Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialised topics. At the 2015 IFPA annual meeting there were 12 themed workshops, three of which are summarized in this report. These workshops related to various aspects of placental biology and collectively covered areas of obesity and the placenta, stem cells of the feto-maternal interface, and placental immunobiology and infection. © 2016 Elsevier Ltd


PURPOSE: To describe success rates and long-term outcomes of conjunctivodacryocystorhinostomy (CDCR) with frosted Jones tubes (FJT) for epiphora with proximal outflow obstruction. METHODS: A retrospective chart review of all patients undergoing external and endoscopic CDCR with FJTs by one author (RAD) was performed between January 1, 2006 and November 1, 2014 at the Casey Eye Institute. Patient demographics, etiology of tearing, concurrent endonasal and eyelid procedures, and FJT size were recorded. After CDCR, follow-up time, tube size changes, tube position, and tearing status were noted. Exclusion criteria included follow up less than 6 months and/or prior CDCR. The study was IRB approved, HIPAA compliant, and adherent to the declaration of Helsinki. RESULTS: Forty-two eyes of 31 patients met the inclusion criteria, with the majority having epiphora from canalicular obstruction (31%) or flaccid canaliculi (31%). Average follow up was 1,088 days. Forty of 42 eyes, or 30 of 31 patients, had complete resolution of tearing after surgery. Twenty of 42 eyes required tube size changes, usually an increase in collar size (45%) and/or decrease in tube length (55%). Six of 42 FJTs were lost, one migrating outward, with an average time to loss between 61 and 1,122 days (mean 817 days). After collars larger than 4 mm became available, only one tube was lost. All epiphora resolved after repeat CDCR. The most common complication was intermittent irritation (17%) near the FJT that resolved after antibiotic-steroid drops and/or tube replacement/cleaning. CONCLUSION: CDCR with FJTs is highly effective in correcting epiphora, and well tolerated by the majority.


PURPOSE: To investigate the presence and microbiology of bacterial biofilms on Jones tubes (JTs) by direct visualization with scanning electron microscopy and polymerase chain reaction (PCR) of representative JTs, and to correlate these findings with inflammation and/or infection related to the JT. METHODS: In this study, prospective case series were performed. JTs were recovered from consecutive patients presenting to clinic for routine cleaning or recurrent irritation/infection. Four tubes were processed for scanning electron microscopy alone to visualize evidence of biofilms. Two tubes underwent PCR alone for bacterial quantification. One tube was divided in half and sent for scanning electron microscopy and PCR. Symptoms related to the JTs were recorded at the time of recovery. RESULTS: Seven tubes were obtained. Five underwent SEM, and 3 out of 5 showed evidence of biofilms (60%). Two of the 3 biofilms demonstrated cocci and the third revealed rods. Three tubes underwent PCR. The predominant bacteria identified were Pseudomonadales (39%), Pseudomonas (16%), and Staphylococcus (14%). Three of the 7 patients (43%) reported irritation and discharge at presentation. Two symptomatic patients, whose tubes were imaged only, revealed biofilms. The third symptomatic patient’s tube underwent PCR only, showing predominantly
Staphylococcus (56%) and Haemophilus (36%) species. Two of the 4 asymptomatic patients also showed biofilms. All symptomatic patients improved rapidly after tube exchange and steroid antibiotic drops.

CONCLUSIONS: Bacterial biofilms were variably present on JTs, and did not always correlate with patients' symptoms. Nevertheless, routine JT cleaning is recommended to treat and possibly prevent inflammation caused by biofilms.


Both the Liaison Committee on Medical Education and the Accreditation Council of Graduate Medical Education require residents to be engaged in teaching to develop skills as educators. Although proposed guidelines for an emergency medicine (EM) resident-as-teachers (RAT) curriculum were published in 2006, little has been published regarding RAT curriculum implementation or outcomes since. A crucial first step in developing a formal RAT curriculum for EM educators to pilot, implement, and evaluate is an assessment of current needs and practices related to RAT curricula in EM residencies. The aim of this study was to conduct a needs assessment of EM residency programs regarding RAT curricular resources and practices. We invited all EM residency programs to participate in a web-based survey assessing their current RAT curricula and needs. 28% responded to our needs assessment. Amongst responding programs, 60% had a RAT curriculum. Of programs with a required medical student rotation, 59% had a RAT curriculum. Of programs without a RAT program, 14% had a program in development, and 18% had a teaching resident program without a curriculum. Most RAT programs (72%) were lecture-based and the majority (66%) evaluated using survey data. 84% of respondent programs demonstrated a desire for a national RAT curriculum. We find that despite national mandates, a large portion of programs do not have a RAT curriculum in place. There is wide variation in core content and curriculum evaluation techniques among available curricula. A majority of respondents report interest in a standardized web-based curriculum as one potential solution to this problem. Our results may help inform collaborative efforts to develop a national EM RAT curriculum.


RATIONALE: Evidence supporting the association of COPD or airflow obstruction with use of solid fuels is conflicting and inconsistent. OBJECTIVE: To assess the association of airflow obstruction with self-reported use of solid fuels for cooking or heating. METHODS: We analysed 18,554 adults from the BOLD study, who had provided acceptable post-bronchodilator spirometry measurements and information on use of solid fuels. The association of airflow obstruction with use of solid fuels for cooking or heating was assessed by sex, within each site, using regression analysis. Estimates were stratified by national income and meta-analysed. We carried out similar analyses for spirometric restriction, chronic cough and chronic phlegm. MEASUREMENTS AND MAIN RESULTS: We found no association between airflow obstruction and use of solid fuels for cooking or heating (ORmen=1.20, 95%CI 0.94-1.53; ORwomen=0.88, 95%CI 0.67-1.15). This was true for low/middle and high income sites. Among never smokers there was also no evidence of an association of airflow obstruction with use of solid fuels (ORmen=1.00, 95%CI 0.57-1.76; ORwomen=1.00, 95%CI 0.76-1.32). Overall, we found no association of spirometric restriction, chronic cough or chronic phlegm with the use of solid fuels. However, we found that chronic phlegm was more likely to be reported among female never smokers and those who had been exposed for >/=20 years. CONCLUSION: Airflow obstruction assessed from post-bronchodilator spirometry was not associated with use of solid fuels for cooking or heating.

PURPOSE: Rapid growth during infancy predicts higher risk of obesity later in childhood. The association between patterns of early life growth and later obesity may differ by race/ethnicity or socioeconomic status (SES), but prior evidence syntheses do not consider vulnerable subpopulations. METHODS: We systemically reviewed published studies that explored patterns of early life growth (0-24 months of age) as predictors of later obesity (>24 months) that were either conducted in racial/ethnic minority or low-SES study populations or assessed effect modification of this association by race/ethnicity or SES. Literature searches were conducted in PubMed and SocINDEX. RESULTS: Ten studies met the inclusion criteria. Faster growth during the first 2 years of life was consistently associated with later obesity irrespective of definition and timing of exposure and outcome measures. Associations were strongest in populations composed of greater proportions of racial/ethnic minority and/or low-SES children. For example, ORs ranged from 1.17 (95% CI: 1.11, 1.24) in a heterogeneous population to 9.24 (95% CI: 3.73, 22.9) in an entirely low-SES nonwhite population. CONCLUSIONS: The impact of rapid growth in infancy on later obesity may differ by social stratification factors such as race/ethnicity and family income. More robust and inclusive studies examining these associations are needed.


PURPOSE: Health insurance coverage affects a patient’s ability to access optimal care, the percentage of insured patients on a clinic’s panel has an impact on the clinic’s ability to provide needed health care services, and there are racial and ethnic disparities in coverage in the United States. Thus, we aimed to assess changes in insurance coverage at community health center (CHC) visits after the Patient Protection and Affordable Care Act (ACA) Medicaid expansion by race and ethnicity. METHODS: We undertook a retrospective, observational study of visit payment type for CHC patients aged 19 to 64 years. We used electronic health record data from 10 states that expanded Medicaid and 6 states that did not, 359 CHCs, and 870,319 patients with more than 4 million visits. Our analyses included difference-in-difference (DD) and difference-in-difference-in-difference (DDD) estimates via generalized estimating equation models. The primary outcome was health insurance type at each visit (Medicaid-insured, uninsured, or privately insured). RESULTS: After the ACA was implemented, uninsured visit rates decreased for all racial and ethnic groups. Hispanic patients experienced the greatest increases in Medicaid-insured visit rates after ACA implementation in expansion states (rate ratio [RR] = 1.77; 95% CI, 1.56-2.02) and the largest gains in privately insured visit rates in nonexpansion states (RR = 3.63; 95% CI, 2.73-4.83). In expansion states, non-Hispanic white patients had twice the magnitude of decrease in uninsured visits compared with Hispanic patients (DD = 2.03; 95% CI, 1.53-2.70), and this relative change was more than 2 times greater in expansion states compared with nonexpansion states (DDD = 2.06; 95% CI, 1.52-2.78). CONCLUSION: The lower rates of uninsured visits for all racial and ethnic groups after ACA implementation suggest progress in expanding coverage to CHC patients; this progress, however, was not uniform when comparing expansion with nonexpansion states and among all racial and ethnic minority subgroups. These findings suggest the need for continued and more equitable insurance expansion efforts to eliminate health insurance disparities.


Dementia is a neurodegenerative disorder with global impact, with the largest proportion of cases occurring in low- and middle-income countries. It is estimated that there are 46.8 million cases globally with approximately 10 million new cases each year or a new case occurring every 3 sec (Prince et al., 2015). For comparison there are 36.7 million HIV cases with an estimated 2 million new cases each year (WHO, 2017). The rise in dementia prevalence is largely due to population ageing, with the oldest being at highest risk. To date there are no diseases modifying medications for Alzheimer’s disease or the other causes of dementia. Academics and
research groups are increasingly focused on prevention or delay of dementia (Brayne and Miller, 2017) and a number of organizations now prioritize dementia, indicating a strong and coherent international effort to address this problem. Examples include the World Health Organisation (WHO), which has established a Global Dementia Observatory; the World Dementia Council; the Organisation for Economic Co-operation and Development (OECD); the U.S. National Alzheimer’s Project Act (NAPA); and the Global Council on Brain Health.


The balance between ovarian folliculogenesis and follicular atresia is critical for female fertility and is strictly regulated by a complex network of neuroendocrine and intra-ovarian signals. Despite the numerous functions executed by granulosa cells (GCs) in ovarian physiology, the role of multifunctional proteins able to simultaneously coordinate/modulate several cellular pathways is unclear. Soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein (alpha-SNAP) is a multifunctional protein that participates in SNARE-mediated membrane fusion events. In addition, it regulates cell-to-cell adhesion, AMPK signaling, autophagy and apoptosis in different cell types. In this study we examined the expression pattern of alpha-SNAP in ovarian tissue and the consequences of alpha-SNAP (M105I) mutation (hyh mutation) in folliculogenesis and female fertility. Our results showed that alpha-SNAP protein is highly expressed in GCs and its expression is modulated by gonadotropin stimuli. On the other hand, alpha-SNAP-mutant mice show a reduction in alpha-SNAP protein levels. Moreover, increased apoptosis of GCs and follicular atresia, reduced ovulation rate, and a dramatic decline in fertility is observed in alpha-SNAP-mutant females. In conclusion, alpha-SNAP plays a critical role in the balance between follicular development and atresia. Consequently, a reduction in its expression/function (M105I mutation) causes early depletion of ovarian follicles and female subfertility.


The primary aim was to compare the difference in time to mesh exposure between mesh placed abdominally versus vaginally. This is a retrospective comparative study of patients presented with vaginal mesh exposure between January 2001 and July 2012. This study compares patients who had undergone vaginally placed mesh procedures to those who had had abdominally placed mesh. Kaplan-Meier survival analysis was used to measure the time to mesh exposure. There were 68 patients with mesh exposure in our cohort. Thirty eight patients had undergone vaginal placement of mesh and 30 patients had abdominal mesh. There was a statistically significant difference in time to mesh exposure between abdominal and vaginal meshes (p < .0001). Mean time to vaginal mesh exposure with abdominal mesh was 59.8 months (95%CI 46.2-73.3) compared to 23 months (95%CI 15.9-30.2) for vaginal mesh. When controlling for age, BMI and surgeon at index surgery, the Hazard Ratio for mesh exposure in our Cox Regression model was 0.53 (95%CI 0.39-0.71) (p < .0001). The mean time to vaginal mesh exposure after abdominal mesh was longer compared to the time to exposure with vaginally placed mesh (60 versus 23 months, p < .0001). These results support the evolving evidence that mesh exposures can occur many years distant from the procedure and warrant some level of surveillance or provision of warning signs by the providers who perform procedures with mesh.


Removing or adding sensory cues from one sensory system during standing balance causes a change in the contribution of the remaining sensory systems, a process referred to as sensory reweighting. While reweighting changes have been described in many studies under steady-state conditions, less is known about the temporal dynamics of reweighting following sudden transitions to different sensory conditions. The present study changed sensory conditions by periodically adding or removing visual (lights On/Off) or proprioceptive cues (surface sway referencing On/Off) in 12 young, healthy subjects. Evidence for changes in sensory contributions to balance was obtained by measuring the time course of medial-lateral sway responses to a constant-amplitude 0.56-Hz sinusoidal stimulus, applied as support surface tilt (proprioceptive contribution), as visual scene tilt (visual contribution), or as binaural galvanic vestibular stimulation (vestibular contribution), and by analyzing the time course of sway variability. Sine responses and variability of body sway velocity showed significant changes following transitions and were highly correlated under steady-state conditions. A dependence of steady-state responses on upcoming transitions was observed, suggesting that knowledge of impending changes can influence sensory weighting. Dynamic changes in sway in the period immediately following sensory transitions were very inhomogeneous across sway measures and in different experimental tests. In contrast to steady-state results, sway response and variability measures were not correlated with one another in the dynamic transition period. Several factors influence sway responses following addition or removal of sensory cues, partly instigated by but also obscuring the effects of reweighting dynamics.

BACKGROUND: Physical symptoms and depression in heart failure (HF) are key drivers of health-related quality of life (HRQOL). Heart failure self-care behaviors are believed to influence how symptoms affect HRQOL. OBJECTIVE: The goal of this study was to determine if HF self-care behaviors moderate the relationships between physical and depressive symptoms and HRQOL. METHODS: In a cohort of adults with moderate to advanced HF, multivariate linear regression was used to evaluate the interaction between self-care behaviors (Self-care of HF index maintenance and management scales) and physical HF symptoms (HF Somatic Perception Scale) on emotional HRQOL (emotional dimension of Minnesota Living With HF Questionnaire). The interaction between self-care behaviors and depression (9-item Patient Health Questionnaire) was evaluated on physical HRQOL (physical dimension of Minnesota Living With HF Questionnaire). RESULTS: The mean age of the sample (N = 202) was 57 +/- 13 years, 50% were women, and 61% had New York Heart Association class III or IV HF. Controlling for age, Seattle HF score, functional ability, and comorbidities, self-care maintenance and management moderated the relationship between physical HF symptoms and emotional HRQOL. Only self-care maintenance moderated the relationship between depression and physical HRQOL. CONCLUSION: In HF, HRQOL is dependent on both the severity of physical and depressive symptoms and the level of engagement in HF self-care behaviors. Future research should consider both self-care behaviors and symptoms when examining patient HRQOL.

Austin, J., Hollingshead, K., & Kaye, J. (2017). Internet Searches and Their Relationship to Cognitive Function in Older Adults: Cross-Sectional Analysis. *Journal of Medical Internet Research, 19*(9), e307. doi:10.2196/jmir.7671


BACKGROUND: Idiopathic intracranial hypertension (IIH) is a neurological disorder characterized by elevated intracranial pressure of unknown cause. Acetazolamide is widely used as the initial treatment option; however, previously published evidence suggests that this drug may also increase the risk of nephrolithiasis. The purpose of this study was to examine daily acetazolamide use and its relationship to nephrolithiasis and compare clinical presentation of IIH between those with and without nephrolithiasis. METHODS: We conducted a case-control study using patient data collected by the Intracranial Hypertension Registry. A total of 670 patients were identified as potential study participants, 19 meeting the case definition of developing a stone during acetazolamide treatment for IIH. From the remaining pool of eligible participants, 40 controls were randomly selected. Two-sample t tests, Fisher exact testing, and exact logistic regression were used to examine differences between cases and controls and to ascertain associations with IIH clinical features and mean daily acetazolamide dosage. RESULTS: Among all eligible patients, 19 (2.8%) developed a stone during acetazolamide treatment for IIH. Among these patients, 17 (89.5%) developed a stone within 1.5 years of initial acetazolamide treatment. Daily acetazolamide use was not significantly related to stone development (odds ratio = 0.95; 95% confidence intervals: 0.86-1.05). Additionally, the relationship between the clinical presentation of IIH at the time of diagnosis (signs and symptoms) and stone development did not reach statistical significance (P > 0.05). CONCLUSIONS: Our results demonstrate that: 1) stone formation during acetazolamide treatment is a relatively infrequent occurrence within the IIH population; 2) among patients who develop a stone, formation is likely to occur within the first year and half; 3) there is no evidence to support the association between acetazolamide daily dosage and stone development; and 4) no unique IIH disease features at the time of diagnosis are associated with stone development. Treatment with acetazolamide should be administered to IIH patients with caution and closely monitored for stone development especially within the first year and a half of treatment.
BACKGROUND: Alzheimer disease (AD) is a very challenging experience for all those affected. Unfortunately, detection of Alzheimer disease in its early stages when clinical treatments may be most effective is challenging, as the clinical evaluations are time-consuming and costly. Recent studies have demonstrated a close relationship between cognitive function and everyday behavior, an avenue of research that holds great promise for the early detection of cognitive decline. One area of behavior that changes with cognitive decline is language use. Multiple groups have demonstrated a close relationship between cognitive function and vocabulary size, verbal fluency, and semantic ability, using conventional in-person cognitive testing. An alternative to this approach which is inherently ecologically valid may be to take advantage of automated computer monitoring software to continually capture and analyze language use while on the computer.

OBJECTIVE: The aim of this study was to understand the relationship between Internet searches as a measure of language and cognitive function in older adults. We hypothesize that individuals with poorer cognitive function will search using fewer unique terms, employ shorter words, and use less obscure words in their searches.

METHODS: Computer monitoring software (WorkTime, Nestersoft Inc) was used to continuously track the terms people entered while conducting searches in Google, Yahoo, Bing, and Ask.com. For all searches, punctuation, accents, and non-ASCII characters were removed, and the resulting search terms were spell-checked before any analysis. Cognitive function was evaluated as a z-normalized summary score capturing five unique cognitive domains. Linear regression was used to determine the relationship between cognitive function and Internet searches by controlling for variables such as age, sex, and education.

RESULTS: Over a 6-month monitoring period, 42 participants (mean age 81 years [SD 10.5], 83% [35/42] female) conducted 2915 searches using these top search engines. Participants averaged 3.08 words per search (SD 1.6) and 5.77 letters per word (SD 2.2). Individuals with higher cognitive function used more unique terms per search (beta=.39, P=.002) and employed less common terms in their searches (beta=1.39, P=.02). Cognitive function was not significantly associated with the length of the words used in the searches.

CONCLUSIONS: These results suggest that early decline in cognitive function may be detected from the terms people search for when they use the Internet. By continuously tracking basic aspects of Internet search terms, it may be possible to detect cognitive decline earlier than currently possible, thereby enabling proactive treatment and intervention.


Control of the dimensions of actin-rich processes like filopodia, lamellipodia, microvilli, and stereocilia requires the coordinated activity of many proteins. Each of these actin structures relies on heterodimeric capping protein (CAPZ), which blocks actin polymerization at barbed ends. Because dimension control of the inner ear’s stereocilia is particularly precise, we studied the CAPZB subunit in hair cells. CAPZB, present at approximately 100 copies per stereocilium, concentrated at stereocilia tips as hair cell development progressed, similar to the CAPZB-interacting protein TWF2. We deleted Capzb specifically in hair cells using Atoh1-Cre, which eliminated auditory and vestibular function. Capzb-null stereocilia initially developed normally but later shortened and disappeared; surprisingly, stereocilia width decreased concomitantly with length. CAPZB2 expressed by in utero electroporation prevented normal elongation of vestibular stereocilia and irregularly widened them. Together, these results suggest that capping protein participates in stereocilia widening by preventing newly elongating actin filaments from depolymerizing.


OBJECTIVE: To evaluate the effect of Medicaid coverage on dental care outcomes, a major health concern for low-income populations. DATA SOURCES: Primary and secondary data on health care use and outcomes for participants in Oregon’s 2008 Medicaid lottery. STUDY DESIGN: We used the lottery's random selection to gauge the causal effects of Medicaid on dental care needs, medication, and emergency department visits for
dental care. DATA COLLECTION: Data were collected for lottery participants over 2 years, including mail surveys (N = 23,777) and in-person questionnaires (N = 12,229). Emergency department (ED) records were matched to lottery participants in Portland (N = 24,646). PRINCIPAL FINDINGS: Medicaid coverage significantly reduced the share of respondents who reported needing dental care (-9.8 percentage points, p < 0.001) or having unmet dental care needs (-13.5 percentage points, p < 0.001). Medicaid doubled the share visiting the ED for dental care (+2.6 percentage points, p = .003) and the use of anti-infective medications often prescribed for dental care, but it had no detectable effect on uncovered dental care or out-of-pocket spending. CONCLUSIONS: Expansion of Medicaid covering emergency dental care substantially reduced unmet need for dental care, increasing ED dental visits and medication use, while not changing patient use of uncovered dental services.


OBJECTIVES: To determine resource utilisation according to age and gender-specific subgroups in two large randomized diagnostic trials. METHODS: We pooled patient-specific data from ACRIN-PA 4005 and ROMICAT II that enrolled subjects with acute chest pain at 14 US sites. Subjects were randomized between a standard work-up and a pathway utilizing cardiac computed tomography angiography (CCTA) and followed for the occurrence of acute coronary syndrome (ACS) and resource utilisation during index hospitalisation and 1-month follow-up. Study endpoints included diagnostic accuracy of CCTA for the detection of ACS as well as resource utilisation. RESULTS: Among 1240 patients who underwent CCTA, negative predictive value of CCTA to rule out ACS remained very high (>/=99.4%). The proportion of patients undergoing additional diagnostic testing and cost increased with age for both sexes (p < 0.001), and was higher in men as compared to women older than 60 years (43.1% vs. 23.4% and $4559 +/-. 3382 vs. $3179 +/-. 2562, p < 0.01; respectively). Cost to rule out ACS was higher in men (p < 0.001) and significantly higher for patients older than 60 years ($2860-5935 in men, p < 0.001). CONCLUSIONS: CCTA strategy in patients with acute chest pain results in varying resource utilisation according to age and gender-specific subgroups, mandating improved selection for advanced imaging. KEY POINTS: * In this analysis, CAD and ACS increased with age and male gender. * CCTA in patients with acute chest pain results in varying resource utilisation. * Significant increase of diagnostic testing and cost with age for both sexes. * Cost to rule out ACS is higher in men and patients >60 years. * Improved selection of subjects for cardiac CTA result in more resource-driven implementation.


PURPOSE: To determine the in vitro accuracy, test-retest repeatability, and interplatform reproducibility of T1 quantification protocols used for dynamic contrast-enhanced MRI at 1.5 and 3 T. METHODS: A T1 phantom with 14 samples was imaged at eight centers with a common inversion-recovery spin-echo (IR-SE) protocol and a variable flip angle (VFA) protocol using seven flip angles, as well as site-specific protocols (VFA with different flip angles, variable repetition time, proton density, and Look-Locker inversion recovery). Factors influencing the accuracy (deviation from reference NMR T1 measurements) and repeatability were assessed using general linear mixed models. Interplatform reproducibility was assessed using coefficients of variation. RESULTS: For the common IR-SE protocol, accuracy (median error across platforms = 1.4-5.5%) was influenced predominantly by T1 sample (P < 10-6 ), whereas test-retest repeatability (median error = 0.2-8.3%) was influenced by the scanner (P < 10-6). For the common VFA protocol, accuracy (median error = 5.7-32.2%) was influenced by field strength (P = 0.006), whereas repeatability (median error = 0.7-25.8%) was influenced by the scanner (P < 0.0001). Interplatform reproducibility with the common VFA was lower at 3 T than 1.5 T (P = 0.004), and lower than that of the common IR-SE protocol (coefficient of variation 1.5T:
Among the site-specific protocols, Look-Locker inversion recovery and VFA (2-3 flip angles) protocols showed the best accuracy and repeatability (errors < 15%). CONCLUSIONS: The VFA protocols with 2 to 3 flip angles optimized for different applications achieved acceptable balance of extensive spatial coverage, accuracy, and repeatability in T1 quantification (errors < 15%). Further optimization in terms of flip-angle choice for each tissue application, and the use of B1 correction, are needed to improve the robustness of VFA protocols for T1 mapping. Magn Reson Med, 2017. (c) 2017 International Society for Magnetic Resonance in Medicine.


Distortion product otoacoustic emissions (DPOAE) testing is a promising alternative to behavioral hearing tests and auditory brainstem response testing of pediatric cancer patients. The central goal of this study is to assess whether significant changes in the DPOAE frequency/emissions curve (DP-gram) occur in pediatric patients in a test-retest scenario. This is accomplished through the construction of normal reference charts, or credible regions, that DP-gram differences lie in, as well as contour probabilities that measure how abnormal (or in a certain sense rare) a test-retest difference is. A challenge is that the data were collected over varying frequencies, at different time points from baseline, and on possibly one or both ears. A hierarchical structural equation Gaussian process model is proposed to handle the different sources of correlation in the emissions measurements, wherein both subject-specific random effects and variance components governing the smoothness and variability of each child’s Gaussian process are coupled together.


Spin-lattice relaxation in the rotating frame magnetic resonance imaging allows for the quantitative assessment of spin-lock contrast within tissues. We describe the utility of spin-lattice relaxation in the rotating frame metrics in characterizing glioblastoma biological heterogeneity. A 84-year-old man presented to our institution with a right frontal temporal mass. Prior tissue sampling from a peripheral nonenhancing lesion was nondiagnostic. Stereotactic image-guided tissue sampling of the nonenhancing T2-fluid-attenuated inversion recovery hyperintense region involving the anterior cingulate gyrus with elevated spin-lattice relaxation in the rotating frame metrics provided a pathologic diagnosis of glioblastoma. This case illustrates the utility of spin-lattice relaxation in the rotating frame magnetic resonance imaging in identifying biologically aggressive regions within glioblastoma. © 2017.


Translation regulation is a fundamental component of gene expression, allowing cells to respond rapidly to a variety of stimuli in the absence of new transcription. The lack of methods for profiling nascent proteomes in distinct cell populations in heterogeneous tissues has precluded an understanding of translational regulation in physiologically relevant contexts. Here, we describe a chemical genetic method that involves orthogonal enzyme-mediated incorporation of a clickable puromycin analogue into nascent polypeptides. Using this method, we show that we can label newly synthesized proteins in a cell-specific manner in cells grown in...
We also show that we can identify the nascent proteome in genetically targeted cell populations using affinity enrichment and tandem mass spectrometry. Our method has the potential to provide unprecedented insights into cell-specific translational regulation in heterogeneous tissues.


BACKGROUND: People with hemophilia (PWH) experience frequent joint bleeding, resulting in pain and functional impairment. Generic and disease-specific patient-reported outcome (PRO) instruments have been used in clinical studies, but rarely in the comprehensive hemophilia care setting. OBJECTIVE: The objective of this study was to assess construct validity of PRO instruments measuring pain, functional impairment, and health-related quality of life in US PWH with a history of joint pain/bleeding. METHODS: Adult male PWH completed 4 PRO instruments (EQ-5D-5L with visual analog scale, Brief Pain Inventory v2 Short Form [BPI], SF-36v2, Hemophilia Activities List [HAL]) and underwent a musculoskeletal examination (Hemophilia Joint Health Score v2.1 [HJHS]). Construct validity between index and domain scores was evaluated by Pearson product-moment correlation coefficient. RESULTS: A total of 381 PWH were enrolled. EQ-5D-5L Mobility correlated with BPI, SF-36v2, and HAL domains related to pain, physical function, and activity of the lower extremities. EQ-5D-5L Self-Care correlated only with HAL Self-Care. EQ-5D-5L Usual Activities correlated with BPI Pain Interference and domains within SF-36v2 and HAL related to pain and physical function/activities (particularly those involving the lower extremities). EQ-5D-5L Pain/Discomfort correlated with Bodily Pain and Physical Summary on SF-36v2, HAL Overall Activity, and all BPI pain domains. EQ-5D-5L Anxiety/Depression correlated with social/emotional/mental aspects of SF-36v2. On BPI, most pain domains correlated with Bodily Pain and Physical Health Summary on SF-36v2 and Overall Activity on HAL. On SF-36v2, Physical Functioning, Role Physical, Bodily Pain, and Physical Health summary scores correlated with all the domains of HAL except Self-Care. For HJHS, Ankle and Total scores correlated with SF-36v2 Physical Functioning and HAL Lying/Sitting, Leg Function, Complex Lower Extremity Activity, and Overall Activity. CONCLUSION: All PRO instruments have high construct validity but provide different levels of detail in describing effects of hemophilia. Instrument choice may depend on individuals' symptoms, treatment planning goals, or outcome tracking research objectives, with consideration for administrative burden.


The efficacy of adenotonsillectomy for relieving obstructive sleep apnoea in children has been firmly established, but its precise effects on cardiorespiratory control are poorly understood. In 375 children enrolled in the Childhood Adenotonsillectomy Trial, randomised to undergo either adenotonsillectomy (n=194) or a strategy of watching waiting (n=181), respiratory rate, respiratory sinus arrhythmia and heart rate were analysed during quiet, non-apnoeic and non-hypopnoeic breathing throughout sleep at baseline and at 7 months using overnight polysomnography. Children who underwent early adenotonsillectomy demonstrated an increase in respiratory rate postsurgery while the watchful waiting group showed no change. Heart rate and respiratory sinus arrhythmia were comparable between both arms. On assessing cardiorespiratory variables with regard to normalisation of clinical polysomnography findings during follow-up, heart rate was reduced in children who had resolution of obstructive sleep apnoea syndrome, while no differences in their respiratory rate or respiratory sinus arrhythmia were observed. Adenotonsillectomy for obstructive sleep apnoea increases baseline respiratory rate during sleep. Normalisation of apnoea-hypopnoea index, spontaneously or via surgery, lowers heart rate. Considering the small average effect size, the clinical significance is uncertain. © ERS 2016.

**BACKGROUND:** Endotracheal intubation remains a cornerstone of early resuscitation of the poisoned patient, but little is known about which substances are associated with intubation. **OBJECTIVES:** Our objective was to describe patient exposures to substances reported to the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) that were managed with intubation between 2010 and 2014. **METHODS:** We performed a retrospective review of cases managed with endotracheal intubation in the ACMT ToxIC Registry from January 1, 2010 through December 31, 2014. Descriptive statistics were used to describe patient exposures. **RESULTS:** A total of 2724 exposures to substances were managed with endotracheal intubation. Intubated patients were 52% male and 82% adults. For all ages taken together, the most common known single-substance exposures managed with intubation were sedative hypnotics (9.8%), antidepressants (8.7%), and opioids (8.0%). The most common single ingestions associated with intubation in various age groups were: opioids (<2 years old), alpha-2 agonists (2-6 years old), antidepressants (7-18 years old), sedative-hypnotics (19-65 years old), and cardiac medications (>65 years old). Multiple substances were involved in 29.0% of exposures. Decontamination and elimination processes were used in 12.8% of patients. **CONCLUSIONS:** The most common substances involved in single- and multiple-substance exposures managed with intubation varied by age group. Most patients were managed with supportive care. Knowledge of substances commonly involved in exposures managed with intubation may inform triage and resource planning in the emergency department resuscitation of critically ill poisoned patients.


Metastatic castration-resistant prostate cancer that has become resistant to docetaxel chemotherapy represents one of the greatest clinical challenges in the management of this disease. Patients in this situation have an expected median survival that is typically less than 18 months, and they frequently suffer from symptoms related to progressive cancer and/or persistent treatment toxicity. More effective treatments for patients with taxane-resistant disease are desperately needed. © 2017, UBM Medica Healthcare Publications. All rights reserved.


Little is known about mechanisms that drive the development of progressive multiple sclerosis (MS), although inflammatory factors, such as macrophage migration inhibitory factor (MIF), its homolog D-dopachrome tautomerase (D-DT), and their common receptor CD74 may contribute to disease worsening. Our findings demonstrate elevated MIF and D-DT levels in males with progressive disease compared with relapsing-remitting males (RRMS) and female MS subjects, with increased levels of CD74 in females vs. males with high MS disease severity. Furthermore, increased MIF and D-DT levels in males with progressive disease were significantly correlated with the presence of two high-expression promoter polymorphisms located in the MIF gene, a -794CATT5-8 microsatellite repeat and a -173 G/C SNP. Conversely, mice lacking MIF or D-DT developed less-severe signs of experimental autoimmune encephalomyelitis, a murine model of MS, thus implicating both homologs as copathogenic contributors. These findings indicate that genetically controlled high MIF expression (and D-DT) promotes MS progression in males, suggesting that these two factors are sex-specific disease modifiers and raising the possibility that aggressive anti-MIF treatment of clinically isolated syndrome or RRMS males with a high-expressor genotype might slow or prevent the onset of progressive MS. Additionally, selective targeting of MIF:CD74 signaling might provide an effective, trackable therapeutic approach for MS subjects of both sexes.

Although endometrial adenocarcinoma is usually treated with surgery, patients with metastatic disease have a poor prognosis. To address the need for better treatment options, molecularly targeted drug therapies are being developed. These targeted therapies rely on accurate mutational profiling of the tumor, which is most often performed on DNA from the primary tumor. Our objective was to compare mutational concordance in primary tumors with their metastases. We genotyped 11 pairs of primary and metastatic endometrial adenocarcinomas using DNA from formalin-fixed paraffin-embedded tissue blocks and semiconductor-based next-generation sequencing. Five of these cases had multiple metastases for comparison. We sequenced 37 known cancer genes that are targets for new drug therapies. A total of 62 mutations were identified in 16 of these 37 genes. The most common mutations were in PIK3CA and PTEN. Overall, there was a 53% discordance in mutations between primary tumors and their paired (33 of 62). The absence of mutations in metastases (25 of 33, 76%) compared with the primary neoplasm was more common than gain of mutations (8 of 33, 24%). There was a 15% discordance rate between paired metastases within individuals (6 of 40), which was significantly less frequent than the rate between primary tumors and their metastases (Fisher exact P value <.0001). Although the sample size is relatively small, our data suggest it may be prudent to test metastases, rather than the primary neoplasm, when using molecularly targeted drug therapies, because isolated metastases may lack mutations detected in the heterogeneous mixture of the tumor’s origin.


INTRODUCTION: Glycerol phenylbutyrate (GPB) is approved in the US for the management of patients 2months of age and older with urea cycle disorders (UCDs) that cannot be managed with protein restriction and/or amino acid supplementation alone. Limited data exist on the use of nitrogen conjugation agents in very young patients. METHODS: Seventeen patients (15 previously on other nitrogen scavengers) with all types of UCDs aged 2months to 2years were switched to, or started, GPB. Retrospective data up to 12months pre-switch and prospective data during initiation of therapy were used as baseline measures. The primary efficacy endpoint of the integrated analysis was the successful transition to GPB with controlled ammonia (<100umol/L and no clinical symptoms). Secondary endpoints included glutamine and levels of other amino acids. Safety endpoints included adverse events, hyperammonemic crises (HACs), and growth and development. RESULTS: 82% and 53% of patients completed 3 and 6months of therapy, respectively (mean 8.85months, range 6days-18.4months). Patients transitioned to GPB maintained excellent control of ammonia and glutamine levels. There were 36 HACs in 11 patients before GPB and 11 in 7 patients while on GPB, with a reduction from 2.98 to 0.88 episodes per year. Adverse events occurring in at least 10% of patients while on GPB were neutropenia, vomiting, diarrhea, pyrexia, hypophagia, cough, nasal congestion, rhinorrhea, rash/papule. CONCLUSION: GPB was safe and effective in UCD patients aged 2months to 2years. GPB use was associated with good short- and long-term control of ammonia and glutamine levels, and the annualized frequency of hyperammonemic crises was lower during the study than before the study. There was no evidence for any previously unknown toxicity of GPB.


BACKGROUND: Although the majority of patients with chronic rhinosinusitis without nasal polyposis (CRSsNP) suffer from bilateral disease, a subset suffer from unilateral disease. Currently, outcomes following endoscopic
sinus surgery (ESS) for medically recalcitrant CRS are inferred from outcomes for patients with bilateral disease.  This study compares outcomes of ESS between patients with unilateral and bilateral disease. METHODS: Patients with CRSsNP who failed appropriate medical therapy and elected ESS were enrolled between 2011 and 2015. Patients were dichotomized according to radiographic evidence of unilateral disease (Lund-Mackay [LM] score = 0 for 1 side) or bilateral disease (LM >/= 1 for both sides). The primary outcome of interest was the 22-item Sino-Nasal Outcome Test (SNOT-22), with secondary outcomes including the Brief Smell Identification Test (BSIT) and the Lund-Kennedy (LK) endoscopy staging system. RESULTS: A total of 190 patients met inclusion criteria consisting of 19 with unilateral (10%) and 171 with bilateral CRSsNP (90%). Both groups were similar across all preoperative demographic factors, SNOT-22, and BSIT scores. Postoperatively, patients with bilateral disease reported greater improvement in mean SNOT-22 scores compared to unilateral disease, but this difference was not statistically or clinically significant (-24.3 +/- 21.1 vs -21.5 +/- 24.0, p = 0.582). Mean LK scores improved for patients with bilateral disease but not unilateral disease, without a difference between groups (-2.0 +/- 3.5 vs -0.4 +/- 2.4, p = 0.090). CONCLUSION: Patients with unilateral CRSsNP experience improvement after ESS comparable to patients with bilateral disease on reported outcome measures.


We hypothesized that constant compression of the knee would mobilize residual synovial fluid and promote successful arthrocentesis. Two hundred and ten knees with grade II-III osteoarthritis were included in this paired design study: (1) conventional arthrocentesis was performed with manual compression and success and volume (milliliters) determined; and (2) the intra-articular needle was left in place, and a circumferential elastomeric brace was tightened on the knee to provide constant compression. Arthrocentesis was attempted again and additional fluid volume was determined. Diagnostic procedural cost-effectiveness was determined using 2017 US Medicare costs. No serious adverse events were noted in 210 subjects. In the 158 noneffusive (dry) knees, sufficient synovial fluid for diagnostic purposes ( >/= 2 ml) was obtained in 5.0% (8/158) without compression and 22.8% (36/158) with compression (p = 0.0001, z for 95% CI = 1.96), and the absolute volume of arthrocentesis fluid obtained without compression was 0.28 +/- 0.79 versus 1.10 +/- 1.81 mL with compression (293% increase, p = 0.0001). In the 52 effusive knees, diagnostic synovial fluid ( >/= 2 ml) was obtained in 75% (39/52) without compression and 100% (52/52) with compression (p = 0.0001, z for 95% CI = 1.96), and the absolute volume of arthrocentesis without compression was 14.7 +/- 3.5 vs 15.5 mL with compression (72.1% increase, p = 0.0002). Diagnostic procedural cost-effectiveness was $655/sample without compression and $387/sample with compression. The new technique of constant compression via circumferential mechanical compression mobilizes residual synovial fluid beyond manual compression improving the success, cost-effectiveness, and yield of diagnostic and therapeutic arthrocentesis in both the effusive and noneffusive knee.


Our previous flow cytometry results demonstrated a significant increase in neutrophils, macrophages/monocytes, and natural killer (NK) cells in dispersed rhesus monkey corpora lutea (CL) after progesterone (P4) levels had fallen below 0.3 ng/ml for >/=3 days during the natural menstrual cycle. In this study, immunohistochemistry revealed the CD11b+ cells (neutrophils, macrophages/monocytes) present in the CL after luteal P4 synthesis ceased were distributed throughout the tissue. CD16+ cells (presumptive NK cells) were observed mainly near the vasculature in functional CL, until their numbers increased and they became widely distributed in regressing CL. To determine if the immune cells that enter luteal tissue during structural regression are functionally different from those that are present during peak function, CD11b+ or CD16+ populations were enriched from mid-late stage (functional) and regressing (days 1.8 ± 0.3 postmenses) CL using antibody-
conjugated magnetic microbeads. Flow cytometry analyses revealed the majority of CD11b+ cells expressed CD14, a protein mainly produced by macrophages/monocytes. The antibody-enriched and depleted fractions were cultured for 24 h, and the media then analyzed for the production of 29 cytokines/chemokines. From the mid-late CL, the CD11b+-enriched fraction produced three cytokines/chemokines, whereas CD16+-enriched cells only produced the chemokine CCL2. However, CD11b+-enriched cells isolated from regressed CL produced eight cytokines/chemokines. The CD16+-enriched cells isolated from regressing CL produced significant levels of only three cytokines. Thus, the CD11b+ cells that appear in the rhesus macaque CL after functional regression produce several cytokines/chemokines that likely play a role in orchestrating structural regression. © The Authors 2017.


The Food and Drug Administration approved Ruxolitinib in 2011 for the treatment of primary myelofibrosis. Five-year safety data showed a higher incidence of skin cancer in patients treated with Ruxolitinib compared to best available therapy for myelofibrosis. This report presents a series of five patients with history of myelofibrosis treated with Ruxolitinib who subsequently developed numerous skin cancers with aggressive biological behavior. Each patient in this report was treated by a Mohs surgeon affiliated with an academic institution. All patients had a history of myelofibrosis and were exposed to Ruxolitinib. Some patients were exposed to other immunomodulatory medications such as Hydroxyurea and Rituximab. The total number of skin cancers and skin cancers with particularly aggressive behavior were noted. All five patients in this series developed numerous skin cancers with aggressive biological behavior during or after therapy with Ruxolitinib. Also, one patient developed lentigo maligna melanoma and another developed metastatic undifferentiated pleomorphic sarcoma. The repeat observation of skin cancers with aggressive features during JAK inhibitor treatment suggests that these medications may promote cutaneous malignant transformation in at risk patients. Further surveillance and testing of JAK kinases regarding the risk of skin cancers is indicated. Copyright © 2017 Journal of Drugs in Dermatology. All Rights Reserved.


RESULTS: A total of 761 VHR were reviewed for a median (range) follow-up of 15 (1-50) mo: there were 291(38%) suture, 303 (40%) low-density and/or mid-density synthetic mesh, and 167(22%) biologic matrix repair. On univariate analysis, there were differences in the three groups including ethnicity, ASA, body mass index, institution, diabetes, primary versus incisional hernia, wound class, hernia size, prior VHR, fascial release, skin flaps, and acute repair. The unadjusted outcomes for SSI (15.1%; 17.8%; 21.0%; P = 0.280) and recurrence (17.8%; 13.5%; 21.5%; P = 0.074) were not statistically different between groups. On multivariate analysis, biologic matrix was associated with a nonsignificant reduction in both SSI and recurrences, whereas synthetic mesh associated with fewer recurrences compared to suture (hazard ratio = 0.60; P = 0.015) and nonsignificant increase in SSI. CONCLUSIONS: Interval estimates favored biologic matrix repair in contaminated VHR; however, these results were not statistically significant. In the absence of higher level evidence, surgeons should carefully balance risk, cost, and benefits in managing contaminated ventral hernia repair. BACKGROUND: Data are lacking to support the choice between suture, synthetic mesh, or biologic matrix in contaminated ventral hernia repair (VHR). We hypothesize that in contaminated VHR, suture repair is associated with the lowest rate of surgical site infection (SSI). METHODS: A multicenter database of all open VHR performed at from 2010-2011 was reviewed. All patients with follow-up of 1 mo and longer were included. The primary outcome was SSI as defined by the Centers for Disease Control and Prevention. The secondary outcome was hernia recurrence (assessed clinically or radiographically). Multivariate analysis (stepwise regression for SSI and Cox proportional hazard model for recurrence) was performed. Copyright © 2016 Elsevier Inc. All rights reserved.


PURPOSE: To assess whether financial or health-related barriers were more common among rural caregivers and whether rural caregivers experienced more caregiving-related difficulties than their urban peers. METHODS: We used data from 7,436 respondents to the Caregiver Module in 10 states from the 2011-2013 Behavioral Risk Factor Surveillance System. Respondents were classified as caregivers if they reported providing care to a family member or friend because of a long-term illness or disability. We classified respondents as living in a rural area if they lived outside of a Metropolitan Statistical Area (MSA). We defined a financial barrier as having an annual household income <$25,000 or not being able see a doctor when needed in the past year because of cost. We defined a health barrier as having multiple chronic health conditions, a disability, or fair or poor self-rated health. FINDINGS: Rural caregivers more frequently had financial barriers than urban caregivers (38.1% vs 31.0%, P = .0001), but the prevalence of health barriers was similar (43.3% vs 40.6%, P = .18). After adjusting for demographic differences, financial barriers remained more common among rural caregivers. Rural caregivers were less likely than their urban peers to report that caregiving created any difficulty in both unadjusted and adjusted models (adjusted prevalence ratio = 0.90; P < .001). CONCLUSIONS: Informal caregivers, particularly in rural areas, face financial barriers. Rural caregivers were less likely than urban caregivers to report caregiving-related difficulties. Rural caregivers' coping strategies or skills in identifying informal supports may explain this difference, but additional research is needed to explore this hypothesis.


