

References

Al Rabadi, L., & Bergan, R. (2016). A way forward for cancer chemoprevention: Think local. *Cancer Prevention Research (Philadelphia, Pa.)*,

As cells progress through carcinogenesis, the associated exponential expansion of genetic and molecular aberrations and resultant heterogeneity make therapeutic success increasingly unattainable. Therapeutic intervention at early stages of carcinogenesis that occur within the primary organ and in the face of a lower burden of molecular aberrations, constitutes a basic tenet of cancer chemoprevention, and provides a situation that favors a greater degree of therapeutic efficacy compared to that of advanced cancer. A longstanding barrier to chemoprevention relates to the requirement for essentially no systemic toxicity, and the fact that when large numbers of people are treated, the emergence of systemic toxicity is almost universal. A rational means to address this in fact relates to a second basic tenet of the chemopreventive strategy: the focus of therapeutic intervention is to disrupt a process that is in essence localized to a single organ. Based upon this consideration, a strategy which is based upon local delivery of therapeutics to an at-risk organ will achieve therapeutic efficacy while avoiding systemic delivery and its associated toxicity. This article will review the rationale for undertaking such an approach, will describe successful clinical achievements based on this strategy, will describe ongoing efforts to expand the impact of this approach and together will highlight the high impact that this approach has already had on the field as well as its extremely high potential for future impact.

Alfadhli, A., Mack, A., Harper, L., Berk, S., Ritchie, C., & Barklis, E. (2016). Analysis of quinolinequinone reactivity, cytotoxicity, and anti-HIV-1 properties. *Bioorganic and Medicinal Chemistry*, 24(21), 5618-5625.

Allensworth, J. J., Troob, S. H., Weaver, T. S., Gonzalez, J. D., Petrisor, D., & Wax, M. K. (2016). Secondary free-flap reconstruction following ablation for acute invasive fungal sinusitis. *The Laryngoscope*,

OBJECTIVE: Acute invasive fungal sinusitis (AIFS) is a frequently fatal infection for which extensive and debilitating surgical debridement is a mainstay of therapy. Resulting defects are

often composite in nature, mandating free tissue-transfer reconstruction. Outcomes data for free flap reconstruction are limited. The purpose of this study was to examine surgical outcomes and survival in patients undergoing free flap transfer following invasive fungal sinusitis. STUDY DESIGN: Retrospective case series. METHODS: Between 1995 and 2015, patients undergoing operative debridement for AIFS were identified. Surgical records were used to identify survivors of acute infection who subsequently underwent free flap reconstructive surgery. Patient demographics, cause of immune compromise, defect description, flap type, perioperative complications, indications for revision surgery, functional outcomes, and long-term survival were reviewed. RESULTS: Forty-four patients were treated for AIFS, of those, 30 (68%) survived acute infection. Ten patients underwent maxillectomy, six with orbital exenteration, and were designated candidates for reconstruction. Eight patients underwent reconstruction. Median time from debridement to reconstruction was 67.5 days. Flap types included latissimus dorsi, scapula, anterolateral thigh, rectus, radial forearm, and fibula. Median follow-up was 7.7 months. No perioperative complications were encountered, and all subjects remained disease-free, able to speak and eat normally without prosthetic supplementation. Seven patients (87%) are currently alive. CONCLUSION: Reconstruction of defects left by invasive fungal sinusitis using free-tissue transfer resulted in successful flap survival, with no disease recurrence for all defects and flap types reviewed. Survivors of AIFS are able to tolerate midface reconstruction, with favorable functional outcomes and survival rates. LEVEL OF EVIDENCE: 4. *Laryngoscope*, 2016.

Amundsen, C. L., Richter, H. E., Menefee, S. A., Komesu, Y. M., Arya, L. A., Gregory, W. T., et al.

(2016). OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: A randomized clinical trial. *Jama*, 316(13), 1366-1374.

Women with refractory urgency urinary incontinence are treated with sacral neuromodulation and onabotulinumtoxinA with limited comparative information. To assess whether onabotulinumtoxinA is superior to sacral neuromodulation in controlling refractory episodes of urgency urinary incontinence. Multicenter open-label randomized trial (February 2012-January 2015) at 9 US medical centers involving 381 women with refractory urgency urinary incontinence. Cystoscopic intradetrusor injection of 200 U of onabotulinumtoxinA (n = 192) or sacral neuromodulation (n = 189). Primary outcome, change from baseline mean number of daily urgency urinary

incontinence episodes over 6 months, was measured with monthly 3-day diaries. Secondary outcomes included change from baseline in urinary symptom scores in the Overactive Bladder Questionnaire Short Form (SF); range, 0-100, higher scores indicating worse symptoms; Overactive Bladder Satisfaction questionnaire; range, 0-100; includes 5 subscales, higher scores indicating better satisfaction; and adverse events. Of the 364 women (mean [SD] age, 63.0 [11.6] years) in the intention-to-treat population, 190 women in the onabotulinumtoxinA group had a greater reduction in 6-month mean number of episodes of urgency incontinence per day than did the 174 in the sacral neuromodulation group (-3.9 vs -3.3 episodes per day; mean difference, 0.63; 95% CI, 0.13 to 1.14; P = .01). Participants treated with onabotulinumtoxinA showed greater improvement in the Overactive Bladder Questionnaire SF for symptom bother (-46.7 vs -38.6; mean difference, 8.1; 95% CI, 3.0 to 13.3; P = .002); treatment satisfaction (67.7 vs 59.8; mean difference, 7.8; 95% CI, 1.6 to 14.1; P = .01) and treatment endorsement (78.1 vs 67.6; mean difference; 10.4, 95% CI, 4.3 to 16.5; P < .001) than treatment with sacral neuromodulation. There were no differences in convenience (67.6 vs 70.2; mean difference, -2.5; 95% CI, -8.1 to 3.0; P = .36), adverse effects (88.4 vs 85.1; mean difference, 3.3; 95% CI, -1.9 to 8.5; P = .22), and treatment preference (92.% vs 89%; risk difference, -3%; 95% CI, -16% to 10%; P = .49). Urinary tract infections were more frequent in the onabotulinumtoxinA group (35% vs 11%; risk difference, -23%; 95% CI, -33% to -13%; P < .001). The need for self-catheterization was 8% and 2% at 1 and 6 months in the onabotulinumtoxinA group. Neuromodulation device revisions and removals occurred in 3%. Among women with refractory urgency urinary incontinence, treatment with onabotulinumtoxinA compared with sacral neuromodulation resulted in a small daily improvement in episodes that although statistically significant is of uncertain clinical importance. In addition, it resulted in a higher risk of urinary tract infections and need for transient self-catheterizations.

Anandakrishnan, R., Zhang, Z., Donovan-Maiye, R., & Zuckerman, D. M. (2016). Biophysical comparison of ATP synthesis mechanisms shows a kinetic advantage for the rotary process. *Proceedings of the National Academy of Sciences of the United States of America*, 113(40), 11220-11225.

Anderson, D. E., Markway, B. D., Bond, D., McCarthy, H. E., & Johnstone, B. (2016). Responses to altered oxygen tension are distinct between human stem cells of high and low chondrogenic capacity. *Stem Cell Research & Therapy*, 7(1), 154.

BACKGROUND: Lowering oxygen from atmospheric level (hyperoxia) to the physiological level (physioxia) of articular cartilage promotes mesenchymal stem cell (MSC) chondrogenesis. However, the literature is equivocal regarding the benefits of physioxic culture on preventing hypertrophy of MSC-derived chondrocytes. Articular cartilage progenitors (ACPs) undergo chondrogenic differentiation with reduced hypertrophy marker expression in hyperoxia but have not been studied in physioxia. This study sought to delineate the effects of physioxic culture on both cell types undergoing chondrogenesis. **METHODS:** MSCs were isolated from human bone marrow aspirates and ACP clones were isolated from healthy human cartilage. Cells were differentiated in pellet culture in physioxia (2 % oxygen) or hyperoxia (20 % oxygen) over 14 days. Chondrogenesis was characterized by biochemical assays and gene and protein expression analysis. **RESULTS:** MSC preparations and ACP clones of high intrinsic chondrogenicity (termed high-GAG) produced abundant matrix in hyperoxia and physioxia. Poorly chondrogenic cells (low-GAG) demonstrated a significant fold-change matrix increase in physioxia. Both high-GAG and low-GAG groups of MSCs and ACPs significantly upregulated chondrogenic genes; however, only high-GAG groups had a concomitant decrease in hypertrophy-related genes. High-GAG MSCs upregulated many common hypoxia-responsive genes in physioxia while low-GAG cells downregulated most of these genes. In physioxia, high-GAG MSCs and ACPs produced comparable type II collagen but less type I collagen than those in hyperoxia. Type X collagen was detectable in some ACP pellets in hyperoxia but reduced or absent in physioxia. In contrast, type X collagen was detectable in all MSC preparations in hyperoxia and physioxia. **CONCLUSIONS:** MSC preparations and ACP clones had a wide range of chondrogenicity between donors. Physioxia significantly enhanced the chondrogenic potential of both ACPs and MSCs compared with hyperoxia, but the magnitude of response was inversely related to intrinsic chondrogenic potential. Discrepancies in the literature regarding MSC hypertrophy in physioxia can be explained by the use of low numbers of preparations of variable chondrogenicity. Physioxic differentiation of MSC preparations of high chondrogenicity significantly decreased hypertrophy-related genes but still produced type X collagen protein. Highly chondrogenic ACP clones had

significantly lower hypertrophic gene levels, and there was little to no type X collagen protein in physioxia, emphasizing the potential advantage of these cells.

Angier, H., Gregg, J., Gold, R., Crawford, C., Davis, M., & DeVoe, J. E. (2014). Understanding how low-income families prioritize elements of health care access for their children via the optimal care model. *BMC Health Services Research*, 14(1)

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Burton, G. A., Jr, Buschmann, J., et al. (2016). RIFM fragrance ingredient safety assessment, 2-hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol, CAS registry number 42822-86-6. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2016). RIFM fragrance ingredient safety assessment, 1-(3,3-dimethylcyclohexyl)pent-4-en-1-one, CAS registry number 56973-87-6. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

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Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2016). RIFM fragrance ingredient safety assessment, 1,3,3-trimethyl-2-norbornanyl acetate, CAS registry number 13851-11-1. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2016). RIFM fragrance ingredient safety assessment, ethylene brassylate, CAS registry number 105-95-3. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

: The use of this material under current conditions is supported by existing information. This

material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using ethylene dodecanedioate (CAS # 54982-83-1) as a suitable read across analog, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra along with data on the target material. The environmental endpoint was completed as described in the RIFM Framework along with data on the suitable read across analog oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2).

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Avila, P. T. (2016). A multidisciplinary response to commercial sexual exploitation of children. *The Nurse Practitioner*, 41(11), 34-40.

Commercial sexual exploitation of children (CSEC) is associated with child abuse, neglect, poverty, homelessness, and societal causes. Sex trafficking is the participation in commercial sex acts in which force, fraud, or coercion occur. This article discusses the scope of CSEC and sex trafficking, and the necessary identification skills and medical evaluations needed to help these patients.

Baird, L. C., Klimo, P., Jr, Flannery, A. M., Bauer, D. F., Beier, A., Durham, S., et al. (2016). Congress of neurological surgeons systematic review and evidence-based guideline for the management of patients with positional plagiocephaly: The role of physical therapy. *Neurosurgery*, 79(5), E630-E631.

BACKGROUND: Evidence-based guidelines are not currently available for the treatment of

positional plagiocephaly and, in particular, for the use of physical therapy for treatment.

OBJECTIVE: To answer the question: "does physical therapy provide effective treatment for positional plagiocephaly?" Treatment recommendations are created based on the available evidence. **METHODS:** The PubMed and the Cochrane Library were queried using MeSH headings and key words relevant to the objective of this systematic review. Abstracts were reviewed, after which studies meeting the inclusion criteria were selected and graded according to their quality of evidence (Classes I-III). Evidentiary tables were constructed that summarized pertinent study results, and recommendations were made based on the quality of the literature (Levels I-III). **RESULTS:** Three studies met criteria for inclusion. Two randomized, controlled trials (Class I and Class II) and 1 prospective study assessing plagiocephaly as a secondary outcome measure (Class III) were included. **CONCLUSION:** Within the limits of this systematic review, physical therapy is significantly more effective than repositioning education as a treatment for positional plagiocephaly. There is no significant difference between physical therapy and a positioning pillow as a treatment for positional plagiocephaly. However, given the American Academy of Pediatrics' recommendation against soft pillows in cribs to ensure a safe sleeping environment for infants, physical therapy must be recommended over the use of a positioning pillow. The full guidelines document can be located at https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly/Chapter_4.

Baird, L. C., Klimo, P., Jr, Flannery, A. M., Bauer, D. F., Beier, A., Durham, S., et al. (2016).

Guidelines: Congress of neurological surgeons systematic review and evidence-based guideline for the management of patients with positional plagiocephaly: The role of physical therapy. *Neurosurgery*, 79(5), E630-E631.

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evidence (Classes I-III). Evidentiary tables were constructed that summarized pertinent study results, and recommendations were made based on the quality of the literature (Levels I-III). RESULTS: Three studies met criteria for inclusion. Two randomized, controlled trials (Class I and Class II) and 1 prospective study assessing plagiocephaly as a secondary outcome measure (Class III) were included. CONCLUSION: Within the limits of this systematic review, physical therapy is significantly more effective than repositioning education as a treatment for positional plagiocephaly. There is no significant difference between physical therapy and a positioning pillow as a treatment for positional plagiocephaly. However, given the American Academy of Pediatrics' recommendation against soft pillows in cribs to ensure a safe sleeping environment for infants, physical therapy must be recommended over the use of a positioning pillow. The full guidelines document can be located at https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly/Chapter_4.

Barajas, R. F., Butowski, N. A., Phillips, J. J., Aghi, M. K., Berger, M. S., Chang, S. M., et al. (2016). The development of reduced diffusion following bevacizumab therapy identifies regions of recurrent disease in patients with high-grade glioma. *Academic Radiology*, 23(9), 1073-1082.

Baumert, M., Pamula, Y., Martin, J., Kennedy, D., Ganesan, A., Kabir, M., et al. (2016). The effect of adenotonsillectomy for childhood sleep apnoea on cardiorespiratory control. *ERJ Open Research*, 2(2)

Beauchamp, G. A., & Hendrickson, R. G. (2016). Delayed salicylate toxicity in a 17-year-old girl with initially undetectable salicylate concentration 3.9 hours after ingestion. *Pediatric Emergency Care*, We report the case of a 17-year-old girl with a 126-mg/kg nonenteric coated aspirin ingestion with nontoxic salicylate concentrations at 1.5 and 3.9 hours postingestion, who developed tinnitus and vomiting an estimated 8 hours postingestion, and who was subsequently found to have a toxic salicylate concentration at 22.7 hours postingestion. This case, as well as previous cases of delayed aspirin therapy, may prompt providers to consider educating patients and their care providers regarding the need to return for further testing if symptoms, such as vomiting or tinnitus, develop after an aspirin ingestion.

Beckman, M., & Mobbs, K. E. (2016). Threatening statements and the therapist-client privilege. *Journal of the American Academy of Psychiatry and the Law*, 44(3), 392-394.

Bei, L., Lee, I., Lee, M. S., Van Stavern, G. P., & McClelland, C. M. (2016). Acute vision loss and choroidal filling delay in the absence of giant-cell arteritis. *Clinical Ophthalmology (Auckland, N.Z.)*, 10, 1573-1578.

Giant-cell arteritis (GCA) is a visually devastating disease that often progresses to severe bilateral vision loss if untreated. Diagnosis of GCA is made challenging by the protean nature of the disease and the lack of a simple test that is both highly sensitive and specific. Choroidal filling delay on fluorescein angiography (FA) has been touted as a highly characteristic feature of GCA-related vision loss, although knowledge of both the sensitivity and specificity of this finding remains unproven. We report our experience of delayed choroidal filling on FA in a series of seven patients referred to an academic neuro-ophthalmology practice due to concern for GCA. Despite the FA findings, our examination, diagnostic testing, and long-term follow-up excluded the diagnosis of GCA in all cases, suggesting that choroidal perfusion abnormalities may occur in the absence of GCA. When evaluating a patient for acute vision loss, the astute clinician must remain cognizant of the limitations of FA in the diagnosis of GCA.

Benedek, G., Vandembark, A. A., Alkayed, N. J., & Offner, H. (2016). Partial MHC class II constructs as novel immunomodulatory therapy for stroke. *Neurochemistry International*,

The worldwide prevalence of stroke continues to rise despite recent successes in treating acute ischemic stroke. With limited patient eligibility and associated risk of tPA and mechanical thrombectomy, new preventive and therapeutic modalities are needed to stave the rising wave of stroke. Inflammation plays a key role in brain damage after cerebral ischemia, and novel therapies that target pro-inflammatory cells have demonstrated promise for treatment for stroke. Partial MHC class II constructs have been shown to prevent and/or reverse clinical signs of various inflammatory diseases such as experimental autoimmune encephalomyelitis, collagen-induced arthritis and experimental autoimmune uveitis, by reducing the number and frequency of activated cells in the damaged CNS. Herein, we review the use of partial MHC class II constructs as a novel treatment for ischemic stroke. These constructs have been shown to reduce infarct

volume and neurological deficit in various cerebral ischemia models in young adult and aging male and female mice. In addition, partial MHC class II constructs were shown to reverse stroke-associated splenic atrophy and promote a protective M2 macrophage/microglia phenotype in the CNS which contributes to tissue repair and recovery after stroke. By addressing remaining STAIR criteria, such as efficacy in large animal models of stroke, these constructs will be prime candidates for clinical trials of acute ischemic stroke.

Bergstrom, C. P., Ruffell, B., Ho, C. M. T., Higano, C. S., Ellis, W. J., Garzotto, M., et al. (2016).

Docetaxel and mitoxantrone before radical prostatectomy in men with high-risk prostate cancer: 10-year follow-up and immune correlates. *Anti-Cancer Drugs*,

Berriochoa, C., Ward, M. C., Weller, M. A., Holliday, E., Kusano, A., Thomas, C. R., et al. (2016).

Applicant interview experiences and postinterview communication of the 2016 radiation oncology match cycle. *International Journal of Radiation Oncology Biology Physics*, 96(3), 514-520.

Bien, J., & Prasad, V. (2016). Future jobs of FDA's haematology-oncology reviewers. *BMJ (Online)*, 354

Bohun, C. M., Woods, P., Winter, C., Mitchell, J., McLarry, J., Weiss, J., et al. (2016). Challenges of intra-institutional transfer of care from paediatric to adult congenital cardiology: The need for retention as well as transition. *Cardiology in the Young*, 26(2), 327-333.

BACKGROUND: Transferring patients with CHD from paediatric to adult care has been challenging, especially across institutions. Within a single institution, some issues such as provider interaction, information exchange, or administrative directives should not play a significant role, and should favour successful transfer. OBJECTIVE: We studied patients who were eligible for transfer to the adult congenital heart disease service within our institution in order to identify factors associated with successful transfer to adult care providers versus failure to transfer. METHODS: Patients above 18 years of age with CHD who were seen by paediatric cardiologists before January, 2008 were identified through a patient-care database. Records were reviewed to determine follow-up between 2008 and 2011 and to determine whether the patient was seen in the adult congenital cardiology clinic, paediatric cardiology clinic, or had no follow-

up, and statistical comparisons were made between groups. RESULTS: After reviewing 916 records, 229 patients were considered eligible for transition to adult congenital cardiology. Of these, 77 (34%) were transferred successfully to adult congenital cardiology, 47 (21%) continued to be seen by paediatric cardiologists, and 105 (46%) were lost to follow-up. Those who transferred successfully differed with regard to complexity of diagnosis, insurance, and whether a formal referral was made by a paediatric care provider. Only a small fraction of the patients who were lost to follow-up could be contacted. CONCLUSION: Within a single institution, with shared information systems, administrations, and care providers, successful transfer from paediatric to adult congenital cardiology was still poor. Efforts for successful retention are just as vital as those for transfer.

Boise, L., Hinton, L., Rosen, H. J., Ruhl, M. C., Dodge, H., Mattek, N., et al. (2016). Willingness to be a brain donor: A survey of research volunteers from 4 Racial/Ethnic groups. *Alzheimer Disease and Associated Disorders*,

INTRODUCTION: Racial and ethnic groups are under-represented among research subjects who assent to brain donation in Alzheimer disease research studies. There has been little research on this important topic. Although there are some studies that have investigated the barriers to brain donation among African American study volunteers, there is no known research on the factors that influence whether or not Asians or Latinos are willing to donate their brains for research.

METHODS: African American, Caucasian, Asian, and Latino research volunteers were surveyed at 15 Alzheimer Disease Centers to identify predictors of willingness to assent to brain donation.

RESULTS: Positive predictors included older age, Latino ethnicity, understanding of how the brain is used by researchers, and understanding of what participants need to do to ensure that their brain will be donated. Negative predictors included African/African American race, belief that the body should remain whole at burial, and concern that researchers might not be respectful of the body during autopsy. DISCUSSION: The predictive factors identified in this study may be useful for researchers seeking to increase participation of diverse ethnic groups in brain donation.

Bourdette, D. (2016). Rituximab for treating multiple sclerosis: Off-label but on target. *Neurology*,

Bradbury, H., & Lifvergren, S. (2016). Action research healthcare: Focus on patients, improve quality, drive down costs. *Healthcare Management Forum*,

We discuss action research healthcare as a transformative approach that continuously innovates in healthcare, attending to the "quadruple" aim. This article is shaped around a decade of evidence in Sweden. At the heart of healthcare action research is the endeavour to "learn by doing" with the participation of key stakeholders, including the patient. Experience suggests that an action research approach is particularly relevant when treating patients with chronic diseases and complex care needs. This inclusion is itself a social learning process and is key to realizing the improved outcomes. Insights from objective quantitative studies are balanced with personal and inter-subjective dialogue that aligns different parts of a system in a movement towards improvement. Close-up non-defensive self-inquiry in the company of colleagues, with trust dynamics building over time, may be a key point of leverage for such systemic improvement activities.

Brasel, K. J., Entwistle, J. W., 3rd, & Sade, R. M. (2016). Should family presence be allowed during cardiopulmonary resuscitation? *The Annals of Thoracic Surgery*, 102(5), 1438-1443.

Burfeind, K. G., Yadav, V., & Marks, D. L. (2016). Hypothalamic dysfunction and multiple sclerosis: Implications for fatigue and weight dysregulation. *Current Neurology and Neuroscience Reports*, 16(11)

Burghardt, K., Verzijl, C., Huang, J., Ingram, M., Song, B., & Hasne, M. -. (2016). Testing modeling assumptions in the west africa ebola outbreak. *Scientific Reports*, 6

Camino, A., Zhang, M., Dongye, C., Pechauer, A. D., Hwang, T. S., Bailey, S. T., et al. (2016).

Automated registration and enhanced processing of clinical optical coherence tomography angiography. *Quantitative Imaging in Medicine and Surgery*, 6(4), 391-401.

BACKGROUND: Motion artifacts degrade the quality of optical coherence tomography angiography (OCTA). Orthogonal registration can eliminate the majority of these artifacts, but some artifacts persist in most clinical images. We evaluate an automated registration algorithm with selective merging and filtering to remove remaining artifacts and improve the quality of images.

METHODS: A 70 kHz commercial spectral domain OCT was used to obtain 3 mm x 3 mm OCTA in 10 healthy, 5 age-related macular degeneration (AMD), and 31 diabetic retinopathy (DR) participants. Projection artifacts were removed and images were segmented into 3 inner retinal plexuses. Amplitude thresholding identified lines containing a residual artifact and correlation between neighboring lines identified distorted stripes. Then the angiograms were registered and the lines selectively merged. A vesselness filter was applied to the resulting images. The images were evaluated for signal-to-noise ratio (SNR), image entropy, vessel connectivity and vessel density. **RESULTS:** Registration and selective merging (RSM) algorithm improved the SNR ($P < 0.02$) compared to orthogonal registration alone. RSM with vesselness filter increased the image entropy ($P < 10^{-8}$) and reduced inter-subject variability (standard error $\leq 3\%$, $n=10$) in healthy eyes. The method improved vessel details and connectivity in OCTA of healthy, DR and neovascular AMD eyes. **CONCLUSIONS:** This automated registration method eliminates residual motion artifacts and enhances the visualization of vessels in OCTA.

Camino, A., Zhang, M., Gao, S. S., Hwang, T. S., Sharma, U., Wilson, D. J., et al. (2016). Evaluation of artifact reduction in optical coherence tomography angiography with realtime tracking and motion correction technology. *Biomedical Optics Express*, 7(10), 3905-3915.

Campbell, M. J., Baehner, F., O'Meara, T., Ojukwu, E., Han, B., Mukhtar, R., et al. (2016).

Characterizing the immune microenvironment in high-risk ductal carcinoma in situ of the breast. *Breast Cancer Research and Treatment*,

PURPOSE: The recent increase in the incidence of ductal carcinoma in situ (DCIS) has sparked debate over the classification and treatment of this disease. Although DCIS is considered a precursor lesion to invasive breast cancer, some DCIS may have more or less risk than is realized. In this study, we characterized the immune microenvironment in DCIS to determine if immune infiltrates are predictive of recurrence. **METHODS:** Fifty-two cases of high-grade DCIS (HG-DCIS), enriched for large lesions and a history of recurrence, were age matched with 65 cases of non-high-grade DCIS (nHG-DCIS). Immune infiltrates were characterized by single- or dual-color staining of FFPE sections for the following antigens: CD4, CD8, CD20, FoxP3, CD68, CD115, Mac387, MRC1, HLA-DR, and PCNA. Nuance multispectral imaging software was used for

image acquisition. Protocols for automated image analysis were developed using CellProfiler. Immune cell populations associated with risk of recurrence were identified using classification and regression tree analysis. RESULTS: HG-DCIS had significantly higher percentages of FoxP3+ cells, CD68+ and CD68+PCNA+ macrophages, HLA-DR+ cells, CD4+ T cells, CD20+ B cells, and total tumor infiltrating lymphocytes compared to nHG-DCIS. A classification tree, generated from 16 immune cell populations and 8 clinical parameters, identified three immune cell populations associated with risk of recurrence: CD8+HLADR+ T cells, CD8+HLADR- T cells, and CD115+ cells. CONCLUSION: These findings suggest that the tumor immune microenvironment is an important factor in identifying DCIS cases with the highest risk for recurrence and that manipulating the immune microenvironment may be an efficacious strategy to alter or prevent disease progression.

Campochiaro, P. A., Lauer, A. K., Sohn, E. H., Mir, T. A., Naylor, S., Anderton, M. C., et al. (2016).

Lentiviral vector gene transfer of Endostatin/Angiostatin for macular degeneration (GEM) study. *Human Gene Therapy*,

Neovascular age-related macular degeneration (NVAMD) is a prevalent cause of vision loss. Intraocular injections of VEGF-neutralizing proteins provide benefit, but many patients require frequent injections for a prolonged period. Benefits are often lost over time due to lapses in treatment. New treatments that sustain anti-angiogenic activity are needed. This study tested the safety and expression profile of a lentiviral Equine Infectious Anemia Virus (EIAV) vector expressing endostatin and angiostatin (RetinoStat(R)). Patients with advanced NVAMD were enrolled at three centers in the United States, and the study eye received a subretinal injection of 2.4×10^4 (n = 3), 2.4×10^5 (n = 3), or 8.0×10^5 transduction units (TU; n = 15). Each of the doses was well-tolerated with no dose-limiting toxicities. There was little or no ocular inflammation. There was one procedure-related serious adverse event (AE), a macular hole, which was managed without difficulty and resolved. There was a vector dose-related increase in aqueous humor levels of endostatin and angiostatin with high reproducibility among subjects within cohorts. Mean levels of endostatin and angiostatin peaked between 12 and 24 weeks after injection of 2.4×10^5 TU or 8.0×10^5 TU at 57-81 ng/mL for endostatin and 15-27 ng/mL for angiostatin, and remained stable through the last measurement at week 48. Long-term follow-up

demonstrated expression was maintained at last measurement (2.5 years in eight subjects and >4 years in two subjects). Despite an apparent reduction in fluorescein angiographic leakage that broadly correlated with the expression levels in the majority of patients, only one subject showed convincing evidence of anti-permeability activity in these late-stage patients. There was no significant change in mean lesion size in subjects injected with 8.0×10^5 TU. These data demonstrate that EIAV vectors provide a safe platform with robust and sustained transgene expression for ocular gene therapy.

Carter-O'Connell, I., Jin, H., Morgan, R. K., Zaja, R., David, L. L., Ahel, I., et al. (2016). Identifying family-member-specific targets of mono-ARTDs by using a chemical genetics approach. *Cell Reports*, 14(3), 621-631.

