterm birth (OR 1.82, 95% CI 0.60-5.59) or low birth weight (OR 1.20, 95% CI 0.57-2.49); however, birth weight more than 4,000 g was significantly reduced (OR 0.50, 95% CI 0.32-0.77). Excessive weight gain statistically increased the odds of pregnancy-induced hypertension (OR 1.96, 95% CI 1.26-3.03) and cesarean delivery (OR 1.40, 95% CI 1.00-1.97) while not appearing to protect against the delivery of low-birth-weight neonates (OR 0.84, 95% CI 0.40-1.78). CONCLUSION: Weight gain below the current guidelines in the super-obese cohort is not associated with an increase in maternal or neonatal risk while decreasing the odds of delivering a macrosomic neonate. Women with BMIs of 50 or higher may warrant separate gestational weight gain recommendations. LEVEL OF EVIDENCE: : II.

Swanson, D. E. W., Polackwich, A. S., Helfand, B. T., Masson, P., Hwong, J., Dugi, D. D., III, et al.

(2014). Penile fracture: Outcomes of early surgical intervention. *Urology*, 84(5), 1117-1121.

Objective To report a series of penile fractures, describing preoperative evaluation, surgical repair, and long-term outcomes. Patients and Methods Medical records from Northwestern Memorial Hospital and Oregon Health & Science University from 2002 to 2011 were reviewed.

Clinical presentation, preoperative evaluation, time from injury, mechanism and site of injury, and presence of urethral injury were assessed. Outcomes including erectile dysfunction, penile curvature, and voiding symptoms were evaluated using International Prostate Symptom Score and International Index of Erectile Function scores. Results Twenty-nine patients with 30 separate episodes of penile fractures presenting to the emergency room were identified. Mean patient age was 43 ± 9.6 years. The time from presentation to the initiation of surgery was 5.5 ± 4.4 hours. Mechanism of injury was intercourse in 26 of 30 fractures with the remaining attributed to masturbation or "rolling over." Immediate surgical repair was offered to all patients. Twenty-seven patients underwent surgery. Urethral injury was noted in 5 of the 27. The site of fracture was at the proximal shaft in 11, mid shaft in 12, and distal shaft in 4 patients. The mean follow-up period was 14.3 ± 15.8 weeks. Nine patients reported new mild erectile dysfunction or penile curvature. One patient reported new irritative voiding symptoms. Conclusion The most common mechanism of penile fracture was from sexual intercourse, and frequent concomitant urethral injuries were observed. The frequency of concomitant urethral injury was higher than in previous studies. Although we observed high incidence of erectile dysfunction or penile curvature with early surgical repair, we retain it as the favored approach.

Tereshchenko, L. G., Henrikson, C. A., Sotoodehnia, N., Arking, D. E., Agarwal, S. K., Siscovick, D. S., et al. (2014). Electrocardiographic deep terminal negativity of the P wave in V1 and risk of sudden cardiac death: The atherosclerosis risk in communities (ARIC) study. *Journal of the American Heart Association*, 3(6), 10.1161/JAHA.114.001387.

BACKGROUND: Identifying individuals at risk for sudden cardiac death (SCD) is of critical importance. Electrocardiographic (ECG) deep terminal negativity of P wave in V1 (DTNPV1), a marker of left atrial abnormality, has been associated with increased risk of all-cause and cardiovascular mortality. We hypothesized that DTNPV1 is associated with increased risk of sudden cardiac death (SCD). METHODS AND RESULTS: This analysis included 15 375 participants (54.1 ± 5.8 years, 45% men, 73% whites) from the Atherosclerosis Risk in Communities (ARIC) study. DTNPV1 was defined from the resting 12-lead ECG as presence of biphasic P wave (positive/negative) in V1 with the amplitude of the terminal negative phase >100 μ V, or one small box on ECG scale. After a median of 14 years of follow-up, 311 cases of SCD occurred. In