Left ventricular hypertrophy (LVH) is prevalent among hypertensive children; however, blood pressure (BP) does not predict its presence. The authors conducted a 1-year prospective cohort study to examine the hypothesis that obesity-related risk factors are associated with left ventricular mass index (LVMI) in hypertensive children, and the association between adiposity and LVMI is mediated by BP-dependent and -independent pathways. A total of 49 hypertensive children were enrolled: 51% were overweight/obese and 41% had LVH at baseline. Children overweight/obese at baseline and follow-up had a greater LVMI increase than those of healthy weight at each visit: mean change of 6.4 g/m(2.7) vs 0.95 g/m(2.7) . Baseline body mass index z score was independently associated with LVMI change (beta=4.08, 1.54-6.61; P=.002). Only pulse pressure and serum aldosterone partially mediated this relationship. Hypertensive youth manifest multiple cardiovascular disease risk factors that worsen over time despite treatment. Of these, adiposity is most associated with LVH and increasing LVMI.
OBJECTIVE: To test whether decline in specific cognitive domains associated with Alzheimer disease neuropathologic change (ADNC) is modified by co-occurrence of other neuropathologies such as Lewy body disease (LBD) or vascular brain injury (VBI). METHODS: Data came from 1,603 autopsied participants evaluated at US Alzheimer's Disease Centers. Standardized z scores in memory, attention, language, and executive function were derived from neuropsychological test scores assessed at each annual visit. Multivariable linear mixed-effects models assessed associations between neuropathologies and longitudinal trajectories of domain scores. RESULTS: Compared to other participants, those with ADNC + LBD generally had worse cognitive trajectories, particularly lower initial executive function and faster attention decline. Participants with ADNC + VBI typically had less impairment and slower decline. Interactions were significant between LBD and ADNC for memory (p = 0.046) and between VBI and ADNC for language (p = 0.03); decline was slower than expected if these neuropathologies acted additively on the rate of decline. In secondary models, these interactions were limited to those with high ADNC (but not intermediate ADNC). In a subset of 260 participants with data on microinfarct location, cortical and subcortical microinfarcts were associated with decline in memory, language, and executive function in those without ADNC, but this effect was reduced among those with ADNC. CONCLUSIONS: ADNC + LBD (but not ADNC + VBI) was associated with poorer executive function and attention compared to other pathology groupings. However, the effect of co-occurring pathologies on cognitive trajectories may depend on the severity of ADNC. Future studies using antemortem biomarkers should seek to replicate these neuropathologic observations.

OBJECT: IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder affecting various anatomical sites, and only recently was identified to affect the dura of the spine. The authors present the second reported case of an intradural extramedullary lesion consistent with IgG4-related spinal disease. METHODS: A literature review was performed that identified 15 other cases of spinal disease, and common features of all known reported spinal IgG4-RD are discussed. RESULTS: Spinal IgG4-RD typically affects males of approximately 50 years of age, and often presents as a T1 and T2 hypo- or isointense lesion that homogenously enhances. Surgical intervention typically involves subtotal resection or biopsy, and histopathologic findings include increased IgG4-positive cells or an IgG4:IgG ratio >40%. The disease responds well to steroids early on, and treatment can include adjuvant therapy such as azathioprine. CONCLUSIONS: Systemic involvement is possible, and, early treatment can quickly minimize disease burden. Thus, increased suspicion would result in early diagnosis and improved prognosis.

PURPOSE: We sought to examine if the method of pregnancy dating at five increasing term gestational ages is associated with increasing neonatal morbidity. MATERIALS AND METHODS: A cohort of women who underwent elective repeat cesarean delivery at >/=37 weeks' gestation were identified from the NICHD MFMU Network registry. We excluded women who were in labor, those carrying a fetus with a congenital anomaly, those with a non-reassuring fetal heart tracing, and those with preeclampsia, preexisting chronic hypertension or diabetes. Composite neonatal morbidity was defined for our study as any of the following: NICU admission, hypotonia, meconium aspiration, seizures, need for ventilator support, NEC, RDS, TTN, hypoglycemia, or neonatal death. We compared composite neonatal morbidity rates among infants born at five different gestational age cutoffs according to their method of pregnancy dating. RESULTS: At 39 and 40 weeks’ gestation, the lowest rate of neonatal complications was seen in pregnancies dated by first trimester...
ultrasound (5.8% and 5.5%, respectively), while those with the highest neonatal morbidity rates were seen when dated by a second or third trimester ultrasound (8.1% and 6.0%, respectively); p < .001. Additionally within each pregnancy dating category, the neonatal morbidity rates declined from 37 to 40 weeks' gestation and then significantly increased at 41 + 0 weeks' gestation. CONCLUSION: Even with suboptimal dating methods, amongst women undergoing elective repeat cesarean delivery, neonatal morbidity was lowest when delivery occurred between 40 and 40 + 6 weeks gestation.


OBJECTIVE: The goal of this article is to highlight mobile technology that is not yet standard of care but could be considered for use in an ototoxicity monitoring programme (OMP) as an adjunct to traditional audiometric testing. Current guidelines for ototoxicity monitoring include extensive test protocols performed by an audiologist in an audiometric booth. This approach is comprehensive, but it may be taxing for patients suffering from life-threatening illnesses and cost prohibitive if it requires serial clinical appointments. With the use of mobile technology, testing outside of the confines of the audiometric booth may be possible, which could create more efficient and less burdensome OMPs. DESIGN: A non-systematic review of new OMP technology was performed. Experts were canvassed regarding the impact of new technology on OMPs. STUDY SAMPLE: OMP devices and technologies that are commercially available and discussed in the literature. RESULTS: The benefits and limitations of portable, tablet-based technology that can be deployed for efficient ototoxicity monitoring are discussed. CONCLUSIONS: New mobile technology has the potential to influence the development and implementation of OMPs and lower barriers to patient access by providing time efficient, portable and self-administered testing options for use in the clinic and in the patient’s home.


PURPOSE: Neutral red (NR) may assist identification of preantral follicles in pieces of cortical tissue prior to cryopreservation in cancer patients requesting fertility preservation. This study is the first to analyze this effect by follicle growth rate after long-term culture in primates. METHODS: Ovarian cortex was obtained from adult rhesus macaques, was cut into fragments, and was incubated with NR. Secondary follicles were readily visualized following NR staining and then were encapsulated into alginate beads and cultured individually for 4 weeks in alphaMEM media supplemented with 10 ng/ml FSH at 5% O2. RESULTS: The survival rates of secondary follicles during culture were similar between those derived from control tissue (71 +/- 13%) and those treated with NR (68 +/- 9%). The proportion of surviving follicles that formed an antrum were also similar in both groups (70 +/- 17% control; 48 +/- 24% NR-treated). Follicle diameters were not different between control follicles (184 +/- 5 mum) and those stained with NR (181 +/- 7 mum) on the day of isolation. The percentages of surviving follicles within three cohorts based on their diameters at week 4 of culture were similar between the control group and NR-stained tissue group, fast-grow follicles (24 +/- 6% vs. 13 +/- 10%), slow-grow follicles (66 +/- 5% vs. 60 +/- 9%), or no-grow (10 +/- 9% vs. 27 +/- 6%), respectively. There were no differences in follicle diameters between groups during the culture period. Pre-exposure of secondary follicles to NR diminished their capacity to produce both estradiol and androstenedione by week 4 of culture, when follicles are exhibiting an antrum. Inhibitory effects of NR on steroid production by slow-grow follicles was less pronounced. CONCLUSIONS: NR does not affect
secondary follicle survival, growth, and antrum formation during long-term culture, but steroid hormone production by fast-grow follicles is compromised. NR can be used as a non-invasive tool for in situ identification of viable secondary follicles in ovarian cortex before tissue cryopreservation without affecting follicle survival and growth in vitro. Whether maturation or developmental competence of oocytes derived from antral follicles in 3D culture that were previously isolated from NR-stained tissue is normal or compromised remains to be determined. Likewise, the functional consequences of pre-exposure to NR prior to ovarian cortical tissue cryopreservation and transplantation are unknown.


OBJECTIVE To determine the scope, source, and mode of transmission of a multifacility outbreak of extensively drug-resistant (XDR) Acinetobacter baumannii. DESIGN Outbreak investigation. SETTING AND PARTICIPANTS Residents and patients in skilled nursing facilities, long-term acute-care hospital, and acute-care hospitals. METHODS A case was defined as the incident isolate from clinical or surveillance cultures of XDR Acinetobacter baumannii resistant to imipenem or meropenem and nonsusceptible to all but 1 or 2 antibiotic classes in a patient in an Oregon healthcare facility during January 2012-December 2014. We queried clinical laboratories, reviewed medical records, oversaw patient and environmental surveillance surveys at 2 facilities, and recommended interventions. Pulsed-field gel electrophoresis (PFGE) and molecular analysis were performed. RESULTS We identified 21 cases, highly related by PFGE or healthcare facility exposure. Overall, 17 patients (81%) were admitted to either long-term acute-care hospital A (n=8), or skilled nursing facility A (n=8), or both (n=1) prior to XDR A. baumannii isolation. Interfacility communication of patient or resident XDR status was not performed during transfer between facilities. The rare plasmid-encoded carbapenemase gene bla OXA-237 was present in 16 outbreak isolates. Contact precautions, chlorhexidine baths, enhanced environmental cleaning, and interfacility communication were implemented for cases to halt transmission. CONCLUSIONS Interfacility transmission of XDR A. baumannii carrying the rare blaOXA-237 was facilitated by transfer of affected patients without communication to receiving facilities.


OBJECTIVE: The aim of this study was to compare the detection of levator ani defects (LAD) between 3-dimensional (3D) ultrasound (US) and 3D magnetic resonance imaging (MRI). METHODS: This is a secondary analysis of the Pelvic Floor Nerve Injury Following Childbirth Study. Nulliparous women underwent a standardized protocol of pelvic floor evaluations between January 2008 and December 2013, prior to pregnancy (V1) and at 2 points postpartum: 6 weeks (V2) and 6 months (V3). Those women who underwent a high-resolution 3D MRI pelvic floor sequence were selected. Comparisons were made to concomitantly acquired 3D perineal US. Eight tomographic slices were examined in the axial plane, each side independently scored with 0 (no defect) or 1 (defect). A similar tomographic approach was applied to the MRI. For both MRI and US, the right and left sides were each scored. A total score of 0 to 8 was given to each side. A dichotomous variable “complete LAD” was defined. Cohen kappa was used as a measurement of agreement of complete LAD between MRI and US. Kendall tau b was used to correlate total scores. RESULTS: On the right side, 80 (90%) of 89 pairs were in agreement (concordant in the diagnosis or not of a “defect”). On the left side, 72 (81%) of 89 pairs were in agreement. Correlations (Cohen kappa) of complete LAD were 0.65 (P < 0.001) on the right and 0.37 (P < 0.001) on the left. Correlations of total scores were 0.47 (P < 0.001) on the right and 0.41 (P < 0.001) on the left. CONCLUSIONS: Moderate agreement was found between 3D US and 3D MRI LAD detection. More LADs and discordance were seen on the left.
Children with Down syndrome (DS) have a remarkably high risk of developing leukemia during childhood; the mechanisms driving that risk are not well understood, and no clear prevention strategies exist. We conducted a nested case-control study in a Texas DS birth cohort to investigate possible links between maternal health, labor/delivery conditions, and leukemia risk. For most of the factors studied there was no evidence of an increased risk of total leukemias, or the subtypes acute lymphoid or acute myeloid leukemia. Ultrasound use showed an almost 2-fold increased odds of leukemia, but this result is likely an example of confounding by indication. There was a pattern of increased risk seen for presence of co-occurring heart anomalies, including tetralogy of Fallot, ventricular septal defects, atrial septal defects, and patent ductus arteriosus. Further investigation of the links between co-occurring heart defects in children with DS and development of leukemia may provide new understanding of cancer mechanisms, and ultimately lead to prevention opportunities for this high-risk population.

Clavicular fractures are common injuries which are traditionally managed non-surgically without clinically significant sequelae. However, they may develop hypertrophic callus formation that compresses the brachial plexus. These cases may present months to years after initial injury with varying degrees of pain, paresthesia and weakness on the affected side, and are usually treated by surgical resection of the hypertrophic callus. We present a case of brachial plexopathy due to hypertrophic clavicular callus causing weakness and paresthesia. The plexopathy was confirmed with imaging and electrodiagnostic studies. This case was unusual in that resolution of symptoms was achieved non-surgically.

BACKGROUND AND AIMS: This study aimed to understand the use of massive transfusion (MT) for gastrointestinal bleeding (GIB). PATIENTS AND METHODS: We performed a retrospective analysis of patients admitted to our medical Intensive Care Unit (ICU) with GIB for the type of bleeding, quantity of blood products transfused, and risk of transfusion-related acute lung injury (TRALI) and death. MT was defined as transfusion of 10 or more units of red blood cell (RBC) within a 24-h period in a 1-unit RBC: 1-unit fresh frozen plasma: and 1-unit platelet ratio. TRALI was defined as development of acute lung injury (ALI), within 6 h of transfusion, with new bilateral pulmonary infiltrates, absence of circulatory overload, or other explanation for ALI. RESULTS: In a 43-month interval, 169 patients were admitted to the ICU with GIB and received blood products, of whom 13 received MT. Ten patients developed TRALI, of whom 7 (70%) had received MT. MT was associated with an increased risk of TRALI (odds ratio [OR]: 17.9, 95% confidence interval [CI]: 2.9-111.2, \( P = 0.002 \)) after adjusting for age, sex, body mass index, baseline vitals, and laboratory data. Death was predicted by MT (OR: 5.6, 95% CI: 1.6-19.7, \( P = 0.007 \)), TRALI (OR: 2.3, 95% CI: 1.1-4.6, \( P = 0.02 \)), and Acute Physiologic Chronic Health Evaluation II score (OR: 1.17 per unit increase, 95% CI: 1.09-1.26, \( P < 0.001 \)) after adjusting for age and sex. CONCLUSIONS: MT for GIB is associated with an increased risk of TRALI and death. Prospective studies assessing the use of MT in this population are needed to understand and improve outcomes.


With the growth of high-throughput proteomic data, in particular time series gene expression data from various perturbations, a general question that has arisen is how to organize inherently heterogenous data into meaningful structures. Since biological systems such as breast cancer tumors respond differently to various stimuli, little is known about exactly how these gene regulatory networks (GRNs) operate under different stimuli. Challenges due to the lack of knowledge not only occur in modeling the dynamics of a GRN but also cause bias or uncertainties in identifying parameters or inferring the GRN structure. This paper describes a new algorithm which enables us to estimate bias error due to the effect of perturbations and correctly identify the common graph structure among biased inferred graph structures. To do this, we retrieve common dynamics of the GRN subject to various perturbations. We refer to the task as “repairing” inspired by “image repairing” in computer vision. The method can automatically correctly repair the common graph structure across perturbed GRNs, even without precise information about the effect of the perturbations. We evaluate the method on synthetic data sets and demonstrate an application to the DREAM data sets and discuss its implications to experiment design.


PURPOSE: To evaluate dose-response relationship in yttrium-90 (90Y) resin microsphere radioembolization for neuroendocrine tumor (NET) liver metastases using a tumor-specific dose estimation based on technetium-99m-labeled macroaggregated albumin (99mTc MAA) single photon emission computed tomography (SPECT)-CT. MATERIALS AND METHODS: Fifty-five tumors (mean size 3.9 cm) in 15 patients (10 women; mean age 57 y) were evaluated. Tumor-specific absorbed dose was estimated using a partition model. Initial (median 2.3 months) follow-up data were available for all tumors; last (median 7.6 months) follow-up data were available for 45 tumors. Tumor response was evaluated using Modified Response Evaluation Criteria in Solid Tumors (mRECIST) on follow-up CT. Tumors with complete or partial response were considered responders. Mean tumor absorbed dose was 231.4 Gy +/- 184.3, and mean nontumor liver absorbed dose was 39.0 Gy +/- 18.0. RESULTS: Thirty-six (65.5%) and 30 (66.7%) tumors showed response at initial and last follow-up, respectively. Mean absorbed doses in responders and nonresponders at initial and last follow-up were 285.8 Gy +/- 191.1 and 128.1 Gy +/- 117.1 (P = .0004) and 314.3 Gy +/- 195.8 and 115.7 Gy +/- 117.4 (P = .0001). Cutoff value of > = 191.3 Gy for tumor-specific absorbed dose predicted tumor response with 93% specificity, whereas < 72.8 Gy predicted nonresponse with 100% specificity at last follow-up. Estimated mean absorbed tumor dose per patient was significantly higher in responders versus nonresponders over the follow-up period (224.5 Gy +/- 90.3 vs 70.0 Gy +/- 28.0; P = .007). CONCLUSIONS: Tumor-specific absorbed dose, estimated with a partition model, was significantly associated with tumor response in NET liver metastases. An estimated dose > = 191.3 Gy predicted treatment response with high sensitivity and specificity.

Alcoholic liver disease is a spectrum of conditions that include alcoholic fatty liver disease, alcoholic hepatitis, and chronic alcoholic liver disease. The diagnosis of alcoholic liver disease remains founded in an accurate patient history and detailed physical examination. Concurrent with the physical examination, objective data from laboratory, imaging, and histologic studies are helpful to confirm a diagnosis of alcoholic liver disease. Novel biomarkers, scoring systems, and imaging modalities are improving the ability to diagnose and manage alcoholic liver disease, but for most practicing clinicians, these have not been adopted widely because of their cost, but also because of limitations and uncertainty in their performance characteristics.

BACKGROUND AND AIMS: Preventing missed appointments, or "no-shows," is an important target in improving efficient patient care and lowering costs in gastrointestinal endoscopy practices. We aimed to investigate whether a nurse telephone call would reduce no-show rates for endoscopic appointments, and to determine if hiring and maintaining a nurse dedicated to pre-endoscopy phone calls is economically advantageous. Our secondary aim was to identify predictors of no-shows to endoscopy appointments. METHODS: We hired and trained a full-time licensed nurse to make a telephone call to patients 7 days before their scheduled upper endoscopy or colonoscopy. We compared this intervention with a previous reminder system involving mailed reminders. The effect of the intervention and impact of other predictors of no-shows were analyzed in 2 similar preintervention and postintervention patient cohorts. A mixed effects logistic regression model was used to estimate the association of the odds of being a no-show to the scheduled appointment and the characteristics of the patient and visit. An analysis of costs was performed that included the startup and maintenance costs of the intervention. RESULTS: We found that a nurse phone call was associated with a 33% reduction in the odds of a no-show visit (odds ratio, 0.67; 95% confidence interval, 0.50–0.91), adjusting for gender, age, partnered status, insurer type, distance from the endoscopy center, and visit type. The recovered reimbursement during the study period was $48,765, with net savings of $16,190 when accounting for the maintenance costs of the intervention; this resulted in a net revenue per annum of $43,173. CONCLUSIONS: We found that endoscopy practices may increase revenue, improve scheduling efficiency, and maximize resource utilization by hiring a nurse to reduce no-shows. Predictors of no-shows to endoscopy included unpartnered or single patients, commercial or managed care, being scheduled for a screening or surveillance colonoscopy.

Alveolar rhabdomyosarcoma (aRMS) is a pediatric soft tissue cancer commonly associated with a chromosomal translocation that leads to the expression of a Pax3:Foxo1 or Pax7:Foxo1 fusion protein, the developmental underpinnings of which may give clues to its therapeutic approaches. In aRMS, the NFkappaB-YY1-miR-29 regulatory circuit is dysregulated, resulting in repression of miR-29 and loss of the associated tumor suppressor activity. To further elucidate the role of NFkappaB in aRMS, we first tested 55 unique sarcoma cell lines and primary cell cultures in a large-scale chemical screen targeting diverse molecular pathways. We
found that pharmacological inhibition of NFkappaB activity resulted in decreased cell proliferation of many of the aRMS tumor cultures. Surprisingly, mice that were orthotopically allografted with aRMS tumor cells exhibited no difference in tumor growth when administered an NFkappaB inhibitor, compared to control. Furthermore, inhibition of NFkappaB by genetically ablating its activating kinase inhibitor, IKKbeta, by conditional deletion in a mouse model harboring the Pax3-Foxo1 chimeric oncogene failed to abrogate spontaneous tumor growth. Genetically engineered mice with conditionally deleted IKKbeta exhibited a paradoxical decrease in tumor latency compared with those with active NFkappaB. However, using a synthetic-lethal approach, primary cell cultures derived from tumors with inactivated NFkappaB showed sensitivity to the BCL-2 inhibitor navitoclax. When used in combination with an NFkappaB inhibitor, navitoclax was synergistic in decreasing the growth of both human and IKKbeta wild-type mouse aRMS cells, indicating that inactivation of NFkappaB alone may not be sufficient for reducing tumor growth, but, when combined with another targeted therapeutic, may be clinically beneficial.


The serotonin transporter is a sodium and chloride-coupled transporter that "pumps" extracellular serotonin into cells. S-citalopram is a drug used to treat depression and anxiety by binding to the serotonin transporter with high-affinity, blocking serotonin reuptake. Here we report an efficient procedure and a set of tools to stabilize, express, purify, and crystallize serotonin transporter-antibody complexes bound to S-citalopram and other antidepressants. Mutations which stabilize the serotonin transporter were identified using an S-citalopram binding assay. Serotonin transporter expressed in baculovirus-transduced HEK293S GnTI- cells, was reconstituted into proteoliposomes and used to raise high-affinity antibodies. We have developed a strategy to discover antibodies that are useful for structural studies. A straightforward approach for the expression of antibody fragments in Sf9 cells has also been established. Transporter-antibody complexes purified using this procedure are well-behaved and readily crystallize, producing complexes with S-citalopram that diffract X-rays to 3-4 A resolution. The strategies developed here can be utilized to determine the structure of other challenging membrane proteins.


PURPOSE: There is currently a wide range of suture knots used in rotator cuff repair. The purpose of this study was to compare a new type of self-locking sliding knot called the Nice knot to the self-locking and sliding Nicky's knot. METHODS: Nice knots and Nicky's knots were tied and subjected to mechanical testing including a pure traction stress and a series of dynamic stresses. Both knots were tied using standard braided suture and reinforced braided suture. The responses to these stresses were measured in the amount of elongation of the knot, maximum effort needed for failure, stiffness of construct and dynamic stiffness. RESULTS: With both knots the standard suture had a lower amount of elongation during the dynamic tests than the reinforced braided suture. The reinforced braided suture showed superior results during maximal effort in the pure traction tests. An increased failure rate occurred due to elongation when a dynamic stress was applied to the reinforced suture in both knot types. During dynamic testing the Nice knot showed a decrease in the amount of elongation (P<0.001). CONCLUSIONS: The Nice knot provides a sliding locking knot option which can decrease the risk of elongation during dynamic stress. LEVEL OF EVIDENCE: Basic Science Study, Biomechanical Study.

BACKGROUND: Retinal dystrophies constitute a group of diseases characterized by clinical variability and pronounced genetic heterogeneity. Retinitis pigmentosa is the most common subtype of hereditary retinal dystrophy and is characterized by a progressive loss of peripheral field vision (Tunnel Vision), eventual loss of central vision, and progressive night blindness. The characteristics of the fundus changes include bone-spicule formations, attenuated blood vessels, reduced and/or abnormal electroretinograms, changes in structure imaged by optical coherence tomography, and subjective changes in visual function. The different syndromic and nonsyndromic forms of retinal dystrophies can be attributed to mutations in more than 250 genes. Molecular diagnosis for patients with retinitis pigmentosa has been hampered by extreme genetic and clinical heterogeneity between retinitis pigmentosa and other forms of retinal dystrophies. Next generation sequencing (NGS) technologies are among the most promising techniques to identify pathogenic variations in retinal dystrophies. PURPOSE: The purpose of this study was to discover the molecular diagnosis for Brazilian patients clinically diagnosed with a retinitis pigmentosa pattern of inheritance by using NGS technologies. MATERIALS AND METHODS: Sixteen patients with the clinical diagnosis of retinitis pigmentosa were included in the study. Their DNA was sequenced in a panel with 132 genes related to retinal dystrophies using the Illumina(R) platform. Sequence analysis and variation calling was performed using Soft Genetics(R), NextGene, and Geneticist Assistant software. The criteria for pathogenicity analysis were established according to the results of prediction programs (Polyphen 2, Mutation taster and MetaCore) and comparison of pathogenic variations found with databases. RESULTS: The identified potentially pathogenic variations were all confirmed by Sanger sequencing. There were 89 variations predicted as pathogenic, but only 10 of them supported the conclusion of the molecular diagnosis. Five of the nine patients were autosomal dominant RP (56%), two (22%) were autosomal recessive RP, and two (22%) were X-linked RP. Nine of the 16 patients (56%) had probably positive or positive results. CONCLUSION: The Next Generation Sequencing used in this study allowed the molecular diagnosis to be confirmed in 56% of the patients and clarified the inheritance pattern of the patient’s retinal dystrophies.


Alternative payment models have been proposed as a way to facilitate patient-centered medical home model implementation, yet little is known about how payment reform translates into changes in care delivery. We conducted site visits, observed operations, and conducted interviews within 3 Federally Qualified Health Center organizations that were part of Oregon’s Alternative Payment Methodology demonstration project. Data were analyzed using an immersion-crystallization approach. We identified several care delivery changes during the early stages of implementation, as well as challenges associated with this new model of payment. Future research is needed to further understand the implications of these changes.


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


This study of a global health research partnership assesses how U.S. fiscal administrative policies impact capacity building at foreign partner institutions. We conducted a case study of a research collaboration between Mbarara University of Science and Technology (MUST) in Mbarara, Uganda, and originally the University of California San Francisco (UCSF), but now Massachusetts General Hospital (MGH). Our case study is based on three of the authors' experiences directing and working with this partnership from its inception in 2003 through 2015. The collaboration established an independent Ugandan non-profit to act as a local fiscal agent and grants administrator and to assure compliance with the Ugandan labour and tax law. This structure, combined with low indirect cost reimbursements from U.S. federal grants, failed to strengthen institutional capacity at MUST. In response to problems with this model, the collaboration established a contracts and grants office at MUST. This office has built administrative capacity at MUST but has also generated new risks and expenses for MGH. We argue that U.S. fiscal administrative practices may drain rather than build capacity at African universities by underfunding the administrative costs of global health research, circumventing host country institutions, and externalising legal and financial risks associated with international work. ABBREVIATIONS: MGH: Massachusetts General Hospital; MUST: Mbarara University of Science and Technology; NIH: National Institutes of Health; UCSF: University of California San Francisco; URI: Uganda Research Institute.


PURPOSE: There are few data available on the experience of minority surgeons in the field of oral and maxillofacial surgery (OMS). Therefore, the purpose of this study was to 1) explore factors that contribute to African Americans choosing OMS as a career, 2) examine satisfaction among minority oral and maxillofacial surgeons with the residency application and training process, 3) report on practice patterns among minority oral and maxillofacial surgeons, and 4) identify perceived bias for or against minority oral and maxillofacial surgeons in an attempt to aid the efforts of OMS residency organizations to foster diversity. MATERIALS AND METHODS: A 19-item survey was sent to 80 OMS practitioners by use of information from the mailing list of the National Society of Oral and Maxillofacial Surgeons, an American Association of Oral and Maxillofacial Surgeons-affiliated organization. All surveys were sent by mail and were followed by a reminder mailing after 8 weeks. Responses returned within 16 weeks were accepted for analysis. RESULTS: Of the 80 mailed surveys, 41 were returned within the 16-week parameter, representing a return rate of 51%. Most of the minority surgeon respondents were married men with a mean age of 60 years who worked as private practitioners. Most respondents practiced on the eastern and western coasts of the United States. Exposure in dental school was the most important factor in selecting OMS as a specialty. Location and prestige were the most important factors in selecting a residency program. Most respondents reported that race did not affect the success of their application to a residency program and did not currently affect the success of their practice. However, 25 to 46% of participants experienced race-related harassment, and 48 to 55% of participants believed there was a bias against African Americans in OMS. CONCLUSIONS: Our data suggest that a substantial number of minority oral and maxillofacial surgeons subjectively perceive race-based bias in their career, although it does not appear to affect professional success.
African giant pouched rats (Cricetomys spp.) are large rodents native to sub-Saharan Africa. Wild-caught pouched rats identified as Cricetomys ansorgei (n = 49) were imported from Tanzania. A survey of gastrointestinal parasitism by fecal flotation revealed the presence of multiple parasites, including Nippostrongylus spp., Heterakis spp., Trichuris spp., Hymenolepis spp., Raillietina spp., and Eimeria spp. Oral self-administered fenbendazole (150 ppm), topical moxidectin (2 mg/kg), pyrantel pamoate (15 mg/kg), piperazine (100 mg/kg daily), and injectable ivermectin (0.25 mg/kg) were used to determine effective treatment options for the gastrointestinal parasites present in the colony. Pyrantel pamoate in a treat vehicle and piperazine in water bottles were easily administered and significantly reduced the numbers of animals shedding Nippostrongylus spp. and Heterakis spp. during the study. Moxidectin and ivermectin were clinically ineffective at reducing fecal egg shedding. Fenbendazole was most effective at clearing infection with Trichuris spp. Although 10 mg/kg praziquantel was ineffective, a single dose of 30 mg/kg praziquantel significantly reduced the number of African pouched rats that shed cestode embryos. A combination treatment may be necessary to successfully treat all parasites present in any given animal.


BACKGROUND: An expedited recovery protocol for management of pediatric blunt solid organ injury (spleen, liver, and kidney) was instituted across two Level 1 Trauma Centers, managed by nine pediatric surgeons within three hospital systems. METHODS: Data were collected for 18 months on consecutive patients after protocol implementation. Patient demographics (including grade of injury), surgeon compliance, National Surgical Quality Improvement Program (NSQIP) complications, direct hospital cost, length of stay, time in the ICU, phlebotomy, and re-admission were compared to an 18-month control period immediately preceding study initiation. RESULTS: A total of 106 patients were treated (control=55, protocol=51). Demographics were similar among groups, and compliance was 78%. Hospital stay (4.6 vs. 3.5 days, p=0.04), ICU stay (1.9 vs. 1.0 days, p=0.02), and total phlebotomy (7.7 vs. 5.3 draws, p=0.007) were significantly less in the protocol group. A decrease in direct hospital costs was also observed ($11,965 vs. $8795, p=0.09). Complication rates (1.8% vs. 3.9%, p=0.86, no deaths) were similar. CONCLUSIONS: An expedited, hemodynamic-driven, pediatric solid organ injury protocol is achievable across hospital systems and surgeons. Through implementation we maintained quality while impacting length of stay, ICU utilization, phlebotomy, and cost. Future protocols should work to further limit resource utilization. TYPE OF STUDY: Retrospective cohort study. LEVEL OF EVIDENCE: Level II.


BACKGROUND: Implantable cardioverter-defibrillator (ICD) recipients require close follow-up that can be difficult for patients who have to travel long distances for clinic follow-up. We aimed to compare clinical outcomes between ICD patients followed-up in a telemedicine video-conferencing clinic (TMVC) and a conventional in-person clinic (CIC). We hypothesized that outcomes of patients followed in the TMVC are noninferior to the CIC. METHODS AND RESULTS: This retrospective study compares time to first appropriate ICD therapy, time to first inappropriate ICD therapy, time to first shock, and overall survival in patients followed in TMVC compared with CIC between 2001 and 2016. Two hundred and eighty-seven patients were followed in the TMVC group and 236 patients in the CIC. The average age of the TMVC and CIC groups was 64.13 +/- 9.38 and 65.23 +/- 8.57 years, respectively (P=0.164). There was no difference in the modified Seattle heart failure
The ability to assess antileukemic drug activity on primary patient samples is a powerful tool in determining potential drug targets and selection of therapeutic agents with biological and functional rationale. We previously described a method for enabling the use of cryopreserved primary acute myeloid leukemia cells in functional drug screens. This method, termed the Novel Method Enabling the Use of Cryopreserved Primary Acute Myeloid Leukemia Cells in Functional Drug Screens (NMC), allows for the maintenance of leukemia cell viability and function over extended periods of time, facilitating the assessment of drug activity in a more naturalistic setting.

**BACKGROUND:**
Antidepressants are established first-line treatments for anxiety disorders, but it is not clear whether they are equally effective across the severity range. To examine the influence of baseline severity on antidepressant efficacy for anxiety disorders, a meta-analysis and meta-regression were conducted.

**AIMS:** To examine the influence of baseline severity on antidepressant efficacy for generalised anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and panic disorder.

**METHOD:** Fifty-six trials of second-generation antidepressants for the short-term treatment of an anxiety disorder were included. Baseline change scores were extracted for placebo and treatment groups in each trial. Mixed effects meta-regression was used to investigate the effects of treatment group, baseline severity and their interaction. Increased baseline severity did not predict greater improvement in drug groups compared with placebo groups.

**RESULTS:** Increased baseline severity did not predict greater improvement in drug groups compared with placebo groups. Standardised regression coefficients of the interaction term between baseline severity and treatment group were 0.04 (95% CI -0.13 to 0.20, P = 0.65) for GAD, -0.06 (95% CI -0.20 to 0.09, P = 0.43) for SAD, 0.04 (95% CI -0.07 to 0.16, P = 0.46) for OCD, 0.16 (95% CI -0.22 to 0.53, P = 0.37) for PTSD and 0.002 (95% CI -0.10 to 0.10, P = 0.96) for panic disorder. For OCD, baseline severity did predict improvement in both placebo and drug groups equally (beta = 0.11, 95% CI 0.05 to 0.17, P = 0.001).

**CONCLUSIONS:** No relationship between baseline severity and drug-placebo difference was found for anxiety disorders. These results suggest that if the efficacy of antidepressants is considered clinically relevant, they may be prescribed to patients with anxiety regardless of symptom severity.

**REFERENCES:**

The ability to assess antileukemic drug activity on primary patient samples is a powerful tool in determining potential drug targets and selection of therapeutic agents with biological and functional rationale. We previously described a method for enabling the use of cryopreserved primary acute myeloid leukemia cells in functional drug screens. This method, termed the Novel Method Enabling the Use of Cryopreserved Primary Acute Myeloid Leukemia Cells in Functional Drug Screens (NMC), allows for the maintenance of leukemia cell viability and function over extended periods of time, facilitating the assessment of drug activity in a more naturalistic setting.
established small molecule inhibitor screens for use on freshly isolated leukemia cells for this purpose. Here we describe a method that produces functional small molecule inhibitor screening results using cryopreserved primary acute myeloid leukemia cells. This method was established to take advantage of biorepositories containing archival material, such as those established by the Children’s Oncology Group, and to enable validation of potential pathway dependencies uncovered by genomic analysis. Various conditions used to thaw and culture cryopreserved specimens were assessed for effect on viability, differentiation, and the ability to recapitulate sensitivity results obtained on fresh samples. The most reproducible results were obtained by quick-thawing and culturing samples in cytokine rich media before performing drug screens. Our data suggest that cytokine-enriched media aids in maintaining the viability and numbers required to perform functional analysis on cryopreserved leukemia cells. This method can aid in producing informative data on therapeutic targeting and precision medicine efforts in leukemia by making use of biorepositories and bio banks.


To test the hypothesis that skeletal muscle myosins can directly influence blood coagulation and thrombosis, ex vivo studies of the effects of myosin on thrombogenesis in fresh human blood were conducted. Addition of myosin to blood augmented the thrombotic responses of human blood flowing over collagen-coated surfaces (300 s^-1 shear rate). Perfusion of human blood over myosin-coated surfaces also caused fibrin and platelet deposition, evidencing myosin’s thrombogenicity. Myosin markedly enhanced thrombin generation in both platelet-rich plasma and platelet-poor plasma, indicating that myosin promoted thrombin generation in plasma primarily independent of platelets. In purified reaction mixtures composed only of factor Xa, factor Va, prothrombin, and calcium ions, myosin greatly enhanced prothrombinase activity. The Gla domain of factor Xa was not required for myosin’s prothrombinase enhancement. When binding of purified clotting factors to immobilized myosin was monitored using biolayer interferometry, factors Xa and Va each showed favorable binding interactions. Factor Va reduced by 100-fold the apparent Kd of myosin for factor Xa (Kd approximately 0.48 nM), primarily by reducing koff, indicating formation of a stable ternary complex of myosin: Xa: Va. In studies to assess possible clinical relevance for this discovery, we found that antimyosin antibodies inhibited thrombin generation in acute trauma patient plasmas more than in control plasmas (P = .0004), implying myosin might contribute to acute trauma coagulopathy. We posit that myosin enhancement of thrombin generation could contribute either to promote hemostasis or to augment thrombosis risk with consequent implications for myosin’s possible contributions to pathophysiology in the setting of acute injuries.


The prefrontal cortex (PFC) is thought to play a critical role in behavioral flexibility by monitoring action–outcome contingencies. How PFC ensembles represent shifts in behavior in response to changes in these contingencies remains unclear. We recorded single-unit activity and local field potentials in the dorsomedial PFC (dmPFC) of male rats during a set-shifting task that required them to update their behavior, among competing options, in response to changes in action–outcome contingencies. As behavior was updated, a subset of PFC ensembles encoded the current trial outcome before the outcome was presented. This novel outcome-prediction encoding was absent in a control task, in which actions were rewarded pseudorandomly, indicating that PFC neurons are not merely providing an expectancy signal. In both control and set-shifting tasks, dmPFC neurons displayed postoutcome discrimination activity, indicating that these neurons also monitor whether a behavior is successful in generating rewards. Gamma-power oscillatory activity increased before the outcome in both tasks but did not differentiate between expected outcomes, suggesting that this measure is not related to set-shifting behavior but reflects expectation of an outcome after action execution.
These results demonstrate that PFC neurons support flexible rule-based action selection by predicting outcomes that follow a particular action. © 2017 the authors.


The purpose of this study was to evaluate glenoid-sided lateralization in reverse shoulder arthroplasty (RSA), and compare bony and prosthetic lateralization. The hypothesis was that stress and displacement would increase with progressive bony lateralization, and be lower with prosthetic lateralization. A 3D finite element analysis (FEA) was performed on a commercially available RSA prosthesis. Stress and displacement were evaluated at baseline and following 5, 10, and 15 mm of bony or prosthetic lateralization. Additional variables included glenosphere size, baseplate orientation, and peripheral screw orientation. Maximum stress for a 36 mm glenosphere without bone graft increased by 137% for the 5 mm graft, 187% for the 10 mm graft, and 196% for the 15 mm graft. Likewise, displacement progressively increased with increasing graft thickness. Stress and displacement were reduced with a smaller glenosphere, inferior tilt of the baseplate, and divergent peripheral screws. Compared to bony lateralization, stress was lower with prosthetic lateralization through the glenosphere or baseplate. Displacement with 5 mm of bony lateralization reached recommended maximal amounts for osseous integration, whereas, this level was not reached until 10-15 mm of prosthetic lateralization. Baseplate stress and displacement in an FEA model is lower with a smaller glenosphere, inferior tilt, and divergent screws. Bony lateralization increases stress and displacement to a greater degree than prosthetic lateralization. It appears that at least 10 mm of prosthetic lateralization is mechanically acceptable during RSA, but only 5 mm of bony lateralization is advised. (c) 2016 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 35:1548-1555, 2017.


BACKGROUND: This study compared the outcome and radiographic humeral adaptations after placement of a traditional-length (TL) or short-stem (SS) humeral component during total shoulder arthroplasty (TSA). The hypothesis was there would be no difference in outcome or radiographic adaptations. METHODS: A multicenter retrospective review was performed of primary TSAs performed with a TL or SS press-fit humeral component. The stems were identical in geometry and coating, with the only variable being stem length. Functional outcome and radiographs were reviewed at a minimum of 2 years postoperatively in 58 TL stems and 56 SSs. RESULTS: There were significant improvements in all range of motion and functional outcome from baseline (P < .001) but no difference between the groups (P > .05). TL stems were placed in anatomical alignment 98% of the time compared with 86% of the SS cases (P = .015), but alignment did not influence outcome. Cortical thinning was more common in the medial metaphysis with the TL stem (74%) than with the SS (50%; P = .008). Partial calcar osteolysis was seen in 31% of TL stems and in 23% of SSs (P = .348). There was no difference in loosening or shift between the 2 groups. CONCLUSION: There is no difference in functional outcome at short-term follow-up between a TL stem and a SS in TSA. The pattern of radiographic adaptations may differ based on stem length. Further study is needed to evaluate the mid- to long-term differences, particularly with regard to calcar osteolysis.


Coenzyme A is an essential metabolite known for its central role in over one hundred cellular metabolic reactions. In cells, Coenzyme A is synthesized de novo in five enzymatic steps with vitamin B5 as the starting metabolite, phosphorylated by pantothenate kinase. Mutations in the pantothenate kinase 2 gene cause a severe form of neurodegeneration for which no treatment is available. One therapeutic strategy is to generate Coenzyme A precursors downstream of the defective step in the pathway. Here we describe the synthesis, characteristics and in vivo rescue potential of the acetyl-Coenzyme A precursor S-acetyl-4′-phosphopantetheine as a possible treatment for neurodegeneration associated with pantothenate kinase deficiency.


Neural encoding of sensory stimuli is typically studied by averaging neural signals across repetitions of the same stimulus. However, recent work has suggested that the variance of neural activity across repeated trials can also depend on sensory inputs. Here we characterize how intertrial variance of the local field potential (LFP) in primary auditory cortex of awake ferrets is affected by continuous natural sound stimuli. We find that natural sounds often suppress the intertrial variance of low-frequency LFP (<16 Hz). However, the amount of the variance reduction is not significantly correlated with the amplitude of the mean response at the same recording site. Moreover, the variance changes occur with longer latency than the mean response. Although the dynamics of the mean response and intertrial variance differ, spectro-temporal receptive field analysis reveals that changes in LFP variance have frequency tuning similar to multiunit activity at the same recording site, suggesting a local origin for changes in LFP variance. In summary, the spectral tuning of LFP intertrial variance and the absence of a correlation with the amplitude of the mean evoked LFP suggest substantial heterogeneity in the interaction between spontaneous and stimulus-driven activity across local neural populations in auditory cortex.


The intent of this contribution is to provide an update of the progress we have made towards developing a method/treatment to permanently sterilize cats. Our approach employs two complementary methodologies: RNA interference (RNAi) to silence genes involved in the central control of reproduction and a virus-based gene therapy system intended to deliver RNAi selectively to the hypothalamus (where these genes are expressed) via the systemic administration of modified viruses. We selected the hypothalamus because it contains neurons expressing Kiss1 and Tac3, two genes essential for reproduction and fertility. We chose the non-pathogenic adeno-associated virus (AAV) as a vector whose tropism could be modified to target the hypothalamus. The issues that must be overcome to utilize this vector as a delivery vehicle to induce sterility include modification of the wild-type AAV to target the hypothalamic region of the brain with a simultaneous reduction in targeting of peripheral tissues and non-hypothalamic brain regions, identification of RNAi targets that will effectively reduce the expression of Kiss1 and Tac3 without off-target effects, and determination if neutralizing antibodies to the AAV serotype of choice are present in cats. Successful resolution of these issues will pave the way for the development of a powerful tool to induce the permanent sterility in cats.
Regions of hypoxia (low oxygen) occur in most solid tumours and cells in these areas are the most aggressive and therapy resistant. In response to decreased oxygen, extensive changes in gene expression mediated by Hypoxia-Inducible Factors (HIFs) contribute significantly to the aggressive hypoxic tumour phenotype. In addition to HIFs, multiple histone demethylases are altered in their expression and activity, providing a secondary mechanism to extend the hypoxic signalling response. In this study, we demonstrate that the levels of HIF-1alpha are directly controlled by the repressive chromatin mark, H3K9me3. In conditions where the histone demethylase KDM4A is depleted or inactive, H3K9me3 accumulates at the HIF-1alpha locus, leading to a decrease in HIF-1alpha mRNA and a reduction in HIF-1alpha stabilisation. Loss of KDM4A in hypoxic conditions leads to a decreased HIF-1alpha mediated transcriptional response and correlates with a reduction in the characteristics associated with tumour aggressiveness, including invasion, migration, and oxygen consumption. The contribution of KDM4A to the regulation of HIF-1alpha is most robust in conditions of mild hypoxia. This suggests that KDM4A can enhance the function of HIF-1alpha by increasing the total available protein to counteract any residual activity of prolyl hydroxylases.