ADP-ribosyltransferases (ARTD1-16) have emerged as major downstream effectors of NAD(+) signaling in the cell. Most ARTDs (ARTD7 and 8, 10-12, and 14-17) catalyze the transfer of a single unit of ADP-ribose from NAD(+) to target proteins, a process known as mono-ADP-ribosylation (MARylation). Progress in understanding the cellular functions of MARylation has been limited by the inability to identify the direct targets for individual mono-ARTDs. Here, we engineered mono-ARTDs to use an NAD(+) analog that is orthogonal to wild-type ARTDs. We profiled the MARylomes of ARTD10 and ARTD11 in vitro, identifying isoform-specific targets and revealing a potential role for ARTD11 in nuclear pore complex biology. We found that ARTD11 targeting is dependent on both its regulatory and catalytic domains, which has important implications for how ARTDs recognize their targets. We anticipate that our chemical genetic strategy will be generalizable to all mono-ARTD family members based on the similarity of the mono-ARTD catalytic domains.

Chappidi, M. R., Chalfin, H. J., Johnson, D. J., Kates, M., Sopko, N. A., Johnson, M. H., et al. (2016).

Longer average blood storage duration is associated with increased risk of infection and overall morbidity following radical cystectomy. *Urologic Oncology*,

BACKGROUND: Patients with bladder cancer undergoing radical cystectomy (RC) experience high rates of perioperative blood transfusions (PBTs) and morbidity. The aim of this study was to evaluate the effect of blood storage duration on the risk of adverse perioperative outcomes in this

high-risk patient population. MATERIALS AND METHODS: In a retrospective review of RC patients from 2010 to 2014 who received PBTs, the average storage duration for all units transfused was used to classify patients as receiving older blood using 3 different definitions (≥ 21 days, ≥ 28 days, and ≥ 35 days). Multivariable Poisson regression models were used to determine the adjusted relative risk of perioperative infections and overall morbidity in those given older blood compared to fresher blood. RESULTS: Of the 451 patients undergoing RC, 205 (45%) received nonirradiated PBTs. In multivariable modeling, increasing average blood storage duration, as a continuous variable, was associated with an increased risk of infections (risk ratio [RR] = 1.08 per day, 95% CI: 1.01-1.17) and overall morbidity (RR = 1.08 per day, 95% CI: 1.01-1.15). Furthermore, ≥ 28 -day blood storage (vs. ≥ 35 -day blood storage (vs. ≥ 28 days may expose RC patients to increased perioperative infections and overall morbidity compared with storage < 28 days. Prospective cohort studies are warranted in cystectomy and other high-risk surgical oncology patients to better determine the effect of blood storage duration.

Chen, Y., Friedman, M., Liu, G., Deodhar, A., & Chu, C. Q. (2016). Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders? *Cytokine*, Inhibition of tumor necrosis factor (TNF) activity has profoundly changed the management of several immune-mediated inflammatory diseases with great benefit for patients. The application of TNF inhibitors (TNFi), however, also brings a new concern, malignancy. We performed a systemic review to collect the studies reporting cancer incidences and risks in TNFi users regardless of indications. TNFi were most frequently used in treating patients with rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD). In RA patients without prior cancer history, the incidences of malignancies ranged from the lowest rate 0 per 1000 person-years in etanercept users regarding lymphoma to the highest rate 35.62 per 1000 person-years in adalimumab users on non-melanoma skin cancer (NMSC), while in those patients with prior cancer history, the recurrent incidences of malignancies ranged from the lowest rate 5.05 per 1000 person-years regarding melanoma to the highest rate 63.20 per 1000 person-years on basal cell carcinoma (BCC) in TNFi users. In IBD patients, incidences ranged from 0 per 1000 person-years in TNFi users on lymphoma to 34.0 per 1000 person-years in infliximab users on overall cancer. However, these incidence rates of overall cancer, lymphoma and melanoma were

not higher in comparison with those patients who were not treated with TNFi. Compared to general population, incidences of lymphoma were elevated in RA patients and rates of NMSC were higher in patients with psoriasis, RA and IBD. In conclusion, cancer incidences vary across different studies, indications, cancer types and studies with different individual TNFi. Treatment with TNFi is not associated with increased malignant risks of overall cancer, lymphoma or melanoma. Results of NMSC risk were inconsistent among studies. A latest prospective registry study demonstrated a small increased risk of squamous cell cancer in RA patients treated with TNFi (one additional case for every 1600years of treatment experience). Further prospective studies are needed to verify whether TNFi users have higher NMSC risk than non-TNFi users.

Cheng, A. (2016). Running behind to move forward. *Family Medicine*, 48(9), 736-737.

Chesler, E. J., Gatti, D. M., Morgan, A. P., Strobel, M., Trepanier, L., Oberbeck, D., et al. (2016).

Diversity outbred mice at 21: Maintaining allelic variation in the face of selection. *G3 (Bethesda, Md.)*,

Multi-parent populations (MPPs) capture and maintain the genetic diversity from multiple inbred founder strains to provide a resource for high-resolution genetic mapping through the accumulation of recombination events over many generations. Breeding designs that maintain a large effective population size with randomized assignment of breeders at each generation can minimize the impact of selection, inbreeding, and genetic drift on allele frequencies. Small deviations from expected allele frequencies will have little effect on the power and precision of genetic analysis, but a major distortion could result in reduced power and loss of important functional alleles. We detected strong transmission ratio distortion in the Diversity Outbred (DO) mouse population on chromosome 2 caused by meiotic drive favoring transmission of the WSB/EiJ allele at the R2d2 locus. The distorted region harbors thousands of polymorphisms derived from the seven non-WSB founder strains and many of these would be lost if the sweep was allowed to continue. To ensure the utility of the DO population to study genetic variation on chromosome 2, we performed an artificial selection against WSB/EiJ alleles at the R2d2 locus. Here we report that we have purged the WSB/EiJ allele from the drive locus while preserving WSB/EiJ alleles in the flanking regions. We observed minimal disruption to allele frequencies

across the rest of the autosomal genome. However, there was a shift in haplotype frequencies of the mitochondrial genome and an increase in the rate of an unusual sex chromosome aneuploidy. The DO population has been restored to genome-wide utility for genetic analysis, but our experience underscores that vigilant monitoring of similar genetic resource populations is needed to ensure their long-term utility.

Chien, J., Novosad, D., & Mobbs, K. E. (2016). The oregon health and science university-oregon state hospital collaboration: Reflections on an evolving public-academic partnership. *Psychiatric Services, 67*(3), 262-264.

Chou, R., Dana, T., Blazina, I., Daeges, M., Bougatsos, C., & Jeanne, T. L. (2016). Screening for dyslipidemia in younger adults: A systematic review for the U.S. preventive services task force. *Annals of Internal Medicine, 165*(8), 560-564.

Background: Dyslipidemia may occur in younger adults (defined as persons aged 21 to 39 years) and is an important risk factor for cardiovascular disease. Screening might identify younger adults with asymptomatic dyslipidemia who may benefit from lipid-lowering therapies. Purpose: To update the 2008 U.S. Preventive Services Task Force review on dyslipidemia screening in younger adults. Data Sources: The Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and MEDLINE through May 2016, and reference lists. Study Selection: Randomized, controlled trials; cohort studies; and case-control studies on screening for or treatment of asymptomatic dyslipidemia in adults aged 21 to 39 years. Data Extraction: The plan was for 1 investigator to abstract data and a second to check their accuracy, and for 2 investigators to independently assess study quality; however, no studies met the inclusion criteria. Data Synthesis: No study evaluated the effects of lipid screening versus no screening, treatment versus no treatment, or delayed versus earlier treatment on clinical outcomes in younger adults. In addition, no study evaluated the diagnostic yield of alternative screening strategies (such as targeted screening of persons with a family history of hyperlipidemia vs. general screening) in younger adults. Limitation: No direct relevant evidence. Conclusion: Direct evidence on the benefits and harms of screening for or treatment of dyslipidemia in younger adults remains unavailable. Estimating the potential effects of screening for dyslipidemia in this

population requires extrapolation from studies performed in older adults. Primary Funding Source: Agency for Healthcare Research and Quality.

Chou, R., Selph, S., Buckley, D. I., Fu, R., Griffin, J. C., Grusing, S., et al. (2016). Comparative effectiveness of fluorescent versus white light cystoscopy for initial diagnosis or surveillance of bladder cancer on clinical outcomes: Systematic review and meta-analysis. *The Journal of Urology*,

PURPOSE: To systematically review the comparative effectiveness of fluorescent versus white light cystoscopy on bladder cancer clinical outcomes. METHODS: Systematic literature searches of Ovid MEDLINE (January 1990 through September 2015), Cochrane databases, and reference lists were performed. Fourteen randomized trials of fluorescent cystoscopy using 5-aminolevulinic acid (5-ALA) or hexaminolevulinic acid (HAL) versus white light cystoscopy for diagnosis of initial or recurrent bladder cancer that reported bladder cancer recurrence, progression, mortality, and harms were selected for review. RESULTS: Fluorescent cystoscopy was associated with decreased risk of bladder cancer recurrence versus white light cystoscopy at short-term (≤ 1 year, 12 trials, RR 0.81, 95% CI 0.70 to 0.93, $I^2=49\%$). However, findings were inconsistent and potentially susceptible to performance and publication bias (strength of evidence [SOE]: low). There were no differences between cystoscopic methods in risk of mortality (3 trials, RR 1.28, 95% CI 0.55 to 2.95, $I^2=41\%$) (SOE: low) or progression (9 trials, RR 0.74, 95% CI 0.52 to 1.03, $I^2=0\%$) (SOE: moderate). Estimates for short-term recurrence (6 trials, RR 0.62, 95% CI 0.38 to 1.00), long-term recurrence (7 trials, RR 0.75, 95% CI 0.62 to 0.92) and progression (4 trials, RR 0.51, 95% CI 0.28 to 0.96) were statistically significant in the subgroup of trials that used HAL, but there were no statistically significant interactions based on the photosensitizer used. Fluorescent cystoscopy was not associated with decreased risk of long-term recurrence in three trials that utilized methods to reduce performance bias with initial cystoscopy (RR 0.96, 95% CI 0.79 to 1.18; $I^2=36\%$). Data on harms were sparse. CONCLUSIONS: Fluorescent cystoscopy was associated with reduced risk of bladder cancer recurrence versus white light cystoscopy; however, additional trials that adequately guard against performance bias are needed to confirm these findings. Fluorescent cystoscopy with HAL may be associated with

decreased risk of progression, but more studies with long-term followup are needed to better understand effects of the photosensitizer used on progression.

Clayburgh, D. R., & Brickman, D. (2016). Triological society best practice: Is esophagoscopy necessary during panendoscopy? *The Laryngoscope*,

Cohen, D. J., Keller, S. R., Hayes, G. R., Dorr, D. A., Ash, J. S., & Sittig, D. F. (2016). Integrating patient-generated health data into clinical care settings or clinical decision-making: Lessons learned from project HealthDesign. *JMIR Human Factors*, 3(2), e26.

BACKGROUND: Patient-generated health data (PGHD) are health-related data created or recorded by patients to inform their self-care and understanding about their own health. PGHD is different from other patient-reported outcome data because the collection of data is patient-driven, not practice- or research-driven. Technical applications for assisting patients to collect PGHD supports self-management activities such as healthy eating and exercise and can be important for preventing and managing disease. Technological innovations (eg, activity trackers) are making it more common for people to collect PGHD, but little is known about how PGHD might be used in outpatient clinics. **OBJECTIVE:** The objective of our study was to examine the experiences of health care professionals who use PGHD in outpatient clinics. **METHODS:** We conducted an evaluation of Project HealthDesign Round 2 to synthesize findings from 5 studies funded to test tools designed to help patients collect PGHD and share these data with members of their health care team. We conducted semistructured interviews with 13 Project HealthDesign study team members and 12 health care professionals that participated in these studies. We used an immersion-crystallization approach to analyze data. Our findings provide important information related to health care professionals' attitudes toward and experiences with using PGHD in a clinical setting. **RESULTS:** Health care professionals identified 3 main benefits of PGHD accessibility in clinical settings: (1) deeper insight into a patient's condition; (2) more accurate patient information, particularly when of clinical relevance; and (3) insight into a patient's health between clinic visits, enabling revision of care plans for improved health goal achievement, while avoiding unnecessary clinic visits. Study participants also identified 3 areas of consideration when implementing collection and use of PGHD data in clinics: (1) developing practice workflows and

protocols related to PGHD collection and use; (2) data storage, accessibility at the point of care, and privacy concerns; and (3) ease of using PGHD data. CONCLUSIONS: PGHD provides value to both patients and health care professionals. However, more research is needed to understand the benefit of using PGHD in clinical care and to identify the strategies and clinic workflow needs for optimizing these tools.

Coleman, K., Robertson, N. D., Dissen, G. A., Neuringer, M. D., Martin, L. D., Cuzon Carlson, V. C., et al. (2016). Isoflurane anesthesia has long-term consequences on motor and behavioral development in infant rhesus macaques. *Anesthesiology*,

BACKGROUND: Experimental evidence correlates anesthetic exposure during early development with neuronal and glial injury and death, as well as behavioral and cognitive impairments, in young animals. Several, although not all, retrospective human studies of neurocognitive and behavioral disorders after childhood exposure to anesthesia suggest a similar association. Few studies have specifically investigated the effects of infant anesthesia exposure on subsequent neurobehavioral development. Using a highly translational nonhuman primate model, the authors investigated the potential dose-dependent effects of anesthesia across the first year of development. METHODS: The authors examined the effects of single or multiple early postnatal isoflurane exposures on subsequent behavioral development in 24 socially reared rhesus macaques. Infants were exposed to 5 h of isoflurane anesthesia once, three times (ISO-3), or not at all (control). The authors assessed reflex development and anxiety using standardized tests. At approximately 1 yr, infants (n = 23) were weaned and housed indoors with 5 to 6 other subjects. The authors recorded their response to this move and reassessed anxiety. RESULTS: Compared to controls, animals exposed to repeated isoflurane (ISO-3) presented with motor reflex deficits at 1 month (median [range]: ISO-3 = 2 [1 to 5] vs. control = 5 [3 to 7]; $P < 0.005$) and responded to their new social environment with increased anxiety (median [range]: ISO-3 = 0.4 bouts/min [0.2 to 0.6]; control = 0.25 bouts/min [0.1 to 0.3]; $P = 0.05$) and affiliative/appeasement behavior (median [range]: ISO-3 = 0.1 [0 to 0.2]; control = 0 bouts/min [0 to 0.1]; $P < 0.01$) at 12 months. There were no statistically significant behavioral alterations after single isoflurane exposure. CONCLUSIONS: Neonatal exposure to isoflurane, particularly

when repeated, has long-term behavioral consequences affecting both motor and socioemotional aspects of behavior.

Corless, C. L. (2016). Next-generation sequencing in cancer diagnostics. *The Journal of Molecular Diagnostics : JMD*, 18(6), 813-816.

This commentary highlights the article by Misyura et al that underscores the use of next-generation sequencing platforms for detection and verification of somatic variants.

Coultas, D. B., Jackson, B. E., Russo, R., Peoples, J., Sloan, J., Singh, K. P., et al. (2016). A lifestyle physical activity intervention for patients with chronic obstructive pulmonary disease a randomized controlled trial. *Annals of the American Thoracic Society*, 13(5), 617-626.

Crabbe, J. C. (2016). Reproducibility of experiments with laboratory animals: What should we do now? *Alcoholism, Clinical and Experimental Research*, 40(11), 2305-2308.

Crawford, J. D., Haller, S. J., Landry, G. J., Abraham, C., Moneta, G. L., Rugonyi, S., et al. (2016).

Intraluminal thrombus is associated with aortic wall weakening in small ruptured abdominal aortic aneurysms. *Journal of Vascular Surgery*, 64(2), 543-544.

Czerniecki, J. M., Turner, A. P., Williams, R. M., Thompson, M. L., Landry, G., Hakimi, K., et al.

(2016). The development and validation of the AMPREDICT model for predicting mobility outcome after dysvascular lower extremity amputation. *Journal of Vascular Surgery*,

OBJECTIVE: The objective of this study was the development of AMPREDICT-Mobility, a tool to predict the probability of independence in either basic or advanced (iBASIC or iADVANCED) mobility 1 year after dysvascular major lower extremity amputation. METHODS: Two prospective cohort studies during consecutive 4-year periods (2005-2009 and 2010-2014) were conducted at seven medical centers. Multiple demographic and biopsychosocial predictors were collected in the periamputation period among individuals undergoing their first major amputation because of complications of peripheral arterial disease or diabetes. The primary outcomes were iBASIC and iADVANCED mobility, as measured by the Locomotor Capabilities Index. Combined data from both studies were used for model development and internal validation. Backwards stepwise

logistic regression was used to develop the final prediction models. The discrimination and calibration of each model were assessed. Internal validity of each model was assessed with bootstrap sampling. RESULTS: Twelve-month follow-up was reached by 157 of 200 (79%) participants. Among these, 54 (34%) did not achieve iBASIC mobility, 103 (66%) achieved at least iBASIC mobility, and 51 (32%) also achieved iADVANCED mobility. Predictive factors associated with reduced odds of achieving iBASIC mobility were increasing age, chronic obstructive pulmonary disease, dialysis, diabetes, prior history of treatment for depression or anxiety, and very poor to fair self-rated health. Those who were white, were married, and had at least a high-school degree had a higher probability of achieving iBASIC mobility. The odds of achieving iBASIC mobility increased with increasing body mass index up to 30 kg/m² and decreased with increasing body mass index thereafter. The prediction model of iADVANCED mobility included the same predictors with the exception of diabetes, chronic obstructive pulmonary disease, and education level. Both models showed strong discrimination with C statistics of 0.85 and 0.82, respectively. The mean difference in predicted probabilities for those who did and did not achieve iBASIC and iADVANCED mobility was 33% and 29%, respectively. Tests for calibration and observed vs predicted plots suggested good fit for both models; however, the precision of the estimates of the predicted probabilities was modest. Internal validation through bootstrapping demonstrated some overoptimism of the original model development, with the optimism-adjusted C statistic for iBASIC and iADVANCED mobility being 0.74 and 0.71, respectively, and the discrimination slope 19% and 16%, respectively. CONCLUSIONS: AMPREDICT-Mobility is a user-friendly prediction tool that can inform the patient undergoing a dysvascular amputation and the patient's provider about the probability of independence in either basic or advanced mobility at each major lower extremity amputation level.

Davarpanah, A. H., Kambadakone, A., Holalkere, N. S., Guimaraes, A. R., Hahn, P. F., & Lee, S. I. (2016). Diffusion MRI of uterine and ovarian masses: Identifying the benign lesions. *Abdominal Radiology*, , 1-10.

De La Chesnaye, E., Mendez, J. P., Lopez-Romero, R., De Los Angeles Romero-Tlalolini, M., Vergara, M. D., Salcedo, M., et al. (2015). FBXW12, a novel F box protein-encoding gene, is deleted or methylated in some cases of epithelial ovarian cancer. *International Journal of Clinical and Experimental Pathology*, 8(9), 10192-10203.

Epithelial ovarian cancer is one of the most lethal of gynecological malignancies. Due to its lack of early symptoms, detection usually occurs when the tumor is no longer confined to the ovary. We previously identified Fbxw15, a gene encoding an F-box protein in the mouse ovary, and showed that its expression is developmentally regulated. Here we report the molecular analysis of its human homologue, FBXW12 in epithelial ovarian tumors. To search for FBXW12 gene mutations, we PCR-amplified and sequenced the coding region of FBXW12, the gene's 5'-untranslated region and the proximal promoter in each of 30 EOC tumors. Promoter methylation was determined by DNA bisulfite conversion, followed by methylation specific PCR. FBXW12 intracellular localization was identified by means of immunohistochemistry. A complete deletion of the gene's coding region, the 5'-UTR and the proximal promoter, was observed in 3 EOC samples. Eight of the remaining 27, had a deletion of the 5'-UTR, and the proximal promoter. FBXW12 mRNA was detected in 2 of the 19 samples without deletions. The methylation specific PCR results demonstrated CpGs methylation in the FBXW12 proximal promoter. Immunohistochemistry assay revealed that within the normal ovary, FBXW12 has an oocyte specific expression, whereas in EOC samples it is present in the ovarian surface epithelium. Our results indicate that the FBXW12 gene is deleted in approximately ten percent of the EOC cases studied; such deletions comprised either the FBXW12 promoter or the mRNA-encoding region. Moreover, FBXW12 could be epigenetically silenced by CpGs methylation in some of these EOC cases.

Deem, S., Yanez, D., Sissons-Ross, L., Broeckel, J. A. E., Daniel, S., & Treggiari, M. (2016).

Randomized pilot trial of two modified endotracheal tubes to prevent ventilator-associated pneumonia. *Annals of the American Thoracic Society*, 13(1), 72-80.

Deodhar, A., Bitman, B., Yang, Y., & Collier, D. H. (2016). The effect of etanercept on traditional metabolic risk factors for cardiovascular disease in patients with rheumatoid arthritis. *Clinical Rheumatology*,

Patients with rheumatoid arthritis (RA) are at an increased risk of cardiovascular disease (CVD). Treatment with tumor necrosis factor inhibitors improves both joint symptoms associated with RA and also CVD risk. This exploratory analysis of a phase 4 study evaluated changes in metabolic risk factors in patients with RA treated with etanercept. Metabolic analytes were measured at baseline, week 12, and week 24 in patients enrolled in a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etanercept in moderately active RA. Patients received either placebo or etanercept 50 mg every week (QW) for 12 weeks, after which all patients received etanercept 50 mg QW through week 24. Levels of metabolic analytes were assessed in all patients, including patients with diabetes and hyperlipidemia, and described descriptively. A total of 210 patients were randomized, 104 to placebo and 106 to etanercept. There were no significant changes in metabolic risk factors from baseline to week 12 or 24 in all patients. Levels of metabolic analytes were similar in patients with diabetes and hyperlipidemia, with some exceptions; fasting glucose and fasting insulin decreased through week 12, and hemoglobin A1C decreased slightly through week 24 in patients with diabetes. Treatment with etanercept did not adversely affect levels of metabolic risk factors for CVD in patients with RA.

Devine, E. B., Alfonso-Cristancho, R., Yanez, N. D., Edwards, T. C., Patrick, D. L., Armstrong, C. A., et al. (2016). Effectiveness of a medical vs revascularization intervention for intermittent leg claudication based on patient-reported outcomes. *JAMA Surgery*, *151*(10), e162024.

Importance: Intermittent claudication (IC) is the most common presentation of infrainguinal peripheral artery disease. Both medical and revascularization interventions for IC aim to increase walking comfort and distance, but there is inconclusive evidence of the comparative benefit of revascularization given the possible risk of limb loss. Objective: To compare the effectiveness of a medical (walking program, smoking cessation counseling, and medications) vs revascularization (endovascular or surgical) intervention for IC in the community, focusing on outcomes of greatest importance to patients. Design, Setting, and Participants: Longitudinal (12-month follow-up) prospective observational cohort study conducted between July 3, 2011, and November 5, 2014, at 15 clinics associated with 11 hospitals in Washington State. Participants were 21 years or older with newly diagnosed or established IC. Interventions: Medical or revascularization interventions. Main Outcomes and Measures: Primary end points were 12-month change scores on the distance,

speed, and stair-climb domains of the Walking Impairment Questionnaire (score range, 0-100). Secondary outcomes were change scores on the Walking Impairment Questionnaire pain domain (score range, 0-100), Vascular Quality of Life Questionnaire (VascuQol) (score range, 1-7), European Quality of Life-5 Dimension Questionnaire (EQ-5D) (score range, 0-1), and Claudication Symptom Instrument (CSI) (score range, 0-4). Results: A total of 323 adults were enrolled, with 282 (87.3%) in the medical cohort. At baseline, the mean duration of disease was longer for participants in the medical cohort, while those in the revascularization cohort reported more severe disease. Other characteristics were well balanced. At 12 months, change scores in the medical cohort reached significance for the following 3 outcomes: speed (5.9; 95% CI, 0.5-11.3; $P = .03$), VascuQol (0.28; 95% CI, 0.08-0.49; $P = .008$), and EQ-5D (0.038; 95% CI, 0.011-0.066; $P = .006$). In the revascularization cohort, there were significant improvements in the following 7 outcomes: distance (19.5; 95% CI, 7.9-31.0; $P = .001$), speed (12.1; 95% CI, 1.4-22.8; $P = .03$), stair climb (11.4; 95% CI, 1.3-21.5; $P = .03$), pain (20.7; 95% CI, 11.0-30.4; $P < .001$), VascuQol (1.10; 95% CI, 0.80-1.41; $P < .001$), EQ-5D (0.113; 95% CI, 0.067-0.159; $P < .001$), and CSI (-0.63; 95% CI, -0.96 to -0.31; $P < .001$). Relative improvements (percentage changes) at 12 months in the revascularization cohort over the medical cohort were observed as follows: distance (39.1%), speed (15.6%), stair climb (9.7%), pain (116.9%), VascuQol (41%), EQ-5D (18%), and CSI (13.5%). Conclusions and Relevance: Among patients with IC, those in the revascularization cohort had significantly improved function (Walking Impairment Questionnaire), better health-related quality of life (VascuQol and EQ-5D), and fewer symptoms (CSI) at 12 months compared with those in the medical cohort, providing important information to inform treatment strategies in the community.

Dickinson, H., Moss, T. J., Gatford, K. L., Moritz, K. M., Akison, L., Fullston, T., et al. (2016). A review of fundamental principles for animal models of DOHaD research: An Australian perspective. *Journal of Developmental Origins of Health and Disease*, 7(5), 449-472.

Epidemiology formed the basis of 'the Barker hypothesis', the concept of 'developmental programming' and today's discipline of the Developmental Origins of Health and Disease (DOHaD). Animal experimentation provided proof of the underlying concepts, and continues to generate knowledge of underlying mechanisms. Interventions in humans, based on DOHaD

principles, will be informed by experiments in animals. As knowledge in this discipline has accumulated, from studies of humans and other animals, the complexity of interactions between genome, environment and epigenetics, has been revealed. The vast nature of programming stimuli and breadth of effects is becoming known. As a result of our accumulating knowledge we now appreciate the impact of many variables that contribute to programmed outcomes. To guide further animal research in this field, the Australia and New Zealand DOHaD society (ANZ DOHaD) Animals Models of DOHaD Research Working Group convened at the 2nd Annual ANZ DOHaD Congress in Melbourne, Australia in April 2015. This review summarizes the contributions of animal research to the understanding of DOHaD, and makes recommendations for the design and conduct of animal experiments to maximize relevance, reproducibility and translation of knowledge into improving health and well-being.

Dixon-Ibarra, A., Driver, S., VanVolkenburg, H., & Humphries, K. (2016). Formative evaluation on a physical activity health promotion program for the group home setting. *Evaluation and Program Planning, 60*, 81-90.

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

D'Souza, S. L., Holub, J. L., Pavic, B. T., & Rodriguez, S. A. (2016). Multicenter evaluation of the utilization of endoscopic ultrasound. *Digestive Endoscopy : Official Journal of the Japan Gastroenterological Endoscopy Society*, 28(7), 738-743.

BACKGROUND AND AIM: There are currently no data regarding the number and type of endoscopic ultrasound (EUS) procedures being carried out in the USA. The aims of the present study are to: (i) estimate the annual number of EUS procedures being carried out in a nationwide database; (ii) describe the indications and types of EUS carried out; and (iii) examine short-term trends in volume. METHODS: Retrospective analysis from the Clinical Outcomes Research Initiative (CORI) of EUS procedures carried out on patients >18 years of age from 1 January 2010 through 31 December 2013. RESULTS: EUS cases (n = 7614) were carried out by 68 endoscopists at 18 sites over the study period, representing 1.7% of the total number of endoscopic procedures. The most common indications were evaluation of a pancreatic mass (14.7%), diagnostic sampling with fine-needle aspiration (14.1%), and evaluation of a pancreatic cyst (14.0%). The number of EUS examinations and cases undergoing same-day endoscopic retrograde cholangiopancreatography (ERCP) increased over the study period (P < 0.0001). Use of general anesthesia or deep sedation increased markedly from 37.8% to 82.8% of procedures (P < 0.0001). CONCLUSIONS: This is the largest survey of EUS practice in the USA. Evaluation of the pancreas accounts for approximately 40% of the indications for EUS. Use of EUS increased over the study period, and the proportion carried out with deep sedation or general anesthesia also increased. These data may have implications regarding the number of endosonographers who should be trained, as well as cost issues pertaining to increasing use of anesthesia providers and same-day ERCP.