unadjusted Cox regression, DTNPV1 was associated with an 8-fold increased risk of SCD (HR 8.21; [95%CI 5.27 to 12.79]). Stratified by race and study center, and adjusted for age, sex, coronary heart disease (CHD), and ECG risk factors, as well as atrial fibrillation (AF), stroke, CHD, and heart failure (HF) as time-updated variables, the risk of SCD associated with DTNPV1 remained significant (2.49, [1.51-4.10]). DTNPV1 improved reclassification: additional 3.4% of individuals were appropriately reclassified into a higher SCD risk group, as compared with traditional CHD risk factors alone. In fully adjusted models DTNPV1 was associated with increased risk of non-fatal events: AF (5.02[3.23-7.80]), CHD (2.24[1.43-3.53]), HF (1.90[1.19-3.04]), and trended towards increased risk of stroke (1.88[0.99-3.57]). CONCLUSION: DTNPV1 is predictive of SCD suggesting its potential utility in risk stratification in the general population.

Theodoroff, S. M., Schuette, A., Griest, S., & Henry, J. A. (2014). Individual patient factors associated with effective tinnitus treatment. *Journal of the American Academy of Audiology, 25*(7), 631-643.

BACKGROUND: Little is known about patient factors that might influence outcomes of tinnitus interventions. Determining such factors would offer insights into why some individuals benefit from tinnitus intervention whereas others do not. PURPOSE: The purpose of this study was to evaluate selected patient factors that may be associated with outcomes of tinnitus intervention. Factors studied include demographics, tinnitus characteristics, psychoacoustic tinnitus measures, audiometric data, and overall physical/emotional health status. RESEARCH DESIGN: A retrospective analysis was performed on data obtained from a controlled clinical study that compared factors associated with tinnitus relief after tinnitus masking and tinnitus retraining therapy. STUDY SAMPLE: A total of 126 military veterans participated in this controlled clinical study. Of these, 89 completed outcome measures at both baseline and 12 mo and were included in the present analysis. DATA COLLECTION AND ANALYSIS: A "responder" to intervention was identified as having a decrease (improvement) of 20 or more points on the Tinnitus Handicap Inventory between baseline and 12 mo. A "nonresponder" did not achieve a 20-point improvement on the Tinnitus Handicap Inventory. Individual patient factors were examined using independent t-tests or chi(2) analysis. A logistic regression model was used to determine how well each factor predicted treatment outcome (responder or nonresponder) while controlling for each of the other factors. RESULTS: Five patient factors were significantly different ($p \leq 0.05$)

between responders and nonresponders. Responders tended to (1) be younger in age; (2) have better low-frequency hearing sensitivity; (3) have greater problems with overall hearing; (4) be more likely to have tinnitus for shorter durations; and (5) perceive their tinnitus to be located "in the head" versus "in the ears." A logistic regression was then performed to determine how well each factor predicted the treatment outcome (responder versus nonresponder) while controlling for each of the other factors. RESULTS from the logistic regression revealed two of the five factors, localization of tinnitus and self-report of hearing problems, to be statistically significant. CONCLUSIONS: Examining the association of individual patient factors to a specific tinnitus intervention yielded several significant findings. Although these findings are not definitive, they reveal the capability that exists to perform these kinds of analyses to investigate relationships between individual patient characteristics and outcomes of intervention for tinnitus. Prospective research using systematic approaches is needed to identify these relationships that would contribute toward the ability to differentially predict outcomes of various tinnitus interventions. Obtaining this information would lead to more targeted therapy and ultimately more effective intervention.

Tratnyek, P. G. (2014). Comment on "evaluation of the kinetic oxidation of aqueous volatile organic compounds by permanganate" by M. G. mahmoodlu, S. M. hassanizadeh, and N. hartog, in science of the total environment (2014) 485-486: 755-763. *Science of the Total Environment*,

Tratnyek, P. G. (2015). Comment on "evaluation of the kinetic oxidation of aqueous volatile organic compounds by permanganate" by M. G. mahmoodlu, S. M. hassanizadeh, and N. hartog, in science of the total environment (2014) 485-486: 755-763. *Science of the Total Environment*, 502, 722-723.