UNLABELLED: Little is known about the factors associated with pain-related outcomes in older adults. In this observational study, we sought to identify patient factors associated with improvements in pain intensity in a national cohort of older veterans with chronic pain. We included 12,924 veterans receiving treatment from the Veterans Health Administration with persistently elevated numeric rating scale scores in 2010 who had not been prescribed opioids in the previous 12 months. We examined: 1) percentage decrease over 12 months in average pain intensity scores relative to average baseline pain intensity score; and 2) time to sustained improvement in average pain intensity scores, defined as a 30% reduction in 3-month scores compared with baseline. Average relative improvement in pain intensity scores from baseline ranged from 25% to 29%; almost two-thirds met criteria for sustained improvement during the 12-month follow-up period. In models, higher baseline pain intensity and older age were associated with greater likelihood of improvement in pain intensity, whereas Veterans Affairs service-connected disability, mental health, and certain pain-related diagnoses were associated with lower likelihood of improvement. Opioid prescription initiation during follow-up was associated with lower likelihood of sustained improvement. The findings call for further characterization of heterogeneity in pain outcomes in older adults as well as further analysis of the relationship between prescription opioids and treatment outcomes. PERSPECTIVE: This study identified factors associated with improvements in pain intensity in a national cohort of older veterans with chronic pain. We found that older veterans frequently show improvements in pain intensity over time, and that opioid prescriptions, mental health, and certain pain diagnoses are associated with lower likelihood of improvement.

Head and neck squamous cell carcinoma (HNSCC) patients have a poor prognosis, with invasion and metastasis as major causes of mortality. The phosphatidylinositol 3-kinase (PI3K) pathway regulates a wide range of cellular processes crucial for tumorigenesis, and PIK3CA amplification and mutation are among the most common genetic alterations in human HNSCC. Compared with the well-documented roles of the PI3K pathway in cell growth and survival, the roles of the PI3K pathway in tumor invasion and metastasis have not
been well delineated. We generated a PIK3CA genetically engineered mouse model (PIK3CA-GEMM) in which wild-type PIK3CA is overexpressed in head and neck epithelium. Although PIK3CA overexpression alone was not sufficient to initiate HNSCC formation, it significantly increased tumor susceptibility in an oral carcinogenesis mouse model. PIK3CA overexpression in mouse oral epithelium increased tumor invasiveness and metastasis by increasing epithelial-mesenchymal transition and by enriching a cancer stem cell phenotype in tumor epithelial cells. In addition to these epithelial alterations, we also observed marked inflammation in tumor stroma. AKT is a central signaling mediator of the PI3K pathway. However, molecular analysis suggested that progression of PIK3CA-driven HNSCC is facilitated by 3-phosphoinositide-dependent protein kinase (PDK1) and enhanced transforming growth factor beta (TGFbeta) signaling rather than by AKT. Examination of human HNSCC clinical samples revealed that both PIK3CA and PDK1 protein levels correlated with tumor progression, highlighting the significance of this pathway. In summary, our results offer significant insight into how PIK3CA overexpression drives HNSCC invasion and metastasis, providing a rationale for targeting PI3K/PDK1 and TGFbeta signaling in advanced HNSCC patients with PIK3CA amplification.


Virtual environments (VEs) have demonstrated promise as a neuropsychological assessment modality and may be well suited for the evaluation of children suspected of having an autism spectrum disorder (ASD). Some recent studies indicate their potential for enhancing reliability, ecologically validity, and sensitivity over traditional neuropsychological evaluation measures. Although research using VEs with ASD is increasing to the degree that several reviews of the literature have been conducted, the reviews to date lack rigor and are not necessarily specific to cognitive or neuropsychological assessment as many focus on intervention. The aim of this project was to comprehensively examine the current literature status of neuropsychological assessment in pediatric ASD using VEs by conducting a systematic review. Specifically, psychometric comparisons of VEs to traditional neuropsychological assessment measures that examined reliability, validity, and/or diagnostic accuracy for pediatric individuals, age 18 and below, with ASD were sought. The search using key words yielded 899 manuscripts, 894 of which were discarded for not meeting inclusion criteria. The remaining five met exclusion criteria. Therefore, the systematic review was modified to a brief report. These findings (or lack thereof) indicate a significant gap in the literature in that psychometric comparisons of these tools for the neuropsychological assessment of pediatric individuals with ASD are lacking. An important future direction of research will be extending the demonstrated incremental validity of VE neuropsychological assessment with other neurodevelopmental (e.g., attention-deficit/hyperactivity disorder) and adult populations to pediatric ASD populations.


Type 1 diabetes requires intensive self-management to avoid acute and long-term health complications. In the past two decades, substantial advances in technology have enabled more effective and convenient self-management of type 1 diabetes. Although proximal technologies (eg, insulin pumps, continuous glucose monitors, closed-loop and artificial pancreas systems) have been the subject of frequent systematic and narrative reviews, distal technologies have received scant attention. Distal technologies refer to electronic systems designed to provide a service remotely and include heterogeneous systems such as telehealth, mobile health applications, game-based support, social platforms, and patient portals. In this Review, we summarise the empirical literature to provide current information about the effectiveness of available distal technologies to improve type 1 diabetes management. We also discuss privacy, ethics, and regulatory considerations, issues of global adoption, knowledge gaps in distal technology, and recommendations for future directions.

**Purpose:** Meaningful use (MU) and Uniform Data Systems (UDSs) are calling for the collection of gender identity (GI) in electronic health record (EHR) systems; however, many transgender and nonconforming (TGNC) patients may not feel safe disclosing their GI and the data collection is not designed to guide care provision. This study explores the complexities surrounding the inclusion of GI in EHR data collection and how it can best serve patients and providers. Methods: Using a semistructured interview format, TGNC patients (n=7) and providers (n=5) who care for TGNC patients were asked about data collection procedures and the use of these data within community health centers in Oregon. Using a constant comparative data analysis methodology, interview transcripts were coded for emergent concepts until overlapping themes were identified. Results: Both patients and providers expressed a need for the EHR to expand upon MU and UDS-recommended fields to include current pronouns and name and gender identifiers in a forward-facing display to prevent misgendering by clinic staff and providers. Furthermore, they both cited the need for a broader range of birth-assigned sex and gender options. TGNC patients and providers disagreed on the scope of health information to be collected as well as who should be tasked with the data collection. Conclusion: These interviews offer us a glimpse into the structural difficulties of creating an EHR system that serves the needs of clinicians while providing safe and culturally competent care to TGNC patients.


**Purpose:** The primary purpose of this study was to determine whether progressive tinnitus management Level 3 skills education workshops conducted at the Bay Pines and Boston Veterans Affairs hospitals result in consistent use of the presented tinnitus management strategies by patients 1-5 years after completing the workshops. Method: In fiscal year (FY) 2015, the tinnitus workshop follow-up form was mailed to all veterans who completed the Level 3 workshops between FY 2010 and FY 2014. Data were compiled to determine which, if any, of the skills taught in the workshops were being used 1-5 years after completion of the workshops and the impact on quality-of-life indicators. Results: All self-management skills were being utilized up to 5 years postcompletion; therapeutic sound was utilized the most. The majority of patients reported an improved ability to manage reactions to tinnitus and improved quality-of-life indicators. Over 90% of patients from both sites recommended the program to others with tinnitus. Conclusion: The self-management skills taught in the progressive tinnitus management Level 3 workshops are sustained over time even when limited resources prevent the full complement of workshops or the involvement of mental health services. The workshops can also be successfully implemented through remote delivery via videoconferencing (telehealth). Supplemental Materials: https://doi.org/10.23641/asha.5370883.


**BACKGROUND:** Multicomponent, interdisciplinary intensive primary care programs target complex patients with the goal of preventing hospitalizations, but programs vary, and their effectiveness is not clear. In this study, we systematically reviewed the impact of intensive primary care programs on all-cause mortality, hospitalization, and emergency department use. METHODS: We searched PubMed, CINAHL, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Reviews of Effects from inception to March 2017. Additional studies were identified from reference lists, hand searching, and consultation with content experts. We included systematic reviews, randomized controlled trials (RCTs), and observational studies of multicomponent, interdisciplinary intensive primary care programs targeting complex patients at high risk of hospitalization or death, with a comparison to usual primary care. Two investigators identified studies and abstracted data using a predefined protocol. Study quality was assessed using the Cochrane risk of bias tool.
RESULTS: A total of 18 studies (379,745 participants) were included. Three major intensive primary care program types were identified: primary care replacement (home-based; three RCTs, one observational study, N = 367,681), primary care replacement (clinic-based; three RCTs, two observational studies, N = 9561), and primary care augmentation, in which an interdisciplinary team was added to existing primary care (five RCTs, three observational studies, N = 2503). Most studies showed no impact of intensive primary care on mortality or emergency department use, and the effectiveness in reducing hospitalizations varied. There were no adverse effects reported. DISCUSSION: Intensive primary care interventions demonstrated varying effectiveness in reducing hospitalizations, and there was limited evidence that these interventions were associated with changes in mortality. While interventions could be grouped into categories, there was still substantial overlap between intervention approaches. Further work is needed to identify program features that may be associated with improved outcomes.


BACKGROUND AND OBJECTIVES: The scope of practice among primary care providers varies, and studies have shown that family physicians' scope may be shrinking. We studied the scope of practice among graduates of residencies associated with Preparing the Personal Physician for Practice (P4) and how length of training and individualized education innovations may influence scope. METHODS: We surveyed graduates 18 months after residency between 2008 and 2014. The survey measured self-reported practice characteristics, scope of practice and career satisfaction. We assessed scope using individual practice components (25 clinical activities, 30 procedures) and a scaled score (P4-SOP) that measured breadth of practice scope. We conducted subgroup analyses according to exposure to innovations over the project period and exposure to specific innovations. RESULTS: No significant differences were found in mean P4-SOP scores between the Pre and Full P4 groups. Compared to national data, P4 graduates reported higher rates for vaginal deliveries (19.3% vs 9.2%), adult inpatient care (48.5% vs 33.7%) and nursing home care (25.4 vs 11.7%) in practice. Graduates exposed to innovations that lengthened training, compared to standard training length, were more likely to include adult hospital care (58.2% vs 38.5%, P=0.002), adult ICU care (30.6% vs 19.2%, P=0.047) and newborn resuscitation (25.6% vs 14%, P=0.028) in their practice and performed 19/30 procedures at higher rates. Graduates of programs with individualized training innovations reported no significant differences in scope compared to graduates without this innovation. CONCLUSIONS: Graduates of residencies engaged in significant educational redesign report a broad scope of practice. Innovations around the length of training may broaden scope and individualized education appears not to constrict scope.


OBJECTIVE: The objective of this assessment is to evaluate the degree of risk of bias in randomized controlled trials published in 2013 and focusing on periodontal regeneration. METHODS: Three reviewers searched and selected the trials based on pre-defined inclusion criteria. Predictor variables [number of authors, primary objective of the study, biomaterial employed, follow-up time periods, split mouth study (yes/no), journal, year of publication, country, scale (single/multi-center) and nature of funding] were extracted and risk of bias assessment using Cochrane risk of bias tool were performed independently by the three reviewers. RESULTS: Seventeen RCTs were included in this assessment. The risk of bias in RCTs published in 2013 with a focus in periodontal regeneration varied significantly with only in less than 30% of the included trials, the overall risk of bias was found to be low, while 41% of trials were designated to have a higher degree of bias. Specifically, when looking at the domains assessed, 70% of the included trials reported an accepted method of sequence generation, blinding (whenever possible), completeness of outcome data or avoided selective outcome reporting. Meanwhile, only 47% of the included trials reported some form of allocation concealment. CONCLUSION: In this assessment, of the included 17 trials, slightly more than 40% of them had a high risk of
bias, underscoring the importance of careful appraisal of trials before implementing the study interventions in clinical practice and the need for more detailed analyses.


BACKGROUND: Supporting day-to-day self-care activities has emerged as a best practice when caring for patients with chronic pain, yet providing this support may introduce challenges for both patients and primary care physicians. It is essential to develop tools that help patients identify the issues and outcomes that are most important to them and to communicate this information to primary care physicians at the point of care.

OBJECTIVE: We describe our process to engage patients, primary care physicians, and other stakeholders in the context of a pilot randomized controlled trial of a patient-centered assessment process implemented in an everyday practice setting. We identify lessons on how to engage stakeholders and improve patient-centered care for those with chronic conditions within the primary care setting.

METHODS: A qualitative analysis of project minutes, interviews, and focus groups was conducted to evaluate stakeholder experiences. Stakeholders included patients, caregivers, clinicians, medical office support staff, health plan administrators, an information technology consultant, and a patient advocate.

RESULTS: Our stakeholders included many patients with no prior experience with research. This approach enriched the applicability of feedback but necessitated extra time for stakeholder training and meeting preparation. Types of stakeholders varied over the course of the project, and more involvement of medical assistants and Information Technology staff was required than originally anticipated.

CONCLUSION: Meaningful engagement of patient and physician stakeholders must be solicited in a well-coordinated manner with broad health care system supports in place to ensure full execution of patient-centered processes.


Accurate kinetic modelling using dynamic PET requires knowledge of the tracer concentration in plasma, known as the arterial input function (AIF). AIFs are usually determined by invasive blood sampling, but this is prohibitive in murine studies due to low total blood volumes. As a result of the low spatial resolution of PET, image-derived input functions (IDIFs) must be extracted from left ventricular blood pool (LVBP) ROIs of the mouse heart. This is challenging because of partial volume and spillover effects between the LVBP and myocardium, contaminating IDIFs with tissue signal. We have applied the geometric transfer matrix (GTM) method of partial volume correction (PVC) to 12 mice injected with \(^{18}\)F-\(^{18}\)FDG affected by a Myocardial Infarction (MI), of which 6 were treated with a drug which reduced infarction size. We utilised high resolution MRI to assist in segmenting mouse hearts into 5 classes: LVBP, infarcted myocardium, healthy myocardium, lungs/body and background. The signal contribution from these 5 classes was convolved with the point spread function (PSF) of the Cambridge split magnet PET scanner and a non-linear fit was performed on the 5 measured signal components. The corrected IDIF was taken as the fitted LVBP component. It was found that the GTM PVC method could recover an IDIF with less contamination from spillover than an IDIF extracted from PET data alone. More realistic values of \((\lambda/\mu)\) were achieved using GTM IDIFs, which were shown to be significantly different \((p < 0.05)\) between the treated and untreated groups. © 1963-2012 IEEE.

Objective: The integration of primary care and public health nursing may provide new opportunities for transforming nursing practice that addresses population health. Effective programs emphasize multilevel approaches that include both downstream (education) and upstream (policy change) actions. The purpose of this article is to identify downstream and upstream nursing actions that integrate public health and primary care practice through two case exemplars concerning disparities in physical activity and nutrition. Methods: Describe two research case exemplars: (1) a secondary analysis of school physical activity policy for female adolescents in 36 public middle schools and (2) a focus group study of African American adults in a community kitchen program. Results: In exemplar 1, school policies lacked population-based standards and presented structural disadvantages to African American girls who were already obese. In exemplar 2, participants found the community kitchen program to be more effective than the federally funded nutrition program. Discussion: Integrating primary care and public health nursing could improve the tailoring of physical activity and nutrition programs to local populations by following core principles of community engagement, infrastructural sustainability, aligned leadership, and data sharing for population health improvement. © 2017 Wiley Periodicals, Inc.


OBJECTIVE: Statistical shape modelling (SSM) of radiographs has been used to explore relationships between altered joint shape and hip osteoarthritis (OA). We aimed to apply SSM to Dual-energy X-ray Absorptiometry (DXA) hip scans, and examine associations between resultant hip shape modes (HSMs), radiographic hip OA (RHOA), and hip pain, in a large population based cohort. METHOD: SSM was performed on baseline hip DXA scans from the Osteoporotic Fractures in Men (MrOS) Study. Associations between the top ten HSMs, and prevalent RHOA from pelvic radiographs obtained 4.6 years later, were analysed in 4100 participants. RHOA was defined as Croft score >/=2. Hip pain was based on pain on walking, hip pain on examination, and Western Ontario and McMaster Universities Arthritis Index (WOMAC). RESULTS: The five HSMs associated with RHOA showed features of either pincer- or cam-type deformities. HSM 1 (increased pincer-type deformity) was positively associated with RHOA [1.23 (1.09, 1.39)] [odds ratio (OR) and 95% CI]. HSM 8 (reduced pincer-type deformity) was inversely associated with RHOA [0.79 (0.70, 0.89)]. HSM 10 (increased cam-type deformity) was positively associated with RHOA [1.21 (1.07, 1.37)]. HSM 3 and HSM 4 (reduced cam-type deformity) were inversely associated with RHOA [0.73 (0.65, 0.83) and 0.82 (0.73, 0.93), respectively]. HSM 3 was inversely related to pain on examination [0.84 (0.76, 0.92)] and walking [0.88, (0.81, 0.95)], and to WOMAC score [0.87 (0.80, 0.93)]. CONCLUSIONS: DXA-derived measures of hip shape are associated with RHOA, and to a lesser extent hip pain, possibly reflecting their role in the pathogenesis of hip OA.


In melanoma, vascular endothelial growth factor-C (VEGF-C) expression and consequent lymphangiogenesis correlate with metastasis and poor prognosis. VEGF-C also promotes tumor immunosuppression, suggesting that lymphangiogenesis inhibitors may be clinically useful in combination with immunotherapy. We addressed this concept in mouse melanoma models with VEGF receptor-3 (VEGFR-3)-blocking antibodies and unexpectedly found that VEGF-C signaling enhanced rather than suppressed the response to immunotherapy. We further found that this effect was mediated by VEGF-C-induced CCL21 and tumor infiltration of naive T cells before immunotherapy because CCR7 blockade reversed the potentiating effects of VEGF-C. In human metastatic melanoma, gene expression of VEGF-C strongly correlated with CCL21 and T cell inflammation, and serum VEGF-C concentrations associated with both T cell activation and expansion after peptide vaccination and clinical response to checkpoint blockade. We propose that VEGF-C potentiates...
immunotherapy by attracting naive T cells, which are locally activated upon immunotherapy-induced tumor cell killing, and that serum VEGF-C may serve as a predictive biomarker for immunotherapy response.


Purpose
To determine the sensitivity and specificity of OCT angiography (OCTA) in the detection of choroidal neovascularization (CNV) in age-related macular degeneration (AMD). Design Prospective case series. Subjects A prospective series of 72 eyes were studied, which included eyes with treatment-naive CNV due to AMD, non-neovascular AMD, and normal controls. Methods All eyes underwent OCTA with a spectral domain OCT. The 3-dimensional angiogram was segmented into separate en face views including the inner retinal angiogram, outer retinal angiogram, and choriocapillaris angiogram. Detection of abnormal flow in the outer retina served as candidate CNV with OCTA. Masked graders reviewed structural OCT alone, en face OCTA alone, and en face OCTA combined with cross-sectional OCTA for the presence of CNV. Main Outcome Measure The sensitivity and specificity of CNV detection compared to the gold standard of fluorescein angiography and OCT was determined for structural spectral domain OCT alone, en face OCTA alone, and with en face OCTA combined with cross-sectional OCTA. Results Of 32 eyes with CNV, both graders identified 26 true positives with en face OCTA alone, resulting in a sensitivity of 81.3%. Four of the 6 false negatives had large subretinal hemorrhage and sensitivity improved to 94% for both graders if eyes with subretinal hemorrhage were excluded. The addition of cross-sectional OCTA along with en face OCTA improved the sensitivity to 100% for both graders. Structural OCT alone also had a sensitivity of 100%. The specificity of en face OCTA alone was 92.5% for grader A and 97.5% for grader B. The specificity of structural OCT alone was 97.5% for grader A and 85% for grader B. Cross-sectional OCTA combined with en face OCTA had a specificity of 97.5% for grader A and 100% for grader B. Conclusions Sensitivity and specificity for CNV detection with en face OCTA combined with cross-sectional OCTA approaches that of the gold standard of fluorescein angiography with OCT, and it is better than en face OCTA alone. Structural OCT alone has excellent sensitivity for CNV detection. False positives from structural OCT can be mitigated with the addition of flow information with OCTA. © 2017 American Academy of Ophthalmology


BACKGROUND: Treatment for hyperphosphatemia in chronic kidney disease (CKD) involves dietary control of phosphorus intake, dialysis, and treatment with oral phosphate binders, none of which were approved by the Federal Food and Drug Administration in pediatric patients at the time of this study. METHODS: This was a phase 2, multicenter study (NCT01574326) with a 2-week, randomized, placebo-controlled, fixed-dose period (FDP) followed by a 6-month, single-arm, open-label, dose-titration period (DTP), with the aim to evaluate the safety and efficacy of sevelamer carbonate (SC) in hyperphosphatemic pediatric patients with CKD. Following a 2-4 week screening phase, pediatric patients with a serum phosphorus level higher than age-appropriate levels were randomized to receive either SC or placebo as powder/tablets in 0.4-1.6 g doses, based on body surface area. The primary efficacy outcome was the change in serum phosphorus from baseline to end of the FDP in the SC versus placebo arms (analysis of covariance). The secondary outcome was mean change in serum phosphorus from baseline to end of DTP by treatment group and overall. Treatment-emergent/serious adverse events (AEs) were recorded. RESULTS: Of 101 enrolled patients (29 centers), 66 completed the study. The majority of patients were adolescents (74%; mean age 14.1 years) and on dialysis (77%). Renal transplant was the main reason for discontinuation. SC significantly reduced serum phosphorus from baseline levels (7.16 mg/dL) during the FDP compared to placebo (least square mean difference - 0.90 mg/dL, p = 0.001) and during the DTP (- 1.18 mg/dL, p < 0.0001). The safety and tolerability of SC and placebo were similar during the FDP, with patients in both groups reporting mild/moderate
gastrointestinal AEs during the DTP. CONCLUSIONS: Sevelamer carbonate significantly lowered serum phosphorus levels in hyperphosphatemic children with CKD, with no serious safety concerns identified.


Background and Aims: The exploration and resolution of ambivalence play an essential role in motivational interviewing (MI) theory. However, most adolescent MI studies have not examined ambivalence as a contributor to behaviour change. This paper reviewed research findings on the role of ambivalence in the adolescent change process. Methods and results: We undertook a narrative review of the published empirical and theoretical literature on ambivalence and mechanisms of change in MI for adolescents and found that current MI evaluations appear to have access to reliable and valid measures of ambivalence in adolescence or neuroimaging methods to evaluate the mechanisms of treatment response. Conclusions: Improved instrumentation is needed to assess adolescents’ ambivalence in clinical and research settings. Innovative methodology, including neuroimaging, may help identify factors mediating relationships between adolescents’ ambivalence and treatment response. © 2016 Society for the Study of Addiction


BACKGROUND: Most patients presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS) undergo noninvasive cardiac testing with a low diagnostic yield. We determined whether a combination of high-sensitivity cardiac troponin I (hs-cTnI) and cardiovascular risk factors might improve selection of patients for cardiac testing. METHODS: We included patients from the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) I and II trials who presented to the ED with acute chest pain and were referred for cardiac testing. Based on serial hs-cTnI measurements and cardiovascular risk factors, we derived and validated the criterion for no need of cardiac testing. We predicted the effect of this criterion on the effectiveness of patient management. RESULTS: A combination of baseline hs-cTnI (<4 ng/L) and cardiovascular risk factors (<2) ruled out ACS with a negative predictive value of 100% in ROMICAT I. We validated this criterion in ROMICAT II, identifying 29% patients as not needing cardiac testing. An additional 5% of patients were identified by adding no change or a decrease between baseline and 2 h hs-cTnI as a criterion. Assuming those patients would be discharged from the ED without cardiac testing, implementation of hs-cTnI would increase ED discharge rate (24.3% to 50.2%, P < 0.001) and decrease the length of hospital stay (21.4 to 8.2 h, P < 0.001), radiation dose (10.2 to 7.7 mSv, P < 0.001), and costs of care (4066 to 3342 US$, P < 0.001). CONCLUSIONS: We derived and validated a criterion for combined hs-cTnI and cardiovascular risk factors that identified acute chest pain patients with no need for cardiac testing and could improve effectiveness of patient management.


BACKGROUND: The presence and extent of coronary artery calcium (CAC) are associated with increased risk for cardiovascular events. We determined whether information on the distribution of CAC and coronary dominance as detected by cardiac computed tomography were incremental to traditional Agatston score (AS) in predicting incident major coronary heart disease (CHD). METHODS AND RESULTS: We assessed total AS and the presence of CAC per coronary artery, per segment, and coronary dominance by computed tomography in participants from the offspring and third-generation cohorts of the Framingham Heart Study. The primary outcome was major CHD (myocardial infarction or CHD death). We performed multivariable Cox
proportional hazards analysis and calculated relative integrated discrimination improvement. In 1268 subjects (mean age, 56.2+/−10.3 years, 63.2% men) with AS >0 and no history of major CHD, a total of 42 major CHD events occurred during median follow-up of 7.4 years. The number of coronary arteries with CAC (hazard ratio, 1.68 per artery; 95% confidence interval, 1.10−2.57; P=0.02) and the presence of CAC in the proximal dominant coronary artery (hazard ratio, 2.59; 95% confidence interval, 1.15−5.83; P=0.02) were associated with major CHD events after multivariable adjustment for Framingham risk score and categories of AS. In addition, measures of CAC distribution improved discriminatory capacity for major CHD events (relative integrated discrimination improvement, 0.14). CONCLUSIONS: Distribution of coronary atherosclerosis, especially CAC in the proximal dominant coronary artery and an increased number of coronary arteries with CAC, predict major CHD events independently of the traditional AS in community-dwelling men and women.


OBJECTIVE: The objective of this work, commissioned by the Academy of Dental Materials, was to review and critically appraise test methods to characterize properties related to critical issues for dental resin composites, including technique sensitivity and handling, polymerization, and dimensional stability, in order to provide specific guidance to investigators planning studies of these properties. METHODS: The properties that relate to each of the main clinical issues identified were ranked in terms of their priority for testing, and the specific test methods within each property were ranked. An attempt was made to focus on the tests and methods likely to be the most useful, applicable, and supported by the literature, and where possible, those showing a correlation with clinical outcomes. Certain methods are only briefly mentioned to be all-inclusive. When a standard test method exists, whether from dentistry or another field, this test has been identified. Specific examples from the literature are included for each test method. RESULTS: The properties for evaluating resin composites were ranked in the priority of measurement as follows: (1) porosity, radiopacity, sensitivity to ambient light, degree of conversion, polymerization kinetics, depth of cure, polymerization shrinkage and rate, polymerization stress, and hygroscopic expansion; (2) stickiness, slump resistance, and viscosity; and (3) thermal expansion. SIGNIFICANCE: The following guidance is meant to aid the researcher in choosing the most appropriate test methods when planning studies designed to assess certain key properties and characteristics of dental resin composites, specifically technique sensitivity and handling during placement, polymerization, and dimensional stability.


OBJECTIVE: Three-column osteotomy (3CO) is a demanding technique that is performed to correct sagittal spinal malalignment. However, the impact of the 3CO level on pelvic or truncal sagittal correction remains unclear. In this study, the authors assessed the impact of 3CO level and postoperative apex of lumbar lordosis on sagittal alignment correction, complications, and revisions. METHODS: In this retrospective study of a multicenter spinal deformity database, radiographic data were analyzed at baseline and at 1- and 2-year follow-up to quantify spinopelvic alignment, apex of lordosis, and resection angle. The impact of 3CO level and apex level of lumbar lordosis on the sagittal correction was assessed. Logistic regression analyses were performed, controlling for cofounders, to investigate the effects of 3CO level and apex level on intraoperative and postoperative complications as well as on the need for subsequent revision surgery. RESULTS: A total of 468 patients were included (mean age 60.8 years, mean body mass index 28.1 kg/m2); 70% of patients were female. The average 3CO resection angle was 25.1 degrees and did not significantly differ with regard to 3CO level. There were no significant correlations between the 3CO level and amount of sagittal vertical axis or pelvic tilt correction. The postoperative apex level significantly correlated with greater correction of pelvic tilt (2 degrees per more caudal level, R = -0.2, p = 0.006). Lower-level 3CO significantly
correlated with revisions for pseudarthrosis (OR = 3.88, p = 0.001) and postoperative motor deficits (OR = 2.02, p = 0.026). CONCLUSIONS In this study, a more caudal lumbar 3CO level did not lead to greater sagittal vertical axis correction. The postoperative apex of lumbar lordosis significantly impacted pelvic tilt. 3CO levels that were more caudal were associated with more postoperative motor deficits and revisions.


Prior data in women suggest that incident clinically undiagnosed radiographic vertebral fractures (VF)s often are symptomatic, but misclassification of incident clinical VF may have biased these estimates. There are no comparable data in men. To evaluate the association of incident clinically undiagnosed radiographic VF with back pain symptoms and associated activity limitations, we used data from the Osteoporotic Fractures in Men (MrOS) Study, a prospective cohort study of community-dwelling men aged >/=65 years. A total of 4396 men completed spine X-rays and symptom questionnaires at baseline and visit 2, about 4.6 years later. Incident clinical VFs during this interval were defined by self-reported clinical diagnosis plus community imaging showing a centrally adjudicated >/=1 increase in semiquantitative (SQ) grade in any thoracic or lumbar vertebral versus baseline study X-rays. Incident radiographic VFs (>/=1 increase in SQ grade between baseline and visit 2 study X-rays) were categorized as radiographic-only (not clinically diagnosed) or radiographic plus clinical (also clinically diagnosed). Multivariable-adjusted log binomial regression was used to calculate prevalence ratios (PRs) and 95% confidence intervals (CIs). Men with incident radiographic plus clinical VF were most likely to have back pain symptoms and associated activity limitation at follow-up. However, versus men without incident VF, those with incident radiographic-only VF also were significantly more likely at follow-up to report any back pain (70% versus 59%; PR, 1.2 [95% CI, 1.1 to 1.3]), severe back pain (8% versus 4%; PR, 1.9 [95% CI, 1.1 to 3.3]), bother from back pain most/all the time (22% versus 13%; PR, 1.7 [95% CI, 1.3 to 2.2]), and limited usual activity from back pain (34% versus 18%; PR, 1.9 [95% CI, 1.5 to 2.4]). Clinically undiagnosed, incident radiographic VFs were associated with an increased likelihood of back pain symptoms and associated activity limitation. Results suggest incident radiographic-only VFs often were symptomatic, and were associated with both new and worsening back pain. Preventing these fractures may reduce back pain and related disability in older men. (c) 2017 American Society for Bone and Mineral Research.


BACKGROUND: Patients in isolated rural communities typically lack access to surgical care. It is not feasible for most rural fist-level hospitals to provide a full suite of surgical specialty services. Comprehensive surgical care thus depends on referral systems. There is minimal literature, however, on the functioning of such systems. METHODS: We undertook a prospective case study of the referral and care coordination process for cardiac, orthopedic, plastic, gynecologic, and general surgical conditions at a district hospital in rural Nepal from 2012 to 2014. We assessed the referral process using the World Health Organization’s Health Systems Framework. RESULTS: We followed the initial 292 patients referred for surgical services in the program. 152 patients (52%) received surgery and four (1%) suffered a complication (three deaths and one patient reported complication). The three most common types of surgery performed were: orthopedics (43%), general (32%), and plastics (10%). The average direct and indirect cost per patient referred, including food, transportation, lodging, medications, diagnostic examinations, treatments, and human resources was US$840, which was over 1.5 times the local district’s per capita income. We identified and mapped challenges according to the World Health Organization’s Health Systems Framework. Given the requirement of intensive human capital, poor quality control of surgical services, and the overall costs of the program, hospital leadership decided to terminate the referral coordination program and continue to build local
surgical capacity. **CONCLUSION:** The results of our case study provide some context into the challenges of rural surgical referral systems. The high relative costs to the system and challenges in accountability rendered the program untenable for the implementing organization.


**OBJECTIVE:** The Medication Research Partnership (MRP), a collaboration between a national commercial health plan and nine addiction treatment centers, implemented organizational and system changes to promote use of federally approved medications for treatment of alcohol and opioid use disorders. **METHOD:** A difference-in-differences analysis examined change over time in the percentage of patients receiving a prescription medication for alcohol or opioid use disorders treated in MRP (n = 9) and comparison (n = 15) sites. **RESULTS:** MRP clinics experienced a 2.4-fold increase in patients receiving an alcohol or opioid prescription (13.2% at baseline to 31.7% at 3 years after MRP initiation); comparison clinics experienced significantly less change (17.6% to 23.5%) with an adjusted difference-in-differences of 12.5% (95% CI [5.4, 19.6], p = .001). MRP sites increased the patients with prescriptions to treat opioid use disorder from 17.0% (baseline) to 36.8% (3 years after initiation), with smaller changes observed in comparison sites (23.2% to 24.0%) and a 3-year post-initiation adjusted difference-in-differences of 19% (95% CI [8.5, 29.5], p = .000). Medications for alcohol use disorders increased in both MRP (9.0% to 26.5%) and comparison sites (11.4% to 23.1%). **CONCLUSIONS:** Promoting the use of medications to support recovery required complex interventions. The Advancing Recovery System Change Model, initially developed in publicly funded systems of care, was successfully adapted for commercial sector use. The model provides a framework for providers and commercial health plans to collaborate and increase patient access to medications.


**Background** - Endovascular treatment with mechanical thrombectomy (MT) is beneficial for acute stroke patients suffering a large vessel occlusion, though treatment efficacy is highly time-dependent. We hypothesized that interhospital transfer to endovascular-capable centers would result in treatment delays and worse clinical outcomes compared to direct presentation. **Methods** - STRATIS was a prospective, multicenter, observational, single-arm study of real-world MT for acute stroke due to anterior-circulation large vessel occlusion performed at 55 sites over 2 years, including 1000 patients with severe stroke and treated within 8 hours. Patients underwent MT with or without IV-tPA, and were admitted to endovascular-capable centers via either interhospital transfer or direct presentation. The primary clinical outcome was functional independence (modified Rankin Score 0-2) at 90 days. We assessed 1) real-world time metrics of stroke care delivery, 2) outcome differences between direct and transfer patients undergoing MT, and 3) the potential impact of local hospital bypass. **Results** - A total of 984 patients were analyzed. Median onset-to-revascularization time was 202.0 minutes for direct vs. 311.5 minutes for transfer patients (p<0.001). Clinical outcomes were better in the direct group with 60.0% (299/498) achieving functional independence, compared to 52.2% (213/408) in the transfer group (odds ratio 1.38, 95% CI 1.06-1.79; p=0.02). Likewise, excellent outcome (modified Rankin Score 0-1) was achieved in 47.4% (236/498) of direct patients vs. 38.0% (155/408) of transfer patients (odds ratio 1.47, 95% CI 1.13-1.92; p=0.005). Mortality did not differ between the two groups (15.1% for direct, 13.7% for transfer; p=0.55). IV-tPA did not impact outcomes. Hypothetical bypass modeling for all
transferred patients suggested that IV-tPA would be delayed by 12 minutes but MT would be performed 91 minutes sooner if patients were routed directly to endovascular-capable centers. If bypass is limited to a 20-mile radius from onset, then IV-tPA would be delayed by 7 minutes and MT performed 94 minutes earlier.

Conclusions - In this large, real-world study, interhospital transfer was associated with significant treatment delays and lower chance of good outcome. Strategies to facilitate more rapid identification of large vessel occlusion and direct routing to endovascular-capable centers for severe stroke patients may improve outcomes. Clinical Trial Registration - URL: http://www.clinicaltrials.gov. Unique identifier: NCT02239640.


ELQ-300 is a preclinical antimalarial drug candidate that is active against liver, blood, and transmission stages of *Plasmodium falciparum*. While ELQ-300 is highly effective when administered in a low multidose regimen, poor aqueous solubility and high crystallinity have hindered its clinical development. To overcome its challenging physiochemical properties, a number of bioreversible alkoxycarbonate ester prodrugs of ELQ-300 were synthesized. These bioreversible prodrugs are converted to ELQ-300 by host and parasite esterase action in the liver and bloodstream of the host. One such alkoxycarbonate prodrug, ELQ-331, is curative against *Plasmodium yoelii* with a single low dose of 3 mg/kg in a murine model of patent malaria infection. ELQ-331 is at least as fully protective as ELQ-300 in a murine malaria prophylaxis model when delivered 24 h before sporozoite inoculation at an oral dose of 1 mg/kg. Here, we show that ELQ-331 is a promising prodrug of ELQ-300 with improved physiochemical and metabolic properties and excellent potential for clinical formulation.


BACKGROUND: Often the clinician is faced with a diagnostic and therapeutic dilemma in patients with concomitant traumatic brain injury (TBI) and hemorrhagic shock (HS), as rapid deterioration from either can be fatal. Knowledge about outcomes after concomitant TBI and HS may help prioritize the emergent management of these patients. We hypothesized that patients with concomitant TBI and HS (TBI + HS) had worse outcomes and required more intensive care compared with patients with only one of these injuries. METHODS: This is a post hoc analysis of the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. TBI was defined by a head Abbreviated Injury Scale score greater than 2. HS was defined as a base excess of -4 or less and/or shock index of 0.9 or greater. The primary outcome for this analysis was mortality at 30 days. Logistic regression, using generalized estimating equations, was used to model categorical outcomes. RESULTS: Six hundred seventy patients were included. Patients with TBI + HS had significantly higher lactate (median, 6.3; interquartile range, 4.7-9.2) compared with the TBI group (median, 3.3; interquartile range, 2.3-4). TBI + HS patients had higher activated prothrombin times and lower platelet counts. Unadjusted mortality was higher in the TBI + HS (51.6%) and TBI (50%) groups compared with the HS (17.5%) and neither group (7.7%). Adjusted odds of death in the TBI and TBI + HS groups were 8.2 (95% confidence interval, 3.4-19.5) and 10.6 (95% confidence interval, 4.8-23.2) times higher, respectively. Ventilator, intensive care unit-free and hospital-free days were lower in the TBI and TBI + HS groups compared with the other groups. Patients with TBI + HS or TBI had significantly greater odds of developing a respiratory complication compared with the neither group. CONCLUSION: The addition of TBI to HS is associated with worse coagulopathy before resuscitation and increased mortality. When controlling for multiple known confounders, the diagnosis of TBI alone or TBI+HS was associated with significantly greater odds of developing respiratory complications. LEVEL OF EVIDENCE: Prognostic study, level II.
In recent years, the population of neurons in the ventral tegmental area (VTA) and substantia nigra (SN) has been examined at multiple levels. The results indicate that the projections, neurochemistry, and receptor and ion channel expression in this cell population vary widely. This review centers on the intrinsic properties and synaptic regulation that control the activity of dopamine neurons. Although all dopamine neurons fire action potentials in a pacemaker pattern in the absence of synaptic input, the intrinsic properties that underlie this activity differ considerably. Likewise, the transition into a burst/pause pattern results from combinations of intrinsic ion conductances, inhibitory and excitatory synaptic inputs that differ among this cell population. Finally, synaptic plasticity is a key regulator of the rate and pattern of activity in different groups of dopamine neurons. Through these fundamental properties, the activity of dopamine neurons is regulated and underlies the wide-ranging functions that have been attributed to dopamine.


In 2007, the United States–Food and Drug Administration (FDA) issued guidance concerning animal models for testing the efficacy of medical countermeasures against variola virus (VARV), the etiologic agent for smallpox. Ectromelia virus (ECTV) is naturally-occurring and responsible for severe mortality and morbidity as a result of mousepox disease in the murine model, displaying similarities to variola infection in humans. Due to the increased need of acceptable surrogate animal models for poxvirus disease, we have characterized ECTV infection in the BALB/c mouse. Mice were inoculated intranasally with a high lethal dose (125 PFU) of ECTV, resulting in complete mortality 10 days after infection. Decreases in weight and temperature from baseline were observed eight to nine days following infection. Viral titers via quantitative polymerase chain reaction (qPCR) and plaque assay were first observed in the blood at 4.5 days post-infection and in tissue (spleen and liver) at 3.5 days post-infection. Adverse clinical signs of disease were first observed four and five days post-infection, with severe signs occurring on day 7. Pathological changes consistent with ECTV infection were first observed five days after infection. Examination of data obtained from these parameters suggests the ECTV BALB/c model is suitable for potential use in medical countermeasures (MCMs) development and efficacy testing.


BACKGROUND: Research examining the role of second opinions in pathology for diagnosis of melanocytic lesions is limited. OBJECTIVE: To assess current laboratory policies, clinical use of second opinions, and pathologists’ perceptions of second opinions for melanocytic lesions. MATERIALS AND METHODS: Cross-sectional data collected from 207 pathologists in 10 US states who diagnose melanocytic lesions. The web-based survey ascertained pathologists’ professional information, laboratory second opinion policy, use of second opinions, and perceptions of second opinion value for melanocytic lesions. RESULTS: Laboratory policies required second opinions for 31% of pathologists and most commonly required for melanoma in situ (26%) and
invasive melanoma (30%). In practice, most pathologists reported requesting second opinions for melanocytic tumors of uncertain malignant potential (85%) and atypical Spitzoid lesions (88%). Most pathologists perceived that second opinions increased interpretive accuracy (78%) and protected them from malpractice lawsuits (62%). CONCLUSION: Use of second opinions in clinical practice is greater than that required by laboratory policies, especially for melanocytic tumors of uncertain malignant potential and atypical Spitzoid lesions. Quality of care in surgical interventions for atypical melanocytic proliferations critically depends on the accuracy of diagnosis in pathology reporting. Future research should examine the extent to which second opinions improve accuracy of melanocytic lesion diagnosis.


Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) provides quantitative metrics (e.g. Ktrans, ve) via pharmacokinetic models. We tested inter-algorithm variability in these quantitative metrics with 11 published DCE-MRI algorithms, all implementing Tofts-Kermode or extended Tofts pharmacokinetic models. Digital reference objects (DROs) with known Ktrans and ve values were used to assess performance at varying noise levels. Additionally, DCE-MRI data from 15 head and neck squamous cell carcinoma patients over 3 time-points during chemoradiotherapy were used to ascertain Ktrans and ve kinetic trends across algorithms. Algorithms performed well (less than 3% average error) when no noise was present in the DRO. With noise, 87% of Ktrans and 84% of ve algorithm-DRO combinations were generally in the correct order. Low Krippendorff’s alpha values showed that algorithms could not consistently classify patients as above or below the median for a given algorithm at each time point or for differences in values between time points. A majority of the algorithms produced a significant Spearman correlation in ve of the primary gross tumor volume with time. Algorithmic differences in Ktrans and ve values over time indicate limitations in combining/comparing data from distinct DCE-MRI model implementations. Careful cross-algorithm quality-assurance must be utilized as DCE-MRI results may not be interpretable using differing software.


AIMS: In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, titrated doses of basal insulin glargine targeting fasting normoglycemia had a neutral effect on cardiovascular outcomes. The dose of insulin required to achieve normoglycemia provides a unique measurement of each individual’s resistance to insulin’s action, and was therefore used to examine the link between insulin resistance and cardiovascular outcomes. MATERIALS AND METHODS: Self-titration of insulin doses targeting a fasting plasma glucose < 5.3 mmol/l (95 mg/dl) was promoted at every visit and cardiovascular and other serious health outcomes were ascertained. All analyses were restricted to participants allocated to insulin glargine, who added it to lifestyle or 1 glucose lowering oral agent at randomization. Normoglycemia was defined as a fasting plasma glucose <5.6 mmol/L and HbA1c <6% at the 2 year visit. The median of the natural logarithm of the insulin doses (expressed per kg of fat-free mass) recorded at every visit from randomization until either the penultimate visit or the first occurrence of a cardiovascular outcome was analyzed. RESULTS: Higher median insulin doses did not reflect incident cardiovascular events overall or in the subset that achieved normoglycemia. When the dose taken before a cardiovascular event or the penultimate visit was analyzed, the adjusted hazard of the composite of cardiovascular death, myocardial infarction or stroke was 0.94 (95%CI 0.88, 1.00) per unit higher dose overall, and 0.91 (95%CI 0.81, 1.01) in the normoglycemic subset. CONCLUSIONS: Insulin resistance may not promote cardiovascular outcomes in people with dysglycemia.