Dudy, S., & Bedrick, S. (2015). Ohsu @ MediaEval 2015: Adapting textual techniques to multimedia search. *CEUR Workshop Proceedings*, , 1436.

Durben, N., & Oleson, D. (2016). Commentary on "sporting activities and quality of life in children with hemophilia: An observational study". *Pediatric Physical Therapy*, 28(4), 459.

Dwan, K., Phillipi, C. A., Steiner, R. D., & Basel, D. (2016). Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database of Systematic Reviews*, 2016(10)

Edwards, M., & Jewell, M. L. (2016). Alloplastic soft tissue support: An overview and clinical experience. *Aesthetic Surgery Journal*, 36(suppl 2), S1-S6.

Enriori, P. J., Chen, W., Garcia-Rudaz, M. C., Grayson, B. E., Evans, A. E., Comstock, S. M., et al. (2016). Alpha-melanocyte stimulating hormone promotes muscle glucose uptake via melanocortin 5 receptors. *Molecular Metabolism*, 5(10), 807-822.

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

Ensrud, K. E., Harrison, S. L., Cauley, J. A., Langsetmo, L., Schousboe, J. T., Kado, D. M., et al.

(2016). Impact of competing risk of mortality on association of weight loss with risk of central body fractures in older men: A prospective cohort study. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*,

To determine the association of weight loss with risk of clinical fractures at the hip, spine and pelvis (central body fractures [CBF]) in older men with and without accounting for the competing risk of mortality, we used data from 4,523 men (mean age 77.5 years). Weight change between baseline and follow-up (mean 4.5 years between examinations) was categorized as moderate loss (loss $\geq 10\%$), mild loss (loss 5% to $\leq 5\%$). Participants were contacted every 4 months after the follow-up examination to ascertain vital status (deaths verified by death certificates) and ask about fractures (confirmed by radiographic reports). Absolute probability of CBF by weight change category was estimated using traditional Kaplan-Meier method and cumulative incidence function accounting for competing mortality risk. Risk of CBF by weight change category was determined using conventional Cox proportional hazards regression and subdistribution hazards models with death as a competing risk. During an average of 8 years, 337 men (7.5%) experienced CBF and 1,569 (34.7%) died before experiencing this outcome. Among men with moderate weight loss, CBF probability was 6.8% at 5 years and 16.9% at 10 years using Kaplan-Meier vs. 5.7% at 5 years and 10.2% at 10 years using a competing risk approach. Men with moderate weight loss compared with those with stable weight had a 1.6-fold higher adjusted risk of CBF (HR 1.59, 95% CI 1.06-2.38) using Cox models that was substantially attenuated in models accounting for competing mortality risk and no longer significant (subdistribution HR 1.16, 95% CI 0.77-1.75). Results were similar in analyses substituting hip fracture for CBF. Older men with weight loss who survive are at increased risk of CBF, including hip fracture. However, ignoring the competing mortality risk among men with weight loss substantially overestimates their longterm fracture probability and relative fracture risk. This article is protected by copyright. All rights reserved.

Ernst, L. L., Harden, C. L., Pennell, P. B., Llewellyn, N., Lau, C., Barnard, S., et al. (2016). Medication adherence in women with epilepsy who are planning pregnancy. *Epilepsia*,

OBJECTIVE: This study examines medication adherence among women with epilepsy via use of

an electronic diary, as part of a prospective multicenter observational study designed to evaluate fertility in women with epilepsy (WWE) versus age-matched controls. METHODS: WWE and healthy age-matched controls, seeking pregnancy, were given an iPod Touch using a customized mobile application (the WEPOD App) for daily data tracking. Eighty-six WWE tracked seizures and antiepileptic drugs (AEDs). Tracking of nonepilepsy medications was optional. Diary data were counted from enrollment date until date of delivery, or up to 12 months if pregnancy was not achieved. Each day that subjects reported missing one or more AED was counted as nonadherence. Because adherence can only be determined in women who track consistently, we elected to include adherence data only for women who tracked >80% of days in the study. RESULTS: Approximately 75% of WWE tracked >80% of days and were included in medication adherence data analysis. In this group, medication adherence rate was 97.71%; 44% of women admitted to missing an AED on at least 1 day. Among the subgroup of WWE who recorded nonepilepsy medications, AED adherence rate was 98.56%, versus 93.91% for non-AEDs. SIGNIFICANCE: The 75% compliance rate with an electronic diary suggests that it may be useful to track medication adherence in future studies and in the clinical setting. In those who tracked, the observed medication adherence rate was considerably higher than the 75% adherence rate seen in previous epilepsy studies. This might be explained in part by selection bias, but may also result from properties of the diary itself (daily reminders, real time feedback given to the provider). Women reported a higher rate of adherence to AEDs than to other prescribed medications and supplements, suggesting that perceived importance of medications likely influences medication adherence, and warrants future study.

Fender, E. A., Killu, A. M., Cannon, B. C., Friedman, P. A., Mcleod, C. J., Hodge, D. O., et al. (2016). Lead extraction outcomes in patients with congenital heart disease. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology*, AIMS: Patients with congenital heart disease (CHD) are at increased risk for intracardiac device malfunction and infection that may necessitate extraction; however, the risk of extraction is poorly understood. This study addresses the safety of extraction in patients with structural heart disease and previous cardiac surgery. METHODS: This retrospective study included 40 CHD and

80 matched control patients, who underwent transvenous lead extractions between 2001 and 2014. Only leads >12 months were included. RESULTS: There were 77 leads in CHD patients and 146 in controls. The mean age was 38 +/- 16 years in CHD patients. Ninety per cent of CHD patients had >=1 cardiac surgeries when compared with 21% of controls (P < 0.001). The number of abandoned leads was significantly different (17 vs. 3, P < 0.001). Lead age was similar with an average duration of 83 +/- 87 months in CHD patients and 62 +/- 65 months in controls (P = 0.24). There was no significant difference in extraction techniques. Manual traction was successful in 40% of CHD patients and 47% of controls, and advanced techniques were used in 60 and 53% of CHD patients and controls, respectively. Complete extraction was achieved in 94% of the patients in both groups. There was no significant difference in complications. CONCLUSION: Lead extraction can be safely performed in patients with CHD. Despite anatomic abnormalities and longer implantation times, the difficulty of lead extraction in patients with CHD is comparable with controls.

Fernando, R., Placzek, E., Reese, E. A., Placzek, A. T., Schwartz, S., Trierweiler, A., et al. (2016).

Elevated serum tetrac in graves' disease: Potential pathogenic role in thyroid-associated ophthalmopathy. *The Journal of Clinical Endocrinology and Metabolism*, , jc20162762.

CONTEXT: The sources and biological impact of 3,3',5,5' tetraiodothyroacetic acid (TA4) are uncertain. CD34+ fibrocytes express several proteins involved in the production of thyroid hormones. They infiltrate the orbit in Graves' disease (GD), an autoimmune process known as thyroid-associated ophthalmopathy. It appears that the thyrotropin receptor (TSHR) plays an important role in the pathogenesis of TAO. OBJECTIVE: To quantify levels of TA4 in healthy subjects and those with Graves' disease. To determine whether fibrocytes generate this TH analogue. To determine whether TA4 influences the actions of TSH and thyroid-stimulating immunoglobulins in orbital fibroblasts. DESIGN/SETTING/PARTICIPANTS: Patients with GD and healthy donors in an academic medical center clinical practice were recruited. MAIN OUTCOME MEASURES: liquid chromatography-tandem mass spectrometry, autoradiography, real-time PCR, hyaluronan immunoassay Results: Serum levels of TA4 are elevated in GD. TA4 levels are positively correlated with those of thyroxine and negatively correlated with serum levels of triiodothyronine. Several cell types in culture generate TA4 from ambient thyroxine, including

fibrocytes, HELA cells, human Muller stem cells, and retinal pigmented epithelial cells.

Propylthiouracil inhibited TA4 generation. TA4 enhances the induction by thyrotropin and thyroid-stimulating immunoglobulins of several participants in the pathogenesis of TAO, including IL-6, hyaluronan synthase-1, prostaglandin endoperoxide H synthase-2, and haluronan production.

CONCLUSION: TA4 may be ubiquitously generated in many tissues and enhances the biological impact of thyrotropin and thyroid-stimulating immunoglobulins in orbital connective tissue. These findings may identify a physiologically important determinant of extra-thyroidal TSH action.

Ferrante, J. M., Friedman, A., Shaw, E. K., Howard, J., Cohen, D. J., & Shahidi, L. (2016). Lessons learned designing and using an online discussion forum for care coordinators in primary care. *Qualitative Health Research*, 26(13), 1851-1861.

Fink, H. A., Litwack-Harrison, S., Taylor, B. C., Bauer, D. C., Orwoll, E. S., Lee, C. G., et al. (2016). Erratum to: Clinical utility of routine laboratory testing to identify possible secondary causes in older men with osteoporosis: The osteoporotic fractures in men (MrOS) study. *Osteoporosis International : A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*,

Flannery, A. M., Tamber, M. S., Mazzola, C., Klimo, P., Jr, Baird, L. C., Tyagi, R., et al. (2016). Congress of neurological surgeons systematic review and evidence-based guidelines for the management of patients with positional plagiocephaly: Executive summary. *Neurosurgery*, 79(5), 623-624.

BACKGROUND: Positional plagiocephaly is a common problem seen by pediatricians, pediatric neurologists, and pediatric neurosurgeons. OBJECTIVE: To create evidence-based guidelines for the treatment of pediatric positional plagiocephaly. METHODS: This guideline was prepared by the Plagiocephaly Guideline Task Force, a multidisciplinary team made up of physician volunteers (clinical experts), medical librarians, and clinical guidelines specialists. The task force conducted a series of systematic literature searches of PubMed and the Cochrane Library, according to standard protocols for each topic addressed in subsequent chapters of this guideline. RESULTS: The systematic literature searches returned 396 abstracts relative to the 4 main topics addressed in this guideline. The results were analyzed and are described in detail in each subsequent

chapter included in this guideline. CONCLUSION: Evidence-based guidelines for the management of infants with positional plagiocephaly will help practitioners manage this common disorder. The full guidelines documents can be located at <https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly>.

- Fleseriu, M., Bodach, M. E., Tumialan, L. M., Bonert, V., Oyesiku, N. M., Patil, C. G., et al. (2016). Guidelines: Congress of neurological surgeons systematic review and evidence-based guideline for pretreatment endocrine evaluation of patients with nonfunctioning pituitary adenomas. *Neurosurgery*, 79(4), E527-E529.
- Forsman, L., & Eliasson, A. -. (2016). Strengths and challenges faced by school-aged children with unilateral CP described by the five to fifteen parental questionnaire. *Developmental Neurorehabilitation*, 19(6), 380-388.
- Foss, M. H., Pou, S., Davidson, P. M., Dunaj, J. L., Winter, R. W., Pou, S., et al. (2016). Diphenylether-modified 1,2-diamines with improved drug properties for development against mycobacterium tuberculosis. *ACS Infectious Diseases*, 2(7), 500-508.
- Frank, J. A., Rojek, N., & Foreman, R. S. (2016). A case of hypertrichosis lanuginosa acquisita as a sign of malignancy. *European Journal of Dermatology : EJD*,
- Franklin, A. E., Gubrud-Howe, P., Sideras, S., & Lee, C. S. (2015). Effectiveness of simulation preparation on novice nurses' competence and self-efficacy in a multiple-patient simulation. *Nursing Education Perspectives*, 36(5), 324-325.
- Frazier, A. D., & Chien, J. (2016). California supreme court limits scope of expert testimony in postprison civil commitment trials. *Journal of the American Academy of Psychiatry and the Law*, 44(3), 390-392.
- Gaissert, H. A., Fernandez, F. G., Allen, M. S., Burfeind, W. R., Block, M. I., Donahue, J. M., et al. (2016). The society of thoracic surgeons general thoracic surgery database: 2016 update on research. *The Annals of Thoracic Surgery*, 102(5), 1444-1451.

The Society of Thoracic Surgeons General Thoracic Surgery Database has grown to more than 500,000 case records. Clinical research supported by the database is increasingly used to advance patient outcomes. This research review from the General Thoracic Surgery Database in 2014 and 2015 discusses 6 recent publications and an ongoing study on longitudinal outcomes in lung cancer surgery from The Society of Thoracic Surgeons Task Force for Linked Registries and Longitudinal Follow-up. A lack of database variables specific for certain uncommon procedures limits the ability to study these operations; inclusion of clinical descriptors for selected infrequent but clinically important thoracic disorders is suggested.

Garcia, H. H., O'Neal, S. E., & Gilman, R. H. (2016). The authors reply. *New England Journal of Medicine*, 375(12), 1196-1197.

Gardell, J. L., & Parker, D. C. (2016). CD40L is transferred to antigen-presenting B cells during delivery of T-cell help. *European Journal of Immunology*,
The delivery of T-cell help to B cells is antigen-specific, MHC-restricted, and CD40L (CD154) dependent. It has been thought that when a T cell recognizes an antigen-presenting B cell, CD40L expressed on the T-cell surface engages with CD40 on the surface of B cells as long as the cells remain conjugated. To study this, we added fluorescently labeled anti-CD40L antibody during overnight incubation of antigen-presenting B cells with antigen-specific T cells. We discovered that CD40L does not remain on the surface of the T cell, but it is transferred to and endocytosed by B cells receiving T-cell help. In the presence of anti-CD40L antibody, transferred CD40L is nearly absent on bystander B cells that are not presenting antigen, and the bystander cells do not become activated. Because transfer of CD40L to B cells correlates with B cell activation, we speculate that persistence of helper T-cell-derived CD40L on or in B cells could permit sustained CD40 signaling enabling survival and proliferation of antigen-presenting B cells following brief interactions with helper T cells in vivo in germinal centers. This article is protected by copyright. All rights reserved.

Gilchuk, I., Gilchuk, P., Sapparapu, G., Lampley, R., Singh, V., Kose, N., et al. (2016). Cross-neutralizing and protective human antibody specificities to poxvirus infections. *Cell*, 167(3), 684-694.e9.

Monkeypox (MPXV) and cowpox (CPXV) are emerging agents that cause severe human infections on an intermittent basis, and variola virus (VARV) has potential for use as an agent of bioterror. Vaccinia immune globulin (VIG) has been used therapeutically to treat severe orthopoxvirus infections but is in short supply. We generated a large panel of orthopoxvirus-specific human monoclonal antibodies (Abs) from immune subjects to investigate the molecular basis of broadly neutralizing antibody responses for diverse orthopoxviruses. Detailed analysis revealed the principal neutralizing antibody specificities that are cross-reactive for VACV, CPXV, MPXV, and VARV and that are determinants of protection in murine challenge models. Optimal protection following respiratory or systemic infection required a mixture of Abs that targeted several membrane proteins, including proteins on enveloped and mature virion forms of virus. This work reveals orthopoxvirus targets for human Abs that mediate cross-protective immunity and identifies new candidate Ab therapeutic mixtures to replace VIG.

Glynn, J. J., Jones, C. M., Anderson, D. E., Pavcnik, D., & Hinds, M. T. (2016). In vivo assessment of two endothelialization approaches on bioprosthetic valves for the treatment of chronic deep venous insufficiency. *Journal of Biomedical Materials Research. Part B, Applied Biomaterials*, 104(8), 1610-1621.

Chronic deep venous insufficiency is a debilitating disease with limited therapeutic interventions. A bioprosthetic venous valve could not only replace a diseased valve, but has the potential to fully integrate into the patient with a minimally invasive procedure. Previous work with valves constructed from small intestinal submucosa (SIS) showed improvements in patients' symptoms in clinical studies; however, substantial thickening of the implanted valve leaflets also occurred. As endothelial cells are key regulators of vascular homeostasis, their presence on the SIS valves may reduce the observed thickening. This work tested an off-the-shelf approach to capture circulating endothelial cells in vivo using biotinylated antikinase insert domain receptor antibodies in a suspended leaflet ovine model. The antibodies on SIS were oriented to promote cell capture and showed positive binding to endothelial cells in vitro; however, no differences were observed in leaflet thickness in vivo between antibody-modified and unmodified SIS. In an alternative approach, valves were pre-seeded with autologous endothelial cells and tested in vivo. Nearly all the implanted pre-seeded valves were patent and functioning; however, no statistical difference

was observed in valve thickness with cell pre-seeding. Additional cell capture schemes or surface modifications should be examined to find an optimal method for encouraging SIS valve endothelialization to improve long-term valve function in vivo. (c) 2015 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 104B: 1610-1621, 2016.

Goloviznina, N. A., Verghese, S. C., Yoon, Y. M., Taratula, O., Marks, D. L., & Kurre, P. (2016).

Mesenchymal stromal cell derived extracellular vesicles promote myeloid biased multipotent hematopoietic progenitor expansion via toll-like receptor engagement. *The Journal of Biological Chemistry,*

Mesenchymal stromal cells (MSC) present in the bone marrow (BM) microenvironment secrete cytokines and angiogenic factors that support the maintenance and regenerative expansion of hematopoietic stem and progenitor cells (HSPC). Here, we tested the hypothesis that extracellular vesicles (EVs) released by MSC contribute to the paracrine crosstalk that shapes hematopoietic function. We systematically characterized EV release by murine stromal cells and demonstrate that MSC-derived EVs prompt a loss of HSPC quiescence with concomitant expansion of murine myeloid progenitors. Our studies reveal that HSPC expansion by MSC EVs is mediated via the MyD88 adapter protein and is partially blocked by treatment with a TLR4 inhibitor. Imaging of fluorescence protein tagged MSC-EVs corroborated their cellular co-localization with TLR4 and endosomal Rab5 compartments in HSPC. The dissection of downstream responses to TLR4 activation reveals that the mechanism by which MSC EVs impact HSPC, involves canonical NF-kappaB signaling and downstream activation of Hif-1alpha and CCL2 target genes. Our aggregate data identify a previously unknown role for MSC-derived EVs in the regulation of hematopoiesis through innate immune mechanisms and illustrate the expansive cell-cell crosstalk in the bone marrow microenvironment.

Gomes, M. M., Wang, L., Jiang, H., Kahl, C. A., & Brigande, J. V. (2016). *A rapid, cost-effective method to prepare recombinant adeno-associated virus for efficient gene transfer to the developing mouse inner ear*

Greene, J. M., Dash, P., Roy, S., McMurtrey, C., Awad, W., Reed, J. S., et al. (2016). MR1-restricted mucosal-associated invariant T (MAIT) cells respond to mycobacterial vaccination and infection in

nonhuman primates. *Mucosal Immunology*,

Studies on mucosal-associated invariant T cells (MAITs) in nonhuman primates (NHP), a physiologically relevant model of human immunity, are handicapped due to a lack of macaque MAIT-specific reagents. Here we show that while MR1 ligand-contact residues are conserved between human and multiple NHP species, three T-cell receptor contact-residue mutations in NHP MR1 diminish binding of human MR1 tetramers to macaque MAITs. Construction of naturally loaded macaque MR1 tetramers facilitated identification and characterization of macaque MR1-binding ligands and MAITs, both of which mirrored their human counterparts. Using the macaque MR1 tetramer we show that NHP MAITs activated *in vivo* in response to both Bacillus Calmette-Guerin vaccination and Mycobacterium tuberculosis infection. These results demonstrate that NHP and human MR1 and MAITs function analogously, and establish a preclinical animal model to test MAIT-targeted vaccines and therapeutics for human infectious and autoimmune disease. *Mucosal Immunology* advance online publication 19 October 2016; doi:10.1038/mi.2016.91.

Gupta, P., Kathawala, R. J., Wei, L., Wang, F., Wang, X., Druker, B. J., et al. (2016). PBA2, a novel inhibitor of imatinib-resistant BCR-ABL T315I mutation in chronic myeloid leukemia. *Cancer Letters*, 383(2), 220-229.

Chronic Myeloid Leukemia (CML) is largely caused by the Philadelphia (Ph) chromosome carrying the Break point Cluster Region-Abelson (BCR-ABL) oncogene. Imatinib is a BCR-ABL-targeted therapy and considered the standard of care in CML management. Resistance to imatinib therapy often develops because of mutations in the BCR-ABL kinase domain. In this study, we evaluated PBA2, a novel BCR-ABL inhibitor, for its anti-cancer activity against BCR-ABL expressing BaF3 cells. PBA2 shows potent activity against wild-type and T315I mutated BaF3 cells as compared with imatinib. PBA2 inhibited the phosphorylation of BCR-ABL and its downstream signaling in BaF3/WT and BaF3/T315I cells. PBA2 inhibited the mRNA expression of BCR-ABL in BaF3/WT and BaF3/T315I cells. Mechanistically, PBA2 increased the cell population in sub G1 phase of the cell cycle, induced apoptosis and elevated ROS production in both BaF3/WT and BaF3/T315I cells. Taken together, our results indicate that PBA2 exhibits anti-proliferative effects and inhibits the imatinib-resistant T315I BCR-ABL mutation. PBA2 may be a novel drug candidate for overcoming the resistance to imatinib in CML patients.

Hamilton, D. K., Kong, C., Hiratzka, J., Contag, A. G., Ailon, T., Line, B., et al. (2016). Patient satisfaction after adult spinal deformity surgery does not strongly correlate with health-related quality of life scores, radiographic parameters or occurrence of complications. *Spine*,

STUDY DESIGN: This is a multicenter retrospective review of prospectively collected cases.

OBJECTIVE: Our objective was to evaluate the relationship between patient satisfaction, HRQoL scores, complications, and radiographic measures at 2 years post-operative follow-up. SUMMARY OF BACKGROUND DATA: For patients receiving operative management for adult spine deformity (ASD), the relationship between health-related quality of life (HRQoL) measures, radiographic parameters, post-operative complications, and self-reported satisfaction remains unclear.

METHODS: Data from 248 patients across 11 centers within the United States who underwent thoracolumbar fusion for ASD and had a minimum of 2 years follow-up was collected. Pre- and post-operative scores were obtained from the Scoliosis Research Society 22-item (SRS-22r), the Oswestry Disability Index (ODI), the 36-Item Short Form Health Survey (SF-36), and the Visual Analogue Scale (VAS). Sagittal vertical axis, coronal C7 plumbline, lumbar lordosis, pelvic tilt, T1 pelvic angle, and the difference between pelvic incidence and lumbar lordosis were assessed using post-operative radiographic films. Satisfaction (SAT) was assessed using the SRS-22r; patients were categorized as highly satisfied (HS) or less satisfied (LS). The correlation between SAT and HRQoL scores, radiographic parameters, and complications was determined. RESULTS: When compared to LS (n = 60) patients, HS (n = 188) patients demonstrated greater improvement in final ODI, SF-36 component scores, SRS-Total, and VAS back scores ($p < 0.05$). The correlations between SAT and the final follow-up and 2 year change from baseline values were moderate for MCS, PCS, and ODI or weak for HRQoL scores ($p < 0.0001$). The HS and LS groups were equal in pre- or final post-operative radiographic parameters. Occurrence of complications had no effect on satisfaction. CONCLUSION: Among operatively treated ASD patients, satisfaction was moderately correlated with some HRQoL measures, and not with radiographic changes or post-operative complications. Other factors, such as patient expectations and relationship with the surgeon, may be stronger drivers of patient satisfaction.

Harvath, T. A., Lindauer, A., & Sexson, K. (2016). Managing complex medication regimens. *The American Journal of Nursing*, 116(11), 43-46.

This article is the first in a series, Supporting Family Caregivers: No Longer Home Alone, published in collaboration with the AARP Foundation. Results of focus groups conducted as part of the AARP Foundation's No Longer Home Alone video project supported evidence that family caregivers aren't being given the information they need to manage the complex care regimens of their family members. This series of articles and accompanying videos aims to help nurses provide caregivers with the tools they need to manage their family member's medications. Each article explains the principles nurses should consider and reinforce with caregivers and is accompanied by a video for the caregiver to watch. The first video can be accessed at <http://links.lww.com/AJN/A74>.

Henkle, E., Aksamit, T., Barker, A., Daley, C. L., Griffith, D., Leitman, P., et al. (2016). Patient-centered research priorities for pulmonary nontuberculous mycobacteria (NTM) infection an NTM research consortium workshop report. *Annals of the American Thoracic Society*, 13(9), S379-S384.

Hicks, M., Hanes, D., & Wahbeh, H. (2016). Expectancy effect in three mind-body clinical trials. *Journal of Evidence-Based Complementary and Alternative Medicine*, 21(4), NP103-NP109.

Hofmann, M. E., & Andresen, M. C. (2016). Vanilloids selectively sensitize thermal glutamate release from TRPV1 expressing solitary tract afferents. *Neuropharmacology*, 101, 401-411.

Vanilloids, high temperature, and low pH activate the transient receptor potential vanilloid type 1 (TRPV1) receptor. In spinal dorsal root ganglia, co-activation of one of these gating sites on TRPV1 sensitized receptor gating by other modes. Here in rat brainstem slices, we examined glutamate synaptic transmission in nucleus of the solitary tract (NTS) neurons where most cranial primary afferents express TRPV1, but TRPV1 sensitization is unknown. Electrical shocks to the solitary tract (ST) evoked EPSCs (ST-EPSCs). Activation of TRPV1 with capsaicin (100 nM) increased spontaneous EPSCs (sEPSCs) but inhibited ST-EPSCs. High concentrations of the ultra-potent vanilloid resiniferatoxin (RTX, 1 nM) similarly increased sEPSC rates but blocked ST-EPSCs. Lowering the RTX concentration to 150 pM modestly increased the frequency of the sEPSCs without causing failures in the evoked ST-EPSCs. The sEPSC rate increased with raising bath temperature to 36 degrees C. Such thermal responses were larger in 150 pM RTX, while the

ST-EPSCs remained unaffected. Vanilloid sensitization of thermal responses persisted in TTX but was blocked by the TRPV1 antagonist capsazepine. Our results demonstrate that multimodal activation of TRPV1 facilitates sEPSC responses in more than the arithmetic sum of the two activators, i.e. co-activation sensitizes TRPV1 control of spontaneous glutamate release. Since action potential evoked glutamate release is unaltered, the work provides evidence for cooperativity in gating TRPV1 plus a remarkable separation of calcium mechanisms governing the independent vesicle pools responsible for spontaneous and evoked release at primary afferents in the NTS.

Hostetler, C. M., Hinde, K., Maninger, N., Mendoza, S. P., Mason, W. A., Rowland, D. J., et al. (2016). Effects of pair bonding on dopamine D1 receptors in monogamous male titi monkeys (*Callicebus cupreus*). *American Journal of Primatology*,
Pair bonding leads to increases in dopamine D1 receptor (D1R) binding in the nucleus accumbens of monogamous prairie voles. In the current study, we hypothesized that there is similar up-regulation of D1R in a monogamous primate, the titi monkey (*Callicebus cupreus*). Receptor binding of the D1R antagonist [¹¹C]-SCH23390 was measured in male titi monkeys using PET scans before and after pairing with a female. We found that within-subject analyses of pairing show significant increases in D1R binding in the lateral septum, but not the nucleus accumbens, caudate, putamen, or ventral pallidum. The lateral septum is involved in a number of processes that may contribute to social behavior, including motivation, affect, reward, and reinforcement. This region also plays a role in pair bonding and paternal behavior in voles. Our observations of changes in D1R in the lateral septum, but not the nucleus accumbens, suggest that there may be broadly similar dopaminergic mechanisms underlying pair bonding across mammalian species, but that the specific changes to neural circuitry differ. This study is the first research to demonstrate neuroplasticity of the dopamine system following pair bonding in a non-human primate; however, substantial variability in the response to pairing suggests the utility of further research on the topic.

Impey, S., Jopson, T., Pelz, C., Tafessu, A., Fareh, F., Zuloaga, D., et al. (2016). Short- and long-term effects of ⁵⁶Fe irradiation on cognition and hippocampal DNA methylation and gene expression.

BMC Genomics, 17(1), 825.

BACKGROUND: Astronauts are exposed to ^{56}Fe ions that may pose a significant health hazard during and following prolonged missions in deep space. We showed previously that object recognition requiring the hippocampus, a structure critical for cognitive function, is affected in 2-month-old mice irradiated with ^{56}Fe ions. Here we examined object recognition in 6-month-old mice irradiated with ^{56}Fe ions, a biological age more relevant to the typical ages of astronauts. Moreover, because the mechanisms mediating the detrimental effects of ^{56}Fe ions on hippocampal function are unclear, we examined changes in hippocampal networks involved in synaptic plasticity and memory, gene expression, and epigenetic changes in cytosine methylation (5mC) and hydroxymethylation (5hmC) that could accompany changes in gene expression. We assessed the effects of whole body ^{56}Fe ion irradiation at early (2 weeks) and late (20 weeks) time points on hippocampus-dependent memory and hippocampal network stability, and whether these effects are associated with epigenetic changes in hippocampal DNA methylation (both 5mC and 5hmC) and gene expression. RESULTS: At the two-week time point, object recognition and network stability were impaired following irradiation at the 0.1 and 0.4 Gy dose, but not following irradiation at the 0.2 Gy dose. No impairments in object recognition or network stability were seen at the 20-week time point at any irradiation dose used. Consistent with this pattern, the significance of pathways for gene categories for 5hmC was lower, though not eliminated, at the 20-week time point compared to the 2-week time point. Similarly, significant changes were observed for 5mC gene pathways at the 2-week time point, but no significant gene categories were observed at the 20-week time point. Only the 5hmC changes tracked with gene expression changes. CONCLUSIONS: Dose- and time-dependent epigenomic remodeling in the hippocampus following ^{56}Fe ion exposure correlates with behavioral changes.