Tseng, J., & Orloff, S. L. (2014). Management of symptomatic polycystic liver disease with hepatic resection. *JAMA Surgery*,

Urbanski, H. F. (2014). Selective targeting of GnRH-II neurons to block ovulation. *Contraception*,
Background: In rhesus macaques, luteinizing hormone (LH) secretion appears to be regulated by two distinct gonadotropin-releasing hormone (GnRH) neuronal populations, which can be

distinguished by their unique anatomical locations and because they express different molecular forms of GnRH (GnRH-I and GnRH-II). Study Design: The effect of estradiol on GnRH gene expression was examined. Results: Estradiol inhibited GnRH-I neurons but stimulated GnRH-II neurons, suggesting that GnRH-II neurons play the dominant role in mediating estradiol-positive feedback and triggering the midcycle preovulatory LH surge. Conclusions: Selective silencing of GnRH-II neurons in women could serve as a novel contraceptive, by blocking ovulation while leaving the rest of the reproductive axis relatively unperturbed.

Van, P. Y., & Schreiber, M. A. (2014). Hematologic issues in the geriatric surgical patient. *Surgical Clinics of North America*,

Geriatric patients are at higher risk for hemorrhagic complications after surgery and traumatic injuries. The elderly population is more likely to take anticoagulant or antiplatelet medications. Chronic disease, autoimmune disease, and nutritional deficiencies can lead to coagulation factor and platelet disorders. One must be familiar with the current anticoagulant and antiplatelet medications, their mechanism of action, and reversal agents to properly care for this group of patients. The new oral anticoagulants do not have Food and Drug Administration (FDA) approved reversal agents, but known procoagulant agents with other FDA indications may be effective.

Vartanian, K. B., Mitchell, H. D., Stevens, S. L., Conrad, V. K., McDermott, J. E., & Stenzel-Poore, M. P. (2014). CpG preconditioning regulates miRNA expression that modulates genomic reprogramming associated with neuroprotection against ischemic injury. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*,

Cytosine-phosphate-guanine (CpG) preconditioning reprograms the genomic response to stroke to protect the brain against ischemic injury. The mechanisms underlying genomic reprogramming are incompletely understood. MicroRNAs (miRNAs) regulate gene expression; however, their role in modulating gene responses produced by CpG preconditioning is unknown. We evaluated brain miRNA expression in response to CpG preconditioning before and after stroke using microarray. Importantly, we have data from previous gene microarrays under the same conditions, which allowed integration of miRNA and gene expression data to specifically identify regulated miRNA

gene targets. CpG preconditioning did not significantly alter miRNA expression before stroke, indicating that miRNA regulation is not critical for the initiation of preconditioning-induced neuroprotection. However, after stroke, differentially regulated miRNAs between CpG- and saline-treated animals associated with the upregulation of several neuroprotective genes, implicating these miRNAs in genomic reprogramming that increases neuroprotection. Statistical analysis revealed that the miRNA targets were enriched in the gene population regulated in the setting of stroke, implying that miRNAs likely orchestrate this gene expression. These data suggest that miRNAs regulate endogenous responses to stroke and that manipulation of these miRNAs may have the potential to acutely activate novel neuroprotective processes that reduce damage. *Journal of Cerebral Blood Flow & Metabolism* advance online publication, 12 November 2014; doi:10.1038/jcbfm.2014.193.

Whorton, M. (2014). Structural biology: Calcium-activated proteins visualized. *Nature*,

Wolfe, B. M., & Belle, S. H. (2014). Long-term risks and benefits of bariatric surgery: A research challenge. *JAMA - Journal of the American Medical Association*, 312(17), 1792-1793.

IMPORTANCE The clinical evidence base demonstrating bariatric surgery's health benefits is much larger than it was when the National Institutes of Health last held a consensus panel in 1991. Still, it remains unclear whether ongoing studies will address critical questions about long-term complication rates and the sustainability of weight loss and comorbidity control. Copyright 2014 American Medical Association. All rights reserved. **OBJECTIVE** To summarize findings from a multidisciplinary workshop convened in May 2013 by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute. The workshop aimed to summarize the current state of knowledge of bariatric surgery, review research findings on the long-term outcomes of bariatric surgery, and establish priorities for future research directions. **EVIDENCE REVIEW** The evidence presented at the workshop was selected by the planning committee for both its quality and duration of follow-up. The data review emphasized randomized clinical trials and large observational studies with long-term follow-up, with or without a control group. **FINDINGS** Several small randomized clinical trials showed greater weight loss and type 2 diabetes mellitus remission compared with nonsurgical treatments within the first