BACKGROUND: Observational reports suggest that supplementation that increases citric acid cycle intermediates via anaplerosis may have therapeutic advantages over traditional medium-chain triglyceride (MCT) treatment of long-chain fatty acid oxidation disorders (LC-FAODs) but controlled trials have not been reported. The goal of our study was to compare the effects of triheptanoin (C7), an anaplerotic seven-carbon fatty acid triglyceride, to trioctanoin (C8), an eight-carbon fatty acid triglyceride, in patients with LC-FAODs. METHODS: A double blinded, randomized controlled trial of 32 subjects with LC-FAODs (carnitine palmitoyltransferase-2, very long-chain acylCoA dehydrogenase, trifunctional protein or long-chain 3-hydroxy acylCoA dehydrogenase deficiencies) who were randomly assigned a diet containing 20% of their total daily energy from either C7 or C8 for 4 months was conducted. Primary outcomes included changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise. Secondary outcomes included body composition, blood biomarkers, and adverse events, including incidence of rhabdomyolysis. RESULTS: Patients in the C7 group increased left ventricular (LV) ejection fraction by 7.4% (p = 0.046) while experiencing a 20% (p = 0.041) decrease in LV wall mass on their resting echocardiogram. They also required a lower heart rate for the same amount of work during a moderate-intensity exercise stress test when compared to patients taking C8. There was no difference in TEE, phosphocreatine recovery, body composition, incidence of rhabdomyolysis, or any secondary outcome measures between the groups. CONCLUSIONS: C7 improved LV ejection fraction and reduced LV mass at rest, as well as lowering heart rate during exercise among patients with LC-FAODs. CLINICAL TRIAL REGISTRATION: Clinicaltrials.gov NCT01379625.


Risky sexual behavior and substance use appear to be interconnected behaviors among adolescents, but data are scarce regarding the extent to which sexual risk behavior is associated with high levels of marijuana and alcohol use, both separately and in combination. 301 adolescents were recruited from a short-term detention facility, and substance use and risky sexual behavior were assessed. We found that adolescents who frequently used marijuana, but not alcohol, reported significantly less risky sex as well as greater intentions to use condoms than either adolescents who frequently used alcohol, but not marijuana, or adolescents who frequently used both substances. Substance use status as a predictor of future risky sexual behavior followed a similar pattern. When designing interventions to reduce substance use in the context of risky sex, it might be especially effective to target efforts toward reducing harm associated with alcohol use, either alone or in combination with marijuana use.


Long-range enhancer interactions critically regulate gene expression, yet little is known about how their coordinated activities contribute to CNS development or how this may, in turn, relate to disease states. By examining the regulation of the transcription factor NFIA in the developing spinal cord, we identified long-range enhancers that recapitulate NFIA expression across glial and neuronal lineages in vivo. Complementary genetic studies found that Sox9-Brn2 and Isl1-Lhx3 regulate enhancer activity and NFIA expression in glial and neuronal populations. Chromatin conformation analysis revealed that these enhancers and transcription factors form distinct architectures within these lineages in the spinal cord. In glioma models, the glia-specific architecture
is present in tumors, and these enhancers are required for NFIA expression and contribute to glioma formation. By delineating three-dimensional mechanisms of gene expression regulation, our studies identify lineage-specific chromatin architectures and associated enhancers that regulate cell fate and tumorigenesis in the CNS.


**Purpose:** To characterize disease burden and medication usage in rural and urban adults aged ≥85 years. **Methods:** This is a secondary analysis of 5 years of longitudinal data starting in the year 2000 from 3 brain-aging studies. Cohorts consisted of community-dwelling adults: 1 rural cohort, the Klamath Exceptional Aging Project (KEAP), was compared to 2 urban cohorts, the Oregon Brain Aging Study (OBAS) and the Dementia Prevention study (DPS). In this analysis, 121 participants were included from OBAS/DPS and 175 participants were included from KEAP. Eligibility was determined based on age ≥85 years and having at least 2 follow-up visits after the year 2000. Disease burden was measured by the Modified Cumulative Illness Rating Scale (MCIRS), with higher values representing more disease. Medication usage was measured by the estimated mean number of medications used by each cohort. **Findings:** Rural participants had significantly higher disease burden as measured by MCIRS, 23.0 (95% CI: 22.3-23.6), than urban participants, 21.0 (95% CI: 20.2-21.7), at baseline. The rate of disease accumulation was a 0.2 increase in MCIRS per year (95% CI: 0.05-0.34) in the rural population. Rural participants used a higher mean number of medications, 5.5 (95% CI: 4.8-6.1), than urban participants, 3.7 (95% CI: 3.1-4.2), at baseline (P <.0001). **Conclusions:** These data suggest that rural and urban Oregonians aged ≥85 years may differ by disease burden and medication usage. Future research should identify opportunities to improve health care for older adults. © 2015 National Rural Health Association


**OBJECTIVES:** To compare outcomes and healthcare utilization of older patients who did versus did not fill opioid prescriptions within 90 days of initiating care for low back pain. **MATERIALS AND METHODS:** For patients ≥65 years with new back pain visits, we used propensity scores to match those who filled no opioid prescriptions to those who filled >2 opioid prescriptions within 90 days (and the first opioid prescription within 30 d) of the index visit. Over 24 months, we examined patient-reported outcomes, healthcare utilization, and subsequent opioid prescription fills. **RESULTS:** Among 1954 patients eligible for matching, 238 (12%) filled >2 opioid prescriptions within 90 days; 200 of these were matched to controls. Patients with versus without early opioid prescriptions had similar patient-reported outcomes but were more likely to have filled >1 opioid prescription 18-24 months after the index visit (odds ratio (95% CI)=2.4 (1.5-3.9)) and to have had >1 visit to the emergency department in the subsequent 24 months (OR 1.6; 95% CI 1.0-2.5). **DISCUSSION:** Among older patients with new back pain visits, filling >2 opioid prescriptions within 90 days of the visit was associated with similar back pain-related outcomes but increased likelihood of filling opioid prescriptions 18-24 months later compared to matched patients who did not fill early opioid prescriptions.

OBJECTIVE: To conduct a scoping literature review to identify practices or programs that promote AYA patient-centered communication. METHODS: Between January and May of 2016, we applied standard scoping review methodology to systematically review articles. We considered peer-reviewed, English language articles written at any phase of intervention research. Both qualitative and quantitative studies were eligible, and no additional search restrictions were applied. We retained articles that included explicit or implicit outcomes for one of the six functions of patient-centered communication in cancer care. At least two independent reviewers assessed the articles. RESULTS: We screened a total of 4072 titles and abstracts, retaining 27 for full-text review. Ultimately, eight titles met the review’s inclusion criteria. We categorized each publication by the action or setting used to improve patient-centered communication, resulting in five categories. Most studies were not included because they did not include a patient-centered communication outcome. CONCLUSION: This area of research is still emerging, as indicated by the small number of eligible studies and predominance of qualitative, descriptive, pilot, and feasibility studies with small sample sizes. PRACTICE IMPLICATIONS: Our results suggest a clear need to develop and evaluate interventions focused on improving patient-centered communication between AYA survivors and their healthcare providers.


OBJECTIVE: Assessment of the effect of the intervention on school adjustment. These findings support the potential for ameliorative effects of interventions targeting critical transitional periods, such as the transition of formal schooling. This school readiness intervention on HPA axis functioning in response to the start of kindergarten. Furthermore, the children's HPA axis response to the start of school mediated the steeper first day of school diurnal cortisol slope on the first day of school, a pattern previously observed among nonmaltreated children. A steeper diurnal cortisol slope predicted teacher ratings of better school adjustment (i.e., academic performance, appropriate classroom behaviors, and engagement in learning) in the fall of kindergarten. Furthermore, the children's HPA axis response to the start of school mediated the effect of the intervention on school adjustment. These findings support the potential for ameliorative effects of interventions targeting critical transitional periods, such as the transition of formal schooling. This school


Maltreated children in foster care are at high risk for dysregulated hypothalamus-pituitary-adrenal (HPA) axis functioning and educational difficulties. The present study examined the effects of a short-term school readiness intervention on HPA axis functioning in response to the start of kindergarten, a critical transition marking entry to formal schooling, and whether altered HPA axis functioning influenced children's school adjustment. Compared to a foster care comparison group, children in the intervention group showed a steeper diurnal cortisol slope on the first day of school, a pattern previously observed among nonmaltreated children. A steeper first day of school diurnal cortisol slope predicted teacher ratings of better school adjustment (i.e., academic performance, appropriate classroom behaviors, and engagement in learning) in the fall of kindergarten. Furthermore, the children's HPA axis response to the start of school mediated the effect of the intervention on school adjustment. These findings support the potential for ameliorative effects of interventions targeting critical transitional periods, such as the transition of formal schooling. This school
readiness intervention appears to influence stress neurobiology, which in turn facilitates positive engagement with the school environment and better school adjustment in children who have experienced significant early adversity.


Wilson’s disease is a well-characterized disorder known to cause liver and brain disease due to abnormal copper deposition. Data regarding copper infiltration of the heart is conflicting, and the risk of heart disease has not been well described. We aimed to determine whether Wilson’s disease is associated with cardiac myopathy, clinically evident in the atria as atrial fibrillation (AF) and in the ventricles as heart failure (HF). We longitudinally assessed 14.3 million patients in the California Healthcare Cost and Utilization Project database from 2005 through 2009 for diagnoses of Wilson’s disease, AF, HF, and covariates using International Classification of Diseases-9th Edition codes. Cirrhosis and appendicitis diagnoses were assessed for positive and negative validation, respectively. We identified 463 patients with Wilson’s disease. As expected in validation analyses, patients with Wilson’s disease had a threefold greater risk of cirrhosis (hazard ratio [HR] 2.85, 95% confidence interval [CI] 2.81 to 2.90, p <0.0001) and no increased risk of appendicitis (HR 0.24, 95% CI 0.04 to 1.71, p = 0.16). Patients with Wilson’s disease exhibited a 29% higher risk of AF after adjusting for age, gender, race, income, hypertension, diabetes, renal disease, hyperlipidemia, obesity, coronary disease, and obstructive sleep apnea (HR 1.29, 95% CI 1.15 to 1.45, p <0.0001). After adjusting for the same covariates, patients with Wilson’s disease had a 55% higher risk of incident HF (HR 1.55, 95% CI 1.41 to 1.71, p <0.0001). Patients with Wilson’s disease have an increased risk of AF and HF, supporting the need for careful surveillance for heart disease. These findings also suggest that the role of copper metabolism in heart disease should be more broadly investigated.


Centella asiatica has been used for centuries to enhance memory. We have previously shown that a water extract of Centella asiatica (CAW) protects against the deleterious effects of amyloid-beta (Abeta) in neuroblastoma cells and attenuates Abeta-induced cognitive deficits in mice. Yet, the neuroprotective mechanism of CAW has yet to be thoroughly explored in neurons from these animals. This study investigates the effects of CAW on neuronal metabolism and oxidative stress in isolated Abeta-expressing neurons. Hippocampal neurons from amyloid precursor protein overexpressing Tg2576 mice and wild-type (WT) littermates were treated with CAW. In both genotypes, CAW increased the expression of antioxidant response genes which attenuated the Abeta-induced elevations in reactive oxygen species (ROS) and lipid peroxidation in Tg2576 neurons. CAW also improved mitochondrial function in both genotypes and increased the expression of electron transport chain enzymes and mitochondrial labeling, suggesting an increase in mitochondrial content. These data show that CAW protects against mitochondrial dysfunction and oxidative stress in Abeta-exposed hippocampal neurons which could contribute to the beneficial effects of the extract observed in vivo. Since CAW also improved mitochondrial function in the absence of Abeta, these results suggest a broader utility for other conditions where neuronal mitochondrial dysfunction occurs.


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


We aimed to examine associations between chronic airflow obstruction (CAO) and unemployment across the world. Cross-sectional data from 26 sites in the Burden of Obstructive Lung Disease (BOLD) study were used to analyse effects of CAO on unemployment. Odds ratios for unemployment in subjects aged 40–65 years were estimated using a multilevel mixed-effects generalised linear model with study site as random effect. Site-by-site heterogeneity was assessed using individual participant data meta-analyses. Out of 18 710 participants, 11.3% had CAO. The ratio of unemployed subjects with CAO divided by subjects without CAO showed large site discrepancies, although these were no longer significant after adjusting for age, sex, smoking and education. The site-adjusted odds ratio (95% CI) for unemployment was 1.79 (1.41–2.27) for CAO cases, decreasing to 1.43 (1.14–1.79) after adjusting for sociodemographic factors, comorbidities and forced vital capacity. Of other covariates that were associated with unemployment, age and education were important risk factors in high-income sites (4.02 (3.53–4.57) and 3.86 (2.80–5.30), respectively), while female sex was important in low- to middle-income sites (3.23 (2.66–3.91)). In the global BOLD study, CAO was associated with increased levels of unemployment, even after adjusting for sociodemographic factors, comorbidities and lung function.


INTRODUCTION: Surgical resection of a lesion that correlates with seizure onset in patients with epilepsy can dramatically improve seizure burden and quality of life. For bilateral hippocampal lesions, bilateral resection comes with a risk of severe cognitive deficits. Responsive neurostimulation (RNS) devices offer a new modality to treat multifocal lesions in a reversible manner including bilateral hippocampal stimulation. We describe technical aspects of Nexframe-assisted placement of bilateral NeuroPace mesial temporal electrodes and case examples. METHODS: Retrospective chart review was performed for 4 patients who underwent bilateral mesial temporal RNS placement for medically intractable epilepsy. Operative techniques were assessed and modified. Ambulatory electrocorticographic recordings and a subanalysis of available data are summarized. RESULTS: Eight electrodes were placed in 4 patients, who were followed for up to 6 months. One out of 8 electrodes was revised due to vector error >3 mm; after surgical technique modification, all subsequent electrodes were reliably placed in a single pass with <2-mm vector error. Using patients’ seizure diaries, seizure semiologies were correlated with ambulatory ECoG recording patterns and subanalyzed; 51.4% were left sided, 15% were right sided, and 33.6% were indeterminate. CONCLUSIONS: We report herein the technical nuances of adapting Nexframe to hippocampal-based depth electrode RNS
system placement. Our group has extensive experience with Nexframe for accurate and safe deep brain stimulation electrode placement. Our preliminary data with bitemporal RNS placement suggest similar accuracy and safety.


Despite significant computational challenges, a number of tools have been developed recently to leverage the mouse to model human disease. Here we review these tools and show how they can be applied in the identification of candidate genes and therapeutic targets as well as mouse models for mechanistic studies and drug validation. © 2017 Elsevier Ltd.


The United States is embroiled in a debate about whether to protect or deport its estimated 11 million unauthorized immigrants, but the fact that these immigrants are also parents to more than 4 million U.S.-born children is often overlooked. We provide causal evidence of the impact of parents’ unauthorized immigration status on the health of their U.S. citizen children. The Deferred Action for Childhood Arrivals (DACA) program granted temporary protection from deportation to more than 780,000 unauthorized immigrants. We used Medicaid claims data from Oregon and exploited the quasi-random assignment of DACA eligibility among mothers with birthdates close to the DACA age qualification cutoff. Mothers’ DACA eligibility significantly decreased adjustment and anxiety disorder diagnoses among their children. Parents’ unauthorized status is thus a substantial barrier to normal child development and perpetuates health inequalities through the intergenerational transmission of disadvantage.


Objective: To report the outcome of adult spinal deformity (ASD) in patients with rod fracture (RF) after thoracolumbar fusion. Methods: Retrospective review of prospective, multicenter database. Operative patients with ASD ≥18 years old with RF after ASD surgery and with a minimum 6-month follow-up after RF were included. Health-related quality of life scores and radiographic alignment were compared with nonparametric paired and independent testing (P &lt; 0.05). Results: A total of 51 of 343 patients with ASD (14.9%) sustained a RF, of whom 44 (86.3%) had at least 6-month follow up after RF (mean age = 61.2 years, mean body mass index = 29.6 kg/m2). Mean total follow-up was 37.8 months (range 24.5–66.7 months). Interbody fusion was used in 26 cases of RF (59.1%) (transforaminal lumbar interbody fusion, n = 17 [65.4%], anterior lumbar interbody fusion, n = 5 [19.2%]). RF was symptomatic in 26 of 44 (59.1%) of patients and discovered incidentally in 18 of 44 patients (40.9%). Overall, 28 RFs were revised (63.6%); 12 of 23 (52.2%) unilateral RF and 16 of 21 (76.2%) bilateral RF at last follow-up. Revision patients were significantly more likely to be symptomatic at the time of RF detection (78.6% vs. 25.0%, P = 0.0006), and had significantly worse Oswestry Disability Index and Scoliosis Research Society-22r pain scores. Conclusions: RFs were detected in 14.9% of patients with ASD and were most common at the L4-L5 and L5-S1 levels. Approximately 63.6% of patients underwent revision surgery. The decision to perform revision surgery may be based predominantly on symptoms referable to the RF, pain, and perceived disability, as radiographic parameters at the time of RF did not differ significantly between patients who did and did not undergo revision. © 2017 Elsevier Inc.
The mixotrophic ciliate, Mesodinium rubrum, is a globally distributed ciliate that relies on the acquisition and use of chloroplasts derived from its cryptophyte prey. The ecology and physiology of the cryptophytes is not well known, nor is it clear how their growth influences M. rubrum blooms. A 4-week survey was conducted in the Columbia River estuary in 2013 during the decline of the annual M. rubrum bloom to better understand how environmental factors influence the dynamics of the cryptophyte prey, Teleaulax amphioxeia. Abundances and division rates of free-living Teleaulax-like cryptophytes were continuously monitored using flow cytometry. Cryptophyte division rates, estimated in situ for the first time using a size-structured division rate model, ranged from 0.2 to 1.5 d⁻¹, with the highest rates observed in accordance with high abundances. These division rates were positively correlated with concentrations of dissolved inorganic nitrogen and phosphorus, suggesting nutrient availability limited the growth of Teleaulax-like cryptophytes at that time. Assuming a minimum ingestion rate of ~1 cryptophyte ciliate 1 day⁻¹, the growth of M. rubrum may have been limited by the low abundance of Teleaulax-like cryptophytes during the M. rubrum bloom decline. Our results highlight the importance of prey availability for understanding the dynamics of red water blooms. © The Author 2017. Published by Oxford University Press. All rights reserved.


OBJECTIVES: We analyzed Twitter tweets and Twitter-provided user data to give geographical, temporal and content insight into the use of social media in the Planned Parenthood video controversy. METHODOLOGY: We randomly sampled the full Twitter repository (also known as the Firehose) (n=30,000) for tweets containing the phrase “planned parenthood” as well as group-defining hashtags “#defundpp” and “#standwithpp.” We used demographic content provided by the user and word analysis to generate charts, maps and timeline visualizations. Chi-square and t tests were used to compare differences in content, statistical references and dissemination strategies. RESULTS: From July 14, 2015, to January 30, 2016, 1,364,131 and 795,791 tweets contained “#defundpp” and “#standwithpp,” respectively. Geographically, #defundpp and #standwithpp were disproportionally distributed to the US South and West, respectively. Word analysis found that early tweets predominantly used “sensational” words and that the proportion of “political” and “call to action” words increased over time. Scatterplots revealed that #standwithpp tweets were clustered and episodic compared to #defundpp. #standwithpp users were more likely to be female [odds ratio (OR) 2.2, confidence interval (CI) 2.0-2.4] and have fewer followers (median 544 vs. 1578, p<.0001). #standwithpp and #defundpp did not differ significantly in their usage of data in tweets. #defundpp users were more likely to link to websites (OR 1.8, CI 1.7-1.9) and to other online dialogs (mean 3.3 vs. 2.0 p<.0001). CONCLUSION: Social media analysis can be used to characterize and understand the content, tempo and location of abortion-related messages in today's public spheres. Further research may inform proabortion efforts in terms of how information can be more effectively conveyed to the public. IMPLICATIONS: This study has implications for how the medical community interfaces with the public with regards to abortion. It highlights how social media are actively exploited instruments for information and message dissemination. Researchers, providers and advocates should be monitoring social media and addressing the public through these modern channels.


Background: Actinic keratosis (AK) can affect large skin areas. Ingenol mebutate (IngMeb) gel (0.015% and 0.05%) is approved for topical treatment of AK in a single contiguous area of ~25 cm². Objective: The study sought to
determine the maximum tolerated dose (MTD), efficacy, and tolerability of IngMeb applied to AK on a contiguous area less than equal to 250 cm2. Methods: Part 1 determined the MTD of IngMeb at 7 concentrations for 2 or 3 days. Part 2 assessed efficacy and tolerability at the MTD and one dose lower for 2 or 3 days vs vehicle. Results: Four dosing regimens with an acceptable benefit-to-risk ratio were identified: 0.018% and 0.027% once daily for 2 or 3 days. Complete clearance at 8 weeks was achieved by 21.3% to 39.1% of IngMeb-treated patients vs 0% to 3.2% treated with vehicle. Composite local skin response scores peaked on the day after the last application, rapidly declined, and were near baseline at 2 weeks. Adverse events were predominantly mild or moderate. Limitations: The study evaluated a limited number of doses in a population of only white patients. Conclusion: IngMeb gel was effective and well tolerated as field treatment of AK on the full face, full scalp, and up to 250 cm2 on the chest.


Ten percent of patients report penicillin allergy, but more than 90% of these individuals can tolerate penicillins. Skin testing remains the optimal method for evaluation of possible IgE-mediated penicillin allergy and is recommended by professional societies, as the harms for alternative antibiotics include antimicrobial resistance, prolonged hospitalizations, readmissions, and increased costs. Removal of penicillin allergy leads to decreased utilization of broad-spectrum antibiotics, such as fluoroquinolones and vancomycin. There is minimal allergic cross-reactivity between penicillins and cephalosporins. IgE-mediated allergy to cephalosporins is usually side-chain specific and may warrant graded challenge with cephalosporins containing dissimilar R1 or R2 group side chains. © 2017 Elsevier Inc.


BACKGROUND: Two decades ago, hypotensive trauma patients requiring emergent laparotomy had a 40% mortality. In the interim, multiple interventions to decrease hemorrhage-related mortality have been implemented, but few have any documented evidence of change in outcomes for patients requiring emergent laparotomy. The purpose of this study was to determine current mortality rates for patients undergoing emergent trauma laparotomy. METHODS: A retrospective cohort of all adult, emergent trauma laparotomies performed in 2012 to 2013 at 12 Level I trauma centers was reviewed. Emergent trauma laparotomy was defined as emergency department (ED) admission to surgical start time in 90 minutes or less. Hypotension was defined as arrival ED systolic blood pressure (SBP) \(\leq 90\) mm Hg. Cause and time to death was also determined. Continuous data are presented as median (interquartile range [IQR]). RESULTS: One thousand seven hundred six patients underwent emergent trauma laparotomy. The cohort was predominately young (31 years; IQR, 24-45), male (84%), sustained blunt trauma (67%), and with moderate injuries (Injury Severity Score, 19; IQR, 10-33). The time in ED was 24 minutes (IQR, 14-39) and time from ED admission to surgical start was 42 minutes (IQR, 30-61). The most common procedures were enterectomy (23%), hepatorrhaphy (20%), enterorrhaphy (16%), and splenectomy (16%). Damage control laparotomy was used in 38% of all patients and 62% of hypotensive patients. The Injury Severity Score for the entire cohort was 19 (IQR, 10-33) and 29 (IQR, 18-41) for the hypotensive group. Mortality for the entire cohort was 21% with 60% of deaths due to hemorrhage. Mortality in the hypotensive group was 46%, with 65% of deaths due to hemorrhage.

CONCLUSION: Overall mortality rate of a trauma laparotomy is substantial (21%) with hemorrhage.
accounting for 60% of the deaths. The mortality rate for hypotensive patients (46%) appears unchanged over the last two decades and is even more concerning, with almost half of patients presenting with an SBP of 90 mm Hg or less dying.


Treatment of patients with triple negative (ER-negative, PR-negative, HER2-negative) breast cancer remains a challenge. Although PARP inhibitors are being evaluated in clinical trials, biomarkers are needed to identify patients that will most benefit from anti-PARP therapy. We determined the response of three PARP inhibitors: veliparib, olaparib, and talazoparib in a panel of eight triple-negative breast cancer cell lines. Therapeutic responses and cellular phenotypes were elucidated using high-content imaging and quantitative immunofluorescence to assess markers of DNA damage (53BP1) and apoptosis (cleaved-PARP). We determined the pharmacodynamic changes in percentage of cells positive for 53BP1, mean number of 53BP1 foci per cell, and percentage of cells positive for cleaved-PARP. Inspired by traditional dose-response measures of cell viability, an EC50 value was calculated for each cellular phenotype for each PARP inhibitor. The EC50 values for both 53BP1 metrics strongly correlated with IC50 values for each PARP inhibitor. Pathway enrichment analysis identified a set of DNA repair and cell cycle associated genes that were associated with 53BP1 response following PARP inhibition. The overall accuracy of our 63 gene set in predicting response to olaparib in seven breast cancer patient-derived xenograft tumors was 86%. In triple-negative breast cancer patients not treated with anti-PARP therapy, the predicted response rate of our gene signature was 45%. These results indicate that 53BP1 is a biomarker of response to anti-PARP therapy in the laboratory, and our DNA damage response gene signature may be used to identify patients who are most likely to respond to PARP inhibition.


OBJECTIVE: To assess the impact of the latest randomized controlled trial (RCT) to each systematic review (SR) in Cochrane Neonatal Reviews. STUDY DESIGN: We selected meta-analyses reporting the typical point estimate of the risk ratio for the primary outcome of the latest study (n=130), mortality (n=128) and the mean difference for the primary outcome (n=44). We employed cumulative meta-analysis to determine the typical estimate after each trial was added, and then performed multivariable logistic regression to determine factors predictive of study impact. RESULTS: For the stated primary outcome, 18% of latest RCTs failed to narrow the confidence interval (CI), and 55% failed to decrease the CI by 20%. Only 8% changed the typical estimate directionality, and 11% caused a change to or from significance. Latest RCTs did not change the typical estimate in 18% of cases, and only 41% changed the typical estimate by at least 10%. The ability to narrow the CI by >20% was negatively associated with the number of previously published RCTs (odds ratio 0.707). Similar results were found in analysis of typical estimates for the outcomes of mortality and mean difference. CONCLUSION: Across a broad range of clinical questions, the latest RCT failed to substantially narrow the CI of the typical estimate, to move the effect estimate or to change its statistical significance in a majority of cases. Investigators and grant peer review committees should consider prioritizing less-studied topics or requiring formal consideration of optimal information size based on extant evidence in power calculations. Journal of Perinatology advance online publication, 7 September 2017; doi:10.1038/jp.2017.126.

OBJECTIVE: To critically appraise the medical education research literature of 2015, and review the highest quality quantitative and qualitative examples. METHODS: 434 EM-related articles were discovered upon a search of ERIC, PsychINFO, PubMED and SCOPUS. These were both quantitative and qualitative in nature. All were screened by two of the authors using previously published exclusion criteria, and the remaining were appraised by all authors using a previously published scoring system. The highest scoring articles were then reviewed. RESULTS: 61 manuscripts were scored, and 10 quantitative and 2 qualitative papers were the highest scoring and are reviewed and summarized in the article. CONCLUSIONS: This installment in this critical appraisal series reviews twelve of the highest quality EM-related medical education research manuscripts published in 2015. This article is protected by copyright. All rights reserved.


OBJECTIVE: To evaluate the effects of epilepsy and antiepileptic drugs (AEDs) used during pregnancy on fetal growth and preterm delivery. METHODS: This study included singleton liveborn infants born to women enrolled in the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2016. Data were collected prospectively through telephone interviews. The prevalence of preterm birth (<37 weeks) and small for gestational age status (SGA) among infants exposed prenatally to AEDs when used by women with epilepsy (WWE) or women without epilepsy (WWOE) was compared with that among infants unexposed to AEDs and born to WWOE. Multivariate log-binomial regression models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). RESULTS: The study population included infants born to 6,777 AED-WWE, 696 AED-WWOE, and 486 no-AED-WWOE. The risk of prematurity was 6.2% for no-AED-WWOE, 9.3% for AED-WWE (RR = 1.5, 95% CI = 1.0-2.1), and 10.5% for AED-WWOE (RR = 1.5, 95% CI = 1.0-2.4). Prenatal exposure to AEDs in WWE and WWOE was associated with a mean lower birth weight of 110 and 136g, respectively, as compared to no-AED-WWOE. The prevalence of SGA was 5.0% for no-AED-WWOE, 10.9% for AED-WWE (RR = 2.0, 95% CI = 1.3-3.0), and 11.0% for AED-WWOE (RR = 1.9, 95% CI = 1.2-2.9). Within users of AEDs in monotherapy, the prevalence of SGA ranged from 7.3% for lamotrigine to 18.5% for topiramate. INTERPRETATION: Women on AEDs during pregnancy, whether for epilepsy or for other neuropsychiatric indications, are at a higher risk of delivering prematurely and giving birth to SGA newborns. The risk may vary by drug. Ann Neurol 2017;82:457-465.


OBJECTIVE: Adenomyosis is a clinical disorder defined by the presence of endometrial glands and stroma within the myometrium, the pathogenesis of which is poorly understood. We postulate that dysregulation of genes and pathways in eutopic endometrium may predispose to ectopic implantation. No study, to our knowledge, has examined the global transcriptome of isolated eutopic endometrium from women with clinically significant adenomyosis. DESIGN: Laboratory-based study with full institutional review board approval and consents. MATERIAL AND METHODS: Endometrial sampling was performed on hysterectomy specimens (proliferative phase) from symptomatic women with pathologically confirmed diffuse adenomyosis (n = 3). Controls (n = 5) were normo-ovulatory patients without adenomyosis. All patients were free from leiomyoma, endometriosis, and hormonal exposures. Isolated purified total RNA was subjected to microarray analysis using the Gene 1.0 ST Affymetrix platform. Data were analyzed with GeneSpring and Ingenuity Pathway analysis. Validation of several genes was undertaken by quantitative real-time reverse transcriptase polymerase chain reaction. RESULTS: Comparison of transcriptomes of proliferative endometrium from women with and without adenomyosis revealed 140 upregulated and 884 downregulated genes in samples from women with adenomyosis compared to controls. Highly differentially expressed genes include those involved in regulation of apoptosis, steroid hormone responsiveness, and proteins involved in extracellular matrix remodeling as well as microRNAs of unknown significance. Affected canonical pathways included
eukaryotic initiation factor 2 signaling, oxidative phosphorylation, mitochondrial dysfunction, estrogen receptor signaling, and mammalian target of rapamycin signaling. CONCLUSION: The eutopic endometrium in patients with adenomyosis has fundamental abnormalities that may predispose to invasion and survival beyond the myometrial interface.


OBJECTIVES: Clinician communication with patients regarding worrisome findings in Prescription Drug Monitoring Programs (PDMPs) may influence patient responses and subsequent care. The authors studied the range of approaches clinicians report when communicating with patients in this situation and how practice policies and procedures may influence this communication. DESIGN: Qualitative interviews of clinician PDMP users. SETTING: Oregon registrants in the state’s PDMP. SUBJECTS: Thirty-three clinicians practicing in pain management, emergency medicine, primary care, psychiatry, dentistry, and surgery. METHODS: The authors conducted semi-structured interviews via telephone with clinicians who routinely used the PDMP. A multidisciplinary team used a grounded theory approach to identify ways clinicians reported using information from the PDMP when communicating with patients, and policies that influenced that communication. RESULTS: Clinicians reported using a range of approaches for communicating about PDMP results, from openly sharing, to questioning patients without disclosing access to the PDMP, to avoiding the conversation. Clinicians also reported practice policies and procedures that influenced communication with their patients about prescribing and ongoing care, including policies that normalized use of the PDMP with all patients and those that facilitated difficult conversations by providing a rationale not to prescribe in certain circumstances. CONCLUSION: Clinicians’ self-reported approaches to sharing PDMP findings and communicating prescribing decisions with patients vary and may be facilitated by appropriate practice policies. Such communication may have implications for patient engagement and alliance building. More research is needed to identify best practices and potential guidelines for effectively communicating about PDMP findings, as this may enhance health outcomes.


Movement toward legalization of cannabis grows in the United States yet little is known about long-term use effects. This study was an initial step in the instrument development of a patient registry questionnaire of cannabis users who will be followed over time. Cannabis-using patients (12 females, 10 males) aged 20–64, were sampled from a Portland, Oregon primary care health center. Respondents completed semi-structured qualitative interviews describing methods of cannabis use, motivations for use, and perceptions of risks and benefits. Qualitative analysis used a content analysis approach to assess and extract salient themes. Patients smoked, inhaled, ingested, and applied a wide variety of cannabis products. All participants but one reported using cannabis for perceived physiological or psychological pain and several used cannabis to alleviate cravings for opioid medications. Other motivations included relief from suicidal thoughts and depression, anxiety, migraines, and neuropathic pain. Relatively few perceived risks as compared to benefits were reported. This study provides relevant insight into how and why these primary care patients use cannabis. Results will be used to construct a quantitative questionnaire for a patient registry that can provide critical information about long-term use effects. © 2017 Policy Studies Organization

Pain-related functional limitations represent an important outcome domain to assess in children and adolescents with chronic pain. The aim of this study was to extend the empirical support of the CALI-21 (21-item Child Activity Limitations Interview), a well-validated measure of activity limitations, using a large, multisite sample and to develop a brief form of the measure with more interpretable scoring. A sample of 1616 youth and 1614 parents completed the CALI-21 at an initial appointment in 1 of 3 pain specialty clinics in the Midwest or Northwest United States, or as part of a research study following this initial visit. All youth also reported on usual pain intensity. CALI-21 data from 1236 youth and parents were used in analyses. Results of the exploratory and confirmatory factor analyses supported a common 2-factor structure (Active and Routine factors) for both child and parent report versions. Using item reduction, the 9 item measure (CALI-9) was developed with both child and parent versions showing good internal consistency and high cross-informant reliability. Initial validity was shown by the ability of the CALI-9 to distinguish by level of pain intensity. Findings suggest that the CALI-9 is a promising brief tool for the evaluation of pain-related activity limitations in youth with chronic pain and for proxy-report by parents. Advantages of the shortened scale include the revised 0-100 point scale, which increases interpretability, and further validation of the subscale scoring to assess specific limitations in active and routine physical functioning domains.


EXECUTIVE SUMMARY: The importance of emotional intelligence (EI) in physicians has attracted attention as researchers begin to focus on the relationship of EI to retention, promotion, and productivity among academic physicians. However, to date, no formal evaluation of EI has been conducted among current department chairs. The objectives of this study were to assess the EI of current chairs of academic radiation oncology departments and to correlate EI with a self-reported assessment of burnout. The authors invited 95 chairs of academic radiation oncology departments to participate in a survey, approved by an institutional review board, consisting of the Trait Emotional Intelligence Questionnaire Short Form (TEIQue-SF) and the abbreviated Maslach Burnout Inventory (a-MBI). TEIQue-SF scores were evaluated for correlation with respondents’ demographics and self-reported burnout scores on the a-MBI. Sixty chairs responded to the survey, for a response rate of 63.2%. The median (interquartile range) TEIQue-SF for the responding cohort was 172 (155-182) out of a maximum possible score of 210. The a-MBI emotional exhaustion and depersonalization subscores were low, with median (interquartile range) scores of 4 (2.25-6.75) and 1 (0-2.75) out of maximum possible scores of 18 and 30, respectively. Higher TEIQue-SF global scores were weakly correlated with decreased burnout. The study results show that academic radiation oncology chairs had a high EI and low rates of self-reported burnout. EI may be of increasing importance with respect to recruitment and retention of academic medical leaders.


Late acute (LA) graft-versus-host disease (GVHD) is persistent, recurrent, or new-onset acute GVHD symptoms occurring >100 days after allogeneic hematopoietic cell transplantation (HCT). The aim of this analysis is to describe the onset, course, morbidity, and mortality of and examine angiogenic factors associated with LA GVHD. A prospective cohort of patients (n = 909) was enrolled as part of an observational study within the Chronic GVHD Consortium. Eighty-three patients (11%) developed LA GVHD at a median of 160 (interquartile range, 128-204) days after HCT. Although 51 out of 83 (61%) achieved complete or partial response to initial therapy by 28 days, median failure-free survival was only 7.1 months (95% confidence interval, 3.4-19.1 months), and estimated overall survival (OS) at 2 years was 56%. Given recently described alterations of circulating angiogenic factors in classic acute GVHD, we examined whether alterations in such factors could be identified in LA GVHD. We first tested cases (n = 55) and controls (n = 50) from the Chronic GVHD Consortium and then validated the findings in 37 cases from Mount Sinai Acute GVHD International
Consortium. Plasma amphiregulin (AREG; an epidermal growth factor [EGF] receptor ligand) was elevated, and an AREG/EGF ratio at or above the median was associated with inferior OS and increased nonrelapse mortality in both cohorts. Elevation of AREG was detected in classic acute GVHD, but not chronic GVHD. These prospective data characterize the clinical course of LA GVHD and demonstrate alterations in angiogenic factors that make LA GVHD biologically distinct from chronic GVHD.


Epidermal growth factor (EGF) is a recently described biomarker of acute GvHD (aGvHD). Whether low plasma EGF prior to hematopoietic cell transplantation (HCT) predisposes to the development of aGvHD, or whether EGF levels fall because of severe aGvHD, is unknown. To evaluate this, we tested plasma samples collected at pre-HCT baseline, day +28 and day +100 during the course of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0402. We found that baseline EGF plasma concentrations were three-fold lower in HCT recipients compared to donors (24.3 vs 76.0 pg/mL, P<0.01). Ninety-one patients (43%) had a markedly low plasma EGF at pre-HCT baseline, defined as <2.7 pg/mL-an optimal cutpoint associated with development of grade III-IV aGvHD. Patients with these low EGF levels at pre-HCT baseline had a 2.9-fold increased risk of grade III-IV aGvHD by day +100. Patients with low EGF at day +28 after HCT had an increased risk of death (relative risk 2.3, P=0.02) by 1 year due to transplant-related toxicities, especially aGvHD. Our results suggest that very low plasma EGF early in the HCT process may predispose patients to an increased risk of death, potentially due to epithelial damage and limited repair capacity. © 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.


While rheumatic heart disease (RHD) is a treatable disease nearly eradicated in the United States, it remains the most common form of acquired heart disease in the developing world. This study used echocardiographic screening to determine the prevalence of RHD in children in American Samoa. Screening took place at a subset of local schools. Private schools were recruited and public schools underwent cluster randomization based on population density. We collected survey information and performed a limited physical examination and echocardiogram using the World Heart Federation protocol for consented school children aged 5-18 years old. Of 2200 students from two private high schools and two public primary schools, 1058 subjects consented and were screened. Overall, 133 (12.9%) children were identified as having either definite (3.5%) or borderline (9.4%) RHD. Of the patients with definitive RHD, 28 subjects had abnormal mitral valves with pathologic regurgitation, three mitral stenosis, three abnormal aortic valves with pathologic regurgitation, and seven borderline mitral and aortic valve disease. Of the subjects with borderline disease, 77 had pathologic mitral regurgitation, 12 pathologic aortic regurgitation, and 7 at least two features of mitral valve disease without pathologic regurgitation or stenosis. Rheumatic heart disease remains a major cause of morbidity and mortality worldwide. The prevalence of RHD in American Samoa (12.9%) is to date the highest reported in the world literature. Echocardiographic screening of school children is feasible, while reliance on murmur and Jones criteria is not helpful in identifying children with RHD.
Carbapenem antibiotics are among the mainstay for treating infections caused by Acinetobacter baumannii, especially in the Northwest United States where carbapenem-resistant A. baumannii remain relatively rare. However, between June 2012 and October 2014, an outbreak of carbapenem-resistant A. baumannii occurred in 16 patients from 5 healthcare facilities in the state of Oregon. All isolates were defined as extensively-drug resistant (XDR). MLST revealed that the isolates belonged to sequence type 2 (international clone 2, IC2), and were greater than 95% similar by rep-PCR analysis. Multiplex PCR revealed the presence of a blaOXA carbapenemase gene, later identified as blaOXA-237 Whole genome sequencing of all isolates revealed a well-supported separate branch within a global A. baumannii phylogeny. Pacific Biosciences (PacBio) SMRT sequencing was also performed on one isolate to gain insight into the genetic location of the carbapenem resistance gene. We discovered that blaOXA-237, flanked on either side by ISAba1 elements in opposite orientations, was carried by a 15,198 bp plasmid designated pORAB01-3, and was present in all 16 isolates. The plasmid also contained genes encoding for: a TonB-dependent receptor, septicolysin, a type IV secretory system conjugative DNA transfer family protein, an integrase, a RepB family plasmid DNA replication initiator protein, an alpha/beta hydrolase, and a BrnT/BrnA type II toxin-antitoxin system. This is the first reported outbreak associated with this specific carbapenemase. Particularly worrisome is that blaOXA-237 was plasmid encoded and found in the most prominent worldwide clonal group IC2, potentially giving pORAB01-3 great capacity for future widespread dissemination.
The brain’s response to radiation exposure is an important concern for patients undergoing cancer therapy and astronauts on long missions in deep space. We assessed whether this response is specific and prolonged and is linked to epigenetic mechanisms. We focused on the response of the hippocampus at early (2-weeks) and late (20-week) time points following whole body proton irradiation. We examined two forms of DNA methylation, cytosine methylation (5mC) and hydroxymethylation (5hmC). Impairments in object recognition, spatial memory retention, and network stability following proton irradiation were observed at the two-week time point and correlated with altered gene expression and 5hmC profiles that mapped to specific gene ontology pathways. Significant overlap was observed between DNA methylation changes at the 2 and 20-week time points demonstrating specificity and retention of changes in response to radiation. Moreover, a novel class of DNA methylation change was observed following an environmental challenge (i.e. space irradiation), characterized by both increased and decreased 5hmC levels along the entire gene body. These changes were mapped to genes encoding neuronal functions including postsynaptic gene ontology categories. Thus, the brain’s response to proton irradiation is both specific and prolonged and involves novel remodeling of non-random regions of the epigenome.


**PURPOSE:** We aimed to identify factors related to technical and clinical success of percutaneous revascularization for blunt renal arterial trauma. METHODS: All cases of percutaneous revascularization for blunt renal arterial trauma were searched in the available literature. We included a case of iatrogenic renal artery occlusion at our institution treated by percutaneous stenting 20 hours after injury. A pooled cohort analysis of percutaneous revascularization for blunt renal artery injury was then performed to analyze factors related to technical and clinical success. Clinical failure was defined as development of new hypertension, serum creatinine rise, or significant asymmetry in split renal function. RESULTS: A total of 53 cases have been reported, and 54 cases were analyzed including our case. Median follow-up was 6 months. Technical success was 88.9% and clinical success was 75%. Of 12 treatment failures (25%), 66.7% occurred during the first postprocedure month. Time from injury to revascularization was not a predictor of clinical success (OR=1.00, P = 0.681). Renal artery occlusion was significantly associated with clinical failure (OR=7.50, P = 0.017) and postintervention antiplatelet therapy was significantly associated with treatment success (OR=0.16, P = 0.043). At 37-month follow-up, the stented renal artery in our case remained patent and the patient was normotensive with preserved glomerular filtration rate. CONCLUSION: Percutaneous revascularization for blunt renal arterial injury resulted in relatively high technical and clinical success. Time-to-revascularization was independent of successful outcomes. Clinical success was significantly associated with a patent renal artery at the time of intervention and with postprocedure antiplatelet therapy.


**ABSTRACT:** Electrical and structural remodeling processes are contributors to the self-perpetuating nature of atrial fibrillation (AF). However, their correlation has not been clarified. In this study, human atrial tissues from the patients with rheumatic mitral valve disease in either sinus rhythm or persistent AF were analyzed using a combined transcriptomic and proteomic approach. An up-regulation in chloride intracellular channel (CLIC) 1, 4, 5 and a rise in type IV collagen were revealed. Combined with the results from immunohistochemistry and electron microscope analysis, the distribution of type IV collagen and effects of fibrosis on myocyte membrane indicated the possible interaction between CLIC and type IV collagen, confirmed by protein structure prediction and co-immunoprecipitation. These results indicate that CLICs play an important role in the development of atrial fibrillation and that CLICs and structural type IV collagen may interact on each other to promote the development of AF in rheumatic mitral valve disease.
OBJECTIVES: Oesophageal squamous cell carcinoma (OSCC) is an aggressive malignancy and the major histological subtype of oesophageal cancer. Although recent large-scale genomic analysis has improved the description of the genetic abnormalities of OSCC, few targetable genomic lesions have been identified, and no molecular therapy is available. This study aims to identify druggable candidates in this tumour. DESIGN: High-throughput small-molecule inhibitor screening was performed to identify potent anti-OSCC compounds. Whole-transcriptome sequencing (RNA-Seq) and chromatin immunoprecipitation sequencing (ChIP-Seq) were conducted to decipher the mechanisms of action of CDK7 inhibition in OSCC. A variety of in vitro and in vivo cellular assays were performed to determine the effects of candidate genes on OSCC malignant phenotypes. RESULTS: The unbiased high-throughput small-molecule inhibitor screening led us to discover a highly potent anti-OSCC compound, THZ1, a specific CDK7 inhibitor. RNA-Seq revealed that low-dose THZ1 treatment caused selective inhibition of a number of oncogenic transcripts. Notably, further characterisation of the genomic features of these THZ1-sensitive transcripts demonstrated that they were frequently associated with super-enhancer (SE). Moreover, SE analysis alone uncovered many OSCC lineage-specific master regulators. Finally, integrative analysis of both THZ1-sensitive and SE-associated transcripts identified a number of novel OSCC oncogenes, including PAK4, RUNX1, DNAJB1, SREBF2 and YAP1, with PAK4 being a potential druggable kinase. CONCLUSIONS: Our integrative approaches led to a catalogue of SE-associated master regulators and oncogenic transcripts, which may significantly promote both the understanding of OSCC biology and the development of more innovative therapies.