Ishikawa, Y., Ito, S., Nagata, K., Sakai, L. Y., & Bächinger, H. P. (2016). Intracellular mechanisms of molecular recognition and sorting for transport of large extracellular matrix molecules.

Proceedings of the National Academy of Sciences of the United States of America, 113(41), E6036-E6044.

Jonkman, N. H., Westland, H., Trappenburg, J. C. A., Groenwold, R. H. H., Bischoff, E. W. M. A., Bourbeau, J., et al. (2016). Do self-management interventions in COPD patients work and which patients benefit most? an individual patient data meta-analysis. *International Journal of COPD*, *11*(1), 2063-2074.

Keefe, D. H., Feeney, M. P., Hunter, L. L., & Fitzpatrick, D. F. (2016). Comparisons of transient evoked otoacoustic emissions using chirp and click stimuli. *Journal of the Acoustical Society of America*, *140*(3), 1949-1973.

Klimo, P., Jr, Lingo, P. R., Baird, L. C., Bauer, D. F., Beier, A., Durham, S., et al. (2016). Congress of neurological surgeons systematic review and evidence-based guideline on the management of patients with positional plagiocephaly: The role of repositioning. *Neurosurgery*, *79*(5), E627-E629.

BACKGROUND: Plagiocephaly, involving positional deformity of the calvarium in infants, is one of the most common reasons for pediatric neurosurgical consultation. OBJECTIVE: To answer the question: "what is the evidence for the effectiveness of repositioning for positional plagiocephaly?" Treatment recommendations are provided based on the available evidence.

METHODS: The National Library of Medicine MEDLINE database and the Cochrane Library were queried using MeSH headings and key words relevant to repositioning as a means to treat plagiocephaly and brachycephaly. Abstracts were reviewed to identify which studies met the inclusion criteria. An evidentiary table was assembled summarizing the studies and the quality of evidence (Classes I-III). Based on the quality of the literature, a recommendation was rendered (Level I, II, or III). RESULTS: There were 3 randomized trials (Class I), 1 prospective cohort study (Class II), and 6 retrospective cohort studies (Class III). Repositioning education was found to be equal to a repositioning device and inferior to a physical therapy program. Five of the 7 cohort studies comparing repositioning with a helmet reported helmets to be better and take less time. CONCLUSION: Within the limits of this systematic review, repositioning education is effective in affording some degree of correction in virtually all infants with positional plagiocephaly or brachycephaly. Most studies suggest that a molding helmet corrects asymmetry more rapidly and to a greater degree than repositioning education. In a Class I study,

repositioning education was as effective as repositioning education in conjunction with a repositioning wrap/device. Another Class I study demonstrated that a bedding pillow was superior to physical therapy for some infants. However, in keeping with the American Academy of Pediatrics' warning against the use of soft positioning pillows in the sleeping environment, the Task Force recommends physical therapy over any positioning device. The full guidelines document can be located at https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly/Chapter_3.

Klimo, P., Jr, Lingo, P. R., Baird, L. C., Bauer, D. F., Beier, A., Durham, S., et al. (2016). Guidelines: Congress of neurological surgeons systematic review and evidence-based guideline on the management of patients with positional plagiocephaly: The role of repositioning. *Neurosurgery*, 79(5), E627-E629.

BACKGROUND: Plagiocephaly, involving positional deformity of the calvarium in infants, is one of the most common reasons for pediatric neurosurgical consultation. OBJECTIVE: To answer the question: "what is the evidence for the effectiveness of repositioning for positional plagiocephaly?" Treatment recommendations are provided based on the available evidence.

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repositioning wrap/device. Another Class I study demonstrated that a bedding pillow was superior to physical therapy for some infants. However, in keeping with the American Academy of Pediatrics' warning against the use of soft positioning pillows in the sleeping environment, the Task Force recommends physical therapy over any positioning device. The full guidelines document can be located at <https://www.cns.org/guidelines/guidelines-management-patients-positional-plagioce> phaly/Chapter_3.

Knope, M. L., Tice, K. A., & Rypkema, D. C. (2016). Site fidelity and homing behaviour of intertidal sculpins revisited. *Journal of Fish Biology*,

To assess the repeatability of an ecological study, this study both partially replicates and extends a previous study on the site fidelity and homing ability of two abundant and ecologically important species of rocky intertidal sculpin fishes, *Oligocottus maculosus* and *Oligocottus snyderi*. A traditional mark and recapture approach was utilized and found that both of these species display high site fidelity to a home range of tidepools and homing ability to these pools, confirming the findings of previous work. Unlike the previous study, however, there was no effect of body size on homing ability and a modelling approach that incorporates encounter probability provided evidence for a sex effect on homing ability. In addition, this study extends the maximum homing ability of *O. snyderi* to 179 m and *O. maculosus* to 218 m, which were the maximum displacement distances for each species in this study, suggesting they may be capable of even greater homing distances. This work, however, finds that homing success was negatively related to displacement distance. These findings suggest adult sculpin populations are likely to be highly sub-structured geographically, possibly contributing to the exceptionally high species richness of the group.

Kohama, S. G., Renner, L., Landauer, N., Weiss, A. R., Urbanski, H. F., Park, B., et al. (2016). Effect of ovarian hormone therapy on cognition in the aged female rhesus macaque. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 36(40), 10416-10424.

Studies of the effect of hormone therapy on cognitive function in menopausal women have been equivocal, in part due to differences in the type and timing of hormone treatment. Here we cognitively tested aged female rhesus macaques on (1) the delayed response task of spatial

working memory, (2) a visuospatial attention task that measured spatially and temporally cued reaction times, and (3) a simple reaction time task as a control for motor speed. After task acquisition, animals were ovariectomized (OVX). Their performance was compared with intact controls for 2 months, at which time no group differences were found. The OVX animals were then assigned to treatment with either a subcutaneous sham implant (OVX), 17-beta estradiol (E) implant (OVX+E) or E implant plus cyclic oral progesterone (OVX+EP). All groups were then tested repeatedly over 12 months. The OVX+E animals performed significantly better on the delayed response task than all of the other groups for much of the 12 month testing period. The OVX+EP animals also showed improved performance in the delayed response task, but only at 30 s delays and with performance levels below that of OVX+E animals. The OVX+E animals also performed significantly better in the visuospatial attention task, particularly in the most challenging invalid cue condition; this difference also was maintained across the 12 month testing period. Simple reaction time was not affected by hormonal manipulation. These data demonstrate that chronic, continuous administration of E can exert multiple beneficial cognitive effects in aged, OVX rhesus macaque females. SIGNIFICANCE STATEMENT: Hormone therapy after menopause is controversial. We tested the effects of hormone replacement in aged rhesus macaques, soon after surgically-induced menopause [ovariectomy (OVX)], on tests of memory and attention. Untreated ovarian-intact and OVX animals were compared with OVX animals receiving estradiol (E) alone or E with progesterone (P). E was administered in a continuous fashion via subcutaneous implant, whereas P was administered orally in a cyclic fashion. On both tests, E-treated animals performed better than the other 3 experimental groups across 1 year of treatment. Thus, in this monkey model, chronic E administered soon after the loss of ovarian hormones had long-term benefits for cognitive function.

Kryscio, R. J., Abner, E. L., Nelson, P. T., Bennett, D., Schneider, J., Yu, L., et al. (2016). The effect of vascular neuropathology on late-life cognition: Results from the SMART project. *The Journal of Prevention of Alzheimer's Disease*, 3(2), 85-91.

BACKGROUND: Cerebral vascular pathology may contribute to cognitive decline experienced by some elderly near death. Given evidence for mixed neuropathologies in advanced age, preventing or reducing cerebrovascular burden in late life may be beneficial. OBJECTIVE: To correlate

measures of cerebral vascular pathology with cognitive trajectories. SETTING: Observational study. PARTICIPANTS: A cohort of 2,274 individuals who came to autopsy at a mean age of 89.3 years and 82 percent of whom had at least two cognitive assessments within the last six years of life was compiled from six centers conducting longitudinal studies. MEASUREMENTS: For each cognitive domain: immediate and delayed memory, language, and naming, three trajectories were examined: good, intermediate, and poor cognition. The probability of a participant belonging to each trajectory was associated with measures of cerebral vascular pathology after adjustment for demographics, APOE, and Alzheimer neuropathology. RESULTS: A large proportion of the cohort (72-94%) experienced good or intermediate cognition in the four domains examined. The presence of arteriosclerosis and the presence of lacunar infarcts doubled the odds of belonging to the poor cognitive trajectory for language when compared to the good trajectory. The presence of lacunar infarcts increased the odds of an intermediate or poor trajectory for immediate and delayed recall while the presence of large artery infarcts increased the odds of poor trajectories for all four cognitive domains examined. Microinfarcts and cerebral amyloid angiopathy had little effect on the trajectories. CONCLUSION: Indicators of cerebral vascular pathology act differently on late life cognition.

Kumar, D. S., Zarraga, I. G., Raitt, M. H., & Balaji, S. (2016). Para-hisian pacing: A paradoxical response? *Journal of Cardiovascular Electrophysiology*,

Kumar, V., Boucher, Y., Liu, H., Ferreira, D., Hooker, J., Catana, C., et al. (2016). Noninvasive assessment of losartan-induced increase in functional microvasculature and drug delivery in pancreatic ductal adenocarcinoma. *Translational Oncology*, 9(5), 431-437.

PURPOSE: Losartan, an angiotensin II receptor blocker, can reduce desmoplasia and enhance drug delivery and efficacy through improving interstitial transport and vascular perfusion in pancreatic ductal adenocarcinoma (PDAC) models in mice. The purpose of this study was to determine whether magnetic resonance imaging (MRI) of magnetic iron oxide nanoparticles (MNPs) and micro-positron emission tomography (PET) measurements could respectively detect improvements in tumor vascular parameters and drug uptake in orthotopic PDAC in mice treated with losartan. METHOD AND MATERIALS: All experiments were approved by the local Institutional

Animal Care and Use Committee. FVB mice with orthotopic PDAC were treated daily with an i.p. injection of losartan (70 mg/kg) or saline (control vehicle) for 5 days. In order to calculate the fractional blood volume, vessel size index, and vessel density index, MRI was performed at 4.7 T following the injection of 3 mg/kg iron ferumoxytol (i.v.). Dynamic PET images were also acquired for 60 minutes using an ^{18}F -5FU tracer dose of 200 μCi and analyzed for time activity curves normalized to muscle. Statistical analyses compared both cohorts using an unpaired two-tailed t test. RESULTS: In comparison to the control treatment, the losartan administration significantly increased the fractional blood volume (mean \pm SEM) [12.1 \pm 1.7 (n=19) vs 6.7 \pm 1.1 (n=20); $P < .02$] and vessel size index (128.2 \pm 35.6 vs 57.5 \pm 18; $P < .05$). Losartan also induced a significant increase in the intratumoral uptake of ^{18}F -5FU by 53% ($P < .0001$). CONCLUSION: MRI using FDA-approved MNPs provides a noninvasive, translatable means of assaying microvascular parameters induced by losartan in pancreatic cancer. PET measurements demonstrated that losartan significantly increased the uptake of ^{18}F -5FU.

Lammers, A., DeLoughery, T., & Prasad, V. (2016). Heparin-induced thrombocytopenia: A tremendous opportunity for randomization. *Blood Coagulation & Fibrinolysis : An International Journal in Haemostasis and Thrombosis*,

Heparin-induced thrombocytopenia and thrombosis (HITT) is both life-threatening with a complex immune-mediated process and clinically challenging to diagnose and treat. What further complicates matters is that thrombocytopenia is a frequently encountered laboratory value but rarely results in clinical signs of HITT. Decades into its initial description, we have anticoagulants with a small therapeutic index and associated high cost. The diagnosis is sometimes equivocal given our current laboratory diagnostics, and can take days to confirm. Furthermore, prior studies that resulted in the approval of anticoagulants for the treatment of heparin-induced thrombocytopenia have been imperfectly designed. Further evaluations of patients with HITT could more adequately define these difficult issues.

Lan, Y., Elwood Madden, A. S., & Butler, E. C. (2016). Transformation of mackinawite to greigite by trichloroethylene and tetrachloroethylene. *Environmental Science: Processes and Impacts*, 18(10), 1266-1273.

Langsetmo, L., Vo, T. N., Ensrud, K. E., Taylor, B. C., Cawthon, P. M., Schwartz, A. V., et al. (2016).

The association between trabecular bone score and lumbar spine volumetric BMD is attenuated among older men with high body mass index. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, 31(10), 1820-1826.

Trabecular bone score (TBS) has been proposed as a dual-energy X-ray absorptiometry (DXA) derived measure of underlying quality of trabecular bone; however, TBS is not considered valid for those with body mass index (BMI) >37 kg/m². Our objective was to determine the association between TBS and lumbar spine (trabecular) volumetric BMD (LS-VBMD) and to examine whether the association varied by BMI and body composition among older men below this clinical threshold. We used regression models to study 3479 men age ≥ 65 years enrolled in the Osteoporotic Fractures in Men (MrOS) study who had TBS from spine DXA scans, LS-VBMD from central quantitative computed tomography, measures of trunk fat and lean mass from DXA, and BMI <37 kg/m². TBS was categorized as normal (n = 925), partially degraded (n = 1747), and degraded (n = 807). TBS was inversely related to BMI, trunk fat mass, and trunk lean mass (all $p < 0.001$). The relationship between TBS and LS-VBMD was nonlinear with magnitude of effect (slope of regression line using standardized variables) ranging from 0.07 (95% CI, -0.02 to 0.15) among those with degraded TBS up to 0.71 (95% CI, 0.54 to 0.89) among those with normal TBS. The relationship was still nonlinear after adjusting for age, clinical site, and either BMI, trunk lean mass, or trunk fat mass. The magnitude of effect relating TBS and LS-VBMD also decreased with increasing BMI (interaction, $p = 0.090$) and increasing trunk lean mass (interaction, $p = 0.001$), but not with increasing trunk fat mass (interaction, $p = 0.224$). In summary, the strength of the association between TBS and LS-VBMD among older men was variable and dependent on BMI and body composition, particularly trunk lean mass. The clinical utility of TBS among older men may be somewhat limited among men with high BMI or high trunk lean mass. (c) 2016 American Society for Bone and Mineral Research.

Lapcharoensap, W., Kan, P., Powers, R. J., Shaw, G. M., Stevenson, D. K., Gould, J. B., et al. (2016).

The relationship of nosocomial infection reduction to changes in neonatal intensive care unit rates of bronchopulmonary dysplasia. *The Journal of Pediatrics*,

OBJECTIVE: To examine whether recent reductions in rates of nosocomial infection have

contributed to changes in rates of bronchopulmonary dysplasia (BPD) in a population-based cohort. **STUDY DESIGN:** This was a retrospective, population-based cohort study that used the California Perinatal Quality Care Collaborative database from 2006 to 2013. Eligible infants included those less than 30 weeks' gestational age and less than 1500 g who survived to 3 days of life. Primary variables of interest were rates of nosocomial infections and BPD. Adjusted rates of nosocomial infections and BPD from a baseline period (2006-2010) were compared with a later period (2011-2013). The correlation of changes in rates across periods for both variables was assessed by hospital of care. **RESULTS:** A total of 22 967 infants from 129 hospitals were included in the study. From the first to second time period, the incidence of nosocomial infections declined from 24.7% to 15% and BPD declined from 35% to 30%. Adjusted hospital rates of BPD and nosocomial infections were correlated positively with a calculated 8% reduction of BPD rates attributable to reductions in nosocomial infections. **CONCLUSIONS:** Successful interventions to reduce rates of nosocomial infections may have a positive impact on other comorbidities such as BPD. The prevention of nosocomial infections should be viewed as a significant component in avoiding long-term neonatal morbidities.

Lee, K. C., Peacock, S., Weinstock, M. A., Zhao, G. A., Knezevich, S. R., Elder, D. E., et al. (2016).

Variation among pathologists' treatment suggestions for melanocytic lesions: A survey of pathologists. *Journal of the American Academy of Dermatology*,

BACKGROUND: The extent of variability in treatment suggestions for melanocytic lesions made by pathologists is unknown. **OBJECTIVE:** We investigated how often pathologists rendered suggestions, reasons for providing suggestions, and concordance with national guidelines.

METHODS: We conducted a cross-sectional survey of pathologists. Data included physician characteristics, experience, and treatment recommendation practices. **RESULTS:** Of 301

pathologists, 207 (69%) from 10 states (California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah, and Washington) enrolled. In all, 15% and 7% reported never and always including suggestions, respectively. Reasons for offering suggestions included improved care (79%), clarification (68%), and legal liability (39%). Reasons for not offering suggestions included referring physician preference (48%), lack of clinical information (44%), and expertise (29%). Training and caseload were associated with offering suggestions (P

< .05). Physician suggestions were most consistent for mild/moderate dysplastic nevi and melanoma. For melanoma in situ, 18 (9%) and 32 (15%) pathologists made suggestions that undertreated or overtreated lesions based on National Comprehensive Cancer Network (NCCN) guidelines, respectively. For invasive melanoma, 14 (7%) pathologists made treatment suggestions that undertreated lesions based on NCCN guidelines. LIMITATIONS: Treatment suggestions were self-reported. CONCLUSIONS: Pathologists made recommendations ranging in consistency. These findings may inform efforts to reduce treatment variability and optimize patterns of care delivery for patients.

Li, B. X., Gardner, R., Xue, C., Qian, D. Z., Xie, F., Thomas, G., et al. (2016). Systemic inhibition of CREB is well-tolerated in vivo. *Scientific Reports*, 6, 34513.

cAMP-response element binding protein (CREB) is a nuclear transcription factor activated by multiple extracellular signals including growth factors and hormones. These extracellular cues activate CREB through phosphorylation at Ser133 by various protein serine/threonine kinases. Once phosphorylated, it promotes its association with transcription coactivators CREB-binding protein (CBP) and its paralog p300 to activate CREB-dependent gene transcription. Tumor tissues of different origins have been shown to present overexpression and/or overactivation of CREB, indicating CREB as a potential cancer drug target. We previously identified 666-15 as a potent inhibitor of CREB with efficacious anti-cancer activity both in vitro and in vivo. Herein, we investigated the specificity of 666-15 and evaluated its potential in vivo toxicity. We found that 666-15 was fairly selective in inhibiting CREB. 666-15 was also found to be readily bioavailable to achieve pharmacologically relevant concentrations for CREB inhibition. Furthermore, the mice treated with 666-15 showed no evidence of changes in body weight, complete blood count, blood chemistry profile, cardiac contractility and tissue histologies from liver, kidney and heart. For the first time, these results demonstrate that pharmacological inhibition of CREB is well-tolerated in vivo and indicate that such inhibitors should be promising cancer therapeutics.

Li, Y., Dillon, T. J., Takahashi, M., Earley, K. T., & Stork, P. J. S. (2016). Protein kinase A-independent ras protein activation cooperates with Rap1 protein to mediate activation of the extracellular signal-regulated kinases (ERK) by cAMP. *Journal of Biological Chemistry*, 291(41), 21584-21595.

Links, A. E., Draper, D., Lee, E., Guzman, J., Valivullah, Z., Maduro, V., et al. (2016). Distributed cognition and process management enabling individualized translational research: The NIH undiagnosed diseases program experience. *Frontiers in Medicine*, 3, 39.

The National Institutes of Health Undiagnosed Diseases Program (NIH UDP) applies translational research systematically to diagnose patients with undiagnosed diseases. The challenge is to implement an information system enabling scalable translational research. The authors hypothesized that similar complex problems are resolvable through process management and the distributed cognition of communities. The team, therefore, built the NIH UDP integrated collaboration system (UDPICS) to form virtual collaborative multidisciplinary research networks or communities. UDPICS supports these communities through integrated process management, ontology-based phenotyping, biospecimen management, cloud-based genomic analysis, and an electronic laboratory notebook. UDPICS provided a mechanism for efficient, transparent, and scalable translational research and thereby addressed many of the complex and diverse research and logistical problems of the NIH UDP. Full definition of the strengths and deficiencies of UDPICS will require formal qualitative and quantitative usability and process improvement measurement.

Loudin, M., Anderson, S., & Schlansky, B. (2016). Bleeding 'downhill' esophageal varices associated with benign superior vena cava obstruction: Case report and literature review. *BMC Gastroenterology*, 16(1), 134.

BACKGROUND: Proximal or 'downhill' esophageal varices are a rare cause of upper gastrointestinal hemorrhage. Unlike the much more common distal esophageal varices, which are most commonly a result of portal hypertension, downhill esophageal varices result from vascular obstruction of the superior vena cava (SVC). While SVC obstruction is most commonly secondary to malignant causes, our review of the literature suggests that benign causes of SVC obstruction are the most common cause actual bleeding from downhill varices. Given the alternative pathophysiology of downhill varices, they require a unique approach to management. Variceal band ligation may be used to temporize acute variceal bleeding, and should be applied on the proximal end of the varix. Relief of the underlying SVC obstruction is the cornerstone of definitive treatment of downhill varices. **CASE PRESENTATION:** A young woman with a benign superior vena cava stenosis due to a tunneled internal jugular vein dialysis catheter presented with

hematemesis and melena. Urgent upper endoscopy revealed multiple 'downhill' esophageal varices with stigmata of recent hemorrhage. As there was no active bleeding, no endoscopic intervention was performed. CT angiography demonstrated stenosis of the SVC surrounding the distal tip of her indwelling hemodialysis catheter. The patient underwent balloon angioplasty of the stenotic SVC segment with resolution of her bleeding and clinical stabilization. CONCLUSION: Downhill esophageal varices are a distinct entity from the more common distal esophageal varices. Endoscopic therapies have a role in temporizing active variceal bleeding, but relief of the underlying SVC obstruction is the cornerstone of treatment and should be pursued as rapidly as possible. It is unknown why benign, as opposed to malignant, causes of SVC obstruction result in bleeding from downhill varices at such a high rate, despite being a less common etiology of SVC obstruction.

Loudin, M., Modiano, N., & Sallay, S. (2016). The reply. *The American Journal of Medicine*, 129(11), e311-e312.

Lucke-Wold, B. P., Logsdon, A. F., Nguyen, L., Eltanahay, A., Turner, R. C., Bonasso, P., et al. (2016). Supplements, nutrition, and alternative therapies for the treatment of traumatic brain injury. *Nutritional Neuroscience*, , 1-13.

Studies using traditional treatment strategies for mild traumatic brain injury (TBI) have produced limited clinical success. Interest in treatment for mild TBI is at an all time high due to its association with the development of chronic traumatic encephalopathy and other neurodegenerative diseases, yet therapeutic options remain limited. Traditional pharmaceutical interventions have failed to transition to the clinic for the treatment of mild TBI. As such, many pre-clinical studies are now implementing non-pharmaceutical therapies for TBI. These studies have demonstrated promise, particularly those that modulate secondary injury cascades activated after injury. Because no TBI therapy has been discovered for mild injury, researchers now look to pharmaceutical supplementation in an attempt to foster success in human clinical trials. Non-traditional therapies, such as acupuncture and even music therapy are being considered to combat the neuropsychiatric symptoms of TBI. In this review, we highlight alternative approaches that have been studied in clinical and pre-clinical studies of TBI, and other

related forms of neural injury. The purpose of this review is to stimulate further investigation into novel and innovative approaches that can be used to treat the mechanisms and symptoms of mild TBI.

Lund, A. W. (2016). Working for tip(DC)s. *Science Translational Medicine*, 8(359)

Madireddy, A., Kosiyatrakul, S. T., Boisvert, R. A., Herrera-Moyano, E., Garcia-Rubio, M. L., Gerhardt, J., et al. (2016). FANCD2 facilitates replication through common fragile sites. *Molecular Cell*, 64(2), 388-404.

Common fragile sites (CFSs) are genomic regions that are unstable under conditions of replicative stress. Although the characteristics of CFSs that render them vulnerable to stress are associated mainly with replication, the cellular pathways that protect CFSs during replication remain unclear. Here, we identify and describe a role for FANCD2 as a trans-acting facilitator of CFS replication, in the absence of exogenous replicative stress. In the absence of FANCD2, replication forks stall within the AT-rich fragility core of CFS, leading to dormant origin activation. Furthermore, FANCD2 deficiency is associated with DNA:RNA hybrid formation at CFS-FRA16D, and inhibition of DNA:RNA hybrid formation suppresses replication perturbation. In addition, we also found that FANCD2 reduces the number of potential sites of replication initiation. Our data demonstrate that FANCD2 protein is required to ensure efficient CFS replication and provide mechanistic insight into how FANCD2 regulates CFS stability.

Madriago, E. J., Punn, R., Geeter, N., & Silverman, N. H. (2016). Routine intra-operative trans-oesophageal echocardiography yields better outcomes in surgical repair of CHD. *Cardiology in the Young*, 26(2), 263-268.

OBJECTIVES: Trans-oesophageal echocardiographic imaging is valuable in the pre- and post-operative evaluation of children and adults with CHD; however, the frequency by which trans-oesophageal echocardiography guides the intra-operative course of patients is unknown.

METHODS: We retrospectively reviewed 1748 intra-operative trans-oesophageal echocardiograms performed between 1 October, 2005 and 31 December, 2010, and found 99 cases (5.7%) that required return to bypass, based in part upon the intra-operative echocardiographic findings.

RESULTS: The diagnoses most commonly requiring further repair and subsequent imaging were

mitral valve disease (20.9%), tricuspid valve disease (16.0%), atrioventricular canal defects (12.0%), and pulmonary valve disease (14.1%). The vast majority of those requiring immediate return to bypass benefited by avoiding subsequent operations and longer lengths of hospital stay. A total of 14 patients (0.8%) who received routine imaging required further surgical repair within 1 week, usually due to disease that developed over ensuing days. Patients who had second post-operative trans-oesophageal echocardiograms in the operating room rarely required re-operations, confirming the benefit of routine intra-operative imaging. CONCLUSIONS: This study represents a large single institutional review of intra-operative trans-oesophageal echocardiography, and confirms its applicability in the surgical repair of patients with CHD. Routine imaging accurately identifies patients requiring further intervention, does not confer additional risk of mortality or prolonged length of hospital stay, and prevents subsequent operations and associated sequelae in a substantial subset of patients. This study demonstrates the utility of echocardiography in intra-operative monitoring of surgical repair and highlights patients who are most likely to require return to bypass, as well as the co-morbidities of such manipulations.

Maggiore, R. J., Callahan, K. E., Tooze, J. A., Parker, I. R., Hsu, T., & Klepin, H. D. (2016). Geriatrics fellowship training and the role of geriatricians in older adult cancer care: A survey of geriatrics fellowship directors. *Gerontology & Geriatrics Education*,
The number of older adults with cancer is growing, necessitating more collaborative training in both geriatric principles and cancer care. We administered a web-based survey to U.S. geriatrics program directors (PDs) addressing cancer-specific training and perspectives on optimal training content and roles for geriatricians in cancer care. Of 140 PDs contacted, 67 (48%) responded. Topics considered very important in training included cancer screening (79%) and cancer-related pain management (70%). Respondents strongly agreed that some of the geriatrician's roles in cancer care included assessing functional status (64%) and assessing physical/cognitive function for goals of care (64%). About half (54%) agreed that having a standardized geriatric oncology curriculum overall was important. The presence of a geriatric oncologist, requiring cancer-based rotations, being affiliated with a cancer center, or being internal vs. family medicine-based did not affect this response. Despite this high level of support, cancer-related skills and knowledge

warrant better definition and integration into current geriatrics training. This survey establishes potential areas for future educational collaborations between geriatrics and oncology training programs.

Mangla, A., & Gupta, S. (2016). Vascular complications post-transcatheter aortic valve procedures. *Indian Heart Journal*, 68(5), 724-731.