2 years of follow-up after bariatric surgery. Large, long-term observational studies have shown durable (>5 years) weight loss, diabetes, and lipid improvements with bariatric surgery. Still unclear are predictors of outcomes, long-term complications, long-term survival, microvascular and macrovascular events, mental health outcomes, and costs. The studies needed to address these knowledge gaps would be expensive and logistically difficult to perform. CONCLUSIONS AND RELEVANCE High-quality evidence shows that bariatric surgical procedures result in greater weight loss than nonsurgical treatments and are more effective at inducing initial type 2 diabetes mellitus remission in obese patients. More information is needed about the long-term durability of comorbidity control and complications after bariatric procedures and this evidence will most likely come from carefully designed observational studies.

Wu, H., Yu, Y., David, L., Ho, Y. S., & Lou, M. F. (2014). Glutaredoxin2 (GRX2) gene deletion induced early on-set of age-dependent cataract in mice. *The Journal of Biological Chemistry*, Glutaredoxin2 (Grx2) is an isozyme of glutaredoxin1 (thioltransferase) present in the mitochondria and nucleus with disulfide reductase and peroxidase activities, and controls thiol/disulfide balance in cells. In this study, we investigated if Grx2 gene deletion could induce faster age-related cataract formation and elucidated the biochemical changes effected by Grx2 gene deletion that may contribute to lens opacity. Slit lamp was used to examine the lenses in Grx2 knockout (KO) mice and age-matched wild-type (WT) mice aged from 1 to 16 months. In the Grx2 null mice, the lens nuclear opacity began at 5 months, 3 months sooner than that of the control mice and the progression of cataract were also much faster than the age-matched controls. Lenses of KO mice contained lower levels of protein thiols and GSH with a significant accumulation of S-glutathionylated proteins. Actin, alphaA-crystallin, and betaB2-crystallin were identified by Western blot and mass spectroscopy as the major S-glutathionylated proteins in the lenses of 16 month-old Grx2 KO mice. Compared with the WT control, the lens of Grx2 KO mouse had only 50% of the activity in complex I, and complex IV, and less than 10% of the ATP pool. It was concluded that Grx2 gene deletion altered the function of lens structural proteins through S-glutathionylation, and also caused severe disturbance in mitochondrial function. These combined alterations affected lens transparency.

Wu, S., Miller, T., Masanz, J., Coarr, M., Halgrim, S., Carrell, D., et al. (2014). Negation's not solved: Generalizability versus optimizability in clinical natural language processing. *PLoS One*, *9*(11), e112774.

A review of published work in clinical natural language processing (NLP) may suggest that the negation detection task has been "solved." This work proposes that an optimizable solution does not equal a generalizable solution. We introduce a new machine learning-based Polarity Module for detecting negation in clinical text, and extensively compare its performance across domains. Using four manually annotated corpora of clinical text, we show that negation detection performance suffers when there is no in-domain development (for manual methods) or training data (for machine learning-based methods). Various factors (e.g., annotation guidelines, named entity characteristics, the amount of data, and lexical and syntactic context) play a role in making generalizability difficult, but none completely explains the phenomenon. Furthermore, generalizability remains challenging because it is unclear whether to use a single source for accurate data, combine all sources into a single model, or apply domain adaptation methods. The most reliable means to improve negation detection is to manually annotate in-domain training data (or, perhaps, manually modify rules); this is a strategy for optimizing performance, rather than generalizing it. These results suggest a direction for future work in domain-adaptive and task-adaptive methods for clinical NLP.

Xie, F., Li, B. X., Alkayed, N. J., & Xiao, X. (2014). Synthesis of 14,15-EET from arachidonic acid using Urea–Hydrogen peroxide as the oxidant. *Synthetic Communications*,
14,15- Epoxyeicosatrienoic acid (14,15-EET) is an endogenous bioactive lipid with pharmacological benefits in multiple cardiovascular diseases. We describe here a practical synthesis of 14,15-EET from arachidonic acid using urea–hydrogen peroxide (UHP) as the oxidant.