Extended-spectrum beta-lactase (ESBL)-producing Enterobacteriaceae strains are increasing in prevalence worldwide. Carbapenem antibiotics are used as a first line of therapy against ESBL-producing Enterobacteriaceae. We examined a cohort of critical care patients for gastrointestinal colonization with carbapenem-resistant ESBL-producing strains (CR-ESBL strains). We cultured samples from this cohort of patients for ESBL-producing Klebsiella spp. and Escherichia coli and then tested the first isolate from each patient for susceptibility to imipenem, doripenem, meropenem, and ertapenem. Multilocus sequence typing was performed on isolates that produced an ESBL and that were carbapenem resistant. Among all patients admitted to an intensive care unit (ICU), 4% were positive for an ESBL-producing isolate and 0.64% were positive for a CR-ESBL strain on surveillance culture. Among the first ESBL-producing E. coli and Klebsiella isolates from the patients’ surveillance cultures, 11.2% were carbapenem resistant. Sequence type 14 (ST14), ST15, ST42, and ST258 were the dominant sequence types detected in this cohort of patients, with ST15 and ST258 steadily increasing in prevalence from 2006 to 2009. Patients colonized by a CR-ESBL strain were significantly more likely to receive antipseudomonal and anti-methicillin-resistant Staphylococcus aureus (anti-MRSA) therapy prior to ICU admission than patients colonized by carbapenem-susceptible ESBL-producing strains. They were also significantly more likely to have received a cephalosporin or a carbapenem antibiotic than patients colonized by carbapenem-susceptible ESBL-producing strains. In conclusion, in a cohort of patients residing in intensive care units within the United States, we found that 10% of the isolates were resistant to at least one carbapenem antibiotic. The continued emergence of carbapenem-resistant ESBL-producing strains is of significant concern, as infections due to these organisms are notoriously difficult to treat.
KEY POINTS: In fetuses, chronic anaemia stimulates cardiac growth; simultaneously, blood flow to the heart muscle itself is increased, and reserve blood flow capacity of the coronary vascular bed is preserved. Here we examined functional adaptations of the capillaries and small blood vessels responsible for delivering oxygen to the anemic fetal heart muscle using contrast-enhanced echocardiography. We demonstrate that coronary microvascular flux rate doubled in anaemic fetuses compared to control fetuses, both at rest and during maximal flow, suggesting reduced microvascular resistance consistent with capillary widening. Cardiac fractional microvascular blood volume was not greater in anaemic fetuses, suggesting that growth of new microvascular vessels does not contribute to the increased flow per volume of myocardium. These unusual changes in microvascular function during anaemia may indicate novel adaptive strategies in the fetal heart.

ABSTRACT: Fetal anaemia causes cardiac adaptations that have immediate and life-long repercussions on heart function and health. It is known that resting and maximal coronary conductance both increase during chronic fetal anaemia, but the coronary microvascular changes responsible for the adaptive response are unknown. Until recently, technical limitations have prevented quantifying functional capillary-level adaptations in the in vivo fetal heart. Our objective was to characterise functional microvascular adaptations in chronically anaemic fetal sheep. Chronically instrumented fetuses were randomized to a control group (n = 11) or were made anaemic by isovolumetric haemorrhage (n = 12) for 1 week prior to myocardial contrast echocardiography at 85% of gestation. Anaemia augmented cardiac mass by 23% without changing body weight. In anaemic fetuses, microvascular blood flow per volume of myocardium was twice that of control fetuses at rest, during vasodilatory hyperaemia, and during hyperaemia plus increased aortic pressure. The elevated blood flow was attributable almost entirely to an increase in microvascular blood flux rate whereas microvascular blood volumes were not different between groups at baseline, during hyperaemia, or with hyperaemia plus increased aortic pressure. Increased coronary microvascular flux rate in response to chronic fetal anaemia is consistent with expected reductions in capillary resistance from capillary diameter widening detected in earlier histological studies.

We have developed a carbon-based, fast-response potentiometric pH microsensor for use as a scanning electrochemical microscopy (SECM) chemical probe to quantitatively map the microbial metabolic exchange between two bacterial species, commensal Streptococcus gordonii and pathogenic Streptococcus mutans. The 25 mum diameter H+ ion-selective microelectrode showed a Nernstian slope of 59 mV/pH and high selectivity against major ions such Na+, K+, Ca2+, and Mg2+. In addition, the unique conductive membrane composition aided us in performing an amperometric approach curve to position the probe and obtain a high-resolution pH map of the microenvironment produced by the lactate-producing S. mutans biofilm. The x-directional pH scan over S. mutans also showed the influence of the pH profile on the metabolic activity of another species, H2O2-producing S. gordonii. When these bacterial species were placed in close spatial proximity, we observed an initial increase in the local H2O2 concentration of approximately 12 +/- 5 muM above S. gordonii, followed by a gradual decrease in H2O2 concentration (>30 min) to almost zero as lactate was produced, and a subsequent decrease in pH with a more pronounced metabolic output of S. mutans. These results were supported by gene expression and confocal fluorescence microscopic studies. Our findings illustrate that H2O2-producing S. gordonii is dominant while the buffering capacity of saliva is valid (approximately pH 6.0) but is gradually taken over by S. mutans as the latter species slowly starts decreasing the local pH to 5.0 or less by producing lactic acid. Our observations demonstrate the unique capability of our SECM chemical probes for studying real-time metabolic interactions between two bacterial species, which would not otherwise be achievable in traditional assays.


Accurate detection and characterization of liver observations to enable HCC diagnosis and staging using LI-RADS requires a technically adequate imaging exam. To help achieve this objective, LI-RADS has proposed technical requirements for CT, MR, and contrast-enhanced ultrasound of liver. This article reviews the technical requirements for liver imaging, including the description of minimum acceptable technical standards, such as the scanner hardware requirements, recommended dynamic imaging phases, and common technical challenges of liver imaging.


Caspases perform critical functions in both living and dying cells; however, how caspases perform physiological functions without killing the cell remains unclear. Here we identify a novel physiological function of caspases at the cortex of Drosophila salivary glands. In living glands, activation of the initiator caspase dronc triggers cortical F-actin dismantling, enabling the glands to stretch as they accumulate secreted products in the lumen. We demonstrate that tango7, not the canonical Apaf-1-adaptor dark, regulates dronc activity at the cortex; in contrast, dark is required for cytoplasmic activity of dronc during salivary gland death. Therefore, tango7 and dark define distinct subcellular domains of caspase activity. Furthermore, tango7-dependent cortical dronc activity is initiated by a sublethal pulse of the inhibitor of apoptosis protein (IAP) antagonist reaper. Our results support a model in which biological outcomes of caspase activation are regulated by differential amplification of IAP antagonists, unique caspase adaptor proteins, and mutually exclusive subcellular domains of caspase activity. Caspases are known for their role in cell death, but they can also participate in other physiological functions without killing the cells. Here the authors show that unique caspase adaptor proteins can regulate caspase activity within mutually-exclusive and independently regulated subcellular domains.


Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system and the most common non-traumatic cause of disability in young adults. Recent research shows that vascular disease risk factors (VDRFs) such as obesity, smoking, hyperlipidemia, hypertension, type II diabetes mellitus, and metabolic syndrome, can influence MS on its onset, disease activity, progression, and resultant disability. This review evaluates the current knowledge on the role of VDRFs on outcomes among people with MS (PwMS) and shows that while VDRF prevalence may or may not be higher among PwMS compared with the general population, its presence can influence MS in myriad ways. Management of VDRFs through early detection and treatment may be a promising approach to improving outcomes in PwMS. © 2017, Touch Briefings. All rights reserved.

Manduca sexta, known as the tobacco hornworm or Carolina sphinx moth, is a lepidopteran insect that is used extensively as a model system for research in insect biochemistry, physiology, neurobiology, development, and immunity. One important benefit of this species as an experimental model is its extremely large size, reaching more than 10 g in the larval stage. M. sexta larvae feed on solanaceous plants and thus must tolerate a substantial challenge from plant allelochemicals, including nicotine. We report the sequence and annotation of the M. sexta genome, and a survey of gene expression in various tissues and developmental stages. The Msex_1.0 genome assembly resulted in a total genome size of 419.4 Mbp. Repetitive sequences accounted for 25.8% of the assembled genome. The official gene set is comprised of 15,451 protein-coding genes, of which 2498 were manually curated. Extensive RNA-seq data from many tissues and developmental stages were used to improve gene models and for insights into gene expression patterns. Genome wide synteny analysis indicated a high level of macrosynteny in the Lepidoptera. Annotation and analyses were carried out for gene families involved in a wide spectrum of biological processes, including apoptosis, vacuole sorting, growth and development, structures of exoskeleton, egg shells, and muscle, vision, chemosensation, ion channels, signal transduction, neuropeptide signaling, neurotransmitter synthesis and transport, nicotine tolerance, lipid metabolism, and immunity. This genome sequence, annotation, and analysis provide an important new resource from a well-studied model insect species and will facilitate further biochemical and mechanistic experimental studies of many biological systems in insects.


OBJECTIVE: The objective was to describe the efficacy of medical abortion using mifepristone and misoprostol for gestations less than 6 weeks. STUDY DESIGN: We searched PubMed and Cochrane databases for articles in any language that examined the success of mifepristone and misoprostol abortion at gestational ages <42 days. Data were independently abstracted by two authors and graded for evidence quality. A pooled analysis of efficacy and a summary odds ratio of abortion failure of <42 days' gestation compared with gestational week 42-49 days were performed for randomized trials as well as for prospective studies. RESULTS: Six randomized controlled trials and nine prospective observational studies met inclusion criteria. Included studies varied greatly in regimens of mifepristone and misoprostol used, and assessment of and timing of outcome of abortion. A pooled proportion of the randomized trials estimated a proportion of unsuccessful abortion of 0.02 (95% confidence interval 0.01-0.03). In the prospective studies, the proportions ranged between 0.02 and 0.17, with considerable heterogeneity in the pooled estimate. However, the two largest observational studies reflected the estimates of the randomized trials (range 0.02-0.03). The summary odds ratios indicated that the odds of unsuccessful abortion were not significantly different between gestational age groups (<42 days versus >42-49 days). DISCUSSION: These analyses support the use of medical abortion at gestational ages <42 days. Efficacy rates are high overall and appear to reflect those observed during the seventh week of pregnancy. Women who prefer to initiate treatment as soon as early pregnancy is diagnosed may do so without delay. IMPLICATIONS: Women can expect success using medical abortion regimens as soon as pregnancy is diagnosed; further research of abortion outcomes disaggregated by gestational age and visualization of the gestational sac is warranted.


OBJECTIVES: Traditionally, the urinary tract has been thought to be sterile in the absence of a clinically identifiable infection. However, recent evidence suggests that the urinary tract harbors a variety of bacterial species, known collectively as the urinary microbiome, even when clinical cultures are negative. Whether these bacteria promote urinary health or contribute to urinary tract disease remains unknown. Emerging evidence indicates that a shift in the urinary microbiome may play an important role in urgency urinary incontinence (UUI). The goal of this prospective pilot study was to determine how the urinary microbiome is different between women with and without UUI. We also sought to identify if characteristics of the urinary
microbiome are associated with UUI severity. METHODS: We collected urine from clinically well-characterized women with UUI (n = 10) and normal bladder function (n = 10) using a transurethral catheter to avoid bacterial contamination from external tissue. To characterize the resident microbial community, we amplified the bacterial 16S rRNA gene by PCR and performed sequencing using Illumina MiSeq. Sequences were processed using the workflow package QIIME. We identified bacteria that had differential relative abundance between UUI and controls using DESeq2 to fit generalized linear models based on the negative binomial distribution. We also identified relationships between the diversity of the urinary microbiome and severity of UUI symptoms with Pearson’s correlation coefficient. RESULTS: We successfully extracted and sequenced bacterial DNA from 95% of the urine samples and identified that there is a polymicrobial community in the female bladder in both healthy controls and women with UUI. We found the relative abundance of 14 bacteria significantly differed between control and UUI samples. Furthermore, we established that an increase in UUI symptom severity is associated with a decrease in microbial diversity in women with UUI. CONCLUSIONS: Our study provides further characterization of the urinary microbiome in both healthy controls and extensively phenotyped women with UUI. Our results also suggest that the urinary microbiome may play an important role in the pathophysiology of UUI and that the loss of microbial diversity may be associated with clinical severity.


BACKGROUND: Recent evidence suggests that exposure to intrauterine inflammation causes acute fetal brain injury and is linked to a spectrum of neurobehavioral disorders. In a rodent model of intrauterine inflammation induced by lipopolysaccharide (LPS) exposure in utero, activated microglia can be detected in the hippocampus of offspring survivors, as late as 60 days postnatal (DPN). Given that the hippocampus is important for learning and memory, these results suggest that in utero inflammation underlies long-term cognitive deficits observed in children/survivors. METHODS: An established mouse model of LPS-induced intrauterine inflammation was used to study hippocampal function from offspring at 44-59 DPN. Microgliosis was examined at 45 DPN. Extracellular field recordings of synaptic transmission were performed on acute hippocampal slices. RESULTS: LPS offspring mice displayed persistent microglial activation and increased CA3-CA1 excitatory synaptic strength, which can be explained in part by an increase in the probability of glutamate release, and reduced long-term synaptic potentiation compared to control mice. CONCLUSIONS: These results offer a mechanistic explanation for the cognitive and behavioral deficits observed in survivors of preterm birth caused by intrauterine inflammation.


Hematopoietic cell transplantation (HCT) is a potentially curative treatment for children and adults with malignant and non-malignant diseases. Despite increasing survival rates, long-term morbidity following HCT is substantial. Neurocognitive dysfunction is a serious cause of morbidity, yet little is known about neurocognitive dysfunction following HCT. To address this gap, collaborative efforts of the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation undertook an expert review of neurocognitive dysfunction following HCT. In this review, we define what constitutes neurocognitive dysfunction, characterize its risk factors and sequelae, describe tools and methods to assess neurocognitive function in HCT recipients, and discuss possible interventions for HCT patients with this condition. This review aims to help clinicians understand the scope of this health-related problem, highlight its impact on well-being of survivors, and to help determine factors that may improve identification of patients at risk for declines in cognitive functioning after HCT. In particular, we review strategies for preventing and treating neurocognitive dysfunction in HCT patients. Lastly, we highlight the
need for well-designed studies to develop and test interventions aimed at preventing and improving neurocognitive dysfunction and its sequelae following HCT.


BACKGROUND: Renin-angiotensin system (RAS) signaling and angiotensin-converting enzyme 2 (ACE2) have been implicated in the pathogenesis of acute respiratory distress syndrome (ARDS). We postulated that repleting ACE2 using GSK2586881, a recombinant form of human angiotensin-converting enzyme 2 (rhACE2), could attenuate acute lung injury. METHODS: We conducted a two-part phase II trial comprising an open-label intrapatient dose escalation and a randomized, double-blind, placebo-controlled phase in ten intensive care units in North America. Patients were between the ages of 18 and 80 years, had an American-European Consensus Criteria consensus diagnosis of ARDS, and had been mechanically ventilated for less than 72 h. In part A, open-label GSK2586881 was administered at doses from 0.1 mg/kg to 0.8 mg/kg to assess safety, pharmacokinetics, and pharmacodynamics. Following review of data from part A, a randomized, double-blind, placebo-controlled investigation of twice-daily doses of GSK2586881 (0.4 mg/kg) for 3 days was conducted (part B). Biomarkers, physiological assessments, and clinical endpoints were collected over the dosing period and during follow-up. RESULTS: Dose escalation in part A was well-tolerated without clinically significant hemodynamic changes. Part B was terminated after 39 of the planned 60 patients following a planned futility analysis. Angiotensin II levels decreased rapidly following infusion of GSK2586881, whereas angiotensin-(1-7) and angiotensin-(1-5) levels increased and remained elevated for 48 h. Surfactant protein D concentrations were increased, whereas there was a trend for a decrease in interleukin-6 concentrations in rhACE2-treated subjects compared with placebo. No significant differences were noted in ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, oxygenation index, or Sequential Organ Failure Assessment score. CONCLUSIONS: GSK2586881 was well-tolerated in patients with ARDS, and the rapid modulation of RAS peptides suggests target engagement, although the study was not powered to detect changes in acute physiology or clinical outcomes. TRIAL REGISTRATION: ClinicalTrials.gov, NCT01597635. Registered on 26 January 2012.


A piezo-scanning fiber endoscopic device architecture is proposed for 3D imaging or ablation. The endoscopic device consists of a piezoelectric membrane that is placed perpendicular to the optical axis, a fiber optic cable that extends out from and actuated by the piezoelectric membrane, and one or multiple lenses for beam delivery and collection. Unlike its counterparts that utilize piezoelectric cylinders for fiber actuation, the proposed architecture offers quasi-static actuation in the axial direction along with resonant actuation in the lateral directions forming a 3D scanning pattern, allowing adjustment of the focus plane. The actuation of the four-quadrant piezoelectric membrane involves driving of two orthogonal electrodes with AC signals for lateral scanning, while simultaneously driving all electrodes for axial scanning and focus adjustment. We have characterized piezoelectric membranes (5–15 mm diameter) with varying sizes to monitor axial displacement behavior with respect to applied DC voltage. We also demonstrate simultaneous lateral and axial actuation on a resolution target, and observe the change of lateral resolution on a selected plane through performing 1D cross-sectional images, as an indicator of focal shift through axial actuation. Based on experimental results, we identify the optical and geometrical parameters for optimal 3D imaging of tissue samples. Our findings reveal that a simple piezoelectric membrane, having comparable dimensions and drive voltage requirement with off-the-shelf MEMS scanner chips, offers tissue epithelial imaging with sub-cellular resolution © 2017 Elsevier B.V.
Piezoelectric actuated fiber-scanners have often been employed in optical imaging of tissues, owing to their compact size, low cost, and high resolution that is accompanied by high frame-rates. Typically having a circular cross-section, the dynamics of the scan pattern is determined by the fiber geometry and material properties. Having circular symmetry, a conventional fiber results in coupling between its orthogonal mechanical modes, as the stiffness along both orthogonal directions (x, y) are theoretically identical. Here, we utilize the mechanical asymmetry of polarization-maintaining fibers to break the circular symmetry and thus mitigate the warping effects in the scan pattern that is encountered in conventional fibers. Through simulations and experiments we observe distinct resonance frequencies difference (28 Hz, which is 6 times the FWHM of the frequency response) for the polarization maintaining fiber, whereas only a few Hz of difference is observed for the conventional fiber resonance frequencies between orthogonal directions that lead to a warped scan pattern. In return, in-resonance scanning of the polarization maintaining fiber produces a clean Lissajous pattern with a wide field of view. The proposed methodology is superior with respect to other studies, as it requires no extra components to be integrated to either the actuator or the fiber itself. Furthermore, it inherently enables polarization dependent imaging modalities without any extra component in the imaging path. © 1989-2012 IEEE.


A 78-year-old immunocompetent man presented with a 3-month history of painless decreased vision and panuveitis with a macular lesion presumed to be due to endogenous endophthalmitis. He had been treated with systemic, intravenous, and intravitreal antibiotics and antifungal agents as well as intravitreal steroids. A culture from a prior vitrectomy had grown a single colony of Aspergillus thought to be a contaminant. The macular lesion enlarged and caused a tractional retinal detachment. The patient underwent surgery including resection of what appeared to be an invasive retinal aspergilloma, from which polymerase chain reaction and histopathology confirmed Aspergillus fumigatus.


This study explores whether for-profit home health agencies responded differently from non-profit agencies to financial incentives embedded in the Medicare prospective payment system. Agencies were able to receive higher reimbursement per patient under the prospective payment system if they adjusted the number of therapy visits or the type of visits for a two-month-long episode. Agencies could also increase reimbursement by treating a patient for multiple episodes of care, because prospective payments were made on a per-episode basis. Using the Medicare Claims and Provider of Services Files from 2001 to 2009, we examine differences between for-profit and non-profit agencies in these practice patterns during the first nine years of the prospective payment system. We find that for-profit agencies were more likely to adopt most of these practice patterns than were non-profit agencies. This finding suggests that for-profit agencies were more responsive to financial incentives, and therefore disproportionately contributed to the increase in Medicare home health spending under the prospective payment system. Policymakers could consider revising the current prospective payment system that gives agencies incentives to distort practice patterns regardless of a patient’s health care needs. Fiscal Studies © 2017 Institute for Fiscal Studies

BACKGROUND: The patient-centered medical home (PCMH) is a primary care delivery model predicated on shared responsibility for patient care among members of an interprofessional team. Effective task sharing may reduce burnout among primary care providers (PCPs). However, little is known about the extent to which PCPs share these responsibilities, and which, if any, of the primary care tasks performed independently by the PCPs (vs. shared with the team) are particularly associated with PCP burnout. A better understanding of the relationship between these tasks and their effects on PCP burnout may help guide focused efforts aimed at reducing burnout. OBJECTIVE: To investigate (1) the extent to which PCPs share responsibility for 14 discrete primary care tasks with other team members, and (2) which, if any, of the primary care tasks performed by the PCPs (without reliance on team members) are associated with PCP burnout. DESIGN: Secondary data analysis of Veterans Health Administration (VHA) survey data from two time periods. PARTICIPANTS: 327 providers from 23 VA primary care practices within one VHA regional network. MAIN MEASURES: The dependent variable was PCP report of burnout. Independent variables included PCP report of the extent to which they performed 14 discrete primary care tasks without reliance on team members; team functioning; and PCP-, clinic-, and system-level variables. KEY RESULTS: In adjusted models, PCP reports of intervening on patient lifestyle factors and educating patients about disease-specific self-care activities, without reliance on their teams, were significantly associated with burnout (intervening on lifestyle: b = 4.11, 95% CI = 0.39, 7.83, p = 0.03; educating patients: b = 3.83, 95% CI = 0.33, 7.32, p = 0.03). CONCLUSIONS: Performing behavioral counseling and self-management education tasks without relying on other team members for assistance was associated with PCP burnout. Expanding the roles of nurses and other healthcare professionals to assume responsibility for these tasks may ease PCP burden and reduce burnout.


Several reports have described excitatory GABA transmission in the suprachiasmatic nucleus (SCN), the master pacemaker of circadian physiology. However, there is disagreement regarding the prevalence, timing, and neuronal location of excitatory GABA transmission in the SCN. Whether GABA is inhibitory or excitatory depends, in part, on the intracellular concentration of chloride ([Cl\textsuperscript{-}]). Here, using ratiometric Cl\textsuperscript{-} imaging, we have investigated intracellular chloride regulation in AVP and VIP-expressing SCN neurons and found evidence suggesting that [Cl\textsuperscript{-}] is higher during the day than during the night in both AVP+ and VIP+ neurons. We then investigated the contribution of the cation chloride cotransporters to setting [Cl\textsuperscript{-}] in these SCN neurons and found that the chloride uptake transporter NKCC1 contributes to [Cl\textsuperscript{-}] regulation in SCN neurons, but that the KCCs are the primary regulators of [Cl\textsuperscript{-}] in SCN neurons. Interestingly, we observed that [Cl\textsuperscript{-}] is differentially regulated between AVP+ and VIP+ neurons-a low concentration of the loop diuretic bumetanide had differential effects on AVP+ and VIP+ neurons, while blocking the KCCs with VU0240551 had a larger effect on VIP+ neurons compared to AVP+ neurons.


BACKGROUND/AIMS: Intraoperative imaging allows near-real-time assessment of stereotactic accuracy during implantation of deep brain stimulation (DBS) electrodes. Such technology can be used to examine factors impacting stereotactic error. METHODS: Intraoperative CT imaging was reviewed in patients undergoing DBS placement at Oregon Health and Sciences University. Coordinates of the target electrode were compared to the operative plan to characterize the magnitude and direction of stereotactic error with respect to side of implantation, target, and electrode approach angles. RESULTS: One hundred sixty-nine leads in 94 patients were examined. Targets were GPi (n = 86), STN (n = 31), and Vim (n = 52). The average Euclidean error was 1.63 mm (SD 0.87). The error magnitude was higher for Vim (1.95 mm) than for GPi (1.44 mm), while STN (1.65 mm) did not differ from either Vim or GPi (ANOVA: F = 6.15, p = 0.003). Electrodes targeting Vim and
STN were significantly more likely to deviate medially compared to those targeting GPi (ANOVA: F = 9.13, p < 0.001). The coronal approach angle affected the error when targeting Vim (rho = 0.338, p = 0.01). These findings were confirmed during multivariate analyses. CONCLUSIONS: This study shows a significant effect of target on the accuracy of electrode placement for DBS. Targeting Vim results in a greater Euclidean error and a greater medial deviation off target. These systematic deviations should be taken into account during electrode implantation.


OBJECTIVES: Acute liver failure (ALF) is classically defined by coagulopathy and hepatic encephalopathy (HE); however, acute liver injury (ALI), i.e., severe acute hepatocyte necrosis without HE, has not been carefully defined nor studied. Our aim is to describe the clinical course of specifically defined ALI, including the risk and clinical predictors of poor outcomes, namely progression to ALF, the need for liver transplantation (LT) and death. METHODS: 386 subjects prospectively enrolled in the Acute Liver Failure Study Group registry between 1 September 2008 through 25 October 2013, met criteria for ALI: International Normalized Ratio (INR)>/=2.0 and alanine aminotransferase (ALT)>/=10 x elevated (irrespective of bilirubin level) for acetaminophen (N-acetyl-p-aminophenol, APAP) ALI, or INR>/>=2.0, ALT>/=10x elevated, and bilirubin>/=3.0 mg/dl for non-APAP ALI, both groups without any discernible HE. Subjects who progressed to poor outcomes (ALF, death, LT) were compared, by univariate analysis, with those who recovered. A model to predict poor outcome was developed using the random forest (RF) procedure. RESULTS: Progression to a poor outcome occurred in 90/386 (23%), primarily in non-APAP (71/179, 40%) vs. only 14/194 (7.2%) in APAP patients comprising 52% of all cases (13 cases did not have an etiology assigned; 5 of whom had a poor outcome). Of 82 variables entered into the RF procedure: etiology, bilirubin, INR, APAP level and duration of jaundice were the most predictive of progression to ALF, LT, or death. CONCLUSIONS: A majority of ALI cases are due to APAP, 93% of whom will improve rapidly and fully recover, while non-APAP patients have a far greater risk of poor outcome and should be targeted for early referral to a liver transplant center.


Background: The recent Fukushima Nuclear Power Plant accident was one of more than 200 serious nuclear/radiation incidents (accidents and disasters) that occurred worldwide since 1945. The current Fukushima disaster is in the recovery phase with the decreasing levels of radiation in the environment. However, fears and stigma related to the perceived risk of radiation exposure persist among the general population. Introduction: To improve on students’ preparedness for social and public health challenges after a radiation incidence, radiation education was provided for undergraduate public health nursing students. Aim: This case study reports the development and implementation of the first class of radiation education in public health nursing, as well as students’ reflections on their class experience. Methods: We included a 90-min radiation class in an undergraduate public health nursing course in Tokyo, Japan. Lectures/discussion on technical and environmental aspects provided the minimally essential content for basic radiation knowledge. After class, all the 65 students were invited to freely write their reflections on the class. With their consent, 61 students’ anonymous written accounts were qualitatively analysed. Results: Five themes emerged: awareness of ignorance about radiation, problems produced by the mass media, becoming knowledgeable about radiation, public health nurses’ role, and trustful and enjoyable lecture. Discussion: The class inspired students to consider social, psychological and relational aspects of knowing and not knowing about radiation and their future professional role. Conclusion and implications for nursing: Once radiation is taught at school, nursing students will emerge as professionals with the belief that radiation is within their professional purview. Education is key to disaster prevention, preparation, response and recovery. Given the ubiquitous nature of health challenges after a radiation incident, radiation education is indispensable for nursing students worldwide. © 2016 International Council of Nurses
The purpose of this report is to provide guidance on the use of otoacoustic emissions (OAEs) as a clinical trial outcome measure for pharmaceutical interventions developed to prevent acquired hearing loss secondary to cochlear insult. OAEs are a rapid, noninvasive measure that can be used to monitor cochlear outer hair cell function. Serial monitoring of OAEs is most clearly established for use in hearing conservation and ototoxicity monitoring programs in which they exhibit more frequent and earlier changes compared with pure-tone audiometry. They also show promise in recent human trials of otoprotectants. Questions remain, however, concerning the most appropriate OAE protocols to use and what constitutes a "significant" OAE response change. Measurement system capabilities are expanding and test efficacy will vary across locations and patient populations. Yet, standardizing minimal measurement criteria and reporting of results is needed including documentation of test-retest variability so that useful comparisons can be made across trials. It is also clear that protocols must be theoretically sound based on known patterns of damage, generate valid results in most individuals tested, be accurate, repeatable, and involve minimal time. Based on the potential value added, OAEs should be included in clinical trials when measurement conditions and time permit.

The Residency Review Committee in Emergency Medicine requires residency programs to deliver at least 5 hours of weekly didactics. Achieving at least a 70 % average attendance rate per resident is required for residency program accreditation, and is used as a benchmark for residency graduation in our program. We developed a web-based, asynchronous curriculum to replace 1 hour of synchronous didactics, and hypothesized that the curriculum would be feasible to implement, well received by learners, and improve conference participation. This paper describes the feasibility and learner acceptability of a longitudinal asynchronous curriculum, and describes its impact on postgraduate year-1(PGY-1) resident conference participation and annual in-training examination scores. Using formal curriculum design methods, we developed modules and paired assessment exercises to replace 1 hour of weekly didactics. We measured feasibility (development and implementation time and costs) and learner acceptability (measured on an anonymous survey). We compared pre- and post-intervention conference participation and in-service training examination scores using a two sample t test. The asynchronous curriculum proved feasible to develop and implement. PGY-1 resident conference participation improved compared to the pre-intervention year (85.6 vs. 62 %; 95 % CI 0.295-0.177; p < 0.001). We are unable to detect a difference between in-training examination results in either the PGY-1 group or across all residents by the introduction of this intervention. 18/31 (58 %) residents completed the post-intervention survey. 83 % reported satisfaction with curriculum changes. Strengths of the curriculum included clarity and timeliness of assignments. Weaknesses included technical difficulties with the online platform. Our curriculum is feasible to develop and implement. Despite technical difficulties, residents report high satisfaction with this new curriculum. Among PGY-1 residents there is improved conference participation compared to the prior year.

Genetic risk factors for autism spectrum disorder (ASD) have yet to be fully elucidated. Postzygotic mosaic mutations (PMMs) have been implicated in several neurodevelopmental disorders and overgrowth syndromes. By leveraging whole-exome sequencing data on a large family-based ASD cohort, the Simons Simplex


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Background - Out-of-hospital cardiac arrest (OHCA) commonly presents with non-shockable rhythms (asystole and pulseless electrical activity (PEA)). Whether antiarrhythmic drugs are safe and effective when these evolve to shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia (VF/VT)) during resuscitation is not known. Methods - Adults with non-traumatic OHCA, vascular access and VF/VT anytime after >1 shock(s) were prospectively randomized, double-blind, to receive amiodarone, lidocaine or placebo by paramedics. Patients presenting with initial shock-refractory VF/VT were previously reported. The current study was a pre-specified analysis in a separate cohort who initially presented with non-shockable OHCA and were randomized upon subsequently developing shock-refractory VF/VT. The primary outcome was survival to hospital discharge; secondary outcomes included discharge functional status and adverse drug-related effects. Results - Of 37,889 patients with OHCA, 3,026 with initial VF/VT and 1,063 with initial non-shockable-turned-shockable rhythms were treatment-eligible, randomized and received their assigned drug. Baseline characteristics among non-shockable-turned-shockable patients were balanced across treatment arms except that placebo recipients included fewer men and were less likely to receive bystander-CPR. Active-drug recipients in this cohort required fewer shocks, supplemental doses of their assigned drug and ancillary antiarrhythmic drugs than placebo-recipients (p<0.05). In all, 16 (4.1%) amiodarone, 11 (3.1%) lidocaine and 6 (1.9%) placebo-treated patients survived to hospital discharge (p=0.24). There was no significant interaction of treatment assignment and discharge survival with the initiating OHCA rhythm (asystole, PEA, or VF/VT); survival in each of these categories was consistently higher with active-drugs, though the trends were not statistically significant. Adjusted absolute differences (95% confidence interval) in survival from non-shockable-turned-shockable arrhythmias with amiodarone vs placebo were 2.3% (-0.3, 4.8), p=0.08 and for lidocaine vs placebo 1.2% (-1.1, 3.6), p=0.30. Over one-half of these survivors were functionally independent or required minimal assistance. Drug-related adverse effects were infrequent. Conclusions - Outcome from non-shockable-turned-shockable OHCA is poor, but not invariably fatal. Though not statistically significant, point estimates for survival were greater after amiodarone or lidocaine than placebo, without increased risk of adverse effects or disability, and consistent with previously observed favorable trends from treatment of initial shock-refractory VF/VT with these drugs. Together the findings may signal a clinical benefit that invites further investigation. Clinical Trial Registration - URL: ClinicalTrials.gov Unique Identifier: NCT01401647.

Collection, we systematically evaluated the potential role of PMMs in autism risk. Initial re-evaluation of published single-nucleotide variant (SNV) de novo mutations showed evidence consistent with putative PMMs for 11% of mutations. We developed a robust and sensitive SNV PMM calling approach integrating complementary callers, logistic regression modeling, and additional heuristics. In our high-confidence call set, we identified 470 PMMs in children, increasing the proportion of mosaic SNVs to 22%. Probands have a significant burden of synonymous PMMs and these mutations are enriched for computationally predicted impacts on splicing. Evidence of increased missense PMM burden was not seen in the full cohort. However, missense burden signal increased in subcohorts of families where probands lacked nonsynonymous germline mutations, especially in genes intolerant to mutations. Parental mosaic mutations that were transmitted account for 6.8% of the presumed de novo mutations in the children. PMMs were identified in previously implicated high-confidence neurodevelopmental disorder risk genes, such as CHD2, CTNNB1, SCN2A, and SYNGAP1, as well as candidate risk genes with predicted functions in chromatin remodeling or neurodevelopment, including ACTL6B, BAZ2B, COL5A3, SSRP1, and UNC79. We estimate that PMMs potentially contribute risk to 3%-4% of simplex ASD case subjects and future studies of PMMs in ASD and related disorders are warranted.

**OBJECTIVE:** To compare strategies for the timing of delivery in women with breast cancer and known cancer stage or hormone receptor subtype, and to determine the optimal gestational age for induction in regards to maternal-fetal outcomes. **STUDY DESIGN:** A decision-analytic model was designed comparing eight different strategies for scheduled delivery at 30, 31, 32, 33, 34, 35, 36, and 37 weeks gestation. Optimal breast cancer treatment was assumed to be delayed until after delivery. Baseline estimates of the stage- and subtype-specific mortality and the impact of delayed cancer treatment on 5-year survival rates were obtained from the literature. Outcomes factored into the model included the risk of intrauterine fetal demise, spontaneous delivery, respiratory distress syndrome, cerebral palsy, and neonatal demise at each gestational age. Univariate sensitivity analyses and Monte Carlo simulations were performed to test the robustness of our model. **RESULTS:** For women with stage I-II breast cancer, delivery at 36 weeks yielded the highest number of overall quality-adjusted life years (QALYs), while maternal QALYs were maximized with delivery at 34 weeks. For stage III and IV disease, maternal QALYs were maximized at 31 and 30 weeks, respectively. For women with estrogen or progesterone receptor-positive, human epidermal receptor-2 negative breast cancer, both maternal QALYs and overall QALYs were maximized with delivery at 36 weeks. More aggressive biological phenotypes were similarly associated with optimal delivery at decreasing gestational age. Our model was heavily driven by the baseline probability of maternal death within 5 years, in addition to the expected progression of disease and decreases in survival rates with each week of non-treatment, and remained robust across reasonable ranges for all variables of interest. **CONCLUSIONS:** For women with breast cancer diagnosed during pregnancy, decisions regarding timing of delivery should take into consideration both cancer stage and hormone receptor subtype.


**INTRODUCTION:** Dupilumab significantly improves signs and symptoms of atopic dermatitis (AD), including pruritus, symptoms of anxiety and depression, and health-related quality of life versus placebo in adults with moderate-to-severe AD. Since the cost-effectiveness of dupilumab has not been evaluated, the objective of this analysis was to estimate a value-based price range in which dupilumab would be considered cost-effective compared with supportive care (SC) for treatment of moderate-to-severe AD in an adult population. **METHODS:** A health economic model was developed to evaluate from the US payer perspective the long-term costs and benefits of dupilumab treatment administered every other week (q2w). Dupilumab q2w was compared with SC; robustness of assumptions and results were tested using sensitivity and scenario analyses. Clinical data were derived from the dupilumab LIBERTY AD SOLO trials; healthcare use and cost data were from health insurance claims histories of adult patients with AD. The annual price of maintenance therapy with dupilumab to be considered cost-effective was estimated for decision thresholds of US$100,000 and $150,000 per quality-adjusted life-year (QALY) gained. **RESULTS:** In the base case, the annual maintenance price for dupilumab therapy to be considered cost-effective would be $28,770 at a $100,000 per QALY gained threshold, and $39,940 at a $150,000 threshold. Results were generally robust to parameter variations in one-way and probabilistic sensitivity analyses. **CONCLUSION:** Dupilumab q2w compared with SC is cost-effective for the treatment of moderate-to-severe AD in US adults at an annual price of maintenance therapy in the range of $29,000-$40,000 at the $100,000-$150,000 per QALY thresholds. **FUNDING:** Sanofi and Regeneron Pharmaceuticals, Inc.
OBJECTIVE Cervical curvature is an important factor when deciding between laminoplasty and laminectomy with posterior spinal fusion (LPSF) for cervical spondylotic myelopathy (CSM). This study compares outcomes following laminoplasty and LPSF in patients with matched postoperative cervical lordosis. METHODS Adults undergoing laminoplasty or LPSF for cervical CSM from 2011 to 2014 were identified. Matched cohorts were obtained by excluding LPSF patients with postoperative cervical Cobb angles outside the range of laminoplasty patients. Clinical outcomes and radiographic results were compared. A subgroup analysis of patients with and without preoperative pain was performed, and the effects of cervical curvature on pain outcomes were examined. RESULTS A total of 145 patients were included: 101 who underwent laminoplasty and 44 who underwent LPSF. Preoperative Nurick scale score, pain incidence, and visual analog scale (VAS) neck pain scores were similar between the two groups. Patients who underwent LPSF had significantly less preoperative cervical lordosis (5.8 degrees vs 10.9 degrees, p = 0.018). Preoperative and postoperative C2-C7 sagittal vertical axis (SVA) and T-1 slope were similar between the two groups. Laminoplasty cases were associated with less blood loss (196.6 vs 325.0 ml, p < 0.001) and trended toward shorter hospital stays (3.5 vs 4.3 days, p = 0.054). The peroperative complication rate was 8.3%; there was no significant difference between the groups. LPSF was associated with a higher long-term complication rate (11.6% vs 2.2%, p = 0.039), with pseudarthrosis accounting for 3 of 5 complications in the LPSF group. Follow-up cervical Cobb angle was similar between the groups (8.8 degrees vs 7.1 degrees, p = 0.454). At final follow-up, LPSF had a significantly lower mean Nurick score (0.9 vs 1.4, p = 0.014). Among patients with preoperative neck pain, pain incidence (36.4% vs 31.3%, p = 0.629) and VAS neck pain (2.1 vs 1.8, p = 0.731) were similar between the groups. Similarly, in patients without preoperative pain, there was no significant difference in pain incidence (19.4% vs 18.2%, p = 0.926) and VAS neck pain (1.0 vs 1.1, p = 0.908). For laminoplasty, there was a significant trend for lower pain incidence (p = 0.010) and higher cervical lordosis, especially when greater than 20 degrees (p = 0.011 and p = 0.018). Mean follow-up was 17.3 months. CONCLUSIONS For patients with CSM, LPSF was associated with slightly greater blood loss and a higher long-term complication rate, but offered greater neurological improvement than laminoplasty. In cohorts of matched follow-up cervical sagittal alignment, pain outcomes were similar between laminoplasty and LPSF patients. However, among laminoplasty patients, greater cervical lordosis was associated with better pain outcomes, especially for lordosis greater than 20 degrees. Cervical curvature (lordosis) should be considered as an important factor in pain outcomes following posterior decompression for multilevel CSM.
Lysine 4 trimethylation of histone H3, which are well-established chromatin marks for active transcription. Our results suggest that Sdp1/2 function as crucial transcriptional coactivators for LIM complexes to specify spinal neuronal identities during development.


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


BACKGROUND: Caregivers are thought to play a major role in helping patients first appraise and then respond to heart failure (HF) symptoms. AIMS: The aims of this study were to: (a) characterise distinct patterns of HF patient-caregiver dyads with respect to symptom appraisal; and (b) link dyadic symptom appraisal to contributions to self-care and caregiver strain. METHODS AND RESULTS: A cross-sectional dyadic descriptive design was used to capture patient and caregiver appraisal of patient HF symptoms (i.e. dyspnoea, fatigue, pain and anxiety). Contributions to self-care were measured using patient and caregiver versions of the Self-Care of Heart Failure Index and the European Heart Failure Self-care Behaviour Scale. Caregiver strain was measured using the Multidimensional Caregiver Strain Index. Multilevel and latent class mixture modelling (LCMM) were used to examine distinct patterns of symptom appraisal. Two patterns of dyadic symptom appraisal were identified: one pattern (n = 24; 38.7%) wherein caregivers appraised patients’ symptoms as being significantly worse than did the patient (labelled as ‘Caregiver > Patient’); and a second pattern (n = 38; 61.3%) wherein patients appraised their symptoms similar to or worse than that as perceived by their caregiver (labelled as ‘Patient Caregiver’). Dyads in the Caregiver > Patient pattern of symptom appraisal reported much better contributions to self-care (symptom response behaviours only), but also greater caregiver strain, compared with dyads in the Patient Caregiver pattern. Greater patient depression and older caregiver age were significant determinants of fitting the Patient Caregiver pattern. CONCLUSION: Differences in how HF patients and caregivers appraise symptoms together must be taken into consideration when examining contributions to HF care and caregiver outcomes.

PURPOSE: The main purposes of the study were to investigate the endocrine function of ovarian tissue transplanted to heterotopic subcutaneous sites and the reproductive competence and telomere length of a nonhuman primate originating from transplanted tissue. METHODS: Ovarian cortex pieces were transplanted into the original rhesus macaques in the arm subcutaneously, in the abdomen next to muscles, or in the kidney. Serum estradiol (E2) and progesterone (P4) concentrations were measured weekly for up to 8 years following tissue transplantation. A monkey derived from an oocyte in transplanted ovarian tissue entered time-mated breeding and underwent controlled ovarian stimulation. Pregnancy and offspring were evaluated. Telomere lengths and oocytes obtained following controlled ovarian stimulation were assessed. RESULTS: Monkeys with transplants in the arm and abdomen had cyclic E2 of 100 pg/ml, while an animal with arm transplants had E2 of 50 pg/ml. One monkey with transplants in the abdomen and kidney had ovulatory cycles for 3 years. A monkey derived from an oocyte in transplanted tissue conceived and had a normal gestation until intrapartum fetal demise. She conceived again and delivered a healthy offspring at term. Controlled ovarian stimulations of this monkey yielded mature oocytes comparable to controls. Her telomere length was long relative to controls. CONCLUSIONS: Heterotopic ovarian tissue transplants yielded long-term endocrine function in macaques. A monkey derived from an oocyte in transplanted tissue was reproductively competent. Her telomere length did not show epigenetically induced premature cellular aging. Ovarian tissue transplantation to heterotopic sites for fertility preservation should move forward cautiously, yet optimistically.


Despite a poor toxicity profile, zidovudine supersedes abacavir (ABC) as an alternative first-line agent in most international treatment guidelines because of concerns about HLA-B*57:01-related ABC-hypersensitivity. We detected one case of HLA-B*57:01 carriage among 513 HIV-infected individuals in Uganda, which, in combination with previous reports, supports the safety of ABC in the region.