Transcatheter aortic valve replacement (TAVR) has rapidly emerged as the standard of care for severe symptomatic aortic stenosis in patients whose comorbidities put them at prohibitive risk for surgical aortic valve replacement (SAVR). Several trials have demonstrated superior outcomes with TAVR compared to medical management alone. TAVR has also shown favorable outcomes in patients at high risk for SAVR. TAVR can be associated with significant vascular complications, which adversely impact outcomes, and operators should be cognizant of their early recognition and appropriate management. In this article, we review the major vascular complications associated with TAVR, along with optimal prevention and management strategies.

Mansoor, S. E., Lü, W., Oosterheert, W., Shekhar, M., Tajkhorshid, E., & Gouaux, E. (2016). X-ray structures define human P2X₃ receptor gating cycle and antagonist action. *Nature*, 538(7623), 66-71.

Masukume, G., Kipersztok, L., Das, D., Shafee, T. M., Laurent, M. R., & Heilman, J. M. (2016). Medical journals and wikipedia: A global health matter. *The Lancet.Global Health*, 4(11), e791-109X(16)30254-6.

Mazzola, C., Baird, L. C., Bauer, D. F., Beier, A., Durham, S., Klimo, P., Jr, et al. (2016). Congress of neurological surgeons systematic review and evidence-based guideline for the diagnosis of patients with positional plagiocephaly: The role of imaging. *Neurosurgery*, 79(5), E625-E626.
BACKGROUND: No evidence-based guidelines exist for the imaging of patients with positional plagiocephaly. OBJECTIVE: The objective of this systematic review and evidence-based guideline is to answer the question, Is imaging necessary for infants with positional plagiocephaly to make a diagnosis? METHODS: The National Library of Medicine Medline database and the Cochrane Library were queried with the use of MeSH headings and key words relevant to imaging as a

means to diagnose plagiocephaly. Abstracts were reviewed, and an evidentiary table was assembled summarizing the studies and the quality of evidence (Classes I-III). Based on the quality of the literature, a recommendation was rendered (Level I, II, or III). RESULTS: A total of 42 full-text articles were selected for review. Of these, 10 were eliminated; thus, 32 full-text were manuscripts selected. There was no Class I evidence, but 2 Class II and 30 Class III studies were included. Three-dimensional cranial topographical imaging, ultrasound, skull x-rays, computed tomography, and magnetic resonance imaging were investigated. CONCLUSION: Clinical examination is most often sufficient to diagnose plagiocephaly (quality, Class III; strength, Level III). Within the limits of this systematic review, the evidence suggests that imaging is rarely necessary and should be reserved for cases in which the clinical examination is equivocal. Many of the imaging studies were not designed to address the diagnostic utility of the imaging modality, and authors were actually assessing the utility of the imaging in longitudinal follow-up, not initial diagnosis. For this reason, some of the studies reviewed were downgraded in Level of Evidence. When needed, 3-dimensional cranial topographical photo, skull x-rays, or ultrasound imaging is almost always sufficient for definitive diagnosis. Computed tomography scanning should not be used to diagnose plagiocephaly, but it may be necessary to rule out craniosynostosis. The full guidelines document can be located at https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly/Chapter_2.

Mazzola, C., Baird, L. C., Bauer, D. F., Beier, A., Durham, S., Klimo, P., Jr, et al. (2016). Guidelines: Congress of neurological surgeons systematic review and evidence-based guideline for the diagnosis of patients with positional plagiocephaly: The role of imaging. *Neurosurgery*, 79(5), E625-E626.

BACKGROUND: No evidence-based guidelines exist for the imaging of patients with positional plagiocephaly. OBJECTIVE: The objective of this systematic review and evidence-based guideline is to answer the question, Is imaging necessary for infants with positional plagiocephaly to make a diagnosis? METHODS: The National Library of Medicine Medline database and the Cochrane Library were queried with the use of MeSH headings and key words relevant to imaging as a means to diagnose plagiocephaly. Abstracts were reviewed, and an evidentiary table was

assembled summarizing the studies and the quality of evidence (Classes I-III). Based on the quality of the literature, a recommendation was rendered (Level I, II, or III). RESULTS: A total of 42 full-text articles were selected for review. Of these, 10 were eliminated; thus, 32 full-text were manuscripts selected. There was no Class I evidence, but 2 Class II and 30 Class III studies were included. Three-dimensional cranial topographical imaging, ultrasound, skull x-rays, computed tomography, and magnetic resonance imaging were investigated. CONCLUSION: Clinical examination is most often sufficient to diagnose plagiocephaly (quality, Class III; strength, Level III). Within the limits of this systematic review, the evidence suggests that imaging is rarely necessary and should be reserved for cases in which the clinical examination is equivocal. Many of the imaging studies were not designed to address the diagnostic utility of the imaging modality, and authors were actually assessing the utility of the imaging in longitudinal follow-up, not initial diagnosis. For this reason, some of the studies reviewed were downgraded in Level of Evidence. When needed, 3-dimensional cranial topographical photo, skull x-rays, or ultrasound imaging is almost always sufficient for definitive diagnosis. Computed tomography scanning should not be used to diagnose plagiocephaly, but it may be necessary to rule out craniosynostosis. The full guidelines document can be located at https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly/Chapter_2.

McDermott, J. E., Mitchell, H. D., Gralinski, L. E., Eisfeld, A. J., Josset, L., Bankhead, A., et al. (2016). The effect of inhibition of PP1 and TNF α signaling on pathogenesis of SARS coronavirus. *BMC Systems Biology*, 10(1)

McDougall, S. J., Guo, H., & Andresen, M. C. (2016). Dedicated C-fibre viscerosensory pathways to central nucleus of the amygdala. *The Journal of Physiology*,
KEY POINTS: Emotions are accompanied by concordant changes in visceral function, including cardiac output, respiration and digestion. One major forebrain integrator of emotional responses, the amygdala, is considered to rely on embedded visceral afferent information, although few details are known. In the present study, we retrogradely transported dye from the central nucleus of the amygdala (CeA) to identify CeA-projecting nucleus of the solitary tract (NTS)

neurons for synaptic characterization and compared them with unlabelled, near-neighbor NTS neurons. Solitary tract (ST) afferents converged onto NTS-CeA second-order sensory neurons in greater numbers, as well as indirectly via polysynaptic pathways. Unexpectedly, all mono- and polysynaptic ST afferent pathways to NTS-CeA neurons were organized exclusively as either transient receptor potential cation channel subfamily V member 1 (TRPV1)-sensitive or TRPV1-resistant, regardless of whether intervening neurons were excitatory or inhibitory. This strict sorting provides viscerosensory signals to CeA about visceral conditions with respect to being either 'normal' via A-fibres or 'alarm' via TRPV1 expressing C-fibres and, accordingly, this pathway organization probably encodes interoceptive status. ABSTRACT: Emotional state is impacted by changes in visceral function, including blood pressure, breathing and digestion. A main line of viscerosensory information processing occurs first in the nucleus of the solitary tract (NTS). In the present study conducted in rats, we examined the synaptic characteristics of visceral afferent pathways to the central nucleus of the amygdala (CeA) in brainstem slices by recording from retrogradely labelled NTS projection neurons. We simultaneously recorded neuron pairs: one dye positive (i.e. NTS-CeA) and a second unlabelled neighbour. Graded shocks to the solitary tract (ST) always (93%) triggered EPSCs at CeA projecting NTS neurons. Half of the NTS-CeA neurons received at least one primary afferent input (classed 'second order') indicating that viscerosensory information arrives at the CeA conveyed via a pathway involving as few as two synapses. The remaining NTS-CeA neurons received viscerosensory input only via polysynaptic pathways. By contrast, approximately 3/4 of unlabelled neighbouring neurons were directly connected to ST. NTS-CeA neurons received greater numbers of ST-related inputs compared to unlabelled NTS neurons, indicating that highly convergent viscerosensory signals reach the CeA. Remarkably, despite multifibre convergence, all single NTS-CeA neurons received inputs derived from only unmyelinated afferents [transient receptor potential cation channel subfamily V member 1 (TRPV1) expressing C-fibres] or only non-TRPV1 ST afferent inputs, and never a combination of both. Such segregation means that visceral afferent information followed separate lines to reach the CeA. Their very different physiological activation profiles mean that these parallel visceral afferent pathways encode viscerosensory signals to the amygdala that may provide interoceptive assessments to impact on behaviours.

McGregor, A. J., Hasnain, M., Sandberg, K., Morrison, M. F., Berlin, M., & Trott, J. (2016). How to study the impact of sex and gender in medical research: A review of resources. *Biology of Sex Differences*, 7(Suppl 1), 46.

There is a growing appreciation by the biomedical community that studying the impact of sex and gender on health, aging, and disease will lead to improvements in human health. Sex- and gender-based comparisons can inform research on disease mechanisms and the development of new therapeutics as well as enhance scientific rigor and reproducibility. This review will assist basic researchers, clinical investigators, as well as epidemiologists, population, and social scientists by providing an annotated bibliography of currently available resource tools on how to consider sex and gender as independent variables in research design and methodology. These resources will assist investigators applying for funding from the National Institutes of Health since all grant applicants will be required (as of January 25, 2016) to address the role of sex as a biological variable in vertebrate animal and human studies.

Morgan, D. L., Eliot, S., Lowe, R. A., & Gorman, P. (2016). Dyadic interviews as a tool for qualitative evaluation. *American Journal of Evaluation*, 37(1), 109-117.

Morgan, T. K., & Beristain, A. G. (2016). Editorial: Uteroplacental mingling: Who's kissing uNK? *Journal of Leukocyte Biology*, 100(4), 637-639.

Morgan, T. K., Jensen, E., Lim, J., & Riggs, R. (2015). Image-guided hyaluronic acid injection and knee bracing significantly improve clinical outcomes for high-grade osteoarthritis. *Sports Medicine - Open*, 1(1), 31.

BACKGROUND: Intra-articular hyaluronic acid (HA) injection is an intermediate option between analgesics and knee joint replacement in patients with osteoarthritis (OA). Our objective was to test whether image-guided HA injections may improve knee OA outcomes after 6 months of treatment independent of potential covariates. METHODS: This is a retrospective case series with multivariate outcome-based analysis of 207 consecutive adult patients with mild to severe knee OA treated at a single out-patient clinic employing fluoroscopy-guided HA injections. We employed a customized pain (scored 0-10) and function (scored 0-120) questionnaire based on the Likert scale to compare baseline scores with 6-month outcomes. Linear and logistic (based on

>9-point score improvement) regression analysis was used to adjust for potential covariates, including grade of disease, patient age, gender, body mass index, smoking history, medical history (e.g., diabetes or heart disease), use of daily pain medications, fish oil supplementation, knee bracing, and physical therapy. RESULTS: Significant covariates included OA grade, knee bracing, and analgesic use. Most of the study subjects were women (124/207, 60 %) and obese (113/207, 55 %). Clinically significant improvements in index scores (>9 points) at 6 months were observed in more than 50 % of cases post-image-guided HA injection. Regression analysis revealed a complimentary affect with knee bracing, especially in severe grade 4 disease (odds ratio 5.5 [1.14-27.0], $P < 0.05$). Daily analgesic use reflected a poor clinical response to treatment. CONCLUSIONS: Our data suggest image-guided HA injections coupled with knee bracing may benefit patients with moderate to severe knee osteoarthritis. KEY POINTS: Image-guided hyaluronic acid injections significantly improve clinical outcomes at 6 months for mild, moderate, and severe knee osteoarthritis. Knee bracing is a significant covariate for clinical improvement in severe grade 4 disease. Daily analgesic use is associated with high-grade disease and less clinical improvement.

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., et al. (2016). Detecting cognitive changes in preclinical alzheimer's disease: A review of its feasibility. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*,

Significant progress has been made in characterizing the biological changes occurring in preclinical Alzheimer's disease (AD). Cognitive dysfunction has been viewed, however, as a late-stage phenomenon, despite increasing evidence that changes may be detected in the decades preceding dementia. In the absence of comprehensive evidence-based guidelines for preclinical cognitive assessment, longitudinal cohort and neuroimaging studies have been reviewed to determine the temporal order and brain biomarker correlates of specific cognitive functions. Episodic memory decline was observed to be the most salient cognitive function, correlating with Igh levels of amyloid deposition and hypoconnectivity across large-scale brain networks. Prospective studies point to early decline in both episodic and semantic memory processing as well as executive functions in the predementia period. The cognitive tests have, however, been

principally those used to diagnose dementia. New procedures are required which target more finely the medial temporal lobe subregions first affected by clinically silent AD pathology.

Moseson, E. M., Wiener, R. S., Golden, S. E., Au, D. H., Gorman, J. D., Laing, A. D., et al. (2016). Patient and clinician characteristics associated with adherence a cohort study of veterans with incidental pulmonary nodules. *Annals of the American Thoracic Society*, 13(5), 651-659.

Mularski, R. A., Hansen, L., Rosenkranz, S. J., Leo, M. C., Nagy, P., & Asch, S. M. (2016). Medical record quality assessments of palliative care for intensive care unit patients do they match the perspectives of nurses and families? *Annals of the American Thoracic Society*, 13(5), 690-698.

Mullins, R. J. (2016). The general's goiter: The outcome of a subtotal thyroidectomy performed on united states army general george catlett marshall. *Journal of the American College of Surgeons*,

Muramoto, O. (2016). Informed consent for the diagnosis of brain death: A conceptual argument. *Philosophy, Ethics, and Humanities in Medicine : PEHM*, 11(1), 8.

BACKGROUND: This essay provides an ethical and conceptual argument for the use of informed consent prior to the diagnosis of brain death. It is meant to enable the family to make critical end-of-life decisions, particularly withdrawal of life support system and organ donation, before brain death is diagnosed, as opposed to the current practice of making such decisions after the diagnosis of death. The recent tragic case of a 13-year-old brain-dead patient in California who was maintained on a ventilator for over 2 years illustrates how such a consent would have made a crucial difference. METHODS: Conceptual, philosophical, and ethical analysis. RESULTS: I first consider a conceptual justification for the use of consent for certain non-beneficial and unwanted medical diagnoses. I suggest that the diagnosis of brain death falls into this category for some patients. Because the diagnostic process of brain death lacks the transparency of traditional death determination, has a unique epistemic structure and a complex risk-benefit profile which differs markedly from case to case, and presents conflicts of interest for physicians and society, I argue that pre-diagnostic counseling and informed consent should be part of the diagnostic process. This approach can be termed as "allow cardiac death", whose parallel logic with "allow natural death" is discussed. I also discuss potential negative impacts on organ donation and

health care cost from this proposal and offer possible mitigation. I show that the pre-diagnostic counseling can improve the possibility for well-thought-out decisions regarding organ donation and terminating life-support system in cases of hopeless prognosis. This approach differs conceptually from the pluralism of the definition of death, such as those in New Jersey and Japan, and it upholds the Uniform Determination of Death Act. CONCLUSIONS: My intention is not to provide an instant panacea for the ongoing impasse of the brain death debate, but to point to a novel conceptual ground for a more pragmatic, and more patient- and family-centered approach. By enabling the family to consent to or decline the diagnostic process of brain death, but not to choose the definition of death, it upholds the current legal definition of death.

Nakajima, E., Walkup, R. D., Shearer, T. R., & Azuma, M. (2016). FK962 induces neurite outgrowth in cultured monkey trigeminal ganglion cells. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie*, PURPOSE: Corneal sensation, cell proliferation, and wound healing all depend on adequate corneal innervation. Disruption of corneal innervation can lead to dry eye and delayed wound healing. Our studies in rats and rabbits show that the substituted fluorobenzamide drug FK962 accelerates the extension of neuronal processes and recovery of corneal sensitivity. The purpose of the present study was 1) to determine whether FK962 induces sprouting and elongation of neurites in cultured monkey trigeminal ganglion cells, and 2) to investigate the involvement of the neurotrophic peptide GDNF in FK962-induced neurite elongation. METHODS: Dissociated, cultured trigeminal ganglion cells, containing neuronal and Schwann cells were cultured for 48 h with or without FK962. Neuronal elongation was evaluated by immunostaining with a neurofilament-specific antibody. Culture with or without GDNF, or with antibody against GDNF, was used to determine the role of GDNF in FK962-induced neurite elongation. RESULTS: FK962 or GDNF were found to significantly induce neurite elongation. The GDNF antibody significantly inhibited elongation induced by FK962. CONCLUSION: GDNF was found to be a mediator of FK962-induced neurite elongation in a relevant primate model. FK962 may be a candidate drug for treatment of neurotrophic disorders in the human cornea.

Noel, M., Wilson, A. C., Holley, A. L., Durkin, L., Patton, M., & Palermo, T. M. (2016). Posttraumatic stress disorder symptoms in youth with vs without chronic pain. *Pain, 157*(10), 2277-2284.

Nogueira, R. G., Zaidat, O. O., Castonguay, A. C., Haussen, D. C., Martin, C. O., Holloway, W. E., et al. (2016). Rescue thrombectomy in large vessel occlusion strokes leads to better outcomes than intravenous thrombolysis alone: A 'real world' applicability of the recent trials. *Interventional Neurology, 5*(3-4), 101-110.

BACKGROUND: The Interventional Management of Stroke III (IMS-III) trial demonstrated no benefit for intravenous recombinant tissue plasminogen activator (IV rt-PA) followed by endovascular therapy versus IV rt-PA alone. However, IMS-III mostly included earlier generation devices. The recent thrombectomy trials have incorporated the stent-retriever technology, but their generalizability remains unknown. METHODS: The North American Solitaire Acute Stroke (NASA) registry recruited patients treated with the Solitaire FR device between March 2012 and February 2013. The NASA-IMS-III-Like Group (NILG baseline NIHSS score ≥ 10 who received IV rt-PA) was compared to the IV rt-PA and IV + intra-arterial (IA)-IMS-III groups and the MR CLEAN, ESCAPE, SWIFT Prime, and REVASCAT trial controls to assess the stent-retriever treatment in the 'real-world' setting. The NILG was also compared to non-IV rt-PA NASA patients to evaluate the impact of IV rt-PA on thrombectomy. RESULTS: A total of 136 of the 354 NASA patients fulfilled criteria for the NILG. Baseline characteristics were well balanced across groups. Time from onset to puncture was higher in NILG than IV+IA-IMS-III patients (274 +/- 112 vs. 208 +/- 47 min, $p = 0.0001$). Reperfusion was higher in NILG than IV+IA-IMS-III patients (74.3 vs. 39.6%, $p < 0.00001$). A 90-day modified Rankin Scale score ≤ 2 was more frequent in the NILG than IV+IA-IMS-III patients (51.9 vs. 40.8%, $p = 0.03$) and MR CLEAN (51.9 vs. 19.1%, $p < 0.00001$), ESCAPE (51.9 vs. 29.3%, $p = 0.0002$), SWIFT Prime (51.9 vs. 35.5%, $p = 0.02$), and REVASCAT (51.9 vs. 28.2%, $p = 0.0003$) controls. Symptomatic intracranial hemorrhage definitions varied across the different studies with rates ranging from 2.7% (ESCAPE) to 11.9% (NILG). The NILG 90-day mortality (24.4%) was higher than in SWIFT Prime but comparable to all other groups. IV rt-PA was an independent predictor of good outcome in NASA (OR = 2.3, 95% CI 1.2-4.7). CONCLUSION: Our results support the 'real-world' applicability of the recent thrombectomy trials.

Nourbakhsh, B., Nunan-Saah, J., Maghzi, A. H., Julian, L. J., Spain, R., Jin, C., et al. (2016).

Longitudinal associations between MRI and cognitive changes in very early MS. *Multiple Sclerosis and Related Disorders*, 5, 47-52.

OBJECTIVES: Cognitive dysfunction in multiple sclerosis (MS) has been primarily examined in patients with advanced disease. Our objective was to study the longitudinal associations between brain magnetic resonance imaging (MRI) metrics and neuropsychological outcomes in patients with early MS. **METHODS:** Relapsing MS patients within 12 months of onset were enrolled in a neuroprotection trial of riluzole versus placebo with up to 36 months of follow-up. MRI metrics included percent brain volume changes measured by SIENAX normalized measurements [normalized brain parenchymal volume (nBPV), normalized normal-appearing white and gray matter volume (nNAWMV and nGMV)] and T2 lesion volume (T2LV). A neuropsychological battery was performed annually. Mixed model regression measured time trends and associations between imaging and neuropsychological outcomes, adjusting for sex, age and education level. **RESULTS:** Forty-three patients (mean age 36 years; 31 females) were enrolled within 7.5 +/- 4.9 months of disease onset. 11.6% of patients with baseline cognitive assessment met conservative criteria for cognitive impairment. Compared to placebo, riluzole had no significant effect on neuropsychological performance; thus, both groups were combined for the association analyses. Baseline T2LV predicted subsequent changes in PASAT ($p=0.006$) and SDMT ($p=0.002$) scores. Longitudinal changes of T2LV were associated with changes in CVLT-II ($p<0.001$). **CONCLUSION:** These findings suggest that cognitive impairment is relatively common in patients with very early MS. Baseline and longitudinal changes in the lesion load may be associated with some of the most frequently identified changes in cognitive function in MS.

Obaseki, D. O., Erhabor, G. E., Gnatiuc, L., Adewole, O. O., Buist, S. A., & Burney, P. G. (2016).

Chronic airflow obstruction in a black african population: Results of BOLD study, ile-ife, nigeria. *Copd*, 13(1), 42-49.

Global estimates suggest that Chronic Obstructive Pulmonary Disease (COPD) is emerging as a leading cause of death in developing countries but there are few spirometry-based general population data on its prevalence and risk factors in sub-Saharan Africa. We used the Burden of Obstructive Lung Disease (BOLD) protocol to select a representative sample of adults aged 40

years and above in Ile-Ife, Nigeria. All the participants underwent spirometry and provided information on smoking history, biomass and occupational exposures as well as diagnosed respiratory diseases and symptoms. Chronic Airflow Obstruction (CAO) was defined as the ratio of post-bronchodilator (BD) one second Forced Expiratory Volume (FEV1) to Forced Vital Capacity (FVC) below the lower limit of normal (LLN) of the population distribution for FEV1/FVC. The overall prevalence of obstruction (post-BD FEV1/FVC < LLN) was 7.7% (2.7% above LLN) using Global Lung Function Initiative (GLI) equations. It was associated with few respiratory symptoms; 0.3% reported a previous doctor-diagnosed chronic bronchitis, emphysema or COPD. Independent predictors included a lack of education (OR 2.5, 95% CI: 1.0, 6.4) and a diagnosis of either TB (OR 23.4, 95% CI: 2.0, 278.6) or asthma (OR 35.4, 95%CI: 4.9, 255.8). There was no association with the use of firewood or coal for cooking or heating. The vast majority of this population (89%) are never smokers. We conclude that the prevalence of CAO is low in Ile-Ife, Nigeria and unrelated to biomass exposure. The key independent predictors are poor education, and previous diagnosis of tuberculosis or asthma.

O'Brien, K. D., Hirsch, I. B., Riddle, M. C., & Probstfield, J. L. (2016). Glucose variability in a 26-week randomized comparison of mealtime treatment with rapid-acting insulin versus GLP-1 agonist in participants with type 2 diabetes at high cardiovascular risk. *Diabetes Care*, 39(10), e188.

Olivier, K. N., Griffith, D. E., Eagle, G., McGinnis II, J. P., Micioni, L., Liu, K., et al. (2016). Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease. *American Journal of Respiratory and Critical Care Medicine*,
Rationale Lengthy multi-drug, toxic, and low efficacy regimens limit management of pulmonary nontuberculous mycobacterial (PNTM) disease. Objective This phase 2 study investigated efficacy and safety of liposomal amikacin for inhalation (LAI) in treatment-refractory PNTM (Mycobacterium avium complex [MAC] or Mycobacterium abscessus) disease. Methods During the double-blind phase, patients were randomly assigned to LAI (590 mg) or placebo once daily added to their multi-drug regimen for 84 days. Both groups could receive open-label LAI for 84 additional days. Primary endpoint was change from baseline to day 84 on a semi-quantitative mycobacterial growth scale. Other endpoints included sputum conversion, 6-minute walk

distance, and adverse events. Measurements and Main Results Modified intent-to-treat population included 89 (LAI=44; placebo=45) patients. Average age was 59 years, 88% were female, 92% were Caucasian; 80 and 59 patients completed study drug dosing during the double-blind and open-label phases, respectively. Primary endpoint was not achieved (P=0.072); however, a greater proportion of the LAI group demonstrated ≥ 1 negative sputum cultures (32% [14/44] vs. 9% [4/45]; P=0.006) and improvement in 6-minute walk test (+20.6 vs. -25.0 meters; P=0.017) at day 84. Treatment effect was predominantly in patients without cystic fibrosis with MAC and was sustained 1 year post-LAI. Most adverse events were respiratory and in some patients led to drug discontinuation. Conclusions Although the primary endpoint was not reached, LAI added to a multi-drug regimen produced improvements in sputum conversion and 6-minute walk distance vs. placebo with limited systemic toxicity in patients with refractory MAC lung disease. Further research is needed. Clinical trial registration available at www.clinicaltrials.gov, ID NCT01315236.

O'Neil, M. E., Callahan, M., Carlson, K. F., Roost, M., Laman-Maharg, B., Twamley, E. W., et al. (2016). Postconcussion symptoms reported by operation enduring Freedom/Operation iraqi freedom veterans with and without blast exposure, mild traumatic brain injury, and posttraumatic stress disorder. *Journal of Clinical and Experimental Neuropsychology*, , 1-10.

Orwoll, E. S., Lapidus, J., Wang, P. Y., Vandenput, L., Hoffman, A., Fink, H., et al. (2016). The limited clinical utility of testosterone, estradiol and sex hormone binding globulin measurements in the prediction of fracture risk and bone loss in older men. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, Measurement of serum testosterone (T) levels is recommended in the evaluation of osteoporosis in older men and estradiol (E2) and sex hormone binding globulin (SHBG) levels are associated with the rate of bone loss and fractures, but the clinical utility of sex steroid and SHBG measurements for the evaluation of osteoporosis in men has not been examined. To evaluate whether measurements of T, E2 and/or SHBG are useful for the prediction of fracture risk or the rate of bone loss in older men, we analyzed longitudinal data from 5487 community-based men participating in the MrOS Study in the US, Sweden and Hong Kong. Serum T, E2 and SHBG levels

were assessed at baseline; incident fractures were self-reported at 4 month intervals with radiographic verification (US), or ascertained via national health records (Sweden, Hong Kong). Rate of bone loss was assessed by serial measures of hip BMD. We used receiver operating characteristic (ROC) curves, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to assess improvement in prediction. Mean age at baseline was 72-75 years and the prevalence of low T levels (59.1 nM), neither sex steroids nor SHBG provided clinically useful improvement in fracture risk discrimination. Similarly, they did not contribute to the prediction of BMD change. In conclusion, there is limited clinical utility of serum E2, T and SHBG measures for the evaluation of osteoporosis risk in elderly men. This article is protected by copyright. All rights reserved.

Pamir, N., Hutchins, P., Ronsein, G., Vaisar, T., Reardon, C. A., Getz, G. S., et al. (2016). Proteomic analysis of HDL from inbred mouse strains implicates APOE associated with HDL in reduced cholesterol efflux capacity via the ABCA1 pathway. *Journal of Lipid Research*, 57(2), 246-257. Cholesterol efflux capacity associates strongly and negatively with the incidence and prevalence of human CVD. We investigated the relationships of HDL's size and protein cargo with its cholesterol efflux capacity using APOB-depleted serum and HDLs isolated from five inbred mouse strains with different susceptibilities to atherosclerosis. Like humans, mouse HDL carried >70 proteins linked to lipid metabolism, the acute-phase response, proteinase inhibition, and the immune system. HDL's content of specific proteins strongly correlated with its size and cholesterol efflux capacity, suggesting that its protein cargo regulates its function. Cholesterol efflux capacity with macrophages strongly and positively correlated with retinol binding protein 4 (RBP4) and PLTP, but not APOA1. In contrast, ABCA1-specific cholesterol efflux correlated strongly with HDL's content of APOA1, APOC3, and APOD, but not RBP4 and PLTP. Unexpectedly, APOE had a strong negative correlation with ABCA1-specific cholesterol efflux capacity. Moreover, the ABCA1-specific cholesterol efflux capacity of HDL isolated from APOE-deficient mice was significantly greater than that of HDL from wild-type mice. Our observations demonstrate that the HDL-associated APOE regulates HDL's ABCA1-specific cholesterol efflux capacity. These findings may be clinically relevant because HDL's APOE content associates with CVD risk and ABCA1 deficiency promotes unregulated cholesterol accumulation in human macrophages.