Yang, O. O., Ali, A., Kasahara, N., Faure-Kumar, E., Bae, J. Y., Picker, L. J., et al. (2014). Short conserved sequences of HIV-1 are highly immunogenic and shift immunodominance. *Journal of Virology*,
Cellular immunity is pivotal in HIV-1 pathogenesis, but 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 148-214 and 250-335, Env 521-606, and Nef 106-148), 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 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-5 boost (weeks 0, 4, 8, and 24 respectively). Although CRV inserts were about a 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 versus the outside regions. The CRV yielded conserved region targeting density that was approximately five-fold that of the WPV. A similar pattern was seen in bronchoalveolar lymphocytes, but quadruple the magnitudes in blood. Overall, these findings demonstrated that the selected conserved regions are highly immunogenic, and that anatomically isolated vaccinations with these regions focuses immunodominance compared to full-length protein vaccination. IMPORTANCE HIV-1 sequence diversity is a major barrier limiting the capability of cellular immunity to contain infection and the ability of vaccines to match circulating viral sequences. To date, vaccines tested in humans have delivered whole proteins or genes for whole proteins, and it is unclear whether including only conserved sequences would yield sufficient cellular immunogenicity. We tested a vaccine delivering genes for four small conserved HIV-1 regions compared to a control vaccine with genes for whole Gag, Env, and Nef. Although the conserved regions ranged from 43 to 86 amino acids and comprised less than one fifth of whole Gag/Env/Nef, the vaccines elicited equivalent total magnitudes of both CD4⁺ and CD8⁺ T lymphocyte responses. These data demonstrate immunogenicity of these small conserved regions, and the potential for a vaccine to steer immunodominance towards conserved epitopes.

Yi, S. S., Ruff, R. R., Jung, M., & Waddell, E. N. (2014). Racial/ethnic residential segregation, neighborhood poverty and urinary biomarkers of diet in new york city adults. *Social Science and*

Medicine, 122, 122-129.

Consuming less sodium and more potassium are components of a healthy diet and reduced cardiovascular disease risk. Racial/ethnic segregation and poverty are both associated with dietary habits, but data linking dietary intake to neighborhood characteristics are limited, particularly in Hispanic and Asian American ethnic enclaves. This study presents relationships between neighborhood-level segregation, poverty and biologic indicators of sodium and potassium consumption. Data were from the 2010 Heart Follow-Up Study, a cross-sectional health survey, which included 24-hour urine collections and self-reported health status (n = 1656). Black, Hispanic, and Asian segregated areas and neighborhood poverty were defined for aggregated zip-code areas. Multivariable models assessed the association between neighborhood segregation and poverty and sodium and potassium intake, after adjustment for individual-level covariates. In unadjusted models, potassium intake (a marker of fruit and vegetable consumption) was lower in high-versus low-Hispanic segregated neighborhoods, and the sodium-potassium ratio was higher in high-versus low black and Hispanic segregated neighborhoods, and in high-versus low-poverty neighborhoods; the sodium-potassium ratio was lower in high-versus low Asian segregated neighborhoods. Segregation and poverty were not independently associated with nutrition biomarkers after adjustment for demographics and for each other; however, practical consideration of neighborhood race/ethnic composition may be useful to understand differences in consumption.

Zachariah, P., Blaschke, G. S., & Weddle, M. (2014). A request for "conversion therapy". *The Virtual Mentor : VM*, 16(11), 877-883.

Zhu, S., & Paoletti, P. (2014). Allosteric modulators of NMDA receptors: Multiple sites and mechanisms. *Current Opinion in Pharmacology*, 20, 14-23.

N-methyl-d-aspartate receptors (NMDARs) are glutamate-gated ion channels that are essential mediators of excitatory neurotransmission and synaptic plasticity. NMDARs are also implicated in a plethora of neuropathological conditions thus receiving strong interest as potential therapeutic targets. Recent years have witnessed major progress in our understanding of the structure and pharmacology of NMDARs with the decoding of the first full-length receptor crystal structures and

the discovery of allosteric modulators acting at novel binding sites and with unique patterns of subunit selectivity. Here we review the properties and structural mechanisms of various allosteric modulators that target NMDARs, emphasizing the newly identified compounds. The expanding pharmacology of NMDARs should help delineate the roles of various NMDAR subtypes in brain function, with potential for drug development.