Dynamic susceptibility contrast-magnetic resonance imaging (DSC-MRI) is widely used to obtain informative perfusion imaging biomarkers, such as the relative cerebral blood volume (rCBV). The related post-processing software packages for DSC-MRI are available from major MRI instrument manufacturers and third-party vendors. One unique aspect of DSC-MRI with low-molecular-weight gadolinium (Gd)-based contrast reagent (CR) is that CR molecules leak into the interstitium space and therefore confound the DSC signal detected. Several approaches to correct this leakage effect have been proposed throughout the years. Amongst the most popular is the Boxerman-Schmainda-Weisskoff (BSW) K2 leakage correction approach, in which the K2 pseudo-first-order rate constant quantifies the leakage. In this work, we propose a new method for the BSW leakage correction approach. Based on the pharmacokinetic interpretation of the data, the commonly adopted R2 * expression accounting for contributions from both intravascular and extravasating CR components is transformed using a method mathematically similar to Gjedde-Patlak linearization. Then, the leakage rate constant (KL ) can be determined as the slope of the linear portion of a plot of the transformed data. Using the DSC data of high-molecular-weight (~750 kDa), iron-based, intravascular Ferumoxytol (FeO), the pharmacokinetic interpretation of the new paradigm is empirically validated. The
primary objective of this work is to empirically demonstrate that a linear portion often exists in the graph of the transformed data. This linear portion provides a clear definition of the Gd CR pseudo-leakage rate constant, which equals the slope derived from the linear segment. A secondary objective is to demonstrate that transformed points from the initial transient period during the CR wash-in often deviate from the linear trend of the linearized graph. The inclusion of these points will have a negative impact on the accuracy of the leakage rate constant, and even make it time dependent.


Vascular smooth muscle cells (VSMCs) represent important modulators of plaque stability in advanced lesions. We previously reported that loss of small proline-rich repeat protein 3 (Sprr3), leads to VSMC apoptosis in a PI3K/Akt-dependent manner and accelerates lesion progression. Here, we investigated the role of Sprr3 in modulating plaque stability in hyperlipidemic ApoE-/− mice. We show that loss of Sprr3 increased necrotic core size and reduced cap collagen content of atheromas in brachiocephalic arteries with evidence of plaque rupture and development of intraluminal thrombi. Moreover, Sprr3-/−/ApoE-/− mice developed advanced coronary artery lesions accompanied by intraplaque hemorrhage and left ventricle microinfarcts. SPRR3 is known to reduce VSMC survival in lesions by promoting their apoptosis. In addition, we demonstrated that Sprr3-/− VSMCs displayed reduced expression of procollagen in a PI3K/Akt dependent manner. SPRR3 loss also increased MMP gelatinase activity in lesions, and increased MMP2 expression, migration and contraction of VSMCs independently of PI3K/Akt. Consequently, Sprr3 represents the first described VSMC modulator of each of the critical features of cap stability, including VSMC numbers, collagen type I synthesis, and protease activity through Akt dependent and independent pathways.


We report a case of severe type I hyperlipoproteinemia caused by autoimmunity against lipoprotein lipase (LPL) in the context of presymptomatic Sjögren’s syndrome. A 7-year-old mixed race (Caucasian/African American) girl was admitted to the intensive care unit at Vanderbilt Children’s Hospital with acute pancreatitis and shock. She was previously healthy aside from asthma and history of Hashimoto’s thyroiditis. Admission triglycerides (TGs) were 2191 mg/dL but returned to normal during the hospital stay and in the absence of food intake. At discharge, she was placed on a low-fat, low-sugar diet. She did not respond to fibrates, prescription fish oil, metformin, or orlistat, and during the following 2 years, she was hospitalized several times with recurrent pancreatitis. Except for a heterozygous mutation in the promoter region of LPL, predicted to have no clinical significance, she had no further mutations in genes known to affect TG metabolism and to cause inherited type I hyperlipoproteinemia, such as APOA5, APOC2, GPIHBP1, or LMF1. When her TG levels normalized after incidental use of prednisone, an autoimmune mechanism was suspected. Immunoblot analyses showed the presence of autoantibodies to LPL in the patient’s plasma. Autoantibodies to LPL decreased by 37% while patient was on prednisone, and by 68% as she subsequently transitioned to hydroxychloroquine monotherapy. While on hydroxychloroquine, she underwent a supervised high-fat meal challenge and showed normal ability to metabolize TG. For the past 3 years and 6 months, she has had TG consistently <250 mg/dL, and no symptoms of, or readmissions for, pancreatitis.


We propose a cause-specific quantile residual life regression where the cause-specific quantile residual life, defined as the inverse of the cumulative incidence function of the residual life distribution of a specific type of events of interest conditional on a fixed time point, is log-linear in observable covariates. The proposed test statistic
for the effects of prognostic factors does not involve estimation of the improper probability density function of the cause-specific residual life distribution under competing risks. The asymptotic distribution of the test statistic is derived. Simulation studies are performed to assess the finite sample properties of the proposed estimating equation and the test statistic. The proposed method is illustrated with a real dataset from a clinical trial on breast cancer. © The Author(s) 2017.


Lymphatic vessels lie at the interface between peripheral sites of pathogen entry, adaptive immunity, and the systemic host. Though the paradigm is that their open structure allows for passive flow of infectious particles from peripheral tissues to lymphoid organs, virus applied to skin by scarification does not spread to draining lymph nodes. Using cutaneous infection by scarification, we analyzed the effect of viral infection on lymphatic transport and evaluated its role at the host-pathogen interface. We found that, in the absence of lymphatic vessels, canonical lymph-node-dependent immune induction was impaired, resulting in exacerbated pathology and compensatory, systemic priming. Furthermore, lymphatic vessels decouple fluid and cellular transport in an interferon-dependent manner, leading to viral sequestration while maintaining dendritic cell transport for immune induction. In conclusion, we found that lymphatic vessels balance immune activation and viral dissemination and act as an "innate-like" component of tissue host viral defense.


AMPARs mediate the briefest synaptic currents in the brain by virtue of their rapid gating kinetics. However, at the mossy fiber-to-unipolar brush cell synapse in the cerebellum, AMPAR-mediated EPSCs last for hundreds of milliseconds, and it has been proposed that this time course reflects slow diffusion from a complex synaptic space. We show that upon release of glutamate, synaptic AMPARs were desensitized by transmitter by >90%. As glutamate levels subsequently fell, recovery of transmission occurred due to the presence of the AMPAR accessory protein stargazin that enhances the AMPAR response to low levels of transmitter. This gradual increase in receptor activity following desensitization accounted for the majority of synaptic transmission at this synapse. Moreover, the amplitude, duration, and shape of the synaptic response was tightly controlled by plasma membrane glutamate transporters, indicating that clearance of synaptic glutamate during the slow EPSC is dictated by an uptake process.


BACKGROUND: Alopecia can occur in captive non-human primates, but its etiology is poorly understood. The purpose of this study was to assess alopecia and hair cortisol in rhesus monkeys and to identify the potential risk factors. METHODS: Subjects were 117 rhesus monkeys at two National Primate Research Centers. Photographs and hair samples were obtained during routine physicals. Photographs were analyzed using Image J software to calculate hair loss, and hair samples were assayed for cortisol. RESULTS: Age, days singly housed, and their interactions contributed to the alopecia model for both facilities. Sex and location changes contributed to the hair cortisol model for Facility 1; sedations contributed for Facility 2. Alopecia and hair cortisol were associated at Facility 1. CONCLUSIONS: Captive management practices can affect alopecia and
hair cortisol. However, there are facility differences in the relationship between alopecia and hair cortisol and in the effect of intrinsic variables and management procedures.


OBJECTIVES: The life-threatening context of heart failure (HF), high variability of the illness and complexity of care place considerable demands on both the adult patient and his/her spouse. The current study examines the role of congruent engagement in HF management behaviors on the depressive symptoms of the couple living with HF. METHOD: A cross-sectional design was used to examine 60 couples living with HF. Multilevel modeling was used to examine partner and within-dyad effects of engagement in HF behaviors on depressive symptoms. RESULTS: Just over one quarter (27%) of couples had both members experiencing at least mild depressive symptoms. Controlling for stage of HF and one’s own level of engagement, one’s partner’s level of engagement was significantly associated with one’s level of depressive symptoms; higher levels of engagement by one’s partner were associated with lower levels of depressive symptoms. Additionally, spouses had lower levels of depressive symptoms when they had similar levels of engagement to their partner with HF; spouses had higher levels of depressive symptoms when they had higher levels of engagement than their partner with HF. CONCLUSION: Findings confirm the importance of screening both members of the couple for depression and fostering collaboration within the couple.


Deficits in social communication, particularly pragmatic language, are characteristic of individuals with autism spectrum disorder (ASD). Speech disfluencies may serve pragmatic functions such as cueing speaking problems. Previous studies have found that speakers with ASD differ from typically developing (TD) speakers in the types and patterns of disfluencies they produce, but fail to provide sufficiently detailed characterizations of the methods used to categorize and quantify disfluency, making cross-study comparison difficult. In this study we propose a simple schema for classifying major disfluency types, and use this schema in an exploratory analysis of differences in disfluency rates and patterns among children with ASD compared to TD and language impaired (SLI) groups. 115 children ages 4-8 participated in the study (ASD = 51; SLI = 20; TD = 44), completing a battery of experimental tasks and assessments. Measures of morphological and syntactic complexity, as well as word and disfluency counts, were derived from transcripts of the Autism Diagnostic Observation Schedule (ADOS). High inter-annotator agreement was obtained with the use of the proposed schema. Analyses showed ASD children produced a higher ratio of content to filler disfluencies than TD children. Relative frequencies of repetitions, revisions, and false starts did not differ significantly between groups. TD children also produced more cued disfluencies than ASD children.


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.


Mesenchymal stem cells (MSCs) have been considered as a potential source for cell-based therapies in arthritic diseases for both their chondrogenic and anti-inflammatory properties. Thus, we examined how MSC-based neocartilage responds to tumour necrosis factor alpha (TNF-alpha) compared to articular chondrocyte (AC)-based neocartilage. Since oxygen tension is altered in arthritic joints, we also examined how increased oxygen tension influences this process. Monolayer-expanded healthy human ACs and bone marrow MSCs were cultured in chondrogenic medium in three-dimensional culture under hypoxia. They were then exposed to TNF-alpha under hypoxic or increased oxygen tension. We found no inherent anti-inflammatory potential of MSC-derived neocartilage as it pertains to the enzymes studied here: more degradative enzymes were upregulated by TNF-alpha in MSCs than in ACs, regardless of the oxygen tension. MSCs were also more sensitive to reoxygenation during TNF-alpha exposure, as indicated by increased proteoglycan loss, increased aggrecanase-generated metabolites, and further upregulation of the major aggrecanases, ADAMTS4 and ADAMTS5. There was also evidence of matrix metalloproteinase (MMP)-mediated aggrecan interglobular domain cleavage and type II collagen loss in response to TNF-alpha in both MSCs and ACs, but more MMPs were further upregulated by reoxygenation in MSCs than in ACs. Our study provides further evidence that consideration of oxygen tension is essential for studying cartilage degradation; for example, neocartilage produced from MSCs may be more sensitive to the negative effects of repeated hypoxia/reoxygenation events than AC-derived neocartilage. Consideration of the differences in responses may be important for cell-based therapies and selection of adjunctive chondroprotective agents.


Background: Musculoskeletal pain is associated with increased fall risk among older men. However, the association of back pain, the most prevalent type of pain in this population, and fall risk is unknown. Methods: We conducted a prospective investigation among 5,568 community-dwelling U.S. men at least 65 years of age from the Osteoporotic Fractures in Men Study (MrOS). Baseline questionnaires inquired about back pain and its location (such as low back), severity, and frequency in the past year. During 1 year of follow-up, falls were summed from self-reports obtained every 4 months. Outcomes were recurrent falls (>1 = 2 falls) and any fall (>1 = 1 fall). Associations of back pain and fall risk were estimated with risk ratios (RRs) and 95% confidence intervals (CIs) from multivariable log-binomial regression models adjusted for age, dizziness, arthritis, knee pain, urinary symptoms, self-rated health, central nervous system medication use, and instrumental activities of daily living. Results: Most (67%) reported any back pain in the past year. During follow-up, 11% had recurrent falls and 25% fell at least once. Compared with no back pain, any back pain was associated with elevated recurrent fall risk (multivariable RR = 1.3, 95% CI: 1.1, 1.5). Multivariable RRs for 1, 2, and 3+ back pain locations were, respectively, 1.2 (95% CI: 1.0, 1.5), 1.4 (1.1, 1.8), and 1.7 (95% CI: 1.3, 2.2). RRs were also elevated for back pain severity and frequency. Back pain was also associated with risk of any fall. Conclusions: Among older men, back pain is independently associated with increased fall risk.

DNA methylation is a central regulator of genome function, and altered methylation patterns are indicative of biological aging and mortality. Age-related cellular, biochemical, and molecular changes in the hippocampus lead to cognitive impairments and greater vulnerability to neurodegenerative disease that varies between the sexes. The role of hippocampal epigenomic changes with aging in these processes is unknown as no genome-wide analyses of age-related methylation changes have considered the factor of sex in a controlled animal model. High-depth, genome-wide bisulfite sequencing of young (3 month) and old (24 month) male and female mouse hippocampus revealed that while total genomic methylation amounts did not change with aging, specific sites in CG and non-CG (CH) contexts demonstrated age-related increases or decreases in methylation that were predominantly sexually divergent. Differential methylation with age for both CG and CH sites was enriched in intergenic and intronic regions and under-represented in promoters, CG islands, and specific enhancer regions in both sexes, suggesting that certain genomic elements are especially labile with aging, even if the exact genomic loci altered are predominantly sex-specific. Lifelong sex differences in autosomal methylation at CG and CH sites were also observed. The lack of genome-wide hypomethylation, sexually divergent aging response, and autosomal sex differences at CG sites was confirmed in human data. These data reveal sex as a previously unappreciated central factor of hippocampal epigenomic changes with aging. In total, these data demonstrate an intricate regulation of DNA methylation with aging by sex, cytosine context, genomic location, and methylation level.


INTRODUCTION: We explored acceptability and feasibility of safer conception methods among HIV-affected couples in Uganda. METHODS: We recruited HIV-positive men and women on antiretroviral therapy (ART) (‘index’) from the Uganda Antiretroviral Rural Treatment Outcomes cohort who reported an HIV-negative or unknown-serostatus partner (‘partner’), HIV-serostatus disclosure to partner, and personal or partner desire for a child within two years. We conducted in-depth interviews with 40 individuals from 20 couples, using a narrative approach with tailored images to assess acceptability of five safer conception strategies: ART for the infected partner, pre-exposure prophylaxis (PrEP) for the uninfected partner, condomless sex timed to peak fertility, manual insemination, and male circumcision. Translated and transcribed data were analyzed using thematic analysis. RESULTS: 11/20 index participants were women, median age of 32.5 years, median of 2 living children, and 80% had HIV-RNA <400 copies/mL. Awareness of HIV prevention strategies beyond condoms and abstinence was limited and precluded opportunity to explore or validly assess acceptability or feasibility of safer conception methods. Four key partnership communication challenges emerged as primary barriers to engagement in safer conception care, including: (1) HIV-serostatus disclosure: Although disclosure was an inclusion criterion, partners commonly reported not knowing the index partner’s HIV status. Similarly, the partner’s HIV-serostatus, as reported by the index, was frequently inaccurate. (2) Childbearing intention: Many couples had divergent childbearing intentions and made incorrect assumptions about their partner’s desires. (3) HIV risk perception: Participants had disparate understandings of HIV transmission and disagreed on the acceptable level of HIV risk to meet reproductive goals. (4) Partnership commitment: Participants revealed significant discord in perceptions of partnership commitment. All four types of partnership miscommunication introduced constraints to autonomous reproductive decision-making, particularly for women. Such miscommunication was common, as only 2 of 20 partnerships in our sample were mutually-disclosed with agreement across all four communication themes. CONCLUSIONS: Enthusiasm for safer conception programming is growing. Our findings highlight the importance of addressing gendered partnership communication regarding HIV disclosure, reproductive goals, acceptable HIV risk, and commitment, alongside technical safer conception advice. Failing to consider partnership dynamics across these domains risks limiting reach, uptake, adherence to, and retention in safer conception programming.
This study describes short-term and long-term healthcare resource utilization (HRU) and costs following an allogeneic hematopoietic stem cell transplant (HSCT) in adult patients with diffuse large B-cell lymphoma (DLBCL) in a real-world setting. Among 101 patients with DLBCL receiving an allogeneic HSCT, HRU and direct healthcare costs for up to three years after the allogeneic HSCT are described. HRU and costs were substantial, with the most intensive HRU and highest healthcare costs observed during the first year after HSCT (38 inpatient days; 68 days with office visits and average healthcare costs of $455,741). Although HRU and costs decreased over time, they remained high even in the third year after HSCT (four inpatient days; 27 days with office visits and average healthcare costs of $72,957). Overall, this study showed that the economic burden following an allogeneic HSCT in DLBCL patients is significant.

Kaposi sarcoma (KS) is an unusual tumor composed of proliferating spindle cells that is initiated by infection of endothelial cells (EC) with KSHV, and develops most often in the setting of immunosuppression. Despite decades of research, optimal treatment of KS remains poorly defined and clinical outcomes are especially unfavorable in resource-limited settings. KS lesions are driven by pathological angiogenesis, chronic inflammation, and oncogenesis, and various in vitro cell culture models have been developed to study these processes. KS arises from KSHV-infected cells of endothelial origin, so EC-lineage cells provide the most appropriate in vitro surrogates of the spindle cell precursor. However, because EC have a limited in vitro lifespan, and as the oncogenic mechanisms employed by KSHV are less efficient than those of other tumorigenic viruses, it has been difficult to assess the processes of transformation in primary or telomerase-immortalized EC. Therefore, a novel EC-based culture model was developed that readily supports transformation following infection with KSHV. Ectopic expression of the E6 and E7 genes of human papillomavirus type 16 allows for extended culture of age- and passage-matched mock- and KSHV-infected EC and supports the development of a truly transformed (i.e., tumorigenic) phenotype in infected cell cultures. This tractable and highly reproducible model of KS has facilitated the discovery of several essential signaling pathways with high potential for translation into clinical settings.

Nationwide utilization of spinal stereotactic body radiotherapy (SBRT) is not known; to address this void, the National Cancer Data Base (NCDB) from 2004 to 2013 was used for analysis. Spinal SBRT was defined as 1-5 fractions (14-32Gy) delivered to the cervical, thoracic, lumbar or sacral spine. From 2004 to 2013, 1044 patients received spinal SBRT, most commonly in single-fraction (38%), three-fraction (26%) and five-fractions (25%). Metastatic spinal disease most commonly originated from the lung (34%), kidney (14%), and blood (9%). The most common insurance status receiving spinal SBRT was private (44%) followed by Medicare (43%), with Medicaid (8%) a distant third. Fifty-six percent of patients were male, and 55% of patients were younger than age 65. 80% of patients were Caucasian, with 13% being African-American. The vast majority (74%) of patients had no Charlson/Deyo comorbidities. The incidence of spinal SBRT gradually increased over time, rising from 2% to 20% of cases from 2004 to 2013. Comprising only 1.4% of spinal metastases radiation in 2004, SBRT rose to a 5.8% share in 2013. In conclusion, SBRT for spine metastases in the United States has more than quadrupled in utilization over a recent ten-year span. Although the majority of spinal SBRT is multi-fraction, the most popular fractionation scheme was single-fraction. It has been most commonly used for Caucasian men under age 65 with private/Medicare insurance and no comorbidities. By far the most
common origin of spinal metastases treated by SBRT was the lung, followed by renal cancer. These results provide a baseline for further prospective investigation.


Introduction: African Americans experience the highest burden of cancer incidence and mortality in the United States and have been persistently less likely to receive interventional care, even when such care has been proven superior to conservative management by randomized controlled trials. The presence of disparities in access to radiation therapy (RT) for African American cancer patients has rarely been examined in an expansive fashion. Methods and materials: An extensive literature search was performed using the PubMed database to examine studies investigating disparities in RT access for African Americans. Results: A total of 55 studies were found, spanning 11 organ systems. Disparities in access to RT for African Americans were most prominently study in cancers of the breast (23 studies), prostate (7 studies), gynecologic system (5 studies), and hematologic system (5 studies). Disparities in RT access for African Americans were prevalent regardless of organ system studied and often occurred independently of socioeconomic status. Fifty of 55 studies (91%) involved analysis of a population-based database such as Surveillance, Epidemiology and End Result (SEER; 26 studies), SEER-Medicare (5 studies), National Cancer Database (3 studies), or a state tumor registry (13 studies). Conclusions: African Americans in the United States have diminished access to RT compared with Caucasian patients, independent of but often in concert with low socioeconomic status. These findings underscore the importance of finding systemic and systematic solutions to address these inequalities to reduce the barriers that patient race provides in receipt of optimal cancer care. © 2017 The Authors.


The physician assistant (PA) profession’s first attempt to characterize the applicant pool for PA education began with publication of the first Annual Report on Physician Assistant Educational Programs in the United States in 1985. The methodology used in the report was limited, however, in identifying the number of unique applicants to PA programs. Collecting accurate and reliable data on the profession’s applicant pool was the primary motivator leading to initiation of the Central Application Service for Physician Assistants (CASPA) in 2001. In the past 15 years, CASPA has provided increasingly valuable data on the profession’s applicant pool, allowing for accurate tracking and analysis of trends in the growth and changing demographics of those applying to PA educational programs. This special report presents a unique analysis of CASPA data that relates the competitiveness of entry into PA programs with that experienced by our colleagues in medicine, for both Doctor of Medicine (MD) and Doctor or Osteopathic Medicine (DO) schools. We present data reflecting the most notable changing demographics of the profession’s applicant and matriculant pools in sex, age, grade point average, and health care experience. We use aggregate data of self-identified race descriptors to compare the contributions of PA, medical, and osteopathic medicine schools to the improvement of diversity within the health professions. To date, the applicant pool of PA programs seems to have kept pace with the expansion of existing programs and the development of new programs. This article poses serious questions for the profession to ponder, as the demographics of those entering PA education change and the number of PA graduates continues to grow.


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 neurons 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.


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

Purpose: Antibodies specific for inhibitory checkpoints PD-1 and CTLA-4 have shown impressive results against solid tumors. This has fueled interest in novel immunotherapy combinations to affect patients who remain refractory to checkpoint blockade monotherapy. However, how to optimally combine checkpoint blockade with agents targeting T-cell costimulatory receptors, such as OX40, remains a critical question.

Experimental Design: We utilized an anti-PD-1-refractory, orthotopically transplanted MMTV-PyMT mammary cancer model to investigate the antitumor effect of an agonist anti-OX40 antibody combined with anti-PD-1. As PD-1 naturally aids in immune contraction after T-cell activation, we treated mice with concurrent combination treatment versus sequentially administering anti-OX40 followed by anti-PD-1.

Results: The concurrent addition of anti-PD-1 significantly attenuated the therapeutic effect of anti-OX40 alone. Combination-treated mice had considerable increases in type I and type II serum cytokines and significantly augmented expression of inhibitory receptors or exhaustion markers CTLA-4 and TIM-3 on T cells. Combination treatment increased intratumoral CD4+ T-cell proliferation at day 13, but at day 19, both CD4+ and CD8+ T-cell proliferation was significantly reduced compared with untreated mice. In two tumor models, sequential combination of anti-OX40 followed by anti-PD-1 (but not the reverse order) resulted in significant increases in therapeutic efficacy. Against MMTV-PyMT tumors, sequential combination was dependent on both CD4+ and CD8+ T cells and completely regressed tumors in approximately 30% of treated animals.

Conclusions: These results highlight the importance of timing for optimized therapeutic effect with combination immunotherapies and suggest the testing of sequencing in combination immunotherapy clinical trials.

PURPOSE: It is essential that hospitals and health professionals establish systems to facilitate patients’ organ donation wishes. Donation education has been neither standardized nor systematic, and resources related to donation processes have not been widely accessible. This report describes 2 free, publicly available educational resources about the organ donation process created to advance the mission of basic education and improve donation processes within hospitals and health care systems. MATERIALS AND METHODS: Members of the Donor Management Task Force of the Organ Donation and Transplantation Alliance (the Alliance) and the Health Resources and Services Administration of the US Department of Health and Human Services convened annually in person and by teleconferencing during the year to develop 2 educational vehicles on organ donation. RESULTS: Two educational products were developed: the Organ Donation Toolbox, an online repository of documents and resources covering all aspects of the donation process, and the Educational Training Video that reviews the basic foundations of a successful hospital donation system. CONCLUSIONS: There is a need for more research and education about the process of organ donation as it relates to the medical and psychosocial care of patients and families before the end of life. The educational products described can help fill this critical need.


Normal blood flow is essential for proper heart formation during embryonic development, as abnormal hemodynamic load (blood pressure and shear stress) results in cardiac defects seen in congenital heart disease (CHD). However, the detrimental remodeling processes that relate altered blood flow to cardiac malformation and defects remain unclear. Heart development is a finely orchestrated process with rapid transformations that occur at the tissue, cell, and subcellular levels. Myocardial cells play an essential role in cardiac tissue maturation by aligning in the direction of stretch and increasing the number of contractile units as hemodynamic load increases throughout development. This study elucidates the early effects of altered blood flow on myofibril and mitochondrial configuration in the outflow tract myocardium in vivo. Outflow tract banding was used to increase hemodynamic load in the chicken embryo heart between Hamburger and Hamilton stages 18 and 24 (~24 h during tubular heart stages). 3D focused ion beam scanning electron microscopy analysis determined that increased hemodynamic load induced changes in the developing myocardium, characterized by thicker myofibril bundles that were more dispered in circumferential orientation, and mitochondria that organized in large clusters around the nucleus. Proteomic mass-spectrometry analysis quantified altered protein composition after banding that is consistent with altered myofibril thin filament assembly and function, and mitochondrial maintenance and organization. Additionally, pathway analysis of the proteomics data identified possible activation of signaling pathways in response to banding, including the renin-angiotensin system (RAS). Imaging and proteomic data combined indicate that myofibril and mitochondrial arrangement in early embryonic stages is a critical developmental process that when disturbed by altered blood flow may contribute to cardiac malformation and defects.


PURPOSE: To report a case of intratumoral gene expression profile discordance in a malignant uveal melanoma, associated with intratumoral heterogeneity based upon histopathologic features. METHODS: The clinical history, fundus findings, imaging and histopathologic features, and DecisionDx-UM gene expression profile results (Castle Biosciences, Inc., Phoenix, AZ, USA) of the tumor were reviewed. RESULTS: A trans-retinal fine-needle aspiration biopsy was performed for a thin, pigmented choroidal tumor in a 33-year-old man. Cells
obtained from this biopsy were tested using the DecisionDx-UM gene expression profile test and the tumor was classified as class 1A. Cytology confirmed melanoma. The patient subsequently elected to undergo enucleation. On microscopic examination of the globe, the tumor was composed primarily of spindle B cells, but had a focal area composed of epithelioid cells. This portion of the tumor was subsequently tested and demonstrated a class 1B gene expression profile. CONCLUSION: Intratumoral discordance in gene expression profile results has been described in uveal melanomas. Here we demonstrate that this discordance may be associated in some cases with intratumoral heterogeneity based upon histopathologic features.


Trace amine-associated receptor 1 (TAAR1) is activated by methamphetamine (MA) and modulates dopaminergic (DA) function. Although DA dysregulation is the hallmark of MA-induced neurotoxicity leading to behavioral and cognitive deficits, the intermediary role of TAAR1 has yet to be characterized. To investigate TAAR1 regulation of MA-induced neurotoxicity, Taar1 transgenic knock-out (KO) and wildtype (WT) mice were administered saline or a neurotoxic regimen of 4 i.p. injections, 2h apart, of MA (2.5, 5, or 10mg/kg). Temperature data were recorded during the treatment day. Additionally, striatal tissue was collected 2 or 7 days following MA administration for analysis of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanilllic acid (HVA), and tyrosine hydroxylase (TH) levels, as well as glial fibrillary acidic protein (GFAP) expression. MA elicited an acute hypothermic drop in body temperature in Taar1-WT mice, but not in Taar1-KO mice. Two days following treatment, DA and TH levels were lower in Taar1-KO mice compared to Taar1-WT mice, regardless of treatment, and were dose-dependently decreased by MA. GFAP expression was significantly increased by all doses of MA at both time points and greater in Taar1-KO compared to Taar1-WT mice receiving MA 2.5 or 5mg/kg. Seven days later, DA levels were decreased in a similar pattern: DA was significantly lower in Taar1-KO compared to Taar1-WT mice receiving MA 2.5 or 5mg/kg. TH levels were uniformly decreased by MA, regardless of genotype. These results indicate that activation of TAAR1 potentiates MA-induced hypothermia and TAAR1 confers sustained neuroprotection dependent on its thermoregulatory effects.


Parenteral nutrition-associated liver disease (PNALD) spectrum ranges from liver enzyme abnormalities to steatosis to fibrosis, and, eventually, cirrhosis from total parenteral nutrition (TPN). The pathophysiology is postulated to be multifactorial. Diagnosis in adults is primarily by exclusion, eliminating other causes of chronic liver disease or cirrhosis, and other factors seen in critically ill or postoperative patients on TPN. Principal treatment is avoiding TPN. If this is not feasible, research supports fish oil-based lipid emulsions in TPN formulations to reduce risk and progression of PNALD. With liver and intestinal failure, liver and intestine transplant is an option. © 2017 Elsevier Inc.


AIMS AND OBJECTIVES: The purpose of this study was to explore the meaning of patient-nurse interaction for older women receiving care in healthcare settings. BACKGROUND: Older women are often overlooked or
misunderstood by the nurses caring for them. Some research exists on nurses’ perception of their interaction with patients, yet few studies have described the meaning of such interaction from the patients’ perspective. METHODS: This was a pilot study using qualitative description as a methodology. Data were filtered through a lens of critical feminist theory to interpret interactions taking place in healthcare settings that are often characterised by paternalism. Seven women between the ages of 66 and 81 were interviewed using a semi-structured guide. RESULTS: Participants had a distinctive perspective on the experience of caring. Their expressions include stories of being cared for themselves by nurses as well as historical recalls of being the one-caring for family members. In these combined stories, the contrast between the nurses who held caring in primacy and those who were distinctly uncaring sheds light on the importance of cultivating a moral ideal of caring and respect for personhood. CONCLUSION: A population of older women who potentially face disabling conditions must rely on direct, meaningful, interaction with nurses to successfully navigate the healthcare system. The findings suggest that these women did not have consistent access to such interaction. IMPLICATIONS FOR PRACTICE: The gathering and interpretation of new narratives about patient-nurse interaction for older women could lead to a deeper understanding of power and civility as it impacts a caring relationship. Further research using a theoretical lens of critical feminism has implications for improving healthcare delivery for older women worldwide.


GABA is a principal neurotransmitter in the hypothalamic suprachiasmatic nucleus (SCN) that contributes to intercellular communication between individual circadian oscillators within the SCN network and the stability and precision of the circadian rhythms. GABA transporters (GAT) regulate the extracellular GABA concentration and modulate GABAA receptor (GABAAR)-mediated currents. GABA transport inhibitors were applied to study how GABAAR-mediated currents depend on the expression and function of GAT. Nipecotic acid inhibits GABA transport and induced an inward tonic current in concentration-dependent manner during whole-cell patch clamp recordings from SCN neurons. Application of either the selective GABA transporter 1 (GAT1) inhibitors NNC711 or SKF89976A, or the GABA transporter 3 (GAT3) inhibitor SNAP5114, produced only small changes of the baseline current. Co-application of GAT1 and GAT3 inhibitors induced a significant GABAAR-mediated tonic current that was blocked by gabazine. GAT inhibitors decreased the amplitude and decay time constant and increased the rise time of spontaneous GABAAR-mediated postsynaptic currents. However, inhibition of GAT did not alter the expression of either GAT1 or GAT3 in the hypothalamus. Thus, GAT1 and GAT3 functionally complement each other to regulate the extracellular GABA concentration and GABAAR-mediated synaptic and tonic currents in the SCN. Co-application of SKF89976A and SNAP5114 (50 microM each) significantly reduced the circadian period of Per1 expression in the SCN by 1.4 hours. Our studies demonstrate that GAT are important regulators of GABAAR-mediated currents and the circadian clock in the SCN.


BACKGROUND: Apnea of prematurity affects a small proportion but large absolute number of late preterm infants, with out-patient management variably utilized despite relative clinical equipoise and potential for improved cost-effectiveness. METHODS: Over a 5-y period, from 2009 to 2013, infants born at >/=34 weeks gestational age at a level IIIb academic center in Boston, Massachusetts, with discharge-delaying apnea, bradycardia, and desaturation (ABD) events were identified. In-patient costs for discharge-delaying ABD events were compared with hypothetical out-patient management. Out-patient costs took into account 4-10 d of in-patient observation for ABD events before caffeine initiation, 3-5 d of additional in-patient observation before discharge, daily caffeine until 43 weeks corrected gestational age, home pulse oximetry monitoring until 44 weeks corrected gestational age, and consideration of variable readmission rates ranging from 0 to 10%. RESULTS: A total of 425 late preterm and term infants were included in our analysis.
Utilization of hypothetical out-patient management resulted in cost savings per eligible patient ranging from $2,422 to $62, dependent upon variable periods of in-patient observation. Sensitivity analysis demonstrated few instances of decreased relative cost-effectiveness. CONCLUSIONS: Out-patient management of discharge-delaying ABD events in a late preterm and term population was a cost-effective alternative to prolonged in-patient observation.


Despite a wealth of evidence for the role of genetics in attention deficit hyperactivity disorder (ADHD), specific and definitive genetic mechanisms have not been identified. Pathway analyses, a subset of gene-set analyses, extend the knowledge gained from genome-wide association studies (GWAS) by providing functional context for genetic associations. However, there are numerous methods for association testing of gene sets and no real consensus regarding the best approach. The present study applied six pathway analysis methods to identify pathways associated with ADHD in two GWAS datasets from the Psychiatric Genomics Consortium. Methods that utilize genotypes to model pathway-level effects identified more replicable pathway associations than methods using summary statistics. In addition, pathways implicated by more than one method were significantly more likely to replicate. A number of brain-relevant pathways, such as RhoA signaling, glycosaminoglycan biosynthesis, fibroblast growth factor receptor activity, and pathways containing potassium channel genes, were nominally significant by multiple methods in both datasets. These results support previous hypotheses about the role of regulation of neurotransmitter release, neurite outgrowth and axon guidance in contributing to the ADHD phenotype and suggest the value of cross-method convergence in evaluating pathway analysis results. (c) 2016 Wiley Periodicals, Inc.


OBJECTIVE: To investigate predictors of time to metastasis among men treated with androgen deprivation therapy for nonmetastatic prostate cancer who developed castration-resistant prostate cancer (CRPC) within the Shared Equal Access Regional Cancer Hospital cohort. METHODS: This is a retrospective analysis of 458 nonmetastatic CRPC men. Metastases were detected in routine bone scans or other imaging tests. Predictors of time to metastasis were analyzed using proportional hazards model with CRPC as time zero. RESULTS: A total of 256 (56%) men were diagnosed with metastatic disease over a median follow-up of 36 months. Metastasis-free survival was 79%, 65%, 52%, 47%, and 41% at 1, 2, 3, 4, and 5 years after CRPC, respectively. In multivariable analysis, Gleason score 8-10 (hazard ratio [HR] = 1.61; P = .026), receiving primary localized treatment (HR = 1.38; P = .028), higher prostate-specific antigen (PSA) levels at CRPC diagnosis (logPSA HR = 1.64; P < .001), and PSA doubling time \(<\) 6 months (HR = 1.42; P = .040) were independently associated with shorter time to metastasis. Race, year of CRPC, age, and time from androgen deprivation therapy to CRPC were not associated with metastasis. CONCLUSION: Among nonmetastatic CRPC men, nearly 60% developed metastatic disease during the first 5 years, with most of the metastasis occurring within the first 3 years. Higher Gleason score, receiving primary treatment, higher PSA, and shorter PSA doubling time were independently associated with shorter time to metastasis. Therefore, these variables can be used to stratify patients according to metastasis risk.

Purposes: To establish the in silico ocular pharmacokinetic modeling for eye drops, and to simulate the dose regimen for FK962 in human choroid/retinal diseases. Methods: Pharmacokinetics for FK962 in vivo was performed by a single instillation of drops containing 0.1% 14C-FK962 in rabbit eyes. Permeation of FK962 across the cornea, sclera, and choroid/retina was measured in vitro. Neurite elongation by FK962 was measured in cultured rat retinal ganglion cells. Parameters from the experimental data were used in an improved in silico model of ocular pharmacokinetics of FK962 in man. Results: The mean concentration of FK962 in ocular tissues predicted by in silico modeling was consistent with in vivo results, validating the in silico model. FK962 rapidly penetrated into the anterior and posterior segments of the eye and then diffused into the vitreous body. The in silico pharmacokinetic modeling also predicted that a dose regimen of 0.0054% FK962 twice per day would produce biologically effective concentrations of FK962 in the choroid/retina, where FK962 facilitates rat neurite elongation. Conclusions: Our in silico model for ocular pharmacokinetics is useful (1) for predicting drug concentrations in specific ocular tissues after topical instillation, and (2) for suggesting the optimal dose regimens for eye drops. The pharmacodynamics for FK962 produced by this model may be useful for clinical trials against retinal neuropathy. © Copyright 2017, Mary Ann Liebert, Inc. 2017.


The working memory (WM) literature contains a number of tasks that vary on dimensions such as when or how memory items are reported. In addition to the ways in which WM tasks are designed to differ, tasks may also diverge according to the strategies participants use during task performance. The present study included seven tasks from the WM literature, each requiring short-term retention of verbal items. Following completion of a small number of trials from each task, individuals completed a self-report questionnaire to identify their primary strategy. Results indicated substantial variation across individuals for a given task, and within the same individual across tasks. Moreover, while direct comparisons between tasks showed that some tasks evinced similar patterns of strategy use despite differing task demands, others showed markedly different patterns of self-reported strategy use. A community detection algorithm, aimed at identifying groups of individuals based on their profile of strategic choices, revealed unique communities of individuals who are dependent on specific strategies under varying demands. Together, the findings suggest that researchers using common WM paradigms should very carefully consider the implications of variation in strategy use when interpreting their findings.


Central neural circuits orchestrate the homeostatic repertoire that maintains body temperature during environmental temperature challenges and alters body temperature during the inflammatory response. This review summarizes the experimental underpinnings of our current model of the CNS pathways controlling the principal thermoeffectors for body temperature regulation: cutaneous vasoconstriction controlling heat loss, and shivering and brown adipose tissue for thermogenesis. The activation of these effectors is regulated by parallel but distinct, effector-specific, core efferent pathways within the CNS that share a common peripheral thermal sensory input. Via the lateral parabrachial nucleus, skin thermal afferent input reaches the hypothalamic preoptic area to inhibit warm-sensitive, inhibitory output neurons which control heat production by inhibiting thermogenesis-promoting neurons in the dorsomedial hypothalamus that project to thermogenesis-controlling premotor neurons in the rostral ventromedial medulla, including the raphe pallidus, that descend to provide the excitation of spinal circuits necessary to drive thermogenic thermal effectors. A distinct population of warm-sensitive preoptic neurons controls heat loss through an inhibitory input to raphe pallidus sympathetic premotor neurons controlling cutaneous vasoconstriction. The model proposed for central thermoregulatory control provides a useful platform for further understanding of the functional organization of central thermoregulation and elucidating the hypothalamic circuitry and neurotransmitters involved in body temperature regulation.

Individuals who perform poorly on measures of the executive function of inhibition have higher anxious arousal in comparison to those with better performance. High anxious arousal is associated with a pro-inflammatory response. Chronically high anxious arousal and inflammation increase one’s risk of developing type 2 diabetes. We sought to evaluate anxious arousal and inflammation as underlying mechanisms linking inhibition with diabetes incidence. Participants (N=835) completed measures of cognitive abilities, a self-report measure of anxious arousal, and donated blood to assess interleukin-6 (IL-6) and glycerated hemoglobin (HbA1c). Individuals with low inhibition were more likely to have diabetes than those with high inhibition due to the serial pathway from high anxious arousal to IL-6. Findings remained when entering other indicators of cognitive abilities as covariates, suggesting that inhibition is a unique cognitive ability associated with diabetes incidence. On the basis of our results, we propose several avenues to explore for improved prevention and treatment efforts for type 2 diabetes.


β-adrenergic receptor (β-AR) blockers may be administered during acute myocardial infarction (MI), as they reduce energy demand through negative chronotropic and inotropic effects and prevent ischemia-induced arrhythmogenesis. However, the direct effects of β-AR blockers on ventricular electrophysiology and intracellular Ca2+ handling during ischemia remain unknown. Using optical mapping of transmembrane potential (with RH237) and sarcoplasmic reticulum (SR) Ca2+ (with the low-affinity indicator Fluo-5N AM), the effects of 15 min of regional ischemia were assessed in isolated rabbit hearts (n = 19). The impact of β-AR inhibition on isolated hearts was assessed by pre-treatment with 100 nM propranolol (Prop) prior to ischemia (n = 7). To control for chronotropy and inotropy, hearts were continuously paced at 3.3 Hz and contraction was inhibited with 20 μM blebbistatin. Untreated ischemic hearts displayed prototypical shortening of action potential duration (APD80) in the ischemic zone (IZ) compared to the non-ischemic zone (NI) at 10 and 15 min ischemia, whereas APD shortening was prevented with Prop. Untreated ischemic hearts also displayed significant changes in SR Ca2+ handling in the IZ, including prolongation of SR Ca2+ reuptake and SR Ca2+ alternans, which were prevented with Prop pre-treatment. At 5 min ischemia, Prop pre-treated hearts also showed larger SR Ca2+ release amplitude in the IZ compared to untreated hearts. These results suggest that even when controlling for chronotropic and inotropic effects, β-AR inhibition has a favorable effect during acute regional ischemia via direct effects on APD and Ca2+ handling. © 2017 Murphy, Wang, Wang, Domondon, Lang, Habecker, Myles and Ripplinger.
shortening of action potential duration (APD80) in the ischemic zone (IZ) compared to the non-ischemic zone (NJ) at 10 and 15 min ischemia, whereas APD shortening was prevented with Prop. Untreated ischemic hearts also displayed significant changes in SR Ca2+ handling in the IZ, including prolongation of SR Ca2+ reuptake and SR Ca2+ alternans, which were prevented with Prop pre-treatment. At 5 min ischemia, Prop pre-treated hearts also showed larger SR Ca2+ release amplitude in the IZ compared to untreated hearts. These results suggest that even when controlling for chronotropic and inotropic effects, beta-AR inhibition has a favorable effect during acute regional ischemia via direct effects on APD and Ca2+ handling.


Summary: Trimodality therapy for resectable esophageal and gastroesophageal junction cancers utilizing preoperative radiotherapy with concurrent carboplatin and paclitaxel-based chemotherapy is being increasingly utilized secondary to the results of the phase III CROSS trial. However, there is a paucity of reports of this regimen as a component of chemoradiotherapy in North America. We aim to report on our clinical experience using a modified CROSS regimen with higher radiotherapy doses. Patients with advanced (cT2–cT4 or node positive) esophageal or gastroesophageal junction carcinoma who received preoperative carboplatin/paclitaxel-based chemoradiotherapy with radiation doses of greater than 41.4 Gray (Gy) followed by esophagectomy were identified from an institutional database. Patient, imaging, treatment, and tumor response characteristics were analyzed. Twenty-four patients were analyzed. All but one tumor had adenocarcinoma histology. The median radiation dose was 50.4 Gy. Pathologic complete response was achieved in 29% of patients, with all receiving 50.4 Gy. Three early postoperative deaths were seen, due in part to acute respiratory distress syndrome and all three patients received 50–50.4 Gy. With a median follow-up of 9.4 months (23 days–2 years), median survival was 24 months. Trimodality therapy utilizing concurrent carboplatin/paclitaxel with North American radiotherapy doses appeared to have similar pathologic complete response rates compared with the CROSS trial, but may be associated with higher toxicity. Although the sample size is small and further follow-up is necessary, radiation doses greater than 41.4 Gy may not be warranted secondary to a potentially increased risk of severe radiation-induced acute lung injury. © 2015 International Society for Diseases of the Esophagus


BACKGROUND: Guidelines for nonoperative management (NOM) of high-grade pancreatic injuries in children have not been established, and wide practice variability exists. The purpose of this study was to evaluate common clinical strategies across multiple pediatric trauma centers to develop a consensus-based standard clinical pathway. METHODS: A multicenter, retrospective review was conducted of children with high-grade (American Association of Surgeons for Trauma grade III-V) pancreatic injuries treated with NOM between 2010 and 2015. Data were collected on demographics, clinical management, and outcomes. RESULTS: Eighty-six patients were treated at 20 pediatric trauma centers. Median age was 9 years (range, 1-18 years). The majority (73%) of injuries were American Association of Surgeons for Trauma grade III, 24% were grade IV, and 3% were grade V. Median time from injury to presentation was 12 hours and median ISS was 16 (range, 4-66). All patients had computed tomography scan and serum pancreatic enzyme levels at presentation, but serial enzyme level monitoring was variable. Pancreatic enzyme levels did not correlate with injury grade or pseudocyst development. Parenteral nutrition was used in 68% and jejunal feeds in 31%. Endoscopic retrograde cholangiopancreatogram was obtained in 25%. An organized peripancreatic fluid collection present for at least 7 days after injury was identified in 59% (42 of 71). Initial management of these included: observation 64%, percutaneous drain 24%, and endoscopic drainage 10% and needle aspiration 2%. Clear
Type 2 diabetes (T2DM) is associated with a significant increase in risk of non-vertebral fractures, but information on the vertebral fracture (VF) risk in subjects with T2DM, particularly among men, is lacking. Furthermore, it is not known whether spine bone mineral density (BMD) can predict the risk of vertebral fracture in T2DM. We sought to examine the effect of diabetes status on prevalent and incident vertebral fracture, and to estimate the effect of lumbar spine BMD (areal and volumetric) as a risk factor for prevalent and incident morphometric vertebral fracture in T2DM (n = 875) and non-diabetic men (n = 4679). We used data from the Osteoporotic Fractures in Men (MrOS) Study, which enrolled men aged >/=65 years. Lumbar spine areal BMD (aBMD) was measured with dual x-ray absorptiometry (DXA), and volumetric BMD (vBMD) by quantitative computed tomography (QCT). Prevalence (7.0% vs.7.7%) and incidence (4.4% vs.4.5%) of vertebral fracture were not higher in T2DM vs. non-diabetic men. The risk of prevalent (OR 1.05, 95% CI 0.78-1.40) or incident vertebral-fracture (OR 1.28 95%CI 0.81-2.00) was not higher in T2DM versus non-diabetic men in models adjusted for age, clinic site, race, BMI and aBMD. Higher spine aBMD was associated with lower risk of prevalent vertebral-fracture in T2DM (OR 0.55, 95% CI 0.48-0.63) and non-diabetic men (OR 0.66, 95% CI 0.5-0.88), (p for interaction = 0.24) and of incident vertebral-fracture in T2DM (OR 0.50, 95% CI 0.41-0.60) and non-diabetic men (OR 0.54, 95% CI 0.33-0.88), (p for interaction = 0.77). Results were similar for vBMD. In conclusion, T2DM was not associated with higher prevalent or incident vertebral-fracture in older men, even after adjustment for BMI and BMD. Higher spine aBMD and vBMD are associated with lower prevalence and incidence of vertebral fracture in T2DM as well as non-diabetic men. This article is protected by copyright. All rights reserved.