Panksepp, J. B., Rodriguez, E. D., & Ryabinin, A. E. (2016). Sweetened-ethanol drinking during social isolation: Enhanced intake, resistance to genetic heterogeneity and the emergence of a distinctive drinking pattern in adolescent mice. *Genes, Brain, and Behavior*,

With its ease of availability during adolescence, sweetened ethanol ('alcopops') is consumed within many contexts. We asked here whether genetically based differences in social motivation are associated with how the adolescent social environment impacts voluntary ethanol intake. Mice with previously described differences in sociability (BALB/cJ, C57BL/6J, FVB/NJ and MSM/MsJ strains) were weaned into isolation or same-sex pairs (postnatal day 21), and then given continuous access to two fluids on postnatal days 34-45: One containing water and the other containing an ascending series of saccharin-sweetened ethanol (3-to-6-to-10%). Prior to the introduction of ethanol (postnatal days 30-33), increased water and food intake was detected in some of the isolation-reared groups, and controls indicated that isolated mice also consumed more 'saccharin-only' solution. Voluntary drinking of 'ethanol-only' was also higher in a subset of the isolated groups on postnatal days 46-49. However, sweetened ethanol intake was increased in all isolated strain-by-sex combinations irrespective of genotype. Surprisingly, blood ethanol concentration was not different between these isolate and socially housed groups 4 hours into the dark phase. Using lickometer-based measures of intake in FVB mice, we identified that a predominance of increased drinking during isolation transpired outside of the typical circadian consumption peak, occurring approximately 8.5 hours into the dark phase, with an associated difference in blood ethanol concentration. These findings collectively indicate that isolate housing leads to increased consumption of rewarding substances in adolescent mice independently of their genotype, and that for ethanol this may be due to when individuals drink during the circadian cycle.

Parchman, M. L., Fagnan, L. J., Dorr, D. A., Evans, P., Cook, A. J., Penfold, R. B., et al. (2016). Study protocol for "healthy hearts northwest": A 2 x 2 randomized factorial trial to build quality improvement capacity in primary care. *Implementation Science : IS*, 11(1), 138.

BACKGROUND: Little attention has been paid to quality improvement (QI) capacity within smaller primary care practices which comprise nearly half of all primary care settings. Strategies for external support to build such capacity include practice facilitation (PF), shared learning

opportunities, and educational outreach. Although PF has proven effectiveness, little is known about the comparative effectiveness of combining these strategies. Here, we describe the protocol of the "Healthy Hearts Northwest" (H2N) study, a randomized trial designed to address these questions while improving risk factors for cardiovascular disease. METHODS/DESIGN: The targeted enrollment is 250 smaller primary care practices across Washington, Oregon, and Idaho. The study is utilizing a two-by-two factorial design to assess four different combinations of practice support: PF alone, PF with educational outreach, PF with shared learning opportunities, or PF with both. A mixed methods approach is being used for evaluation and will include data from (1) baseline and follow-up practice and staff surveys; (2) baseline and quarterly clinical performance measurement from each practice on four cardiovascular risk factors: appropriate aspirin use, blood pressure control, lipid management and smoking cessation support; and (3) a quality improvement capacity assessment (QICA) survey used by external practice facilitators to guide improvement efforts. DISCUSSION: Results from this study will inform future large-scale practice improvement initiatives by providing comparisons of promising external practice support strategies and advance our understanding of how to build QI capacity in primary care. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02839382.

Parent, A. S., Pinson, A., Woods, N., Chatzi, C., Vaaga, C. E., Bensen, A., et al. (2016). Early exposure to aroclor 1254 in vivo disrupts the functional synaptic development of newborn hippocampal granule cells. *The European Journal of Neuroscience*, Neurogenesis in the dentate gyrus is sensitive to endogenous and exogenous factors that influence hippocampal function. Ongoing neurogenesis and the integration of these new neurons throughout life thus may provide a sensitive indicator of environmental stress. We examined the effects of Aroclor 1254 (A1254), a mixture of polychlorinated biphenyls (PCBs), on the development and function of newly-generated dentate granule cells. Early exposure to A1254 has been associated with learning impairment in children, suggesting potential impact on the development of hippocampus and/or cortical circuits. Oral A1254 (from the 6th day of gestation to postnatal day 21) produced the expected increase in PCB levels in brain at postnatal day 21, which persisted at lower levels into adulthood. A1254 did not affect the proliferation or survival of newborn neurons in immature animals nor did it cause overt changes in neuronal morphology.

However, A1254 occluded the normal developmental increase in sEPSC frequency in the 3rd post-mitotic week without altering the average sEPSC amplitude. Our results suggest that early exposure to PCBs can disrupt excitatory synaptic function during a period of active synaptogenesis, and thus could contribute to the cognitive effects noted in children exposed to PCBs. This article is protected by copyright. All rights reserved.

Park, J. -, Mancini, M., Carlson-Kuhta, P., Nutt, J. G., & Horak, F. B. (2016). Quantifying effects of age on balance and gait with inertial sensors in community-dwelling healthy adults. *Experimental Gerontology, 85*, 48-58.

Perry, C. K., Ackert, E., Sallis, J. F., Glanz, K., & Saelens, B. E. (2016). Places where children are active: A longitudinal examination of children's physical activity. *Preventive Medicine, 93*, 88-95.

Pfefferbaum, A., Rohlfing, T., Pohl, K. M., Lane, B., Chu, W., Kwon, D., et al. (2016). Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. *Cerebral Cortex, 26*(10), 4101-4121.

Pfeiffer, P. N., Valenstein, M., Ganoczy, D., Henry, J., Dobscha, S. K., & Piette, J. D. (2016). Pilot study of enhanced social support with automated telephone monitoring after psychiatric hospitalization for depression. *Social Psychiatry and Psychiatric Epidemiology*,
BACKGROUND: Following discharge, patients hospitalized for depression are at high risk for poor retention in outpatient care and adverse outcomes. AIMS: Pilot tests a post-hospital monitoring and enhanced support program for depression. METHOD: 48 patients at a Veterans Affairs Medical Center discharged following a depression-related inpatient stay received weekly visits or phone calls for 6 months from their choice of either a family member/friend (n = 19) or a certified peer support specialist (n = 29). Participants also completed weekly automated telephone monitoring calls assessing depressive symptoms and antidepressant medication adherence. RESULTS: Over 90% of participants were more satisfied with their care due to the service. The mean change from baseline to 6 months in depression symptoms was -7.9 (p 0.10), respectively. CONCLUSIONS: Increased contact with a chosen support person coupled with automated telephone monitoring after psychiatric hospitalization is an acceptable service for

patients with depression. Those who received the service, and particularly those supported by a family member/friend, experienced reductions in symptoms of depression.

Phan, L., Rugonyi, S., & Grimm, C. (2016). Visualization of chicken embryo heart motion. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging and Visualization*, , 1-15.

Placzek, A. T., Ferrara, S. J., Hartley, M. D., Sanford-Crane, H. S., Meinig, J. M., & Scanlan, T. S. (2016). Sobetirome prodrug esters with enhanced blood-brain barrier permeability. *Bioorganic & Medicinal Chemistry*, 24(22), 5842-5854.

There is currently great interest in developing drugs that stimulate myelin repair for use in demyelinating diseases such as multiple sclerosis. Thyroid hormone plays a key role in stimulating myelination during development and also controls the expression of important genes involved in myelin repair in adults. Because endogenous thyroid hormone in excess lacks a generally useful therapeutic index, it is not used clinically for indications other than hormone replacement; however, selective thyromimetics such as sobetirome offer a therapeutic alternative. Sobetirome is the only clinical-stage thyromimetic that is known to cross the blood-brain-barrier (BBB) and we endeavored to increase the BBB permeability of sobetirome using a prodrug strategy. Ester prodrugs of sobetirome were prepared based on literature reports of improved BBB permeability with other carboxylic acid containing drugs and BBB permeability was assessed in vivo. One sobetirome prodrug, ethanolamine ester 11, was found to distribute more sobetirome to the brain compared to an equimolar peripheral dose of unmodified sobetirome. In addition to enhanced brain levels, prodrug 11 displayed lower sobetirome blood levels and a brain/serum ratio that was larger than that of unmodified sobetirome. Thus, these data indicate that an ester prodrug strategy applied to sobetirome can deliver increased concentrations of the active drug to the central nervous system (CNS), which may prove useful in the treatment of CNS disorders.

Pleil, K. E., Helms, C. M., Sobus, J. R., Daunais, J. B., Grant, K. A., & Kash, T. L. (2016). Effects of chronic alcohol consumption on neuronal function in the non-human primate BNST. *Addiction Biology*, 21(6), 1151-1167.

Alterations in hypothalamic-pituitary-adrenal axis function contribute to many of the adverse

behavioral effects of chronic voluntary alcohol drinking, including alcohol dependence and mood disorders; limbic brain structures such as the bed nucleus of the stria terminalis (BNST) may be key sites for these effects. Here, we measured circulating levels of several steroid hormones and performed whole-cell electrophysiological recordings from acutely prepared BNST slices of male rhesus monkeys allowed to self-administer alcohol for 12 months or a control solution. Initial comparisons revealed that BNST neurons in alcohol-drinking monkeys had decreased membrane resistance, increased frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) with no change in spontaneous excitatory postsynaptic currents (sEPSCs). We then used a combined variable cluster analysis and linear mixed model statistical approach to determine whether specific factors including stress and sex hormones, age and measures of alcohol consumption and intoxication are related to these BNST measures. Modeling results showed that specific measures of alcohol consumption and stress-related hormone levels predicted differences in membrane conductance in BNST neurons. Distinct groups of adrenal stress hormones were negatively associated with the frequency of sIPSCs and sEPSCs, and alcohol drinking measures and basal neuronal membrane properties were additional positive predictors of inhibitory, but not excitatory, PSCs. The amplitude of sEPSCs was highly positively correlated with age, independent of other variables. Together, these results suggest that chronic voluntary alcohol consumption strongly influences limbic function in non-human primates, potentially via interactions with or modulation by other physiological variables, including stress steroid hormones and age.

Prasad, V. (2016). Precision medicine in diffuse large B-cell lymphoma: Hype or hope? *European Journal of Cancer (Oxford, England : 1990)*, 68, 22-26.

Prasad, V., Wang, R., Afifi, S. H., & Mailankody, S. (2016). The rising price of cancer drugs-A new old problem? *JAMA Oncology*,

Puy, C., Tucker, E. I., Ivanov, I. S., Gailani, D., Smith, S. A., Morrissey, J. H., et al. (2016). Platelet-derived short-chain polyphosphates enhance the inactivation of tissue factor pathway inhibitor by activated coagulation factor XI. *PLoS One*, 11(10), e0165172.

INTRODUCTION: Factor (F) XI supports both normal human hemostasis and pathological thrombosis. Activated FXI (FXIa) promotes thrombin generation by enzymatic activation of FXI,

FIX, FX, and FV, and inactivation of alpha tissue factor pathway inhibitor (TFPIalpha), in vitro. Some of these reactions are now known to be enhanced by short-chain polyphosphates (SCP) derived from activated platelets. These SCPs act as a cofactor for the activation of FXI and FV by thrombin and FXIa, respectively. Since SCPs have been shown to inhibit the anticoagulant function of TFPIalpha, we herein investigated whether SCPs could serve as cofactors for the proteolytic inactivation of TFPIalpha by FXIa, further promoting the efficiency of the extrinsic pathway of coagulation to generate thrombin. METHODS AND RESULTS: Purified soluble SCP was prepared by size-fractionation of sodium polyphosphate. TFPIalpha proteolysis was analyzed by western blot. TFPIalpha activity was measured as inhibition of FX activation and activity in coagulation and chromogenic assays. SCPs significantly accelerated the rate of inactivation of TFPIalpha by FXIa in both purified systems and in recalcified plasma. Moreover, platelet-derived SCP accelerated the rate of inactivation of platelet-derived TFPIalpha by FXIa. TFPIalpha activity was not affected by SCP in recalcified FXI-depleted plasma. CONCLUSIONS: Our data suggest that SCP is a cofactor for TFPIalpha inactivation by FXIa, thus, expanding the range of hemostatic FXIa substrates that may be affected by the cofactor functions of platelet-derived SCP.

Quimson-Guevarra, P., & Jones, T. G. (2016). Post-atkins determination of intellectual disability in a death penalty case in oregon. *Journal of the American Academy of Psychiatry and the Law*, 44(3), 394-396.

Raess, P. W., Cascio, M. J., Fan, G., Press, R., Druker, B. J., Brewer, D., et al. (2016). Concurrent STAT3, DNMT3A and TET2 mutations in T-LGL leukemia with molecularly distinct clonal hematopoiesis of indeterminate potential. *American Journal of Hematology*,

Ranasinghe, S., Lamothe, P. A., Soghoian, D. Z., Kazer, S. W., Cole, M. B., Shalek, A. K., et al. (2016). Antiviral CD8+ T cells restricted by human leukocyte antigen class II exist during natural HIV infection and exhibit clonal expansion. *Immunity*, 45(4), 917-930.

CD8+ T cell recognition of virus-infected cells is characteristically restricted by major histocompatibility complex (MHC) class I, although rare examples of MHC class II restriction have been reported in Cd4-deficient mice and a macaque SIV vaccine trial using a recombinant cytomegalovirus vector. Here, we demonstrate the presence of human leukocyte antigen (HLA)

class II-restricted CD8+ T cell responses with antiviral properties in a small subset of HIV-infected individuals. In these individuals, T cell receptor beta (TCRbeta) analysis revealed that class II-restricted CD8+ T cells underwent clonal expansion and mediated killing of HIV-infected cells. In one case, these cells comprised 12% of circulating CD8+ T cells, and TCRalpha analysis revealed two distinct co-expressed TCRalpha chains, with only one contributing to binding of the class II HLA-peptide complex. These data indicate that class II-restricted CD8+ T cell responses can exist in a chronic human viral infection, and may contribute to immune control.

Rice, A. L., Butenhoff, C. L., Teama, D. G., Röger, F. H., Khalil, M. A. K., & Rasmussen, R. A. (2016). Atmospheric methane isotopic record favors fossil sources flat in 1980s and 1990s with recent increase. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(39), 10791-10796.

Rice, T. W., Apperson-Hansen, C., DiPaola, L. M., Semple, M. E., Lerut, T. E. M. R., Orringer, M. B., et al. (2016). Worldwide esophageal cancer collaboration: Clinical staging data. *Diseases of the Esophagus*, *29*(7), 707-714.

Rice, T. W., Chen, L. -, Hofstetter, W. L., Smithers, B. M., Rusch, V. W., Wijnhoven, B. P. L., et al. (2016). Worldwide esophageal cancer collaboration: Pathologic staging data. *Diseases of the Esophagus*, *29*(7), 724-733.

Rice, T. W., Lerut, T. E. M. R., Orringer, M. B., Chen, L. -, Hofstetter, W. L., Smithers, B. M., et al. (2016). Worldwide esophageal cancer collaboration: Neoadjuvant pathologic staging data. *Diseases of the Esophagus*, *29*(7), 715-723.

Richard, N. P., Pippa, R., Cleary, M. M., Puri, A., Tibbitts, D., Mahmood, S., et al. (2016). Combined targeting of SET and tyrosine kinases provides an effective therapeutic approach in human T-cell acute lymphoblastic leukemia. *Oncotarget*,
Recent evidence suggests that inhibition of protein phosphatase 2A (PP2A) tumor suppressor activity via the SET oncoprotein contributes to the pathogenesis of various cancers. Here we demonstrate that both SET and c-MYC expression are frequently elevated in T-ALL cell lines and

primary samples compared to healthy T cells. Treatment of T-ALL cells with the SET antagonist OP449 restored the activity of PP2A and reduced SET interaction with the PP2A catalytic subunit, resulting in a decrease in cell viability and c-MYC expression in a dose-dependent manner. Since a tight balance between phosphatases and kinases is required for the growth of both normal and malignant cells, we sought to identify a kinase inhibitor that would synergize with SET antagonism. We tested various T-ALL cell lines against a small-molecule inhibitor screen of 66 compounds targeting two-thirds of the tyrosine kinome and found that combined treatment of T-ALL cells with dovitinib, an orally active multi-targeted small-molecule receptor tyrosine kinase inhibitor, and OP449 synergistically reduced the viability of all tested T-ALL cell lines. Mechanistically, combined treatment with OP449 and dovitinib decreased total and phospho c-MYC levels and reduced ERK1/2, AKT, and p70S6 kinase activity in both NOTCH-dependent and independent T-ALL cell lines. Overall, these results suggest that combined targeting of tyrosine kinases and activation of serine/threonine phosphatases may offer novel therapeutic strategies for the treatment of T-ALL.

Richards, J. R., Lange, R. A., Arnold, T. C., & Horowitz, B. Z. (2016). Dual cocaine and methamphetamine cardiovascular toxicity: Rapid resolution with labetalol. *The American Journal of Emergency Medicine*,

Ritchie, K., Ropacki, M., Albala, B., Harrison, J., Kaye, J., Kramer, J., et al. (2016). Recommended cognitive outcomes in preclinical alzheimer's disease: Consensus statement from the european prevention of alzheimer's dementia project. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*,

The Horizon 2020/IMI European Prevention of Alzheimer's Dementia (EPAD) project will undertake large-scale proof-of-concept trials in predementia AD. Within EPAD, the monitoring of cognitive trajectories in the preclinical period will constitute a central outcome measure; however, there are currently no clear guidelines as to how this should be achieved as most measures have been developed for the period around dementia diagnosis. The EPAD Scientific Advisory Group for Clinical and Cognitive Outcomes identified appropriate cognitive measures based on a literature search covering both cognitive correlates of preclinical brain changes from

imaging studies and cognitive changes observed over time in nondementia population cohorts developing incident dementia. These measures were evaluated according to the following criteria: validity, coherence with biomarker changes, psychometric properties, cross-cultural suitability, availability of alternative forms, and normative data limited practice effects. The resulting consensus statement provides recommendations for both future drug trials and research into preclinical Alzheimer's disease.

Robertson, D. J., Lee, J. K., Boland, C. R., Dominitz, J. A., Giardiello, F. M., Johnson, D. A., et al. (2016). Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: A consensus statement by the US multi-society task force on colorectal cancer. *The American Journal of Gastroenterology*,
The use of the fecal occult blood test (FOBT) for colorectal cancer (CRC) screening is supported by randomized trials demonstrating effectiveness in cancer prevention and widely recommended by guidelines for this purpose. The fecal immunochemical test (FIT), as a direct measure of human hemoglobin in stool has a number of advantages relative to conventional FOBT and is increasingly used relative to that test. This review summarizes current evidence for FIT in colorectal neoplasia detection and the comparative effectiveness of FIT relative to other commonly used CRC screening modalities. Based on evidence, guidance statements on FIT application were developed and quality metrics for program implementation proposed. *Am J Gastroenterol* advance online publication, 18 October 2016; doi:10.1038/ajg.2016.492.

Rodriguez, M. I., Seuc, A., Say, L., & Hindin, M. J. (2016). Episiotomy and obstetric outcomes among women living with type 3 female genital mutilation: A secondary analysis. *Reproductive Health*, 13(1), 1-7.

Rompala, K. S., Cirino, N., Rosenberg, K. D., Fu, R., & Lambert, W. E. (2016). Prenatal depression screening by certified nurse-midwives, Oregon. *Journal of Midwifery and Women's Health*, 61(5), 599-605.

Rudy, C. C., Ballard, C., Broberg, C., & Hunter, A. J. (2016). Platypnea-orthodeoxia syndrome: A case of chronic paroxysmal hypoxemia. *Journal of General Internal Medicine*,

A 75-year-old man with chronic (30-year) unexplained paroxysmal hypoxemia presented with postural hypoxemia and desaturation consistent with a clinical manifestation of platypnea-orthodeoxia syndrome. His history included a lack of significant past pulmonary disease, yet with intermittent need for oxygen supplementation. On admission he was found to have an interatrial shunt through a patent foramen ovale. Device closure by percutaneous catheterization led to sustained resolution of symptoms. Platypnea-orthodeoxia syndrome is a rare but important consideration in the differential diagnosis of hypoxemia, as it represents a potentially curable cause of hypoxemia, with missed diagnosis leading to possible patient morbidity if untreated. Even more importantly, an astute and careful history and physical examination are integral to the diagnosis of this rare but likely under-recognized syndrome.

Salgado, V. E., Cavassoni, D., Gonçalves, A. P. R., Pfeifer, C., Moraes, R. R., & Schneider, L. F. (2017). Photoinitiator system and water effects on C=C conversion and solubility of experimental etch-and-rinse dental adhesives. *International Journal of Adhesion and Adhesives*, 72, 6-9.

Schabel, M. C., Roberts, V. H. J., Lo, J. O., Platt, S., Grant, K. A., Frias, A. E., et al. (2016). Functional imaging of the nonhuman primate placenta with endogenous blood oxygen level-dependent contrast. *Magnetic Resonance in Medicine*, 76(5), 1551-1562.

Schafer, C. T., Fay, J. F., Janz, J. M., & Farrens, D. L. (2016). Decay of an active GPCR: Conformational dynamics govern agonist rebinding and persistence of an active, yet empty, receptor state. *Proceedings of the National Academy of Sciences of the United States of America*, 113(42), 11961-11966.

Schlansky, B., & Orloff, S. L. (2016). Promise and pitfalls of using alpha-fetoprotein in liver transplantation allocation for hepatocellular carcinoma. *JAMA Surgery*,

Schwab, P., Sayles, H., Bergman, D., Cannon, G. W., Michaud, K., Mikuls, T. R., et al. (2016). Utilization of care outside the veterans affairs health care system by US veterans with rheumatoid arthritis. *Arthritis Care & Research*,
OBJECTIVES: Many veterans enrolled in Veterans Affairs (VA) also receive care through other

healthcare systems. Both VA and non-VA healthcare use must therefore be considered when conducting research in this population. This study characterized dual care utilization in veterans with rheumatoid arthritis (RA) and explored associations with RA disease activity. METHODS: Through a questionnaire mailed to RA patients at three VA sites, veterans reported medical services by non-VA primary care and subspecialty providers, comorbidities, non-VA medications, and hospitalizations. Disease activity score (DAS)-28 and Multidimensional Health Assessment Questionnaire (MD-HAQ) were recorded during VA clinic visits, and respondent groups compared. RESULTS: Of the 510 participants surveyed, 318 (62%) responded. Respondents were older (69 vs. 66 years, $p=0.006$), more likely non-smokers (80% vs. 67%, $p=0.001$) and had lower disease activity (DAS-28 3.3 vs. 3.8, $p<0.001$; MD-HAQ 0.8 vs. 0.9, $p=0.01$) than non-respondents ($n=192$, 38%). The respondents with a non-VA provider ($n=130$, 41%) were older (71 vs. 68 years, $p=0.001$) and had more education (14 vs. 13 years, $p=0.021$) than non-dual care users. Only 6% of respondents reported having a non-VA rheumatologist; with 2% receiving a non-VA prescribed biologic or disease-modifying anti-rheumatic drug. CONCLUSION: In this study, VA beneficiaries with RA had lower dual-care utilization than previously reported for the general VA population, with few patients receiving dual rheumatology care or non-VA RA medications. This survey suggests that most US Veterans with RA who access VA care use the VA as their primary source of arthritis care. This article is protected by copyright. All rights reserved.

Sharma, K. J., Esakoff, T. F., Guillet, A., Burwick, R. M., & Caughey, A. B. (2016). Pregnancies complicated by both preeclampsia and growth restriction between 34 and 37 weeks gestation are associated with adverse perinatal outcomes. *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*, , 1-14.

OBJECTIVE: To determine whether adverse outcomes were more common in late preterm pregnancies complicated by preeclampsia and growth restriction compared to those affected by preeclampsia alone. METHODS: This was a retrospective cohort study of 8,927 singleton pregnancies with preeclampsia. Pregnancies with small for gestational age (SGA) neonates (birthweight <10th percentile) were compared to those appropriate for gestational age (AGA) neonates. Maternal outcomes included cesarean delivery (CD) rate, CD for fetal heart rate (FHR)

abnormalities, abruption, postpartum hemorrhage (PPH), maternal transfusion, acute renal failure, and peripartum cardiomyopathy. Neonatal outcomes studied included respiratory distress syndrome (RDS), jaundice, hypoglycemia, seizure, asphyxia, neonatal death, and intrauterine fetal demise (IUFD). RESULTS: Women with preeclampsia and SGA infants were more likely to experience abruption (5.3% vs 3.0%, $p < 0.001$), higher CD rate (66.5% vs 55.0%, $p < 0.001$), and higher likelihood of a CD for FHR abnormalities (21.7% vs 10.0%, $p < 0.001$). SGA infants were more likely to experience adverse neonatal outcomes including RDS (10.1% vs 4.9%, $p < 0.001$), jaundice (59.8% vs 39.2%, $p < 0.001$), hypoglycemia (8.9% vs 3.9%, $p < 0.001$), asphyxia (0.6% vs 0.2%, $p = 0.015$), and IUFD (1.5% versus 0.3%, $p < 0.001$). CONCLUSIONS: Preeclamptic women and their neonates were more likely to experience adverse perinatal outcomes when SGA pregnancies were compared to those with AGA neonates.

Shatzel, J. J., Connelly, K. J., & DeLoughery, T. G. (2016). Thrombotic issues in transgender medicine: A review. *American Journal of Hematology,*

Clinicians, including hematologists, are more frequently encountering transgender individuals in practice; however, most lack training on the management and complications of transgender medicine. Hormonal therapy forms the backbone of medical interventions for patients undergoing gender transition. While supplementing an individual's intrinsic sex hormone is associated with a variety of hematologic complications including increased rates of venous thrombosis, cardiovascular events, erythrocytosis, and malignancy, the risks of supplementing with opposing sex hormones are not well understood. Data on the hematologic complications of these therapies are accumulating but remain limited, and clinicians have little experience with their management. This review highlights the current interventions available in transgender medicine and related potential hematologic complications, and it suggests simple, evidence-based management going forward. This article is protected by copyright. All rights reserved.

Sheridan, D. C., Hendrickson, R. G., Beauchamp, G., Laurie, A., Fu, R., & Horowitz, B. Z. (2016).

Adolescent intentional abuse ingestions: Overall 10-year trends and regional variation. *Pediatric Emergency Care,*

OBJECTIVE: Adolescent intentional ingestions remain a significant public health problem in the

United States with little research to date on the over-the-counter or prescription medicines that adolescents abuse. These data are important for anticipatory guidance by primary care providers, preventive health, and poison center outreach. METHODS: This was an observational study using the American Association of Poison Control Centers National Poison Data System. The study population consisted of all cases of patients aged 13 to 19 years from 2004 to 2013 with a coding of "intentional abuse." RESULTS: There were 95,695 patient calls that were coded for intentional abuse between 2004 and 2013 for adolescents aged 13 to 19 years. The most common agent reportedly ingested in intentional-abuse cases was antihistamine and/or decongestant with dextromethorphan, and this agent remained the most common throughout the 10-year study period. The next 4 most common agents remained similar across the study period as well and included ethanol, benzodiazepines, dextromethorphan alone, and marijuana. These 5 agents remained the most commonly reported across the study period for all US regions (West, Midwest, South Northeast, and US territories). CONCLUSIONS: Over a recent 10-year period, common cough preparations remain the most commonly reported intentional abuse ingestion among all years and regions for adolescents.

Shifera, A. S., Pennesi, M. E., Yang, P., & Lin, P. (2016). Ultra-wide-field fundus autofluorescence findings in patients with acute zonal occult outer retinopathy. *Retina (Philadelphia, Pa.)*,
PURPOSE: To determine whether ultra-wide-field fundus autofluorescence (UWFFAF) findings in acute zonal occult outer retinopathy correlated well with perimetry, optical coherence tomography, and electroretinography findings. METHODS: Retrospective observational study on 16 eyes of 10 subjects with AZOOR seen at a single referral center from October 2012 to March 2015 who had UWFFAF performed. Chi-square analysis was performed to compare categorical variables, and Mann-Whitney U test used for comparisons of nonparametric continuous variables. RESULTS: All eyes examined within 3 months of symptom onset (five of the five eyes) had diffusely hyperautofluorescent areas on UWFFAF. The remaining eyes contained hypoautofluorescent lesions with hyperautofluorescent borders. In 11/16 (68.8%) eyes, UWFFAF showed the full extent of lesions that would not have been possible with standard fundus autofluorescence centered on the fovea. There were 3 patterns of spread: centrifugal spread (7/16, 43.8%), centripetal spread (5/16, 31.3%), and centrifugal + centripetal spread (4/16,

25.0%). The UWFFAF lesions corresponded well with perimetric, optical coherence tomography, and electroretinography abnormalities. CONCLUSION: The UWFFAF along with optical coherence tomography can be useful in the evaluation and monitoring of acute zonal occult outer retinopathy patients.

Shindo, M. (2016). Focused lateral approach for targeted parathyroidectomy. *Operative Techniques in Otolaryngology - Head and Neck Surgery*, 27(3), 157-161.

Simmons, J., Gould, M. K., Iaccarino, J., Slatore, C. G., & Wiener, R. S. (2016). Systems-level resources for pulmonary nodule evaluation in the united states: A national survey. *American Journal of Respiratory and Critical Care Medicine*, 193(9), 1063-1065.

Simpson, E. L., Bieber, T., Guttman-Yassky, E., Beck, L. A., Blauvelt, A., Cork, M. J., et al. (2016).

Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *The New England Journal of Medicine*,

Background Dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha, inhibits signaling of interleukin-4 and interleukin-13, type 2 cytokines that may be important drivers of atopic or allergic diseases such as atopic dermatitis. Methods In two randomized, placebo-controlled, phase 3 trials of identical design (SOLO 1 and SOLO 2), we enrolled adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment. Patients were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment and a reduction of 2 points or more in that score from baseline at week 16. Results We enrolled 671 patients in SOLO 1 and 708 in SOLO 2. In SOLO 1, the primary outcome occurred in 85 patients (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo ($P < 0.001$ for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo ($P < 0.001$ for both comparisons). In addition, in

the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo ($P < 0.001$ for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups.

Conclusions In two phase 3 trials of identical design involving patients with atopic dermatitis, dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo. Trials of longer duration are needed to assess the long-term effectiveness and safety of dupilumab. (Funded by Sanofi and Regeneron Pharmaceuticals; SOLO 1 ClinicalTrials.gov number, NCT02277743 ; SOLO 2 ClinicalTrials.gov number, NCT02277769 .).

Sivaswamy, L. (2016). Pediatric intracranial hypertension. *Pediatric Neurology Briefs*, 30(10), 39.

Investigators from the Ohio State University, Oregon Health and Science University and Rosalind Franklin School of Medicine examined the presenting manifestations, demographics and treatment strategies in children enrolled in the Intracranial Hypertension Registry (IHR).

Smith, M. L., Hostetler, C. M., Heinricher, M. M., & Ryabinin, A. E. (2016). Social transfer of pain in mice. *Science Advances*, 2(10), e1600855.

A complex relationship exists between the psychosocial environment and the perception and experience of pain, and the mechanisms of the social communication of pain have yet to be elucidated. The present study examined the social communication of pain and demonstrates that "bystander" mice housed and tested in the same room as mice subjected to inflammatory pain or withdrawal from morphine or alcohol develop corresponding hyperalgesia. Olfactory cues mediate the transfer of hyperalgesia to the bystander mice, which can be measured using mechanical, thermal, and chemical tests. Hyperalgesia in bystanders does not co-occur with anxiety or changes in corticosterone and cannot be explained by visually dependent emotional contagion or stress-induced hyperalgesia. These experiments reveal the multifaceted relationship between the social environment and pain behavior and support the use of mice as a model system for

investigating these factors. In addition, these experiments highlight the need for proper consideration of how experimental animals are housed and tested.

Snyder, H. M., Asthana, S., Bain, L., Brinton, R., Craft, S., Dubal, D. B., et al. (2016). Sex biology contributions to vulnerability to alzheimer's disease: A think tank convened by the women's alzheimer's research initiative. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*,

More than 5 million Americans are living with Alzheimer's disease (AD) today, and nearly two-thirds of Americans with AD are women. This sex difference may be due to the higher longevity women generally experience; however, increasing evidence suggests that longevity alone is not a sufficient explanation and there may be other factors at play. The Alzheimer's Association convened an expert think tank to focus on the state of the science and level of evidence around gender and biological sex differences for AD, including the knowledge gaps and areas of science that need to be more fully addressed. This article summarizes the think tank discussion, moving forward a research agenda and funding program to better understand the biological underpinnings of sex- and gender-related disparities of risk for AD.

Spencer, P. S., Mazumder, R., Palmer, V. S., & Oregon-Uganda Research Team on Nodding Syndrome. (2016). Response to R. colebunders: Helminth infections in nodding syndrome. *Journal of the Neurological Sciences*,

Stevens, K. R., Jr, & Toffler, W. L. (2016). Euthanasia and physician-assisted suicide. *Jama*, 316(15), 1599.

Steyger, P. S. (2015). Novel aminoglycoside antibiotics show reduced ototoxicity risk. *Hearing Journal*, 68(4), 32-35.

Stout, N. L., Silver, J. K., Raj, V. S., Rowland, J., Gerber, L., Cheville, A., et al. (2016). Toward a national initiative in cancer rehabilitation: Recommendations from a subject matter expert group. *Archives of Physical Medicine and Rehabilitation*, 97(11), 2006-2015.

The health care delivery system in the United States is challenged to meet the needs of a

growing population of cancer survivors. A pressing need is to optimize overall function and reduce disability in these individuals. Functional impairments and disability affect most patients during and after disease treatment. Rehabilitation health care providers can diagnose and treat patients' physical, psychological, and cognitive impairments in an effort to maintain or restore function, reduce symptom burden, maximize independence and improve quality of life in this medically complex population. However, few care delivery models integrate comprehensive cancer rehabilitation services into the oncology care continuum. The Rehabilitation Medicine Department of the Clinical Center at the National Institutes of Health with support from the National Cancer Institute and the National Center for Medical Rehabilitation Research convened a subject matter expert group to review current literature and practice patterns, identify opportunities and gaps regarding cancer rehabilitation and its support of oncology care, and make recommendations for future efforts that promote quality cancer rehabilitation care. The recommendations suggest stronger efforts toward integrating cancer rehabilitation care models into oncology care from the point of diagnosis, incorporating evidence-based rehabilitation clinical assessment tools, and including rehabilitation professionals in shared decision-making in order to provide comprehensive cancer care and maximize the functional capabilities of cancer survivors. These recommendations aim to enable future collaborations among a variety of stakeholders to improve the delivery of high-quality cancer care.

Sullivan, E. V., Lane, B., Kwon, D., Meloy, M. J., Tapert, S. F., Brown, S. A., et al. (2016). Structural brain anomalies in healthy adolescents in the NCANDA cohort: Relation to neuropsychological test performance, sex, and ethnicity. *Brain Imaging and Behavior*, , 1-14.

Sun, C. J., Ma, A., Tanner, A. E., Mann, L., Reboussin, B. A., Garcia, M., et al. (2016). Depressive symptoms among latino sexual minority men and latina transgender women in a new settlement state: The role of perceived discrimination. *Depression Research and Treatment*, 2016, 4972854. Background. Little is known about the role of discrimination on depression among Latino sexual and gender identity minorities. This manuscript examined the relationship between ethnic/racial discrimination and sexual discrimination on clinically significant depressive symptoms among Latino sexual minority men (i.e., gay and bisexual men and other men who have sex with men)

and Latina transgender women. Methods. A community-based participatory research partnership recruited participants (N = 186; 80.6% cisgender men) in North Carolina to a social network-based HIV intervention. Using baseline data, we quantified the amount of perceived discrimination and conducted mixed-effects logistic regression analyses to examine correlates of clinically significant depressive symptoms. Results. A high percentage of participants reported ethnic/racial discrimination (73.7%) and sexual discrimination (53.8%). In the multivariable models, ethnic/racial discrimination, sexual discrimination, masculinity, fatalism, and social support were significantly associated with clinically significant depressive symptoms. Discussion. Improving mental health requires multilevel interventions that address pertinent individual, interpersonal, and system level factors.

Suszko, J., Danko, C., & Fett, N. (2016). Periarticular swelling and skin thickening involving the proximal interphalangeal joints. *The American Journal of Dermatopathology*, 38(11), 858.

Suszko, J., Danko, C., & Fett, N. (2016). Periarticular swelling and skin thickening involving the proximal interphalangeal joints. *The American Journal of Dermatopathology*, 38(11), 822-823.

Switzer, G. E., Bruce, J., Kiefer, D. M., Kobusingye, H., Drexler, R., Besser, R. M., et al. (2016).

HRQoL among older related HSC donors (>60 yrs.) is equivalent to that of younger related donors (18-60 yrs.): An RDSafe study. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

The increasing number of older adults with blood-related disorders and the introduction of reduced intensity conditioning regimens has led to increases in hematopoietic stem cell (HSC) transplantation among older adults and a corresponding increase in the age of siblings who donate HSCs to these patients. Data regarding the donation-related experiences of older donors is lacking. The Related Donor Safety Study (RDSafe) aimed to examine/compare health-related quality of life (HRQoL) of older versus younger HSC donors. 60 peripheral blood stem cell (PBSC) donors ages 18-60 and 104 PBSC donors age >60 completed validated questionnaires at pre-donation, 4 weeks and 1 year post-donation. Prior to donation, older donors had poorer general physical health ($t=-3.27$; $p=.001$) but better mental health ($t=2.11$; $p<.05$). There were no age differences in multiple other donation-related factors. At 4 weeks post-donation, there were no

group differences in general physical/mental health, but older donors were less likely to report donation-related pain ($t=-2.26$; $p<.05$) and concerns ($t=-3.38$; $p=.001$). At both 4 weeks and 1 year post-donation, there were no significant differences in the percentage of each age group feeling physically back to normal or in the number of days it took donors to feel completely well. There was no evidence that increasing age within the older donor group was associated with poorer donation-related HRQoL. Taken together, these data support the current practice of HSC donation by sibling donors above age 60, providing no evidence of worsening HRQoL up to one year after donation in individuals up to age 76.

Tamber, M. S., Nikas, D., Beier, A., Baird, L. C., Bauer, D. F., Durham, S., et al. (2016). Congress of neurological surgeons systematic review and evidence-based guideline on the role of cranial molding orthosis (helmet) therapy for patients with positional plagiocephaly. *Neurosurgery*, 79(5), E632-E633.

BACKGROUND: No evidence-based guidelines exist on the role of cranial-molding orthosis (helmet) therapy for patients with positional plagiocephaly. **OBJECTIVE:** To address the clinical question: "Does helmet therapy provide effective treatment for positional plagiocephaly?" and to make treatment recommendations based on the available evidence. **METHODS:** The US National Library of Medicine Medline database and the Cochrane Library were queried by using MeSH headings and key words relevant to the objective of this systematic review. Abstracts were reviewed, after which studies meeting the inclusion criteria were selected and graded according to their quality of evidence (Classes I-III). Evidentiary tables were constructed that summarized pertinent study results, and, based on the quality of the literature, recommendations were made (Levels I-III). **RESULTS:** Fifteen articles met criteria for inclusion into the evidence tables. There was 1 prospective randomized controlled trial (Class II), 5 prospective comparative studies (Class II), and 9 retrospective comparative studies (Class II). **CONCLUSION:** There is a fairly substantive body of nonrandomized evidence that demonstrates more significant and faster improvement of cranial shape in infants with positional plagiocephaly treated with a helmet in comparison with conservative therapy, especially if the deformity is severe, provided that helmet therapy is applied during the appropriate period of infancy. Specific criteria regarding the measurement and quantification of deformity and the most appropriate time window in infancy

for treatment of positional plagiocephaly with a helmet remains elusive. In general, infants with a more severe presenting deformity and infants who are helmeted early in infancy tend to have more significant correction (and even normalization) of head shape. The full guidelines document can be located at https://www.cns.org/guidelines/guidelines-management-patients-positional-plagiocephaly/Chapter_5.

Tamber, M. S., Nikas, D., Beier, A., Baird, L. C., Bauer, D. F., Durham, S., et al. (2016). Guidelines: Congress of neurological surgeons systematic review and evidence-based guideline on the role of cranial molding orthosis (helmet) therapy for patients with positional plagiocephaly. *Neurosurgery*, 79(5), E632-E633.

BACKGROUND: No evidence-based guidelines exist on the role of cranial-molding orthosis (helmet) therapy for patients with positional plagiocephaly. OBJECTIVE: To address the clinical question: "Does helmet therapy provide effective treatment for positional plagiocephaly?" and to make treatment recommendations based on the available evidence. METHODS: The US National Library of Medicine Medline database and the Cochrane Library were queried by using MeSH headings and key words relevant to the objective of this systematic review. Abstracts were reviewed, after which studies meeting the inclusion criteria were selected and graded according to their quality of evidence (Classes I-III). Evidentiary tables were constructed that summarized pertinent study results, and, based on the quality of the literature, recommendations were made (Levels I-III). RESULTS: Fifteen articles met criteria for inclusion into the evidence tables. There was 1 prospective randomized controlled trial (Class II), 5 prospective comparative studies (Class II), and 9 retrospective comparative studies (Class II). CONCLUSION: There is a fairly substantive body of nonrandomized evidence that demonstrates more significant and faster improvement of cranial shape in infants with positional plagiocephaly treated with a helmet in comparison with conservative therapy, especially if the deformity is severe, provided that helmet therapy is applied during the appropriate period of infancy. Specific criteria regarding the measurement and quantification of deformity and the most appropriate time window in infancy for treatment of positional plagiocephaly with a helmet remains elusive. In general, infants with a more severe presenting deformity and infants who are helmeted early in infancy tend to have more significant correction (and even normalization) of head shape. The full guidelines document

can be located at <https://www.cns.org/guidelines/guidelines-management-patients-positional-plagioce> phaly/Chapter_5.

Teotia, P., Chopra, D. A., Dravid, S. M., Van Hook, M. J., Qiu, F., Morrison, J., et al. (2016).

Generation of functional human retinal ganglion cells with target specificity from pluripotent stem cells by chemically defined recapitulation of developmental mechanism. *Stem Cells (Dayton, Ohio)*,

Glaucoma is a complex group of diseases wherein a selective degeneration of retinal ganglion cells (RGCs) lead to irreversible loss of vision. A comprehensive approach to glaucomatous RGC degeneration may include stem cells to functionally replace dead neurons through transplantation and understand RGCs vulnerability using a disease in a dish stem cell model. Both approaches require the directed generation of stable, functional, and target-specific RGCs from renewable sources of cells, that is, the embryonic stem cells and induced pluripotent stem cells. Here, we demonstrate a rapid and safe, stage-specific, chemically defined protocol that selectively generates RGCs across species, including human, by recapitulating the developmental mechanism. The de novo generated RGCs from pluripotent cells are similar to native RGCs at the molecular, biochemical, functional levels. They also express axon guidance molecules, and discriminate between specific and nonspecific targets, and are nontumorigenic. *Stem Cells* 2016.

Tham, S. W., Palermo, T. M., Holley, A. L., Zhou, C., Stubhaug, A., Furberg, A. S., et al. (2016). A population-based study of quantitative sensory testing in adolescents with and without chronic pain. *Pain*,

Quantitative sensory testing (QST) has been used to characterize pain sensitivity in individuals with and without pain conditions. Research remains limited in pediatric populations, hindering the ability to expand the utility of QST toward its potential application in clinical settings and clinical predictive value. The aims of this study were to examine pain sensitivity using QST in adolescents with chronic pain compared to adolescents without chronic pain and identify predictors of pain sensitivity. A population-based study conducted from 2010 to 2011 provided data on 941 adolescents, 197 were classified as having chronic pain and 744 were classified without chronic pain. Self-reported data on pain characteristics, psychological functioning, and QST responses

were examined. The findings revealed lower pressure pain threshold and tolerance on the trapezius (P 's = 0.03) in adolescents with chronic pain compared to adolescents without chronic pain, but no differences on heat or cold-pressor pain tasks. Female sex (P 's = 0.02) and poorer psychological functioning (P 's = 0.02) emerged as significant predictors of greater pain sensitivity across all pain modalities. Exploratory analyses revealed several associations between clinical pain characteristics and QST responses within the chronic pain cohort. Findings from this large pediatric sample provide comprehensive data that could serve as normative data on QST responses in adolescents with and without chronic pain. These findings lay the groundwork toward developing future QST research and study protocols in pediatric populations, taking into consideration sex and psychological distress.

Theiler, J., Yoon, H., Yusim, K., Picker, L. J., Fruh, K., & Korber, B. (2016). Epigraph: A vaccine design tool applied to an HIV therapeutic vaccine and a pan-filovirus vaccine. *Scientific Reports*, 6, 33987.

Epigraph is an efficient graph-based algorithm for designing vaccine antigens to optimize potential T-cell epitope (PTE) coverage. Epigraph vaccine antigens are functionally similar to Mosaic vaccines, which have demonstrated effectiveness in preliminary HIV non-human primate studies. In contrast to the Mosaic algorithm, Epigraph is substantially faster, and in restricted cases, provides a mathematically optimal solution. Epigraph furthermore has new features that enable enhanced vaccine design flexibility. These features include the ability to exclude rare epitopes from a design, to optimize population coverage based on inexact epitope matches, and to apply the code to both aligned and unaligned input sequences. Epigraph was developed to provide practical design solutions for two outstanding vaccine problems. The first of these is a personalized approach to a therapeutic T-cell HIV vaccine that would provide antigens with an excellent match to an individual's infecting strain, intended to contain or clear a chronic infection. The second is a pan-filovirus vaccine, with the potential to protect against all known viruses in the Filoviridae family, including ebolaviruses. A web-based interface to run the Epigraph tool suite is available (<http://www.hiv.lanl.gov/content/sequence/EPIGRAPH/epigraph.html>).

Theologis, A. A., Mundis, G. M., Jr, Nguyen, S., Okonkwo, D. O., Mummaneni, P. V., Smith, J. S., et al.

(2016). Utility of multilevel lateral interbody fusion of the thoracolumbar coronal curve apex in adult deformity surgery in combination with open posterior instrumentation and L5-S1 interbody fusion: A case-matched evaluation of 32 patients. *Journal of Neurosurgery.Spine*, , 1-12.

OBJECTIVE The aim of this study was to evaluate the utility of supplementing long thoracolumbar posterior instrumented fusion (posterior spinal fusion, PSF) with lateral interbody fusion (LIF) of the lumbar/thoracolumbar coronal curve apex in adult spinal deformity (ASD). **METHODS** Two multicenter databases were evaluated. Adults who had undergone multilevel LIF of the coronal curve apex in addition to PSF with L5-S1 interbody fusion (LS+Apex group) were matched by number of posterior levels fused with patients who had undergone PSF with L5-S1 interbody fusion without LIF (LS-Only group). All patients had at least 2 years of follow-up. Percutaneous PSF and 3-column osteotomy (3CO) were excluded. Demographics, perioperative details, radiographic spinal deformity measurements, and HRQoL data were analyzed. **RESULTS** Thirty-two patients were matched (LS+Apex: 16; LS: 16) (6 men, 26 women; mean age 63 +/- 10 years). Overall, the average values for measures of deformity were as follows: Cobb angle > 40 degrees , sagittal vertical axis (SVA) > 6 cm, pelvic tilt (PT) > 25 degrees , and mismatch between pelvic incidence (PI) and lumbar lordosis (LL) > 15 degrees . There were no significant intergroup differences in preoperative radiographic parameters, although patients in the LS+Apex group had greater Cobb angles and less LL. Patients in the LS+Apex group had significantly more anterior levels fused (4.6 vs 1), longer operative times (859 vs 379 minutes), and longer length of stay (12 vs 7.5 days) (all $p < 0.01$). For patients in the LS+Apex group, Cobb angle, pelvic tilt (PT), lumbar lordosis (LL), PI-LL (lumbopelvic mismatch), Oswestry Disability Index (ODI) scores, and visual analog scale (VAS) scores for back and leg pain improved significantly ($p < 0.05$). For patients in the LS-Only group, there were significant improvements in Cobb angle, ODI score, and VAS scores for back and leg pain. The LS+Apex group had better correction of Cobb angles (56% vs 33%, $p = 0.02$), SVA (43% vs 5%, $p = 0.46$), LL (62% vs 13%, $p = 0.35$), and PI-LL (68% vs 33%, $p = 0.32$). Despite more LS+Apex patients having major complications (56% vs 13%; $p = 0.02$) and postoperative leg weakness (31% vs 6%, $p = 0.07$), there were no intergroup differences in 2-year outcomes. **CONCLUSIONS** Long open posterior instrumented fusion with or without multilevel LIF is used to treat a variety of coronal and sagittal adult

thoracolumbar deformities. The addition of multilevel LIF to open PSF with L5-S1 interbody support in this small cohort was often used in more severe coronal and/or lumbopelvic sagittal deformities and offered better correction of major Cobb angles, lumbopelvic parameters, and SVA than posterior-only operations. As these advantages came at the expense of more major complications, more leg weakness, greater blood loss, and longer operative times and hospital stays without an improvement in 2-year outcomes, future investigations should aim to more clearly define deformities that warrant the addition of multilevel LIF to open PSF and L5-S1 interbody fusion.

Tiwari, S., Raman, J., Reddy, V., Ghetler, A., Tella, R. P., Han, Y., et al. (2016). Towards translation of discrete frequency infrared spectroscopic imaging for digital histopathology of clinical biopsy samples. *Analytical Chemistry*, 88(20), 10183-10190.

Fourier transform infrared (FT-IR) spectroscopic imaging has been widely tested as a tool for stain-free digital histology of biomedical specimens, including for the identification of infiltration and fibrosis in endomyocardial biopsy samples to assess transplant rejection. A major barrier in clinical translation has been the slow speed of imaging. To address this need, we tested and report here the viability of using high speed discrete frequency infrared (DFIR) imaging to obtain stain-free biochemical imaging in cardiovascular samples collected from patients. Images obtained by this method were classified with high accuracy by a Bayesian classification algorithm trained on FT-IR imaging data as well as on DFIR data. A single spectral feature correlated with instances of fibrosis, as identified by the pathologist, highlights the advantage of the DFIR imaging approach for rapid detection. The speed of digital pathologic recognition was at least 16 times faster than the fastest FT-IR imaging instrument. These results indicate that a fast, on-site identification of fibrosis using IR imaging has potential for real time assistance during surgeries. Further, the work describes development and applications of supervised classifiers on DFIR imaging data, comparing classifiers developed on FT-IR and DFIR imaging modalities and identifying specific spectral features for accurate identification of fibrosis. This addresses a topic of much debate on the use of training data and cross-modality validity of IR measurements. Together, the work is a step toward addressing a clinical diagnostic need at acquisition time scales that make IR imaging technology practical for medical use.

Tovar, K. R., & Westbrook, G. L. (2017). Modulating synaptic NMDA receptors. *Neuropharmacology*, *112*(Pt A), 29-33.

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

Tsujimoto, A., Barkmeier, W. W., Takamizawa, T., Watanabe, H., Johnson, W. W., Latta, M. A., et al.

(2016). Relationship between mechanical properties and bond durability of short fiber-reinforced resin composite with universal adhesive. *European Journal of Oral Sciences*, *124*(5), 480-489.

The purpose of this study was to determine the relationship between mechanical properties and bond durability of short fiber-reinforced resin composite with universal adhesive. As controls, micro-hybrid and nano-hybrid resin composites were tested. The universal adhesives used were Scotchbond Universal, Adhese Universal, and G-Premio Bond. The fracture toughness and flexural properties of resin composites, and shear bond strength and shear fatigue strength of universal adhesive with resin composite using both total-etch and self-etch modes were determined. In the results, short fiber-reinforced resin composite showed significantly higher fracture toughness than did micro-hybrid and nano-hybrid resin composites. The flexural strength and modulus of short fiber-reinforced and nano-hybrid resin composites were significantly lower than were those of

micro-hybrid resin composites. Regardless of etching mode, the shear bond strength of universal adhesives with short fiber-reinforced resin composite did not show any significant differences from micro-hybrid and nano-hybrid resin composites. The shear fatigue strength of universal adhesives with short fiber-reinforced resin composite and micro-hybrid resin composites were significantly higher than that of nano-hybrid resin composites. The results of this study suggest that the mechanical properties of short fiber-reinforced resin composite improve their bond durability with universal adhesive.

van der Heijde, D., Deodhar, A., Fleischmann, R., Mease, P. J., Rudwaleit, M., Nurminen, T., et al. (2016). Early disease activity or clinical response predict long-term outcomes with certolizumab pegol in axial spondyloarthritis or psoriatic arthritis. *Arthritis Care & Research*, Objective Early identification of patients unlikely to achieve good long-term disease control with anti-TNF therapy in axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) is important for physicians following treat-to-target recommendations. Here we assess associations between disease activity or clinical response during the first 12 weeks (wks) of treatment and attainment of treatment targets at Wk48 in axSpA and PsA patients receiving certolizumab pegol (CZP).
Methods The relationship between disease activity or clinical response during the first 12 wks of treatment, and achievement of Wk48 targets (axSpA: ASDAS-CRP inactive disease or BASDAI 5.1 at Wk12, compared to 73% (57/78) of patients with DAS28(CRP) <2.6. Similar results were observed regardless of disease activity measure used. Clinical response at Wk12 also predicted Wk48 outcomes, though to a lesser extent than disease activity. Conclusion Using disease activity and clinical response state during the first 12 wks of CZP treatment, it was possible to identify a subset of axSpA and PsA patients unlikely to achieve long-term treatment goals. This article is protected by copyright. All rights reserved.

Van, P. Y., & Schreiber, M. A. (2016). Contemporary thromboprophylaxis of trauma patients. *Current Opinion in Critical Care*,

PURPOSE OF REVIEW: The traumatically injured patient is at high risk for developing venous thromboembolism. Clinical practice guidelines developed by the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma recognize the importance of

initiating thromboprophylaxis, but the guidelines lack specific recommendations regarding the timing and dose of pharmacologic thromboprophylaxis. We review the literature regarding initiation of thromboprophylaxis in different injuries, the use of inferior vena cava filters, laboratory monitoring, dosing regimens, and the use of antiplatelet therapy. RECENT FINDINGS: Use of pharmacologic thromboprophylaxis with invasive intracranial monitors is not associated with increased bleeding complications. The initiation of low-molecular-weight heparin (LMWH) prophylaxis 48 h postinjury in blunt solid organ injury is not associated with an increase in the rate of failed nonoperative management. Antiplatelet therapy in conjunction with LMWH may help to prevent venous thromboembolism. SUMMARY: In the setting of blunt traumatic brain and solid organ injury, initiation of pharmacologic thromboprophylaxis 48 h after injury is not associated with increased bleeding complications. There is no consensus or clear data showing which dosing regimen of LMWH is most effective or whether routine laboratory measurements are beneficial for determining effective thromboprophylaxis.

Vaughan Dickson, V., Lee, C. S., Yehle, K. S., Mola, A., Faulkner, K. M., & Riegel, B. (2016).

Psychometric testing of the self-care of coronary heart disease inventory (SC-CHDI). *Research in Nursing & Health*,

Although coronary heart disease (CHD) requires a significant amount of self-care, there are no instruments available to measure self-care in this population. The purpose of this study was to test the psychometric properties of the Self-Care of Coronary Heart Disease Inventory (SC-CHDI). Using the Self-Care of Chronic Illness theory, we developed a 22-item measure of maintenance, management, and confidence appropriate for persons with stable CHD and tested it in a convenience sample of 392 adults (62% male, mean age 61.4 +/- 9.6 years). Factorial validity was tested with confirmatory factor analysis. Convergent validity was tested with the Medical Outcomes Study MOS-SAS Specific Adherence Scale and the Decision Making Competency Inventory (DMCI). Cronbach alpha and factor determinacy scores (FDS) were calculated to assess reliability. Two multidimensional self-care scales were confirmed: self-care maintenance included "consultative behaviors" (e.g., taking medicines as prescribed) and "autonomous behaviors" (e.g., exercising 30 minute/day; FDS = .87). The multidimensional self-care management scale included "early recognition and response" (e.g., recognizing symptoms)

and "delayed response" (e.g., taking an aspirin; FDS = .76). A unidimensional confidence factor captured confidence in each self-care process ($\alpha = .84$). All the self-care dimensions were associated with treatment adherence as measured by the MOS-SAS. Only self-care maintenance and confidence were associated with decision-making (DCMI). These findings support the conceptual basis of self-care in patients with CHD as a process of maintenance that includes both consultative and autonomous behaviors, and management with symptom awareness and response. The SC-CHDI confidence scale is promising as a measure of self-efficacy, an important factor influencing self-care. (c) 2016 Wiley Periodicals, Inc.

Ventres, W., & Gross, P. (2016). Getting started: A call for storytelling in family medicine education. *Family Medicine, 48*(9), 682-687.

Verma, V., Shostrom, V. K., Kumar, S. S., Zhen, W., Hallemeier, C. L., Braunstein, S. E., et al. (2016). Multi-institutional experience of stereotactic body radiotherapy for large (≥ 5 centimeters) non-small cell lung tumors. *Cancer*,
BACKGROUND: Stereotactic body radiotherapy (SBRT) is the standard of care for patients with nonoperative, early-stage non-small cell lung cancer (NSCLC) measuring ≥ 5 cm is considerably less defined, with the existing literature limited to small, single-institution reports. The current multi-institutional study reported outcomes evaluating the largest such population reported to date. METHODS: Clinical/treatment characteristics, outcomes, toxicities, and patterns of failure were assessed in patients with primary NSCLC measuring ≥ 5 cm without evidence of distant/lymph node metastasis who underwent SBRT using ≥ 5 cm reported to date, indicate that SBRT is a safe and efficacious option. *Cancer* 2016. (c) 2016 American Cancer Society.