Short chain fatty acids (SCFA) are metabolites of intestinal bacteria resulting from fermentation of dietary fiber. SCFA are protective in various animal models of inflammatory disease. We investigated the effects of exogenous administration of SCFAs, particularly propionate, on uveitis using an inducible model of experimental autoimmune uveitis (EAU). Oral SCFA administration attenuated uveitis severity in a mouse strain-dependent manner through regulatory T cell induction among lymphocytes in the intestinal lamina propria (LPL) and cervical lymph nodes (CLN). SCFA also suppressed effector T cell induction in the CLN and mesenteric lymph nodes (MLN). Alterations in intestinal morphology and gene expression demonstrated in the EAU model prior to the onset of uveitis were blunted by oral SCFA administration. Using a Kaede transgenic mouse, we demonstrated enhanced leukocyte trafficking between the intestine and the eye in EAU. Propionate suppressed T effector cell migration between the intestine and the spleen in EAU Kaede mice. In conclusion, our findings support exogenous administration of SCFAs as a potential treatment strategy for uveitis through the stabilization of subclinical intestinal alterations that occur in inflammatory diseases including uveitis, as well as prevention of trafficking of leukocytes between the gastrointestinal tract and extra-intestinal tissues.


Type 2 diabetes (T2DM) is associated with a significant increase in risk of non-vertebral fractures, but information on the vertebral fracture (VFs) risk in subjects with T2DM, particularly among men, is lacking. Furthermore, it is not known whether spine bone mineral density (BMD) can predict the risk of vertebral-fracture in T2DM. We sought to examine the effect of diabetes status on prevalent and incident vertebral fracture, and to estimate the effect of lumbar spine BMD (areal and volumetric) as a risk factor for prevalent and incident morphometric vertebral fracture in T2DM (n = 875) and non-diabetic men (n = 4679). We used data from the Osteoporotic Fractures in Men (MrOS) Study, which enrolled men aged >/=65 years. Lumbar spine areal BMD (aBMD) was measured with dual x-ray absorptiometry (DXA), and volumetric BMD (vBMD) by quantitative computed tomography (QCT). Prevalence (7.0% vs.7.7%) and incidence (4.4% vs.4.5%) of vertebral fracture were not higher in T2DM vs. non-diabetic men. The risk of prevalent (OR 1.05, 95% CI 0.78-1.40) or incident vertebral-fracture (OR 1.28 95%CI 0.81-2.00) was not higher in T2DM versus non-diabetic men in models adjusted for age, clinic site, race, BMI and aBMD. Higher spine aBMD was associated with lower risk of prevalent vertebral-fracture in T2DM (OR 0.55, 95% CI 0.48-0.63) and non-diabetic men (OR 0.66, 95% CI 0.5-0.88), (p for interaction = 0.24) and of incident vertebral-fracture in T2DM (OR 0.50, 95% CI 0.41-0.60) and non-diabetic men (OR 0.54, 95% CI 0.33-0.88), (p for interaction = 0.77). Results were similar for vBMD. In conclusion, T2DM was not associated with higher prevalent or incident vertebral-fracture in older men, even after adjustment for BMI and BMD. Higher spine aBMD and vBMD are associated with lower prevalence and incidence of vertebral fracture in T2DM as well as non-diabetic men. This article is protected by copyright. All rights reserved.

Objectives: We explored the association between stressful life events and postpartum depressive symptoms among non-Hispanic American Indian and Alaska Native (AI/AN) mothers. Methods: We analyzed self-reports of stressful life events and depressive symptoms from 298 AI/AN respondents and conducted logistic regression to examine their association. Results: Of the AI/AN mothers who responded, 29.7% reported depressive symptoms during their second postpartum year. Partner-related and traumatic stressful life events were significantly associated with increased risk of postpartum depressive symptoms. Conclusions: AI/AN women should receive intensive screening for depression through the second postpartum year. Programs that address stressful life events may be part of a plan to decrease postpartum depression. © Centers for American Indian and Alaska Native Health Colorado School of Public Health/University of Colorado Anschutz Medical Campus.

INTRODUCTION: Underserved populations have been overlooked or underrepresented in research based on data from diabetes registries. We estimated diabetes prevalence using a cohort developed from the electronic health records of 3 networks of safety net clinics that provide care to underserved populations. METHODS: ADVANCE (Accelerating Data Value Across a National Community Health Center Network) is a partnership of the OCHIN Community Health Information Network (OCHIN), the Health Choice Network (HCN), and the Fenway Health Institute (FHI), representing 97 federally qualified health centers (FQHCs) and 744 clinic sites in 22 US states. Among 952,316 adults with a body mass index (BMI) measurement and at least 2 outpatient visits in 2012 to 2014, we calculated diabetes prevalence using outpatient diagnoses, diagnostic laboratory results, or dispenses of anti-hyperglycemic agents no more than 730 days apart. We calculated prevalence by age, sex, race, Hispanic ethnicity, and BMI class. RESULTS: The crude prevalence of diabetes was 14.4%. Men had a higher prevalence than women (16.5% vs 13.2%); diabetes prevalence increased across age categories. White patients had the lowest prevalence (11.4%) and Hawaiian/Pacific Islanders, the highest prevalence (21.9%), with prevalence ranging from 15.2% to 16.5% for other race/ethnicities. The association between BMI class and diabetes prevalence was similar across all racial/ethnic groups. CONCLUSION: The ADVANCE diabetes cohort offers an opportunity to conduct epidemiologic and comparative effectiveness research on underserved and underrepresented individuals, who have a higher prevalence of diabetes than the general US population.
effective drugs that inhibit PCSK9 have become available to the clinician, a better understanding of the biological roles of PCSK9 is warranted.


Most accelerator-based space radiation experiments have been performed with single ion beams at fixed energies. However, the space radiation environment consists of a wide variety of ion species with a continuous range of energies. Due to recent developments in beam switching technology implemented at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), it is now possible to rapidly switch ion species and energies, allowing for the possibility to more realistically simulate the actual radiation environment found in space. The present paper discusses a variety of issues related to implementation of galactic cosmic ray (GCR) simulation at NSRL, especially for experiments in radiobiology. Advantages and disadvantages of different approaches to developing a GCR simulator are presented. In addition, issues common to both GCR simulation and single beam experiments are compared to issues unique to GCR simulation studies. A set of conclusions is presented as well as a discussion of the technical implementation of GCR simulation.


We summarize content from the opening thematic session of the 20th anniversary meeting for Biomechanics and Neural Control of Movement (BANCOM). Scientific discoveries from the past 20 years of research are covered, highlighting the impacts of rapid technological, computational, and financial growth on motor control research. We discuss spinal-level communication mechanisms, relationships between muscle structure and function, and direct cortical movement representations that can be decoded in the control of neuroprostheses. In addition to summarizing the rich scientific ideas shared during the session, we reflect on research infrastructure and capacity that contributed to progress in the field, and outline unresolved issues and remaining open questions.


Interest in deep space exploration underlines the needs to investigate the effects of exposure to combined sources of space radiation. The lung is a target organ for radiation, and exposure to protons and heavy ions as radiation sources may lead to the development of degenerative disease and cancer. In this study, we evaluated the pro-fibrotic and epigenetic effects of exposure to protons (150 MeV/nucleon, 0.1 Gy) and heavy iron ions ((56)Fe, 600 MeV/nucleon, 0.5 Gy) alone or in combination (protons on Day 1 and (56)Fe on Day 2) in C57BL/6 male mice 4 weeks after irradiation. Exposure to (56)Fe, proton or in combination, did not result in histopathological changes in the murine lung. At the same time, combined exposure to protons and (56)Fe resulted in pronounced molecular alterations in comparison with either source of radiation alone. Specifically, we observed a substantial increase in the expression of cytokine Il13, loss of expression of DNA methyltransferase Dnmt1, and reactivation of LINE-1, SINE B1 retrotransposons, and major and minor satellites. Given the deleterious potential of the observed effects that may lead to development of chronic lung injury, pulmonary fibrosis, and cancer, future studies devoted to the investigation of the long-term effects of combined exposures to proton and heavy ions are clearly needed.

**PURPOSE:** To develop a complete and consistent prescription drug monitoring program (PDMP) data set for use by drug safety researchers in evaluating patterns of high-risk use and potential abuse of scheduled drugs.

**METHODS:** Using publically available data references from the US Food and Drug Administration and the Centers for Disease Control and Prevention, we developed a strategic methodology to assign drug categories based on pharmaceutical class for the majority of prescriptions in the PDMP data set. We augmented data elements required to calculate morphine milligram equivalents and assigned duration of action (short-acting or long acting) properties for a majority of opioids in the data set. **RESULTS:** About 10% of prescriptions in the PDMP data set did not have a vendor-assigned drug category, and 20% of opioid prescriptions were missing data needed to calculate risk metrics. Using inclusive methods, 19,133,167 (>99.9%) of prescriptions in the PDMP data set were assigned a drug category. For the opioid category, augmenting data elements resulted in 10,760,669 (99.8%) having required values to calculate morphine milligram equivalents and evaluate duration of action properties. **CONCLUSIONS:** Drug safety researchers who require a complete and consistent PDMP data set can use the methods described here to ensure that prescriptions of interest are assigned consistent drug categories and complete opioid risk variable values. Copyright (c) 2016 John Wiley & Sons, Ltd.


Endochin-like quinolones (ELQs) are potent and specific inhibitors of cytochrome bc1 from Plasmodium falciparum and Toxoplasma gondii and show promise for novel antiparasitic drug development. To determine whether the mitochondrial electron transport chain of Leishmania parasites could be targeted similarly for drug development, we investigated the activity of 134 structurally diverse ELQs. A cohort of ELQs was selectively toxic to amastigotes of Leishmania mexicana and L. donovani, with 50% inhibitory concentrations (IC50s) in the low micromolar range, but the structurally similar hydroxynaphthoquinone buparvaquone was by far the most potent inhibitor of electron transport, ATP production, and intracellular amastigote growth. Cytochrome bc1 is thus a promising target for novel antileishmanial drugs, and further improvements on the buparvaquone scaffold are warranted for development of enhanced therapeutics.


**PURPOSE:** We reviewed fertility outcomes of vasectomy reversal at a high surgical volume center in men with the same female partner as before vasectomy. **MATERIALS AND METHODS:** We retrospectively studied a prospective database. All vasectomy reversals were performed by a single surgeon (EFF). Patients who underwent microsurgical vasectomy reversal and had the same female partner as before vasectomy were identified from 1978 to 2011. Pregnancy and live birth rates, procedure type (bilateral vasovasostomy, bilateral vasoepididymostomy, unilateral vasovasostomy or unilateral vasoepididymostomy), patency rate, time from reversal and spouse age were evaluated. **RESULTS:** We reviewed the records of 3,135 consecutive microsurgical vasectomy reversals. Of these patients 524 (17%) who underwent vasectomy reversal had the same female partner as before vasectomy. Complete information was available on 258 patients (49%), who had a 94% vas patency rate. The clinical pregnancy rate was 83% by natural means compared to 60% in our general vasectomy reversal population (p <0.0001). On logistic regression analysis controlling for female partner and patient ages, years from vasectomy and vasectomy reversal with the same female partner the OR was 2 (p <0.007). Average time from vasectomy was 5.7 years. Average patient and female partner age at reversal was 38.9 and 33.2 years, respectively. **CONCLUSIONS:** Outcomes of clinical pregnancy and live birth rates are higher in men who undergo microsurgical vasectomy reversal with the same female partner. These
outcomes may be related to a shorter interval from vasectomy, previous fertility and couple motivation.


BACKGROUND: Heparin-induced thrombocytopenia (HIT) complicated by severe thrombocytopenia and thrombosis can pose significant treatment challenges. Use of alternative anticoagulants in this setting may increase bleeding risks, especially in patients who have a protracted disease course. Additional therapies are lacking in this severely affected patient population. METHODS: We describe three patients with HIT who had severe thromboembolism and prolonged thrombocytopenia refractory to standard treatment but who achieved an immediate and sustained response to IVIg therapy. The mechanism of action of IVIg was evaluated in these patients and in five additional patients with severe HIT. The impact of a common polymorphism (H/R 131) in the platelet IgG receptor FcγRIIa on IVIg-mediated inhibition of platelet activation was also examined. RESULTS: At levels attained in vivo, IVIg inhibits HIT antibody-mediated platelet activation. The constant domain of IgG (Fc) but not the antigen-binding portion (Fab) is required for this effect. Consistent with this finding, IVIg had no effect on HIT antibody binding in a solid-phase HIT immunoassay (platelet factor 4 enzyme-linked immunoassay). The H/R131 polymorphism in FcγRIIa influences the susceptibility of platelets to IVIg treatment, with the HH131 genotype being most susceptible to IVIg-mediated inhibition of antibody-induced activation. However, at high doses of IVIg, activation of platelets of all FcγRIIa genotypes was significantly inhibited. All three patients did well on long-term anticoagulation therapy with direct oral anticoagulants. CONCLUSIONS: These studies suggest that IVIg treatment should be considered in patients with HIT who have severe disease that is refractory to standard therapies.


BACKGROUND: Younger workers are more likely to be injured on the job than older workers. Investigation tends to focus on work-related explanatory factors but often neglects non-work-related causes. AIMS: To identify both work- and non-work-related factors that contribute to younger workers’ injuries in seasonal work. METHODS: Two surveys of a set of seasonal parks and recreation workers were conducted measuring health and safety behaviours and self-reported injuries. RESULTS: Seventy per cent reported an injury at work over the summer. Among young workers, each additional year of age was associated with an almost 50% increase in injury rate (P < 0.05). Odds of injury in women were three times those for men (P < 0.05). We observed a linear relationship between average hours worked per week and injuries (P < 0.001). Alcohol abuse (P < 0.05) was also associated with injuries. CONCLUSIONS: Higher injury rates among younger workers in this sample is multifactorial and encompasses both work and non-work factors and suggest that more global approaches are required to address young worker safety.


Although balance and gait deteriorate as a person ages, it is unknown if all balance and gait measures change similarly across the adult age span. We developed the Instrumented Stand and Walk test (ISAW) to provide a quick quantification of key components of balance and walking: postural sway, anticipatory postural adjustments during step initiation, gait, and turning using body-worn, inertial sensors. Our aims were to characterize how different balance and gait measures change with age and to identify key age-related
measures of mobility, in a wide age range of healthy, community-dwelling adults. A total of 135 healthy, community-dwelling subjects of age range 21-89 years with no history of falls were enrolled. Subjects wore inertial sensors on the wrists, ankles, sternum and lumbar area; 37 reliable and valid measures of postural sway, step initiation, gait and turning were computed. Univariate and multivariate regression analyses were performed to examine how the measures changed with age. Several distinct correlation patterns between age and ISAW measures were observed: linear deterioration, deterioration after plateau, and subtle, or no, worsening. Spatial, but not temporal, measures of gait were age-related. The strongest age correlation was found for centroidal frequency of mediolateral postural sway (r = -0.50, p < 0.001). A hierarchical regression model revealed that age was the most important predictor of mediolateral centroidal frequency, with lower sway frequencies associated with older age, independent of gender, weight, and height. Our results showed that balance and gait represent independent control systems for mobility and not all balance and gait measures deteriorate the same way with age. Postural sway during stance was more strongly related to age than any gait, gait initiation or turning measure.


Background: A low proportion of adults with cancer are recruited to clinical trials. Cancer Council Victoria provides funding to clinical trial sites through its statewide Cancer Trials Management Scheme (CTMS). Historically, there appeared to be a relationship between budget-allocated funding and the number of patients recruited. A randomized controlled trial was conducted to test whether additional funding in 2013 would increase trial recruitment. Methods: A total of 18 trial centers ("sites") received usual CTMS funds, whereas 16 intervention sites received usual funds plus additional funds, proportional to recruitment in 2011; additional payments to sites in the intervention group ranged from $6,750 to $234,000 AUD (approximately $6750-$234,000 USD at the time). This represented an average 11.8% (interquartile range [IQR], 8.0%, 12.3%) increase in sites' budgets. Sites were required to use the funds with the aim of increasing recruitment. The study end point was the number of new participants recruited to trials in 2013. An online survey assessed strategies used to increase recruitment. Results: The median number of new trial recruits per site in 2013 was 21 (IQR, 5-39) in the control arm and 12.5 (IQR, 3.5-44.5) in the intervention arm. The ratio of new trial recruitment numbers at the intervention sites compared with control sites in 2013, adjusting for respective 2012 numbers and institution type, was 0.99 (95% CI, 0.69, 1.43; P = .96). The survey revealed most intervention sites used funding to increase staffing. Conclusions: Additional funding at a site level did not lead to a contemporaneous increase in trial recruitment.


BACKGROUND: Primary drivers (PDs) of adult cervical deformity (ACD) have not been described in relation to pre- and early postoperative alignment or degree of correction. OBJECTIVE: To define the PDs of ACD to understand the impact of driver region on global postoperative compensatory mechanisms. METHODS: Primary cervical deformity driver/vertebral apex level were determined: CS = cervical; CTJ = cervicothoracic junction; TH = thoracic; SP = spinopelvic. Patients were evaluated if surgery included PD apex, based on the lowest instrumented vertebra (LV); CS: LV ≤ C7, CTJ: LV ≤ T3, TH: LV ≤ T12. Cervical and thoracolumbar alignment was measured preoperatively and 3 mo (3M) postoperatively. PD groups were compared with analysis of variance/Pearson chi 2, paired t-tests. RESULTS: Eighty-four ACD patients met inclusion criteria. Thoracic drivers (n = 26) showed greatest preoperative cervical and global malalignment against other PD: higher thoracic kyphosis, pelvic incidence-lumbar lordosis (PI-LL), T1 slope C2-T3 sagittal vertical axis (SVA), and C0-2 angle (P < .05). Differences in baseline-3M alignment changes were observed between surgical PD groups, in PI-LL, LL, T1 slope minus cervical lordosis (TS-CL), cervical SVA, C2-T3 SVA (P < .05). Main changes were between TH and CS driver groups: TH patients had greater PI-LL (4.47 degrees vs -0.87 degrees, P =
.049), TS-CL (-19.12 degrees vs -4.30, P = .050), C2-C7 SVA (-18.12 vs -4.30 mm, P = .007), and C2-T3 SVA (-24.76 vs 8.50 mm, P = .002) baseline-3M correction. CTJ drivers trended toward greater LL correction compared to CS drivers (-6.00 degrees vs 0.88 degrees, P = .050). Patients operated at CS driver level had a difference in the prevalence of 3M TS-CL modifier grades (0 = 35.7%, 1 = 0.0%, 2 = 13.3%, P = .030). There was a significant difference in 3M chin-brow vertical angle modifier grade distribution in TH drivers (0 = 0.0%, 1 = 35.9%, 2 = 14.3%, P = .049). CONCLUSION: Characterizing ACD patients by PD type reveals differences in pre- and postoperative alignment. Evaluating surgical alignment outcomes based on PD inclusion is important in understanding alignment goals for ACD correction.

Patel, M. S., Raza, S. S., Bhakta, A., Ewing, T., Bukur, M., Vagefi, P. A., . . . Malinoski, D. J. (2016). Patients on state organ donor registries receive similar levels of intensive care compared to those who are not: an opportunity to increase public intent to donate. Clinical Transplantation, 30(6), 682-687. doi:10.1111/ctr.12734

The intent to donate organs is affected by the public perception that patients on state registries receive less aggressive life-saving care in order to allow organ donation to proceed. However, the association between first person authorization to donate organs and the actual care received by eventual organ donors in hospitals is unknown. From August 2010 to April 2011, all eight organ procurement organizations in United Network for Organ Sharing Region 5 prospectively recorded demographic data and organ utilization rates on all donors after neurologic determination of death (DNDDs). Critical care and physiologic parameters were also recorded at referral for imminent neurologic death and prior to authorization for donation to reflect the aggressiveness of provided care. There were 586 DNDDs and 23% were on a state registry. Compared to non-registered DNDDs, those on state registries were older but were noted to have similar critical care parameters at both referral and authorization. Furthermore, there was no significant difference in organs procured per donor or organs transplanted per donor between registered and non-registered DNDDs. Thus, DNDDs who are on state donor registries receive similar levels of intensive care compared to non-registered donors. The association noted in this study may therefore help to dispel a common misperception that decreases the intent to donate.


OBJECTIVE: In the kidney disease clinic setting, higher-than-usual blood pressure is often ascribed to recent dietary sodium indiscretion. While clinical trials demonstrate a clear relationship between salt intake and blood pressure on the population level, it is uncertain whether real-world variation in sodium intake within individual chronic kidney disease (CKD) patients is associated with fluctuations in blood pressure. METHODS: We analyzed data from the Phosphorus Normalization Trial, in which participants with CKD eating their usual diets completed at least three 24-hour urine collections over 9 months, from which we measured sodium. Blood pressure was measured at the time of 24-hour urine collections. For each individual participant, we assessed the slope of the relationship between sodium intake and mean arterial blood pressure (MAP). RESULTS: Among 119 participants (mean age 67 years and mean estimated glomerular filtration rate 31 mL/minute/1.73 m2), there was substantial variation in sodium intake as measured by 24-hour urine collections (mean intake 3,903 mg/day, standard deviation 1037 mg/day). Individual participants had highly variable associations between their sodium intake and their MAP; 47% (n = 56) had inverse associations between sodium and MAP, whereas the remainder had positive (salt-sensitive) associations. CONCLUSIONS: Among CKD patients, there is substantial variation in sodium intake but no predictable relationship between dietary sodium and blood pressure in individuals. The frequent dismissal of elevated blood pressure readings as related to recent sodium intake in clinic may be a misapplication of large-scale population data to explain individual variability and may contribute to clinical inertia regarding high blood pressure treatment.

**BACKGROUND:** Between 45 and 95% of children with Autism Spectrum Disorder (ASD) present sensory features that affect their daily functioning. However, the data in the scientific literature are not conclusive regarding the evolution of sensory features in children with ASD. The main objective of this study was to analyze the sensory features of children within the age of 3-4 (T1) when they received their ASD diagnosis and two years later (T2) when they started school. **METHODS:** We conducted a prospective cohort study to assess sensory features in 34 children with ASD over time. The data were collected using a standardized assessment tool, the Sensory Profile. **RESULTS:** Our analyses show that sensory features in children with ASD are stable from the age of three to six years. The stability of sensory scores is independent of correction by covariates, such as cognitive level and autism severity scores. **CONCLUSIONS:** Children with ASD have sensory features that persist from the time of diagnosis at the age of 3 to 4 years to school age. This persistence of sensory features from an early age underscores the need to support these children and their parents. Sensory features should be detected early and managed to improve functional and psychosocial outcomes.


Protective postural responses, including stepping, to recover equilibrium are critical for fall prevention and are impaired in people with Parkinson’s disease (PD) with freezing of gait (FoG). Improving protective postural responses through training may reduce falls in this population. However, motor learning, the basis of neurorehabilitation, is also impaired in people with PD and, in particular, people with PD who experience freezing. It is unknown whether people with PD who freeze can improve protective postural responses, and whether these improvements are similar to nonfreezers. Our goal was to assess whether people with freezing can improve protective postural responses and retain these improvements similarly to nonfreezers. Twenty-eight people with PD (13 freezers, 15 nonfreezers) were enrolled. Improvement in protective postural responses was assessed over the course of 25 forward and 25 backward support surface translations (delivered in pseudo-random order). Postural responses were re-assessed 24h later to determine whether improvements were retained. People who freeze did not improve or retain improvement in protective postural responses as well as nonfreezers in our primary outcome variable, center of mass (COM) displacement after perturbations (post hoc across group assessments: freezers- p=0.14 and nonfreezers- p=0.001, respectively). However, other protective stepping outcomes, including margin of stability, step length, and step time, improved similarly across groups. Significant improvements were retained in both groups. In conclusion, people with PD who freeze exhibited reduced ability to improve protective postural responses in some, but not all, outcome variables. Additional training may be necessary to improve protective postural responses in people with PD who freeze.


After a brief review of current restorative materials and classifications, this article discusses the latest developments in polymer-based direct filling materials, with emphasis on products and studies available in the last 10 years. This will include the more recent bulk fill composites and self-adhesive materials, for which clinical evidence of success, albeit somewhat limited, is already available. The article also introduces the latest cutting edge research topics on new materials for composite restorations, and an outlook for the future of how those may help to improve the service life of dental composite restorations.

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


PURPOSE: Colorectal cancer (CRC) is the third leading cause of cancer death in the United States, yet 1 in 3 Americans have never been screened for CRC. Annual screening using fecal immunochemical tests (FITs) is often a preferred modality in populations experiencing CRC screening disparities. Although multiple studies evaluate the clinical effectiveness of FITs, few studies assess patient preferences toward kit characteristics. We conducted this community-led study to assess patient preferences for FIT characteristics and to use study findings in concert with clinical effectiveness data to inform regional FIT selection. METHODS: We collaborated with local health system leaders to identify FITs and recruit age eligible (50 to 75 years), English or Spanish speaking community members. Participants completed up to 6 FITs and associated questionnaires and were invited to participate in a follow-up focus group. We used a sequential explanatory mixed-methods design to assess participant preferences and rank FIT kits. First, we used quantitative data from user testing to measure acceptability, ease of completion, and specimen adequacy through a descriptive analysis of 1) fixed response questionnaire items on participant attitudes toward and experiences with FIT kits, and 2) a clinical assessment of adherence to directions regarding collection, packaging, and return of specimens. Second, we analyzed qualitative data from focus groups to refine FIT rankings and gain deeper insight into the pros and cons associated with each tested kit. FINDINGS: Seventy-six FITs were completed by 18 participants (Range, 3 to 6 kits per participant). Over half (56%, n = 10) of the participants were Hispanic and 50% were female (n = 9). Thirteen participants attended 1 of 3 focus groups. Participants preferred FITs that were single sample, used a probe and vial for sample collection, and had simple, large-font instructions with colorful pictures. Participants reported challenges using paper to catch samples, had difficulty labeling tests, and emphasized the importance of having care team members provide verbal instructions on test completion and follow-up support for patients with abnormal results. FIT rankings from most to least preferred were OC-Light, Hemosure iFOB Test, InSure FIT, QuickVue, OneStep+, and Hemoccult ICT. CONCLUSIONS: FIT characteristics influenced patient’s perceptions of test acceptability and feasibility. Health system leaders, payers, and clinicians should select FITs that are both clinically effective and incorporate patient preferred test characteristics. Consideration of patient preferences may facilitate FIT return, especially in populations at higher risk for experiencing CRC screening disparities.


BACKGROUND & AIMS: Wilson disease is a disorder of copper (Cu) misbalance caused by mutations in the ATPase copper transporting beta gene (ATP7B). ATP7B is highly expressed in the liver—the major site of Cu accumulation in patients with Wilson disease. The intestine also expresses ATP7B, but little is known about the contribution of intestinal ATP7B to normal intestinal homeostasis or to Wilson disease manifestations. We characterized the role of ATP7B in mouse intestinal organoids and tissues. METHODS: We collected intestinal tissues from ATP7B-knockout (Atp7b/-/-) and control mice, and establish 3-dimensional enteroids. Immunohistochemistry and X-ray fluorescence were used to characterize the distribution of ATP7B and Cu in tissues. Electron microscopy, histologic analyses, and immunoblotting were used to determine the effects of ATP7B loss. Enteroids derived from control and ATP7B-knockout mice were incubated with excess Cu or with
Cu-chelating reagents; effects on cell fat content and ATP7B levels and localization were determined by fluorescent confocal microscopy. RESULTS: ATP7B maintains a Cu gradient along the duodenal crypt-villus axis and buffers Cu levels in the cytosol of enterocytes. These functions are mediated by rapid Cu-dependent enlargement of ATP7B-containing vesicles and increased levels of ATP7B. Intestines of Atp7b−/− mice had reduced Cu storage pools in intestine, Cu depletion, accumulation of triglyceride-filled vesicles in enterocytes, mis-localization of apolipoprotein B, and loss of chylomicrons. In primary 3-dimensional enteroids, administration of excess Cu or Cu chelators impaired assembly of chylomicrons. CONCLUSIONS: ATP7B regulates vesicular storage of Cu in mouse intestine. ATP7B buffers Cu levels in enterocytes to maintain a range necessary for formation of chylomicrons. Misbalance of Cu and lipid in the intestine could account for gastrointestinal manifestations of Wilson disease.


Background and Objective: Advanced analytic methods for synthesizing evidence about complex interventions continue to be developed. In this paper, we emphasize that the specific research question posed in the review should be used as a guide for choosing the appropriate analytic method. Methods: We present advanced analytic approaches that address four common questions that guide reviews of complex interventions: (1) How effective is the intervention? (2) For whom does the intervention work and in what contexts? (3) What happens when the intervention is implemented? and (4) What decisions are possible given the results of the synthesis? Conclusion: The analytic approaches presented in this paper are particularly useful when each primary study differs in components, mechanisms of action, context, implementation, timing, and many other domains. © 2017 The Author(s).


Adeno-associated virus (AAV) entry is determined by its interactions with specific surface glycans and a proteinaceous receptor(s). Adeno-associated virus receptor (AAVR) (also named KIAA0319L) is an essential cellular receptor required for the transduction of vectors derived from multiple AAV serotypes, including the evolutionarily distant serotypes AAV2 and AAV5. Here, we further biochemically characterize the AAV-AAVR interaction and define the domains within the ectodomain of AAVR that facilitate this interaction. By using a virus overlay assay, it was previously shown that the major AAV2 binding protein in membrane preparations of human cells corresponds to a glycoprotein with a molecular mass of 150 kDa. By establishing a purification procedure, performing further protein separation by two-dimensional electrophoresis, and utilizing mass spectrometry, we now show that this glycoprotein is identical to AAVR. While we find that AAVR is an N-linked glycosylated protein, this glycosylation is not a strict requirement for AAV2 binding or functional transduction. Using a combination of genetic complementation with deletion constructs and virus overlay assays with individual domains, we find that AAV2 functionally interacts predominantly with the second Ig-like polycystic kidney disease (PKD) repeat domain (PKD2) present in the ectodomain of AAVR. In contrast, AAV5 interacts primarily through the first, most membrane-distal, PKD domain (PKD1) of AAVR to promote transduction. Furthermore, other AAV serotypes, including AAV1 and -8, require a combination of PKD1 and PKD2 for optimal transduction. These results suggest that despite their shared dependence on AAVR as a critical entry receptor, different AAV serotypes have evolved distinctive interactions with the same receptor. © 2017 American Society for Microbiology.

BACKGROUND: The increasing adoption of electronic health records (EHRs) has been associated with a number of unintended negative consequences with provider efficiency and job satisfaction. To address this, there has been a dramatic increase in the use of medical scribes to perform many of the required EHR functions. Despite this rapid growth, little has been published on the training or assessment tools to appraise the safety and efficacy of scribe-related EHR activities. Given the number of reports documenting that other professional groups suffer from a number of performance errors in EHR interface and data gathering, scribes likely face similar challenges. This highlights the need for new assessment tools for medical scribes.

OBJECTIVE: The objective of this study was to develop a virtual video-based simulation to demonstrate and quantify the variability and accuracy of scribes’ transcribed notes in the EHR.

METHODS: From a pool of 8 scribes in one department, a total of 5 female scribes, intent on pursuing careers in health care, with at least 6 months of experience were recruited for our simulation study. We created three simulated patient-provider scenarios. Each scenario contained a corresponding medical record in our simulation instance of our EHR. For each scenario, we video-recorded a standardized patient-provider encounter. Five scribes with at least 6 months of experience both with our EHR and in the specialty of the simulated cases were recruited. Each scribe watched the simulated encounter and transcribed notes into a simulated EHR environment. Transcribed notes were evaluated for interscribe variability and compared with a gold standard for accuracy.

RESULTS: All scribes completed all simulated cases. There was significant interscribe variability in note structure and content. Overall, only 26% of all data elements were unique to the scribe writing them. The term data element was used to define the individual pieces of data that scribes perceived from the simulation. Note length was determined by counting the number of words varied by 31%, 37%, and 57% between longest and shortest note between the three cases, and word economy ranged between 23% and 71%. Overall, there was a wide inter- and intrascribe variation in accuracy for each section of the notes with ranges from 50% to 76%, resulting in an overall positive predictive value for each note between 38% and 81%. CONCLUSIONS: We created a high-fidelity, video-based EHR simulation, capable of assessing multiple performance indicators in medical scribes. In this cohort, we demonstrate significant interscribe variability in note structure and content. Overall, only 26% of all data elements were unique to the scribe writing them. The term data element was used to define the individual pieces of data that scribes perceived from the simulation. Note length was determined by counting the number of words varied by 31%, 37%, and 57% between longest and shortest note between the three cases, and word economy ranged between 23% and 71%. Overall, there was a wide inter- and intrascribe variation in accuracy for each section of the notes with ranges from 50% to 76%, resulting in an overall positive predictive value for each note between 38% and 81%. CONCLUSIONS: We created a high-fidelity, video-based EHR simulation, capable of assessing multiple performance indicators in medical scribes. In this cohort, we demonstrate significant variability both in terms of structure and accuracy in clinical documentation. This form of simulation can provide a valuable tool for future development of scribe curriculum and assessment of competency.


Nivolumab (Opdivo, Bristol Meyer Squibb, New York, NY) and pembrolizumab (Keytruda, Merck, Kenilworth, NJ) are the first two US Food and Drug Administration (FDA)-approved monoclonal antibodies targeting programmed death-1 (PD-1). Nivolumab and pembrolizumab work by interfering with the interaction between PD-1 and programmed death ligand-1 (PD-L1), whose unimpeded interaction downregulates T cells allowing cancer cells to evade immune surveillance. These drugs have earned a series of FDA approvals for melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), urothelial cancer, classical Hodgkin lymphoma, and renal cell cancer. In this review we will summarize the data for efficacy and toxicity for these two agents. We conclude that they represent two valuable but interchangeable...
alternatives to target their approved indications. We will discuss how this can help global payers seeking to contain the cost of cancer therapeutics that continues to spiral out of control.


Importance: A common justification for high cancer drug prices is the sizable research and development (R&D) outlay necessary to bring a drug to the US market. A recent estimate of R&D spending is $2.7 billion (2017 US dollars). However, this analysis lacks transparency and independent replication. Objective: To provide a contemporary estimate of R&D spending to develop cancer drugs. Design, Setting, and Participants: Analysis of US Securities and Exchange Commission filings for drug companies with no drugs on the US market that received approval by the US Food and Drug Administration for a cancer drug from January 1, 2006, through December 31, 2015. Cumulative R&D spending was estimated from initiation of drug development activity to date of approval. Earnings were also identified from the time of approval to the present. The study was conducted from December 10, 2016, to March 2, 2017. Main Outcomes and Measures: Median R&D spending on cancer drug development. Results: Ten companies and drugs were included in this analysis. The 10 companies had a median time to develop a drug of 7.3 years (range, 5.8-15.2 years). Five drugs (50%) received accelerated approval from the US Food and Drug Administration, and 5 (50%) received regular approval. The median cost of drug development was $648.0 million (range, $157.3 million to $1950.8 million). The median cost was $757.4 million (range, $203.6 million to $2601.7 million) for a 7% per annum cost of capital (or opportunity costs) and $793.6 million (range, $219.1 million to $2827.1 million) for a 9% opportunity costs. With a median of 4.0 years (range, 0.8-8.8 years) since approval, the total revenue from sales of these 10 drugs since approval was $67.0 billion compared with total R&D spending of $7.2 billion ($9.1 billion, including 7% opportunity costs). Conclusions and Relevance: The cost to develop a cancer drug is $648.0 million, a figure significantly lower than prior estimates. The revenue since approval is substantial (median, $1658.4 million; range, $204.1 million to $22275.0 million). This analysis provides a transparent estimate of R&D spending on cancer drugs and has implications for the current debate on drug pricing.


PURPOSE: The College of American Pathologists offers blinded proficiency testing (PT) for laboratories performing HFE genetic tests for hereditary hemochromatosis (common C282Y and H63D variants). This study used 10 years of PT data to determine laboratory performance for HFE analytical genotyping and clinical interpretation. METHODS: Laboratories were graded for accuracy of genotype determination (six possible C282Y/H63D genotypes) and clinical interpretation regarding whether the genotype was likely to have contributed to iron overload in a hypothetical patient. RESULTS: The analytical genotyping error rate was low (0.73%) in 7,663 results (from 257 unique laboratories). Genotyping errors were significantly higher in C282Y heterozygous, H63D homozygous, and C282Y homozygous samples, in non-American laboratories, and in laboratories with lower testing volume. Analytical sensitivity and specificity were >98.5 and >99.5%. The interpretive error rate (4.3%) was higher than the genotyping error rate, with two problematic genotypes (C282Y heterozygous and H63D homozygous) accounting for 77% of total interpretive errors. There was a time-dependent improvement in the interpretation of the clinical significance of HFE genotypes. CONCLUSIONS: HFE molecular genetic testing, performed by non-US Food and Drug Administration-approved laboratory-developed tests, demonstrated excellent accuracy, sensitivity, and specificity. Clinical interpretations were more heterogeneous, probably owing to the low clinical penetrance of some common HFE genotypes. Genet Med 18 12, 1206-1213.

Purpose To determine whether gadolinium remains in juvenile nonhuman primate tissue after maternal exposure to intravenous gadoteridol during pregnancy. Materials and Methods Gravid rhesus macaques and their offspring (n = 10) were maintained, as approved by the institutional animal care and utilization committee. They were prospectively studied as part of a pre-existing ongoing research protocol to evaluate the effects of maternal malnutrition on placental and fetal development. On gestational days 85 and 135, they underwent placental magnetic resonance imaging after intravenous gadoteridol administration. Amniocentesis was performed on day 135 prior to administration of the second dose of gadoteridol. After delivery, the offspring were followed for 7 months. Tissue samples from eight different organs and from blood were harvested from each juvenile macaque. Gadolinium levels were measured by using inductively coupled plasma mass spectrometry. Results Gadolinium concentration in the amniotic fluid was 0.028 x 10^-5 %ID/g (percentage injected dose per gram of tissue) 50 days after administration of one gadoteridol dose. Gadolinium was most consistently detected in the femur (mean, 2.5 x 10^-5 %ID/g; range, [0.81-4.1] x 10^-5 %ID/g) and liver (mean, 0.15 x 10^-5 %ID/g; range, [0.0-0.26] x 10^-5 %ID/g). Levels were undetectable in the remaining sampled tissues, with the exception of one juvenile skin sample (0.07 x 10^-5 %ID/g), one juvenile spleen sample (0.039 x 10^-5 %ID/g), and one juvenile brain (0.095 x 10^-5 %ID/g) and kidney (0.13 x 10^-5 %ID/g) sample. Conclusion The presence of gadoteridol in the amniotic fluid after maternal injection enables confirmation that it crosses the placenta. Extremely low levels of gadolinium are found in juvenile macaque tissues after in utero exposure to two doses of gadoteridol, indicating that a very small amount of gadolinium persists after delivery. (c) RSNA, 2017.


Dental impression making is the process of creating a negative form of the teeth and oral tissues, into which gypsum or other die materials can be processed to create working analogues. Contemporary dentistry generates new information every year and digital dentistry is becoming established and influential. Although dentists should stay abreast of new technologies, some of the conventional materials and time-tested techniques remain widely used. It is important to review the impression-making process to ensure that practitioners have up-to-date information about how to safely and effectively capture the exact form of the oral tissues to provide optimal patient management.


OBJECTIVE: The goals of this study were to determine baseline and postbariatric surgical characteristics associated with type 2 diabetes remission and if, after controlling for differences in weight loss, diabetes remission was greater after Roux-en-Y gastric bypass (RYGBP) than laparoscopic gastric banding (LAGB). RESEARCH DESIGN AND METHODS: An observational cohort of obese participants was studied using generalized linear mixed models to examine the associations of bariatric surgery type and diabetes remission rates for up to 3 years. Of 2,458 obese participants enrolled, 1,868 (76%) had complete data to assess diabetes status at both baseline and at least one follow-up visit. Of these, 627 participants (34%) were classified with diabetes: 466 underwent RYGBP and 140 underwent LAGB. RESULTS: After 3 years, 68.7% of RYGBP and 30.2% of LAGB
participants were in diabetes remission. Baseline factors associated with diabetes remission included a lower weight for LAGB, greater fasting C-peptide, lower leptin-to-fat mass ratio for RYGBP, and a lower hemoglobin A1c without need for insulin for both procedures. After both procedures, greater postsurgical weight loss was associated with remission. However, even after controlling for differences in amount of weight lost, relative diabetes remission rates remained nearly twofold higher after RYGBP than LAGB.

CONCLUSIONS: Diabetes remission up to 3 years after RYGBP and LAGB was proportionally higher with increasing postsurgical weight loss. However, the nearly twofold greater weight loss-adjusted likelihood of diabetes remission in subjects undergoing RYGBP than LAGB suggests unique mechanisms contributing to improved glucose metabolism beyond weight loss after RYGBP.


UNLABELLED: Pain involving several body regions generally represents nervous system pathophysiology shifting from predominantly peripheral to more central. In adults, higher widespread pain scores are clinically meaningful and confer risk for poor response to treatment. It is unknown whether widespread pain is similarly important in children. To address this gap, we conducted an observational study examining 1) associations between widespread pain and functional impairment and health-related quality of life (HRQOL) in clinical pediatric samples, and 2) associations among sociodemographic factors and pain catastrophizing with widespread pain scores. Participants were 166 children aged 10 to 18 years from 3 samples (acute pain, presurgery, chronic pain). Children self-reported pain intensity, pain catastrophizing, functional impairment, and HRQOL. Children indicated pain locations on a body diagram, which was coded using the American College of Rheumatology definition of widespread pain. Results revealed higher widespread pain scores were associated with greater functional impairment with routine activities (F = 3.15, P = .02) and poorer HRQOL (F = 3.29, P = .02), adjusting for pain intensity, study group, and demographic characteristics. Older age (B = .11, P = .02), and Hispanic ethnicity (B = .67, P = .04) were associated with higher widespread pain scores. Findings support incorporating evaluation of widespread pain into pediatric pain assessment. Future research is needed to examine the longitudinal effect of widespread pain on children’s treatment outcomes.

PERSPECTIVE: This article examines the association between widespread pain scores and functional impairment and HRQOL in community and clinical samples of children. Assessment of the spatial distribution of the pain experience provides unique information that may identify children at risk for poorer health.