Vesco, K. K., Leo, M. C., Karanja, N., Gillman, M. W., McEvoy, C. T., King, J. C., et al. (2016). One-year postpartum outcomes following a weight management intervention in pregnant women with obesity. *Obesity, 24*(10), 2042-2049.

Vidal, A. C., Howard, L. E., Sun, S. X., Cooperberg, M. R., Kane, C. J., Aronson, W. J., et al. (2016). Obesity and prostate cancer-specific mortality after radical prostatectomy: Results from the shared equal access regional cancer hospital (SEARCH) database. *Prostate Cancer and Prostatic*

Diseases,

BACKGROUND: At the population level, obesity is associated with prostate cancer (PC) mortality. However, few studies analyzed the associations between obesity and long-term PC-specific outcomes after initial treatment. **METHODS:** We conducted a retrospective analysis of 4268 radical prostatectomy patients within the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Cox models accounting for known risk factors were used to examine the associations between body mass index (BMI) and PC-specific mortality (PCSM; primary outcome). Secondary outcomes included biochemical recurrence (BCR) and castration-resistant PC (CRPC). BMI was used as a continuous and categorical variable (normal <25 kg/m², overweight 25-29.9 kg/m² and obese 30 kg/m²). Median follow-up among all men who were alive at last follow-up was 6.8 years (interquartile range=3.5-11.0). During this time, 1384 men developed BCR, 117 developed CRPC and 84 died from PC. Hazard ratios were analyzed using competing-risks regression analysis accounting for non-PC death as a competing risk. **RESULTS:** On crude analysis, higher BMI was not associated with risk of PCSM (P=0.112), BCR (0.259) and CRPC (P=0.277). However, when BMI was categorized, overweight (hazard ratio (HR) 1.99, P=0.034) and obesity (HR 1.97, P=0.048) were significantly associated with PCSM. Obesity and overweight were not associated with BCR or CRPC (all P0.189). On multivariable analysis adjusting for both clinical and pathological features, results were little changed in that obesity (HR=2.05, P=0.039) and overweight (HR=1.88, P=0.061) were associated with higher risk of PCSM, but not with BCR or CRPC (all P0.114) with the exception that the association for overweight was no longer statistical significant. **CONCLUSIONS:** Overweight and obesity were associated with increased risk of PCSM after radical prostatectomy. If validated in larger studies with longer follow-up, obesity may be established as a potentially modifiable risk factor for PCSM. *Prostate Cancer and Prostatic Diseases* advance online publication, 4 October 2016; doi:10.1038/pcan.2016.47.

Vyleta, N. P., Borges-Merjane, C., & Jonas, P. (2016). Plasticity-dependent, full detonation at hippocampal mossy fiber-CA3 pyramidal neuron synapses. *Elife*, 5, 10.7554/eLife.17977. Mossy fiber synapses on CA3 pyramidal cells are 'conditional detonators' that reliably discharge postsynaptic targets. The 'conditional' nature implies that burst activity in dentate gyrus granule cells is required for detonation. Whether single unitary excitatory postsynaptic potentials (EPSPs)

trigger spikes in CA3 neurons remains unknown. Mossy fiber synapses exhibit both pronounced short-term facilitation and uniquely large post-tetanic potentiation (PTP). We tested whether PTP could convert mossy fiber synapses from subdetonator into detonator mode, using a recently developed method to selectively and noninvasively stimulate individual presynaptic terminals in rat brain slices. Unitary EPSPs failed to initiate a spike in CA3 neurons under control conditions, but reliably discharged them after induction of presynaptic short-term plasticity. Remarkably, PTP switched mossy fiber synapses into full detonators for tens of seconds. Plasticity-dependent detonation may be critical for efficient coding, storage, and recall of information in the granule cell-CA3 cell network.

Wadhwa, H., Terris, M. K., Aronson, W. J., Kane, C. J., Amling, C. L., Cooperberg, M. R., et al. (2016).

Long-term oncological outcomes of apical positive surgical margins at radical prostatectomy in the shared equal access regional cancer hospital cohort. *Prostate Cancer and Prostatic Diseases*, BACKGROUND: Approximately 29-38% of all positive surgical margins (PSMs) at radical prostatectomy (RP) involve the apex. The prognostic significance of apical PSM remains unclear. We therefore compared the long-term oncologic outcomes of men with apical PSMs to those with negative PSMs, apical and other PSMs, and other PSMs at RP. METHODS: The SEARCH (Shared Equal Access Regional Cancer Hospital) database was used to identify 4031 men with prostate cancer (PCa) managed with RP with complete pathologic grade and stage data. Margin status was categorized as negative, apex only, or other positive. Multivariable Cox regression models adjusted for pathologic stage and grade were developed to test the relationship between margin status and biochemical recurrence (BCR), metastases and PCa death. RESULTS: In the final cohort, 34.3% had PSMs, whereas 65.7% had negative margins. Univariable analysis showed that compared with negative margins, apex-only PSM was associated with BCR (hazard ratio (HR): 1.4 [1.1-1.8]), but not metastases or PCa death, whereas apex and other PSMs were associated with BCR (HR: 3.3 [2.8-4]) and metastases (HR: 1.8 [1.02-3.1]) but not PCa death. Nonapical PSMs were associated with BCR (HR: 2.7 [2.4-3.1]), metastases (1.7 [1.2-2.5]) and PCa death (1.8 [1.05-3]). On multivariable analysis, apex-only, apex and other, and nonapical PSMs were associated with BCR but margin status was not associated with metastases or PCa death. CONCLUSIONS: In a large cohort of men undergoing RP, those with PSMs at the prostatic

apex had lower BCR, metastases, or PCa death compared with those with PSMs at other locations. When adjusted for pathologic stage and grade, however, PSMs were associated with BCR but not long-term oncologic outcomes. These data confirm that men with apex-only PSMs may not be ideal candidates for adjuvant therapy after RP. *Prostate Cancer and Prostatic Diseases* advance online publication, 4 October 2016; doi:10.1038/pcan.2016.45.

Wallace, A. H., Dalziel, S. R., Cowan, B. R., Young, A. A., Thornburg, K. L., & Harding, J. E. (2016). Long-term cardiovascular outcome following fetal anaemia and intrauterine transfusion: A cohort study. *Archives of Disease in Childhood*,

Wangpraseurt, D., Jacques, S. L., Petrie, T., & Kuhl, M. (2016). Monte carlo modeling of photon propagation reveals highly scattering coral tissue. *Frontiers in Plant Science*, 7, 1404. Corals are very efficient at using solar radiation, with photosynthetic quantum efficiencies approaching theoretical limits. Here, we investigated potential mechanisms underlying such outstanding photosynthetic performance through extracting inherent optical properties of the living coral tissue and skeleton in a massive faviid coral. Using Monte Carlo simulations developed for medical tissue optics it is shown that for the investigated faviid coral, the coral tissue was a strongly light scattering matrix with a reduced scattering coefficient of $\mu_s' = 10 \text{ cm}^{-1}$ (at 636 nm). In contrast, the scattering coefficient of the coral skeleton was $\mu_s' = 3.4 \text{ cm}^{-1}$, which facilitated the efficient propagation of light to otherwise shaded coral tissue layers, thus supporting photosynthesis in lower tissues. Our study provides a quantification of coral tissue optical properties in a massive faviid coral and suggests a novel light harvesting strategy, where tissue and skeletal optics act in concert to optimize the illumination of the photosynthesizing algal symbionts embedded within the living coral tissue.

Warshaw, E. M., Hagen, S. L., Sasseville, D., Maibach, H. I., DeKoven, J. G., Belsito, D. V., et al. (2016). Occupational contact dermatitis in north american mechanics and repairers referred for patch testing: Retrospective analysis of cross-sectional data from the north american contact dermatitis group 1998 to 2014. *Dermatitis : Contact, Atopic, Occupational, Drug*,
BACKGROUND: Contact dermatoses are common in mechanic and repair occupations.
OBJECTIVES: This study aimed to (1) estimate the prevalence of occupationally related contact

dermatitis among mechanics/repairers patch tested from 1998 to 2014 by the North American Contact Dermatitis Group, (2) characterize responsible allergens and irritants, and their sources, and (3) compare results among 3 occupational subgroups (mechanics, electrical/electronic, and other). METHODS: A cross-sectional analysis of patients patch tested by the North American Contact Dermatitis Group between 1998 and 2014. RESULTS: Of 38,784 patients patch tested, 691 (1.8%) were mechanics/repairers. Male sex (93.5%) and hand involvement (59.5%) were common overall. Occupationally related skin disease was more prevalent among vehicle and mobile equipment mechanics/repairers (52.7%) and other mechanics/repairers (41.4%) than electrical/electronic equipment mechanics/repairers (21.3%). Overall, carba mix, thiuram mix, and methylchloroisothiazolone/methylisothiazolone were the most common occupation-related clinically relevant allergens. Gloves, automotive vehicles, solvents, oils, lubricants, and fuels were the most common sources of responsible allergens. CONCLUSIONS: Common occupationally related allergens included rubber accelerators and the preservative methylchloroisothiazolone/methylisothiazolone.

Willcocks, R. J., Triplett, W. T., Forbes, S. C., Arora, H., Senesac, C. R., Lott, D. J., et al. (2016).

Magnetic resonance imaging of the proximal upper extremity musculature in boys with duchenne muscular dystrophy. *Journal of Neurology*,

There is a pressing need for biomarkers and outcomes that can be used across disease stages in Duchenne muscular dystrophy (DMD), to facilitate the inclusion of a wider range of participants in clinical trials and to improve our understanding of the natural history of DMD. Quantitative magnetic resonance imaging (qMRI) and spectroscopy (MRS) biomarkers show considerable promise in both the legs and forearms of individuals with DMD, but have not yet been examined in functionally important proximal upper extremity muscles such as the biceps brachii and deltoid. The primary objective of this study was to examine the feasibility of implementing qMRI and MRS biomarkers in the proximal upper extremity musculature, and the secondary objective was to examine the relationship between MR measures of arm muscle pathology and upper extremity functional endpoints. Biomarkers included MRS and MRI measures of fat fraction and transverse relaxation time (T₂). The MR exam was well tolerated in both ambulatory and non-ambulatory boys. qMR biomarkers differentiated affected and unaffected participants and

correlated strongly with upper extremity function ($r = 0.91$ for biceps brachii T 2 versus performance of upper limb score). These qMR outcome measures could be highly beneficial to the neuromuscular disease community, allowing measurement of the quality of functionally important muscles across disease stages to understand the natural history of DMD and particularly to broaden the opportunity for clinical trial participation.

Winn, S. R., Scherer, T., Thony, B., & Harding, C. O. (2016). High dose sapropterin dihydrochloride therapy improves monoamine neurotransmitter turnover in murine phenylketonuria (PKU). *Molecular Genetics and Metabolism*, 117(1), 5-11.

Central nervous system (CNS) deficiencies of the monoamine neurotransmitters, dopamine and serotonin, have been implicated in the pathophysiology of neuropsychiatric dysfunction in phenylketonuria (PKU). Increased brain phenylalanine concentration likely competitively inhibits the activities of tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH), the rate limiting steps in dopamine and serotonin synthesis respectively. Tetrahydrobiopterin (BH4) is a required cofactor for TH and TPH activity. Our hypothesis was that treatment of hyperphenylalaninemic Pah(enu2/enu2) mice, a model of human PKU, with sapropterin dihydrochloride, a synthetic form of BH4, would stimulate TH and TPH activities leading to improved dopamine and serotonin synthesis despite persistently elevated brain phenylalanine. Sapropterin (20, 40, or 100mg/kg body weight in 1% ascorbic acid) was administered daily for 4 days by oral gavage to Pah(enu2/enu2) mice followed by measurement of brain biopterin, phenylalanine, tyrosine, tryptophan and monoamine neurotransmitter content. A significant increase in brain biopterin content was detected only in mice that had received the highest sapropterin dose, 100mg/kg. Blood and brain phenylalanine concentrations were unchanged by sapropterin therapy. Sapropterin therapy also did not alter the absolute amounts of dopamine and serotonin in brain but was associated with increased homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), dopamine and serotonin metabolites respectively, in both wild type and Pah(enu2/enu2) mice. Oral sapropterin therapy likely does not directly affect central nervous system monoamine synthesis in either wild type or hyperphenylalaninemic mice but may stimulate synaptic neurotransmitter release and subsequent metabolism.

Wong, T. E., Nguyen, T., Shah, S. S., Brogan, T. V., & Witmer, C. M. (2016). Antithrombin concentrate use in pediatric extracorporeal membrane oxygenation: A multicenter cohort study. *Pediatric Critical Care Medicine*,

Wood, A. M., Frey, H. A., Tuuli, M. G., Caughey, A. B., Odibo, A. O., Macones, G. A., et al. (2016). Optimal admission cervical dilation in spontaneously laboring women. *American Journal of Perinatology*, 33(2), 188-194.

OBJECTIVE: To estimate the impact of admission cervical dilation on the risk of cesarean in spontaneously laboring women at term. STUDY DESIGN: Secondary analysis of a prospective cohort study of women admitted in term labor with a singleton gestation. Women with rupture of membranes before admission, induction of labor, or prelabor cesarean were excluded. The association between cesarean and cervical dilation at admission was estimated, and results were stratified by parity. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated, using cervical dilation ≥ 6 cm as the reference group. Cesarean for arrest was secondarily explored. RESULTS: A total of 2,033 spontaneously laboring women met inclusion criteria. Women admitted at ≥ 6 cm (13.2 vs. 3.5%; RR 3.73; 95% CI 1.94-7.17). The increased risk was noted in nulliparous (16.8 vs. 7.1%; RR 2.35; 95% CI 0.90-6.13) and multiparous (11.0 vs. 2.5%; RR 4.36; 95% CI 1.80-10.52) women, but was statistically significant only in multiparous women. CONCLUSIONS: Decreasing cervical dilation at admission, particularly < 6 cm, is a modifiable risk factor for cesarean, especially in multiparous women. This should be considered in the decision-making process about timing of admission in term labor.

Wyatt, T. R., Bowen, J., Mann, K., Regehr, G., & Cianciolo, A. T. (2016). Coming in from the cold-physician professional development as deepening participation in the healthcare community. *Teaching and Learning in Medicine*, 28(4), 358-361.

This Conversation Starters article presents a selected research abstract from the 2016 Association of American Medical Colleges Southern Region Group on Educational Affairs annual spring meeting. The abstract is paired with the integrative commentary of three experts who shared their thoughts stimulated by the pilot study. These thoughts probe the concept of patient

"ownership" and suggest an alternative way of conceptualizing physicians' total dedication to patient care.

Xuan, C., Xu, L. -, Tian, Q. -, Li, H., Wang, Q., He, G. -, et al. (2016). Dimethylarginine dimethylaminohydrolase 2 (DDAH 2) gene polymorphism, asymmetric dimethylarginine (ADMA) concentrations, and risk of coronary artery disease: A case-control study. *Scientific Reports*, 6

Yee, L. M., Sandoval, G., Bailit, J., Reddy, U. M., Wapner, R. J., Varner, M. W., et al. (2016). Maternal and neonatal outcomes with early compared with delayed pushing among nulliparous women. *Obstetrics and Gynecology*, 128(5), 1039-1047.

OBJECTIVE: To describe factors associated with delayed pushing and evaluate the relationship between delayed pushing and perinatal outcomes in nulliparous women with singleton term gestations. METHODS: This was a secondary analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Assessment of Perinatal Excellence cohort of 115,502 women and their neonates born in 25 U.S. hospitals from 2008 to 2011. Nulliparous women with singleton, cephalic, nonanomalous term births who achieved 10-cm cervical dilation were included. Women in whom pushing was delayed by 60 minutes or greater (delayed group) were compared with those who initiated pushing within 30 minutes (early group). Multivariable regression analyses were used to assess the independent association of delayed pushing with mode of delivery, length of the second stage, and other maternal and perinatal outcomes (significance defined as $P < .05$). RESULTS: Of 21,034 women in the primary analysis sample, pushing was delayed in 18.4% ($n=3,870$). Women who were older, privately insured, or non-Hispanic white as well as those who had induction or augmentation of labor, diabetes, or epidural analgesia were more likely to have delayed pushing. Delayed pushing was more common when the second stage began during daytime hours or in hospitals with dedicated 24-hour obstetric anesthesia, although differences were small. After adjusting for differences in baseline and labor characteristics including center, women in the delayed group had longer mean durations of the second stage (191 compared with 84 minutes, $P < .001$) and of active pushing (86 compared with 76 minutes, $P < .001$). Delayed pushing was associated with greater rates of cesarean delivery (11.2% compared with 5.1%; adjusted odds ratio [OR] 1.86, 95% confidence interval [CI] 1.63-

2.12), operative vaginal delivery (adjusted OR 1.26, 95% CI 1.14-1.40), postpartum hemorrhage (adjusted OR 1.43, 95% CI 1.05-1.95), and blood transfusion (adjusted OR 1.51, 95% CI 1.04-2.17). Delayed pushing was not associated with increased odds of adverse neonatal outcomes compared with early pushing. CONCLUSION: In this large birth cohort, delayed pushing was associated with longer second stage duration, increased odds of cesarean delivery, and increased odds of postpartum hemorrhage, but was not associated with neonatal morbidity.

Yorgason, J. T., Calipari, E. S., Ferris, M. J., Karkhanis, A. N., Fordahl, S. C., Weiner, J. L., et al.

(2016). Social isolation rearing increases dopamine uptake and psychostimulant potency in the striatum. *Neuropharmacology*, *101*, 471-479.

Social isolation rearing (SI) is a model of early life stress that results in neurobiological alterations leading to increased anxiety-like behaviors. These animals also exhibit an increased propensity to administer psychostimulants, such as cocaine; however, the mechanisms governing this increased addiction vulnerability remain to be elucidated. Long-term stressors have been shown to produce important alterations in nucleus accumbens core (NAc) function. The NAc regulates motivated and goal-directed behaviors, and individual differences in NAc function have been shown to be predictive of addiction vulnerability. Rats were reared in group (GH; 4/cage) or SI (1/cage) conditions from weaning (PD 28) into early adulthood (PD 77) and dopamine release was assessed using voltammetry in brain slices containing the NAc and dorsomedial striatum. SI rats exhibited enhanced dopamine release and uptake in both regions compared to GH rats. In regard to psychostimulant effects directly at the dopamine transporter (DAT), methylphenidate and amphetamine, but not cocaine, inhibited uptake more in SI than GH rats. The increased potencies were positively correlated with uptake rates, suggesting that increased potencies of amphetamine-like compounds are due to changes in DAT function. Cocaine's effects on uptake were similar between rearing conditions, however, cocaine enhanced evoked dopamine release greater in SI than GH rats, suggesting that the enhanced cocaine reinforcement in SI animals involves a DAT independent mechanism. Together, the results provide the first evidence that greater psychostimulant effects in SI compared to GH rats are due to effects on dopamine terminals related to uptake dependent and independent mechanisms.

Yu, Y., Petrik, I., Chacon, K. N., Hosseinzadeh, P., Chen, H., Blackburn, N. J., et al. (2016). Effect of circular permutation on the structure and function of type 1 blue copper center in azurin. *Protein Science : A Publication of the Protein Society*,

Type 1 copper (T1Cu) proteins are electron transfer (ET) proteins involved in many important biological processes. While the effects of changing primary and secondary coordination spheres in the T1Cu ET function have been extensively studied, no report has explored the effect of the overall protein structural perturbation on active site configuration or reduction potential of the protein, even though the protein scaffold has been proposed to play a critical role in enforcing the entatic or "rack-induced" state for ET functions. We herein report circular permutation of azurin by linking the N- and C-termini and creating new termini in the loops between 1st and 2nd beta strands or between 3rd and 4th beta strands. Characterization by electronic absorption, electron paramagnetic spectroscopies, as well as crystallography and cyclic voltammetry revealed that, while the overall structure and the primary coordination sphere of the circular permuted azurins remain the same as those of native azurin, their reduction potentials increased by 18 and 124 mV over that of WTaz. Such increases in reduction potentials can be attributed to subtle differences in the hydrogen-bonding network in secondary coordination sphere around the T1Cu center. This article is protected by copyright. All rights reserved.

Zaugg, T. L., Thielman, E. J., Griest, S., & Henry, J. A. (2016). Subjective reports of trouble tolerating sound in daily life versus loudness discomfort levels. *American Journal of Audiology*, , 1-5.

Purpose: A retrospective analysis of tonal and speech loudness discomfort levels (LDLs) relative to a subjective report of sound tolerance (SRST) was performed to explore the relation between the 2 commonly used clinical measures. Method: Tonal LDLs and SRST were measured for 139 U.S. military veterans who were recruited into a study providing intervention for tinnitus. Spearman's rank correlation coefficients were computed to assess the relation between the tonal and speech LDLs and the SRST. Results: Only weak correlations were found between tonal LDLs and SRST and between speech LDLs and SRST. Conclusion: If LDLs ratings of SRST measured the same phenomenon, the measures would be strongly negatively correlated. The weak correlations found between the measures suggest that LDLs do not accurately represent a patient's ability to tolerate sound in daily life.

Zhang, M., Hwang, T. S., Dongye, C., Wilson, D. J., Huang, D., & Jia, Y. (2016). Automated quantification of nonperfusion in three retinal plexuses using projection-resolved optical coherence tomography angiography in diabetic retinopathy. *Investigative Ophthalmology & Visual Science*, 57(13), 5101-5106.

Purpose: The purpose of this study was to evaluate an automated algorithm for detecting avascular area (AA) in optical coherence tomography angiograms (OCTAs) separated into three individual plexuses using a projection-resolved technique. Methods: A 3 x 3 mm macular OCTA was obtained in 13 healthy and 13 mild nonproliferative diabetic retinopathy (NPDR) participants. A projection-resolved algorithm segmented OCTA into three vascular plexuses: superficial, intermediate, and deep. An automated algorithm detected AA in each of the three plexuses that were segmented and in the combined inner-retinal angiograms. We assessed the diagnostic accuracy of extrafoveal and total AA using segmented and combined angiograms, the agreement between automated and manual detection of AA, and the within-visit repeatability. Results: The sum of extrafoveal AA from the segmented angiograms was larger in the NPDR group by 0.17 mm² (P 0.8). The pooled SDs of AA were small compared with the difference in mean for control and NPDR groups. Conclusions: An algorithm to detect AA in OCTA separated into three individual plexuses using a projection-resolved algorithm accurately distinguishes mild NPDR from control eyes. Automatically detected AA agrees with manual delineation and is highly repeatable.

Zhang, Q. S., Tang, W., Deater, M., Phan, N., Marcogliese, A. N., Li, H., et al. (2016). Metformin improves defective hematopoiesis and delays tumor formation in fanconi anemia mice. *Blood*, Fanconi anemia is an inherited bone marrow failure disorder associated with a high incidence of leukemia and solid tumors. Bone marrow transplantation is currently the only curative therapy for the hematopoietic complications of this disorder. However, long-term morbidity and mortality remain very high and new therapeutics are badly needed. Here we show that the widely used diabetes drug metformin improves hematopoiesis and delays tumor formation in *Fancd2*^{-/-} mice. Metformin is the first compound reported to improve both of these Fanconi anemia phenotypes. Importantly, the beneficial effects are specific to Fanconi anemia mice, and not seen in the wild-type controls. In this preclinical model of Fanconi anemia, metformin outperformed the current standard of care, oxymetholone, by improving peripheral blood counts in *Fancd2*^{-/-} mice

significantly faster. Metformin increased the size of the hematopoietic stem cell compartment and enhanced quiescence in hematopoietic stem and progenitor cells. In tumor-prone *Fancd2*^{-/-} *Trp53*^{+/-} mice, metformin delayed the onset of tumors and significantly extended the tumor-free survival time. In addition, we found that metformin and the structurally related compound aminoguanidine reduced DNA damage and ameliorated spontaneous chromosome breakage and radials in human Fanconi anemia patient-derived cells. Our results also indicate that aldehyde detoxification might be one of the mechanisms by which metformin reduces DNA damage in Fanconi anemia cells.

Zhu, F., Panwar, B., Dodge, H. H., Li, H., Hampstead, B. M., Albin, R. L., et al. (2016). COMPASS: A computational model to predict changes in MMSE scores 24-months after initial assessment of alzheimer's disease. *Scientific Reports*, 6, 34567.

We present COMPASS, a COmputational Model to Predict the development of Alzheimer's diSease Spectrum, to model Alzheimer's disease (AD) progression. This was the best-performing method in recent crowdsourcing benchmark study, DREAM Alzheimer's Disease Big Data challenge to predict changes in Mini-Mental State Examination (MMSE) scores over 24-months using standardized data. In the present study, we conducted three additional analyses beyond the DREAM challenge question to improve the clinical contribution of our approach, including: (1) adding pre-validated baseline cognitive composite scores of ADNI-MEM and ADNI-EF, (2) identifying subjects with significant declines in MMSE scores, and (3) incorporating SNPs of top 10 genes connected to APOE identified from functional-relationship network. For (1) above, we significantly improved predictive accuracy, especially for the Mild Cognitive Impairment (MCI) group. For (2), we achieved an area under ROC of 0.814 in predicting significant MMSE decline: our model has 100% precision at 5% recall, and 91% accuracy at 10% recall. For (3), "genetic only" model has Pearson's correlation of 0.15 to predict progression in the MCI group. Even though addition of this limited genetic model to COMPASS did not improve prediction of progression of MCI group, the predictive ability of SNP information extended beyond well-known APOE allele.

Zhu, S., & Gouaux, E. (2017). Structure and symmetry inform gating principles of ionotropic glutamate receptors. *Neuropharmacology*, 112(Pt A), 11-15.

Ionotropic glutamate receptors (iGluRs) transduce signals derived from release of the excitatory neurotransmitter glutamate from pre-synaptic neurons into excitation of post-synaptic neurons on a millisecond time-scale. In recent years, the elucidation of full-length iGluR structures of NMDA, AMPA and kainate receptors by X-ray crystallography and single particle cryo-electron microscopy has greatly enhanced our understanding of the interrelationships between receptor architecture and gating mechanism. Here we briefly review full-length iGluR structures and discuss the similarities and differences between NMDA receptors and non-NMDA iGluRs. We focus on distinct conformations, including ligand-free, agonist-bound active, agonist-bound desensitized and antagonist-bound conformations as well as modulator and auxiliary protein-bound states. These findings provide insights into structure-based mechanisms of iGluR gating and modulation which together shape the amplitude and time course of the excitatory postsynaptic potential. This article is part of the Special Issue entitled 'Ionotropic glutamate receptors'.

Ziu, M., Dunn, I. F., Hess, C., Fleseriu, M., Bodach, M. E., Tumialan, L. M., et al. (2016). Guidelines: Congress of neurological surgeons systematic review and evidence-based guideline on posttreatment follow-up evaluation of patients with nonfunctioning pituitary adenomas. *Neurosurgery*, 79(4), E541-E543.

Zive, D. M., Cook, J., Yang, C., Sibell, D., Tolle, S. W., & Lieberman, M. (2016). Implementation of a novel electronic health record-embedded physician orders for life-sustaining treatment system. *Journal of Medical Systems*, 40(11), 245.

In April 2015, Oregon Health & Science University (OHSU) deployed a web-based, electronic medical record-embedded application created by third party vendor Vynca Inc. to allow real-time education, and completion of Physician Orders for Life Sustaining Treatment (POLST). Forms are automatically linked to the Epic Systems electronic health record (EHR) patient header and submitted to a state Registry, improving efficiency, accuracy, and rapid access to and retrieval of these important medical orders. POLST Forms, implemented in Oregon in 1992, are standardized portable medical orders used to document patient treatment goals for end-of-life care. In 2009,

Oregon developed the first POLST-only statewide registry with a legislative mandate requiring POLST form signers to register the form unless the patient opts out. The Registry offers 24/7 emergency access to POLST Forms for Emergency Medical Services, Emergency Departments, and Acute Care Units. Because POLST is intended for those nearing end of life, immediate access to these forms at the time of an emergency is critical. Delays in registering a POLST Form may result in unwanted treatment if the paper form is not immediately available. An electronic POLST Form completion system (ePOLST) was implemented to support direct Registry submission. Other benefits of the system include single-sign-on, transmission of HL7 data for patient demographics and other relevant information, elimination of potential errors in form completion using internalized logic, built-in real-time video and text-based education materials for both patients and health care professionals, and mobile linkage for signature capture.