The space radiation environment includes energetic charged particles that may impact cognitive performance. We assessed the effects of (16)O ion irradiation on cognitive performance of C57BL/6J x DBA/2J F1 (B6D2F1) mice at OHSU (Portland, OR) one month following irradiation at Brookhaven National Laboratory (BNL, Upton, NY). Hippocampus-dependent contextual fear memory and hippocampus-independent cued fear memory of B6D2F1 mice were tested. (16)O ion exposure enhanced cued fear memory. This effect showed a bell-shaped dose response curve. Cued fear memory was significantly stronger in mice irradiated with (16)O ions at a dose of 0.4 or 0.8 Gy than in sham-irradiated mice or following irradiation at 1.6 Gy. In contrast to cued fear memory, contextual fear memory was not affected following (16)O ion irradiation at the doses used in this study. These data indicate that the amygdala might be particularly susceptible to effects of (16)O ion exposure.

Accurate subclassification of aggressive B cell lymphomas (ABCLs) requires integration of morphologic, immunohistochemical (IHC), and cytogenetic information. Optimal strategies have not been well defined for diagnosis of high grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (HGBLwR) and double expressor lymphomas with MYC and BCL2 protein overexpression. One hundred and eighty seven ABCLs were investigated with complete IHC and FISH analysis. Morphologic and IHC analysis was insufficient to identify clinically relevant HGBLwR. Approximately, 75% of cases classified as HGBLwR showed conventional DLBCL morphologic features. Fourteen percent of MYC-rearranged cases were negative by IHC. Conversely, 60% of cases positive for MYC by IHC did not demonstrate a MYC rearrangement. Analysis by FISH without MYC and BCL2 IHC would miss 41 cases of double expressor lymphoma. Complete IHC and FISH analysis is recommended in the evaluation of all ABCLs.


STUDY DESIGN: A retrospective data collection study with application of metastatic spine scoring systems.

OBJECTIVES: To apply the Tomita and revised Tokuhashi scoring systems to a surgical cohort at a single academic institution and analyze spine-related surgical morbidity and mortality rates. SUMMARY OF BACKGROUND DATA: Surgical management of metastatic spine patients requires tools that can accurately predict patient survival, as well as knowledge of morbidity and mortality rates. METHODS: An Oregon Health & Science University (OHSU) Spine Center surgical database was queried (years 2002-2010) to identify patients with an ICD-9 code indicative of metastatic spine disease. Patients whose only surgical treatment was vertebral augmentation were not included. Scatter plots of survival versus the Tomita and revised Tokuhashi metastatic spine scoring systems were statistically analyzed. Spine-related morbidity and mortality rates were calculated. RESULTS: Sixty-eight patients were identified: 45 patients’ (30 male patients, mean age 45 y) medical records included operative, morbidity, and mortality statistic data and 38 (26 male patients, mean age 54 y) contained complete metastatic spine scoring system data. Of the 38 deceased spine metastatic patients, 8 had renal cell, 7 lung, 4 breast, 2 chondrosarcoma, 2 prostate, 11 other, and 4 unknown primary cancers. Linear regression analysis revealed R values of 0.2570 and 0.2009 for the revised Tokuhashi and Tomita scoring systems, respectively. Overall transfusion, infection, morbidity, and mortality rates were 33% and 9%, and 42% and 9%, respectively. CONCLUSIONS: Application of metastatic prognostic scoring systems to a retrospective surgical cohort revealed an overall poor correlation with the Tomita and revised Tokuhashi predictive survival models. Morbidity and mortality rates concur with those in the medical literature. This study underscores the difficulty in utilizing metastatic spine scoring systems to predict patient survival. We believe a scoring system based on cancer type is needed to account for changes in treatment paradigms with improved patient survival over time.


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.


OBJECTIVE: Operatively, video-assisted thoracoscopic sympathectomy (VATS) involves pleural entry and poses risk in small children and patients with pulmonary disease. A conventional posterior sympathectomy is more invasive than VATS. We investigated a cadaveric feasibility study of a minimal access posterior approach for endoscopic extrapleural sympathectomy and discuss this minimal approach in children with cardiac sympathectomy. METHODS: A posterior endoscopic extrapleural approach for thoracic sympathectomy was performed using lightly embalmed cadavers; surgical corridor depth, width, and associated pleural violation were recorded. Two pediatric cases undergoing secondary prevention for breakthrough cardiac dysrhythmias using this approach are discussed: case 1, a 9-year-old girl with refractory long QT syndrome; and case 2, a 13-year-old boy with hypertrophic cardiomyopathy. RESULTS: The cadaveric study supported 100% identification of a craniocaudal-oriented sympathetic chain using an 18-mm tubular retractor, and a 10% pleural violation rate. There were no clinically significant pneumothoraces in either proof of concept cases. CONCLUSIONS: Minimal access posterior extrapleural sympathectomy is feasible to expose the sympathetic chain in the thoracic region with good visualization using either endoscopic or microscopic magnification. Single-position bilateral thoracic sympathectomy can be performed in pediatric patients with life-threatening ventricular arrhythmias. Based on the cadaveric study and the 2 preliminary cases, we believe that a posterior minimal access approach allows safe and effective access to the thoracic sympathetic chain for causes requiring sympathectomy using single positioning, with minimal risk of pneumothorax or Horner syndrome.


OBJECTIVES: Binaural pitch fusion is the fusion of stimuli that evoke different pitches between the ears into a single auditory image. Individuals who use hearing aids or bimodal cochlear implants (CIs) experience abnormally broad binaural pitch fusion, such that sounds differing in pitch by as much as 3-4 octaves are fused across ears, leading to spectral averaging and speech perception interference. The goal of this study was to determine if adult bilateral CI users also experience broad binaural pitch fusion. DESIGN: Stimuli were pulse trains delivered to individual electrodes. Fusion ranges were measured using simultaneous, dichotic presentation of reference and comparison stimuli in opposite ears, and varying the comparison stimulus to find the range that fused with the reference stimulus. RESULTS: Bilateral CI listeners had binaural pitch fusion ranges varying from 0 to 12 mm (average 6.1 +/- 3.9 mm), where 12 mm indicates fusion over all electrodes in the array. No significant correlations of fusion range were observed with any subject factors related to age, hearing loss history, or hearing device history, or with any electrode factors including interaural electrode pitch mismatch, pitch match bandwidth, or within-ear electrode discrimination abilities. CONCLUSIONS: Bilateral CI listeners have abnormally broad fusion, similar to hearing aid and bimodal CI listeners. This broad fusion may explain the variability of binaural benefits for speech perception in quiet and in noise in bilateral CI users.

**PURPOSE:** The aim of this study was to examine the performance of laboratories offering assessment for myotonic dystrophy type 1 (DM1) using external proficiency testing samples. DM1, a dominant disorder, has a prevalence of 1:20,000 due to the expansion of CTG trinucleotide repeats in the DMPK gene. **METHODS:** External proficiency testing administered by the College of American Pathologists/American College of Medical Genetics and Genomics distributes three samples twice yearly. Responses from 2003 through the first distribution of 2013 were analyzed after stratification by location (United States/international). Both the repeat sizes (analytic validity) and clinical interpretations were assessed. **RESULTS:** Over the 21 distributions, 45 US and 29 international laboratories participated. Analytic sensitivity for detecting and reporting expanded repeats (>\/=50) was 99.2% (382/385 challenges) and 97.1% (133/137 challenges), respectively. Analytic specificity (to within two repeats of the consensus) was 99.2% (1,790/1,805 alleles) and 98.6% (702/712 alleles), respectively. Clinical interpretations were correct for 99.3% (450/453) and 98.2% (224/228) of positive challenges and in 99.9% (936/937) and 99.6% (455/457) of negative challenges, respectively. Of four incorrect interpretations made in the United States, two were probably due to sample mix-up. **CONCLUSION:** This review of laboratory performance regarding laboratory-developed genetic tests indicates very high performance for both the analytic and interpretative challenges for DM1.


**BACKGROUND AND AIMS:** Breast cancer is the most common cancer in women and the second leading cause of cancer-related deaths in this population. Breast cancer related deaths have declined due to screening and adjuvant therapies, yet a driving clinical need exists to better understand the cause of the deadliest aspect of breast cancer, metastatic disease. Breast cancer metastasizes to several distant organs, the liver being the third most common site. To date, very few murine models of hepatic breast cancer exist. **METHODS:** In this study, a novel murine model of liver breast cancer using the MDA-MB-231 cell line is introduced as an experimental (preclinical) model. **RESULTS:** Histological typing revealed consistent hepatic breast cancer tumor foci. Common features of the murine model were vascular invasion, lung metastasis and peritoneal seeding. **CONCLUSIONS:** The novel murine model of hepatic breast cancer established in this study provides a tool to be used to investigate mechanisms of hepatic metastasis and to test potential therapeutic interventions.


**PURPOSE:** Nondisclosure of terminal prognosis in the context of intercultural interactions can cause moral distress among health care providers guided exclusively by informed consent. However, cultural humility can show that revealing and withholding prognostic information are two equally valid paths to the goal of protecting the patient from harm. **DESIGN:** Assumptions and history giving rise to the preference for truth telling in the United States(US) are examined. Principles of biomedical ethics are described within the context of US, Chinese, and Latin American cultures. The process of cultural competence in the delivery of health care services is explained and introduces the concept of cultural humility. **IMPLICATIONS FOR PRACTICE:** By focusing more on biases and assumptions brought forth from the dominant culture, health care providers may experience less moral distress and convey increased caring in the context of intercultural interactions and nondisclosure of prognosis of a terminal illness.

The provision of optimal end-of-life care to Hispanics receiving hospice care requires familiarity with hospice-specific variables. For example, a preference for nondisclosure of terminal prognosis in some Hispanics is incongruous with traditional hospice practice. In addition, the Spanish word for hospice, “hospicio,” has negative connotations about abandonment of loved ones. Added to cultural considerations are socioeconomic considerations. Many marginalized Hispanic individuals may experience distinct challenges when enrolling in hospice due to socioeconomic hardships relating to poverty, citizenship, and lack of insurance. This systematic integrative review examines the research literature on Hispanics and hospice to report on the state of the science for this topic. Reviewed articles were identified systematically using computer research databases and inclusion and exclusion criteria. Of the 21 reviewed articles, many are survey and low-inference qualitative designs with limited validity and trustworthiness. Most survey instruments were not validated for Spanish language or Hispanic culture. None of the qualitative studies included theoretical sampling or follow-up interviews. Few study designs considered heterogeneity within the Hispanic population. Interpreting results cautiously, there is evidence that some Hispanics find some satisfaction with hospice care in spite of cultural incongruities and socioeconomic challenges. Future research calls for intervention studies and high-inference qualitative designs to gain insight into hospice experiences and what constitutes quality hospice care from the perspectives of Hispanic subgroups. Assessing quality and designing interventions for these end-of-life cultural and socioeconomic issues will improve end-of-life care and facilitate the hospice philosophy of promoting emotional growth at end of life.


Objective: To compare primary indications for cesarean delivery among patients with different female genital mutilation (FGM) status. Methods: The present secondary analysis included data from women who underwent trial of labor resulting in cesarean delivery at 28 obstetric centers in six African countries between November 1, 2001, and March 31, 2003. Associations between cesarean delivery indications and FGM status were assessed using descriptive statistics and multivariable multinomial logistic regression. Results: Data from 1659 women (480 patients with no type of FGM and 1179 patients with FGM [any type]) were included; cesarean delivery indications were collapsed into five categories (fetal indications, maternal factors, stage 1 arrest, stage 2 arrest, and other). The incidence of a clear medical indication for cesarean delivery did not differ between the groups (P=0.320). Among patients without a clear indication for cesarean delivery, women with FGM were more likely to have undergone cesarean delivery for maternal factors (adjusted relative risk ratio [aRRR] 3.92, 95% confidence interval [CI] 1.3–11.71), stage 1 arrest (aRRR 7.74, 95% CI 1.33–45.07), stage 2 arrest (aRRR 6.63, 95% CI 3.74–11.73), or other factors (aRRR 2.41, 95% CI 1.04–5.60) rather than fetal factors compared with women who had no type of FGM. Conclusion: Among women with unclear medical indications, FGM was associated with cesarean delivery being performed for maternal factors or arrest disorders. © 2017 World Health Organization; licensed by John Wiley & Sons Ltd on behalf of International Federation of Gynecology and Obstetrics.


PURPOSE: To develop a model using wearable inertial sensors to assess the performance of orthopaedic residents while performing a diagnostic knee arthroscopy. METHODS: Fourteen subjects performed a diagnostic arthroscopy on a cadaveric right knee. Participants were divided into novices (5 postgraduate year 3 residents), intermediates (5 postgraduate year 4 residents), and experts (4 faculty) based on experience. Arm movement data were collected by inertial measurement units (Opal sensors) by securing 2 sensors to each
upper extremity (dorsal forearm and lateral arm) and 2 sensors to the trunk (sternum and lumbar spine). Kinematics of the elbow and shoulder joints were calculated from the inertial data by biomechanical modeling based on a sequence of links connected by joints. Range of motion required to complete the procedure was calculated for each group. Histograms were used to compare the distribution of joint positions for an expert, intermediate, and novice. RESULTS: For both the right and left upper extremities, skill level corresponded well with shoulder abduction-adduction and elbow pronosupination. Novices required on average 17.2 degrees more motion in the right shoulder abduction-adduction plane than experts to complete the diagnostic arthroscopy ($P = .03$). For right elbow pronosupination (probe hand), novices required on average 23.7 degrees more motion than experts to complete the procedure ($P = .03$). Histogram data showed novices had markedly more variability in shoulder abduction-adduction and elbow pronosupination compared with the other groups. CONCLUSIONS: Our data show wearable inertial sensors can measure joint kinematics during diagnostic knee arthroscopy. Range-of-motion data in the shoulder and elbow correlated inversely with arthroscopic experience. Motion pattern-based analysis shows promise as a metric of resident skill acquisition and development in arthroscopy. CLINICAL RELEVANCE: Wearable inertial sensors show promise as metrics of arthroscopic skill acquisition among residents.


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


BACKGROUND: The prevalence of obesity in America continues to grow significantly. Awareness and understanding of the disease of obesity and treatment options for it appear to be lacking among the general US population. OBJECTIVE: This study aimed to identify misperceptions in diagnosis and treatment of obesity, struggles Americans face in obtaining treatment, consequences of obesity, and perceived barriers to weight loss. SETTING: University hospital, United States. METHODS: A survey of 1509 adults was completed in September 2016 using AmeriSpeak, a probability-based panel designed to be representative of the US household population. The survey included oversamples of blacks and Hispanics. The study analyzed quantitative data from structured interviews and presents descriptive statistics related to public attitudes toward obesity. RESULTS: Of Americans, 81% consider obesity to be the most serious health problem facing the nation, tying cancer as the top issue and landing ahead of diabetes (72%), heart disease (72%), mental illness (65%), and HIV infection and AIDS (46%). Nearly all Americans (94%) agree that obesity itself, even when no other diseases are present, increases the risk for early death. Most Americans overestimate the effectiveness of some obesity treatments, such as diet and exercise alone. Many overweight and obese Americans do not consult a doctor at all about their issues of excess weight. CONCLUSIONS: There is increased awareness about the serious consequences of obesity, but there is still a lack of understanding about the reasons and best treatment modalities for the disease.
STUDY DESIGN: Clinical case series. OBJECTIVE: This study sought to clarify symptoms, diagnostic criteria, and treatment of C4 radiculopathy, and the role of diagnostic C4 root block in this entity. SUMMARY OF BACKGROUND DATA: Although well understood cervical dermatomal/myotomal syndromes have been described for symptoms originating from impingement on the C2, C3, C5, C6, C7, and C8 roots, less has been written about the syndrome(s) associated with the C4 root. METHODS: The senior author reviewed surgical records and describes his personal experience with the diagnosis and treatment of C4 radiculopathy. RESULTS: A total of 712 procedures for cervical radiculopathy without myelopathy were reviewed. Among that cohort, 13 procedures involved the C4 root only and five procedures involved two level procedures including the C4 root. Patients described pain as involving the axial cervical region, paraspinal muscles, trapezius muscle, and interscapular region. No patient described pain over the anterior chest wall or radiating distal to the shoulder, one described pain over the medial clavicle. All patients who were offered surgery had a positive response to a diagnostic C4 transforaminal single nerve root block. Thirteen patients underwent posterior foraminotomy (five at two levels) and five patients underwent an anterior discectomy and fusion at C3-4. Mean Oswestry Disability Index score significantly declined; preoperative score 24.3 (range 14-29), postoperative score 9.7 (range 2-18; \( P = 0.003 \)) at \( \geq 3 \) months. Mean Short Form-36v2 score significantly increased; preoperative score 34.2 (range 20-40.2), postoperative score 73.7 (range 40.5-88.3, \( P = 0.001 \)) at \( \geq 3 \) months. CONCLUSION: C4 root symptoms overlap those of the C3 and C5 roots and are very similar to facet mediated pain. Asymptomatic C4 foraminal stenosis may be a common imaging finding, it can be difficult to diagnose C4 radiculopathy clinically. Diagnostic C4 root block can make an accurate diagnosis and lead to successful surgical outcomes. LEVEL OF EVIDENCE: 4.

In sickle cell disease (SCD), abnormal microvascular function combined with chronic anaemia predisposes patients to perfusion-demand mismatch. We hypothesized that skeletal muscle and myocardial perfusion, normalized to the degree of anaemia, is reduced at basal-state compared to controls, and that this defect is ameliorated by hydroxyurea (HC; also termed hydroxyurea) therapy. Twenty-one SCD patients, of whom 15 were treated with HC, and 27 controls underwent contrast-enhanced ultrasound (CEU) perfusion imaging of the forearm as well as the myocardium. HC treatment was associated with lower white cell and reticulocyte counts, and higher fetal haemoglobin and total haemoglobin levels. When corrected for the degree of anaemia in SCD patients, skeletal flow in HC-treated patients was significantly higher than in untreated SCD patients (217.7 ± 125.4 vs. 85.9 ± 40.2, \( P = 0.018 \)). Similarly, when normalized for both anaemia and increased myocardial work, resting myocardial perfusion was also significantly higher in HC-treated patients compared with untreated SCD patients (0.53 ± 0.47 vs. 0.13 ± 0.07, \( P = 0.028 \)). Haemoglobin F (HbF) levels correlated with skeletal muscle microvascular flow (\( r = 0.55, P = 0.01 \)). In conclusion, patients with SCD not on HC therapy have resting flow deficits in both skeletal muscle and myocardial flow. HC therapy normalizes flow and there is a direct correlation with HbF levels. Clinical trial registration ClinicalTrials.gov Identifier: NCT01602809; https://clinicaltrials.gov/ct2/show/NCT01602809?term=sACHDEV&rank=9.

INTRODUCTION: Childhood maltreatment is associated with later obesity, but the underlying mechanisms are unknown. The objective of this study was to estimate the extent to which depression mediates the associations between childhood maltreatment and BMI in adolescence through adulthood. METHODS: Data
on a cohort of 13,362 adolescents in the National Longitudinal Study of Adolescent to Adult Health (Wave I [1994-1995] to Wave IV [2008-2009]) were analyzed in 2015-2016. Classes of maltreatment experienced prior to age 12 years were statistically identified using latent class analysis. Gender-stratified latent growth curve analysis was used to estimate total effects of maltreatment classes on latent BMI trajectory (aged 13-31 years) and indirect effects of maltreatment classes that occurred through latent depression trajectory (aged 12-31 years). RESULTS: Four latent maltreatment classes were identified: high abuse and neglect; physical abuse dominant; supervisory neglect dominant; and no/low maltreatment. In girls, compared with no/low maltreatment, supervisory neglect dominant (coefficient=0.3, 95% CI=0.0, 0.7) and physical abuse dominant (coefficient=0.6, 95% CI=0.1, 1.2) maltreatment were associated with faster gain in BMI. Change in depression over time fully mediated the association of BMI slope with physical abuse dominant maltreatment, but not with supervisory neglect dominant maltreatment. In boys, high abuse and neglect maltreatment was associated with marginally greater BMI at baseline (coefficient=0.7, 95% CI= -0.1, 1.5); this association was not mediated by depression. CONCLUSIONS: Although maltreatment was associated with depression and BMI trajectories from adolescence to adulthood, depression only mediated associations with physical abuse dominant maltreatment in girls.


BACKGROUND: Proximal junctional kyphosis (PJK) is a well-recognized complication in patients undergoing posterior instrumented fusion procedures for adult spinal deformity. Strategies that reduce rates of PJK have the potential to improve the safety of these operations and decrease cost by eliminating the need for revision surgery. OBJECTIVE: To present a set of surgical techniques that can decrease rates of PJK in adults undergoing surgery for spinal deformity. METHODS: We summarize the use of vertebroplasty, transverse process hooks, terminal rod contouring, and ligament augmentation as means to reduce rates of PJK. RESULTS: We present PJK prevention strategies and a video technique guide that are safe, technically feasible, and add minimal operative time to these surgical procedures. When applied to appropriate high-risk patients, these techniques have the potential to dramatically reduce rates of PJK, which improves quality of life and decreases the cost associated with this treating adult spinal deformity. CONCLUSION: PJK prevention strategies represent a critical area for improvement in surgery for adult spinal deformity. We present a summary of techniques that are safe, feasible, and add minimal time to the overall procedure. These techniques warrant investigation in a thoughtful, prospective manner, but are supported by existing data and compelling biomechanical rationale. Our hope is that these strategies can be applied, particularly in high-risk patients, to help reduce rates of PJK.


OBJECTIVES: The long-term outcome of patients with psychogenic nonepileptic seizures (PNES) is of importance given the disabling symptoms and tendency to affect patients early in their productive years. Health care utilization (HCU) is an important outcome measure reflecting overall health status and costs. There is little information regarding long-term HCU following diagnosis of PNES. METHODS: We retrospectively reviewed records of Veterans diagnosed with PNES during epilepsy monitoring unit (EMU) evaluation. For the three-year period following diagnosis of PNES, we reviewed emergency department (ED) visits, hospitalizations, outpatient clinic visits, and radiology procedures. We compared the three years following PNES diagnosis with the three years preceding diagnosis. We also compared patients with PNES and patients with epileptic seizures (ES). RESULTS: Emergency department visits and hospitalizations were more frequent in patients with PNES compared with those in patients with ES (p=0.01). There was no overall improvement in HCU during the three-year interval following diagnosis of PNES. A transient decrease during the year following diagnosis was not sustained over three-year follow-up. Pain complaints rather than seizures were the most common reason for presentation, whereas the opposite was true for patients with ES (p<0.01). There was a sharp decrease in
neurology outpatient visits ($p<0.001$) and a decrease in primary care visits ($p<0.05$) after PNES was diagnosed. Total outpatient visits were unchanged. CONCLUSIONS: Overall HCU did not improve during the three years following diagnosis of PNES, compared with three years preceding diagnosis. The results add to studies documenting poor seizure outcomes following diagnosis of PNES and underscore the need for more effective and comprehensive treatments, addressing comorbid symptoms.


As forward genetic screens in zebrafish become more common, the number of mutants that cannot be identified by gross morphology or through transgenic approaches, such as many nervous system defects, has also increased. Screening for these difficult to visualize phenotypes demands techniques such as whole-mount in situ hybridization (WISH) or antibody staining, which require tissue fixation. To date, fixed tissue has not been amenable for generating libraries for whole genome sequencing (WGS). Here, we describe a method for utilizing genomic DNA from fixed tissue and a bioinformatics suite for WGS-based mapping of zebrafish mutants. We tested our protocol using two known zebrafish mutant alleles, gpr126st49 and egr2bfh227, both of which cause myelin defects. As further proof of concept we mapped a novel mutation, stl64, identified in a zebrafish WISH screen for myelination defects. We linked stl64 to chromosome 1 and identified a candidate nonsense mutation in the F-box and WD repeat domain containing 7 (fbxw7) gene. Importantly, stl64 mutants phenocopy previously described fbxw7vu56 mutants, and knock-down of fbxw7 in wild-type animals produced similar defects, demonstrating that stl64 disrupts fbxw7 Together, these data show that our mapping protocol can map and identify causative lesions in mutant screens which require tissue fixation for phenotypic analysis.


Summary Background: The role of the Chief Research Informatics Officer (CROI) is emerging in academic health centers to address the challenges clinical researchers face in the increasingly digitalized, data-intensive healthcare system. Most current CROIs are the first officers in their institutions to hold that role. To date there is very little published information about this role and the individuals who serve it. Objective: To increase our understanding of the CROI role, the leaders who serve it, and the factors associated with their success in their organizations. Methods: The Clinical Research Informatics Working Group of the American Medical Informatics Association (AMIA) conducted a national survey of CROIs in the United States and convened an expert panel of CROIs to discuss their experience during the 2016 AMIA Annual Symposium. Results: CROIs come from diverse academic backgrounds. Most have advance training and extensive experience in biomedical informatics but the majority have been CROIs for less than three years. CROIs identify funding, data governance, and advancing data analytics as their major challenges. Conclusion: CROIs play an important role in helping shape the future of clinical research, innovation, and data analytics in healthcare in their organizations. They share many of the same challenges and see the same opportunities for the future of the field. Better understanding the background and experience of current CROIs can help define and develop the role in other organizations and enhance their influence in the field of research informatics. © Schattauer 2017.

Since the 2007 Diabetes Surgery Summit in Rome, Italy, and the subsequent publishing of the world’s first guidelines for the surgical treatment of type 2 diabetes (T2D), much new evidence regarding the efficacy and safety of metabolic surgery has emerged. Additional observational cohort studies support the superior effects of surgery over medical treatment with respect to glycemic control, weight loss, and even reduction in mortality and microvascular complications associated with T2D. Furthermore, new safety data suggest that the perioperative morbidity and mortality of metabolic surgery (5% and 0.3%, respectively) are now similar to that of common low-risk procedures, such as cholecystectomy and hysterectomy. The largest advance, however, has been the completion of 11 randomized controlled trials from around the globe that compare surgery with medical treatment of T2D. These studies with follow-up duration of 1-5 years involve nearly 800 patients without surgical mortality and with major complication rates of less than 5% and a reoperation rate of 8%. All but 1 of the 11 randomized controlled trials have shown the superiority of surgery over medical management at achieving remission or glycemic improvement. Surgery was also superior to medical treatment with respect to improving cardiovascular risk factors, such as weight loss and dyslipidemia, while reducing medication burden. This new efficacy and safety evidence should help guide physicians across the globe to the appropriate use of surgery as an effective treatment for patients suffering from T2D and obesity.


STUDY DESIGN: A retrospective review of large, multicenter adult spinal deformity (ASD) database. OBJECTIVE: The aim of this study was to build a model based on baseline demographic, radiographic, and surgical factors that can predict clinically significant proximal junctional kyphosis (PJF) and proximal junctional failure (PJF). SUMMARY OF BACKGROUND DATA: PJF and PJK are significant complications and it remains unclear what are the specific drivers behind the development of either. There exists no predictive model that could potentially aid in the clinical decision making for adult patients undergoing deformity correction. METHODS: Inclusion criteria: age ≥18 years, ASD, at least four levels fused. Variables included in the model were demographics, primary/revision, use of three-column osteotomy, upper-most instrumented vertebra (UIV)/lower-most instrumented vertebra (LIV) levels and UIV implant type (screw, hooks), number of levels fused, and baseline sagittal radiographs [pelvic tilt (PT), pelvic incidence and lumbar lordosis (PI-LL), thoracic kyphosis (TK), and sagittal vertical axis (SVA)]. PJK was defined as an increase from baseline of proximal junctional angle ≥20 degrees with concomitant deterioration of at least one SRS-Schwab sagittal modifier grade from 6 weeks postop. PJF was defined as requiring revision for PJK. An ensemble of decision trees were constructed using the C5.0 algorithm with five different bootstrapped models, and internally validated via a 70:30 data split for training and testing. Accuracy and the area under a receiver operator characteristic curve (AUC) were calculated. RESULTS: Five hundred ten patients were included, with 357 for model training and 153 as testing targets (PJF: 37, PJK: 102). The overall model accuracy was 86.3% with an AUC of 0.89 indicating a good model fit. The seven strongest (importance ≥0.95) predictors were age, LIV, pre-operative SVA, UIV implant type, UIV, pre-operative PT, and pre-operative PI-LL. CONCLUSION: A successful model (86% accuracy, 0.89 AUC) was built predicting either PJF or clinically significant PJK. This model can set the groundwork for preop point of care decision making, risk stratification, and need for prophylactic strategies for patients undergoing ASD surgery. LEVEL OF EVIDENCE: 3.


Prothrombin complex concentrates (PCCs) have been associated with a possible risk of thromboembolic complications, potentially attributable to an increased ratio of the plasma concentration of factor II (FII) to antithrombin (AT). We developed a mathematical model to examine the relationship between amounts of
PCC or therapeutic plasma administered, and plasma levels of FII and AT. The model showed that PCC produces substantial increases in plasma levels of FII but only small changes in AT, increasing the FII:AT ratio. Therapeutic plasma was shown to have only modest effects on levels of FII or AT, unless high doses are used. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Shad, M. U. (2017). What do we know about insight into illness and its association with the underlying biology of schizophrenia? Schizophr Res. doi:10.1016/j.schres.2017.08.017


OBJECTIVE: To characterize stimulation of taste fibers in the facial nerve following cochlear implantation. PATIENT: A 34-year old presented with reversible dysgeusia following activation of a cochlear implant. INTERVENTION: Reprogramming targeted to specific offending electrodes reduced symptom intensity. Computed tomography demonstrated dehiscence of the bone separating the labyrinthine segment of the facial nerve and the basal turn of the cochlea in proximity to the electrode array. RESULTS: Dysgeusia was attributed to stimulation of taste fibers in the facial nerve by electrodes 13 to 16 of the cochlear implant array located in the superior-most portion of the basal turn. CONCLUSIONS: Dysgeusia following cochlear implant activation has not previously been reported. This likely results from stimulation of taste fibers through dehiscence of the bone separating the labyrinthine segment of the Fallopian canal and the basal turn of the cochlea. While in some cases of apparent dehiscence there may be thin bone present, recognition of this potential anatomic feature may influence the choice of which ear and which electrode design to implant.


BACKGROUND: The assessment of capillary refill time (CRT) is a common physical examination technique. However, despite its importance and its widespread use, there is little standardization, which can lead to inaccurate assessments. OBJECTIVE: In this article, we assessed how different physicians estimate CRT. We hypothesized that when different physicians are presented with the same recordings of CRT, clinicians will, on average, provide different CRT estimates. METHODS: Using recordings of different fingertip compressions, physicians assessed and documented when capillary refill had returned to normal. Videos were recorded of the fingertips only, with no other identifying markers or subject characteristics provided. Videos were shown at one-quarter speed to allow time for recognition and response to the capillary refill. The primary outcome was physician estimates of CRT for each video recording. RESULTS: An analysis of variance regression revealed significant differences in physician estimates of CRT when examining the same CRT videos from 34 subjects. Further regression analyses reveal the importance of controlling for the physician that is examining the patient when predicting a patient’s CRT. CONCLUSIONS: Results indicate that some physicians gave, on average, slower CRT estimates, whereas others gave, on average, faster CRT estimates. Objective approaches and innovations in assessment of capillary refill have the potential to increase the diagnostic accuracy of this important clinical examination finding.

OBJECTIVE: Bupropion is often categorized as a newer generation antidepressant and assessed with serotonin reuptake inhibitors as a lower risk than older tricyclic antidepressants (TCAs). The objective of this study was to compare outcomes in adolescent suicide from ingestions between bupropion and TCA medications.

STUDY DESIGN: An analysis of the National Poison Data System for exposures coded "suspected suicide" in adolescents (age: 13-19) was undertaken for the years 2013-2016 and included TCAs or bupropion. We compared clinical effects, therapies and medical outcomes.

RESULTS: Over the four-year period there were 2253 bupropion and 1496 TCA adolescent suspected suicide calls. There was a significant linear increase in bupropion ingestions over the four years. Across all years, there were on average 189.2 (95% CI: 58.1-320.4; p = .01) more ingestions of bupropion than TCA. When comparing bupropion to a TCA, ingestions of bupropion were significantly more likely to be accompanied by seizure (30.7% vs 3.9%; p < .01), to be admitted (74.8% vs 61.6%; p < .01) and medical outcomes to be coded as a major outcome (19.3% vs 10.0%; p < .01). The number of cases with death or major clinical outcome for both increased over the four-year period. Ingestions of bupropion were less likely to have hypotension (2.7% vs 8.0%; p < .01) and less likely to be intubated (5.6% vs 16.4%; p < .01) as compared to ingestions of TCA.

CONCLUSIONS: Adolescents who overdose on a single medication in a suicide attempt with bupropion have a statistically significant higher incidence of major outcomes and seizures. The risks of bupropion as a potential means of suicidal gesture by overdose must be considered, and weighed against its benefits and side effect profile when choosing an appropriate agent for the treatment of depression in adolescents.


OBJECTIVE: The etonogestrel (ENG) subdermal implant can cause frequent breakthrough bleeding in some users. The objective of this study was to evaluate whether a short course of tamoxifen reduces bleeding/spotting days compared to placebo in ENG implant users. STUDY DESIGN: In this double-blind trial, we randomized ENG implant users with frequent or prolonged bleeding or spotting to tamoxifen 10 mg or placebo twice daily for 7 days, to be started after 3 consecutive days of bleeding/spotting. Treatment was repeated as needed up to three times in 180 days. Subjects completed a daily text message bleeding diary. A sample size of 56 provided 80% power to detect a difference of 6 days of bleeding/spotting per 30 days by two-sample t test. Ovulation was monitored by urinary metabolites of progesterone. RESULTS: From March 2014 to February 2015, 56 women enrolled. Fifty-one completed at least 30 days of follow up, and 34 completed 180 days. Compared to women randomized to placebo, women randomized to tamoxifen reported 5 fewer days of bleeding/spotting over 30 days (95% confidence interval [CI] -9.9 to -0.9, p = .05), and 15.2 more continuous bleeding-free days (95% CI 2.8-27.5 days, p = .02) after first use of study drug. Conclusions could not be drawn after 30 days due to higher-than-expected dropout. No ovulation was detected. CONCLUSION: First use of tamoxifen by ENG implant users reduces bleeding/spotting days and provides a longer cessation of bleeding/spotting than placebo, without compromising ovulation suppression. Further study is needed to determine whether this effect is maintained with repeat use. IMPLICATIONS: Women with frequent ENG implant-related breakthrough bleeding may experience a reduction in bleeding/spotting days and an
increase in continuous bleeding-free days in the month following first use of tamoxifen. This short course of tamoxifen was well tolerated with bleeding cessation noted within a median of 5 days.


Influence of the conditions for aerobic oxidation of catalysed by the MnxEFG protein complex on the morphology, structure and reactivity of the resulting biogenic manganese oxides (MnOx) is explored. Physical characterisation of MnOx includes scanning and transmission electron microscopy, and X-ray photoelectron and K-edge Mn, Fe X-ray absorption spectroscopy. This characterisation reveals that the MnOx materials share the structural features of birnessite, yet differ in the degree of structural disorder. Importantly, these biogenic products exhibit strikingly different morphologies that can be easily controlled. Changing the substrate-to-protein ratio produces MnOx either as nm-thin sheets, or rods with diameters below 20 nm, or a combination of the two. Mineralisation in solutions that contain makes solids with significant disorder in the structure, while the presence of facilitates formation of more ordered materials. The (photo)oxidation and (photo)electrocatalytic capacity of the MnOx minerals is examined and correlated with their structural properties. © 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim


Crisaborole and dupilumab represent the first 2 Food and Drug Administration (FDA)-approved therapies for atopic dermatitis (AD) in more than 15 years, and there are many promising drugs currently in development. This new wave of therapeutics capitalizes on the large body of work clarifying the pathogenesis of AD over the last several decades. In particular, type 2 cytokine-driven inflammation and skin barrier dysfunction are key processes underlying AD pathogenesis.


BACKGROUND AND OBJECTIVES: The optimal curriculum for training family physicians for rural practice within a traditional urban-based residency is not defined. We used the scope of practice among recent family medicine graduates of residencies associated with Preparing the Personal Physician for Practice (P4), practicing in small communities, to identify rural curriculum components. METHODS: We surveyed graduates 18 months after residency between 2007 and 2014. The survey measured self-reported practice characteristics, including community size, and scope of practice. We compared the subgroups according to practice community size. RESULTS: Compared to graduates in larger communities, those practicing in small communities were more likely to report a broader scope of clinical practice including: adult hospital care (59% vs 35%), vaginal deliveries (23% vs 12%), C sections as primary surgeon (14% vs 5%) and assistant (21% vs 8%), newborn hospital care (45% vs 24%), and procedures such as endometrial biopsy (46% vs 33%), joint injections and aspirations (89% vs 79%), and fracture care (58% vs 42%). Graduates in small communities were also more often engaged in assessing community health needs (78% vs 64%) and developing community interventions (67% vs 51%) compared to graduates in larger communities. In contrast, graduates in small communities were less likely to have integrated behavioral health (26% vs 46%) and case management support (37% vs 52%). CONCLUSIONS: A rural practice curriculum should include training toward a broad medical scope of practice as well as skills in community-oriented primary care and integrated behavioral health.
OBJECTIVE: Although previous reports suggest that surgery can improve the pain and disability of cervical spinal deformity (CSD), techniques are not standardized. Our objective was to assess for consensus on recommended surgical plans for CSD treatment. METHODS: Eighteen CSD cases were assembled, including a clinical vignette, cervical imaging (radiography, computed tomography/magnetic resonance imaging), and full-length standing radiography. Fourteen deformity surgeons (10 orthopedic, 4 neurosurgery) were queried regarding recommended surgical plans. RESULTS: There was marked variation in treatment plans across all deformity types. Even for the least complex deformities (moderate midcervical apex kyphosis), there was lack of agreement on approach (50% combined anterior-posterior, 25% anterior only, 25% posterior only), number of anterior (range, 2-6) and posterior (range, 4-16) fusion levels, and types of osteotomies. As the kyphosis apex moved caudally (cervical-thoracic junction/upper thoracic spine) and for cases with chin-on-chest kyphosis, >80% of surgeons agreed on a posterior-only approach and >70% recommended a pedicle subtraction osteotomy or vertebral column resection, but the range in number of anterior (4-8) and posterior (4-27) fusion levels was exceptionally broad. Cases of cervical/cervical-thoracic scoliosis had the least agreement for approach (48% posterior only, 33% combined anterior-posterior, 17% anterior-posterior-anterior or posterior-anterior-posterior, 2% anterior only) and had broad variation in the number of anterior (2-5) and posterior (6-19) fusion levels, and recommended osteotomies (41% pedicle subtraction osteotomy/vertebral column resection). CONCLUSIONS: Among a panel of deformity surgeons, there was marked lack of consensus on recommended surgical approach, osteotomies, and fusion levels for CSD. Further study is warranted to assess whether specific surgical treatment approaches are associated with better outcomes.

OBJECTIVE: Using a simple simulation, we illustrate why associations estimated from studies restricted to preterm births cannot be interpreted causally. DESIGN, SETTING, AND POPULATION: Data simulation involving a hypothetical cohort of fetuses who may be healthy or have one or more of four pathological factors (termed A through D, increasing in severity) with known effects on gestational length and risk of mortality. We focus on babies born \( \leq 32 \) weeks of gestation. METHODS: We visually represent the simulated population and compare the association between A (which may represent preeclampsia) and neonatal death. We then repeat the exercise with D (standing in for chorioamnionitis) as the exposure of interest. MAIN OUTCOME MEASURES: Odds ratios of neonatal death in the simulated data. RESULTS: In most weeks, and for both A and D, the calculated odds ratios are substantially biased and underestimate the true risk of neonatal death associated with each pathology. For example, factor A has a true causal odds ratio of 1.50, yet it appears protective among births \( \leq 32 \) weeks (estimated crude odds ratio = 0.39, gestational age-adjusted odds ratio = 0.71). CONCLUSIONS: Among very preterm births, virtually all babies are born with pathologies that increase risk of adverse outcomes. Thus, babies exposed to one factor (e.g., preeclampsia) are compared with babies who have a mix of other pathologies. Such selection bias affects studies carried out among very preterm births (e.g., where preeclampsia appears to reduce risk of neonatal outcomes). FUNDING: JMS is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, United States National Institutes of Health (grant number R00 HD079658-03). This article is protected by copyright. All rights reserved.
Polymerization shrinkage stress of resin-based materials have been related to several unwanted clinical consequences, such as enamel crack propagation, cusp deflection, marginal and internal gaps, and decreased bond strength. Despite the absence of strong evidence relating polymerization shrinkage to secondary caries or fracture of posterior teeth, shrinkage stress has been associated with post-operative sensitivity and marginal stain. The latter is often erroneously used as a criterion for replacement of composite restorations. Therefore, an indirect correlation can emerge between shrinkage stress and the longevity of composite restorations or resin-bonded ceramic restorations. The relationship between shrinkage and stress can be best studied in laboratory experiments and a combination of various methodologies. The objective of this review article is to discuss the concept and consequences of polymerization shrinkage and shrinkage stress of composite resins and resin cements. Literature relating to polymerization shrinkage and shrinkage stress generation, research methodologies, and contributing factors are selected and reviewed. Clinical techniques that could reduce shrinkage stress and new developments on low-shrink dental materials are also discussed.


**PURPOSE:** Clinical trials have demonstrated the efficacy of bladder-preserving chemoradiation therapy (BPT) in muscle-invasive bladder cancer but have differed in the radiation therapy dose/fractionations, radiation therapy targets, and concurrent chemotherapy regimens used. No data exist on the technical and practical approaches actually used in clinical practice throughout the United States when delivering BPT. We performed a survey to explore radiation oncologists’ practice patterns. **METHODS AND MATERIALS:** We conducted an electronic survey of US radiation oncologists regarding the management of patients with cT2-3N0M0 transitional cell muscle-invasive bladder cancer. The instrument included questions regarding the types of patients treated with BPT, as well as several aspects of treatment delivery. Descriptive statistics were reported for all responses. Pearson chi2 tests were used for univariate analysis. **RESULTS:** In total, 277 physicians completed our survey. Most respondents (58%) stated that they only treated 1 to 3 patients in the prior year. Seventy-four percent of respondents primarily treated patients deemed unfit for cystectomy, while only 28% saw patients prior to cystectomy for consultation to discuss BPT. The majority of radiation oncologists used conventional fractionation (91%) instead of hypofractionation (7.6%), but more variability existed for radiation therapy targets. Sixty percent used a small pelvis field, 29% used a whole-pelvis field, and 12% treated the bladder only. There was increased use of hypofractionation (29%) and bladder-only radiation therapy (34%) in patients who were not candidates for cystectomy or chemotherapy (P < .001). Cisplatin-based concurrent chemotherapy was most commonly preferred (89%). In non-cisplatin candidates, most respondents preferred 5-fluorouracil plus mitomycin C (32%) or carboplatin (32%). Intensity modulated radiation therapy use and midtreatment cystoscopy re-evaluation were variable, while hyperfractionation use was low. **CONCLUSIONS:** Our study describes radiation oncologists’ practice patterns for patients undergoing BPT. Although there are areas of consistency, variability exists in many technical and practical aspects of treatment delivery. Further research and education are needed to determine the optimal radiation therapy target, dose/fractionation, and concurrent chemotherapy regimen.


The bacterial manganese oxidase MnxG of the Mnx protein complex is unique among multicopper oxidases (MCOs) in carrying out a two-electron metal oxidation, converting Mn(II) to MnO2 nanoparticles. The reaction occurs in two stages: Mn(II) → Mn(III) and Mn(III) → MnO2. In a companion study, we show that the electron transfer from Mn(II) to the low-potential type 1 Cu of MnxG requires an activation step, likely forming a hydroxide bridge at a dinuclear Mn(II) site. Here we study the second oxidation step, using pyrophosphate (PP) as a Mn(III) trap. PP chelates Mn(III) produced by the enzyme and subsequently allows it to become a substrate for the second stage of the reaction. EPR spectroscopy confirms the presence of Mn(III) bound to the
enzyme. The Mn(III) oxidation step does not involve direct electron transfer to the enzyme from Mn(III), which is shown by kinetic measurements to be excluded from the Mn(II) binding site. Instead, Mn(III) is proposed to disproportionate at an adjacent polynuclear site, thereby allowing indirect oxidation to Mn(IV) and recycling of Mn(II). PP plays a multifaceted role, slowing the reaction by complexing both Mn(II) and Mn(III) in solution, and also inhibiting catalysis, likely through binding at or near the active site. An overall mechanism for Mnx-catalyzed MnO2 production from Mn(II) is presented. © 2017 American Chemical Society.


The bacterial protein complex Mnx contains a multicopper oxidase (MCO) MnxG that, unusually, catalyzes the two-electron oxidation of Mn(II) to MnO2 biomineral, via a Mn(III) intermediate. Although Mn(III)/Mn(II) and Mn(IV)/Mn(III) reduction potentials are expected to be high, we find a low reduction potential, 0.38 V (vs Normal Hydrogen Electrode, pH 7.8), for the MnxG type 1 Cu2+, the electron acceptor. Indeed the type 1 Cu2+ is not reduced by Mn(II) in the absence of molecular oxygen, indicating that substrate oxidation requires an activation step. We have investigated the enzyme mechanism via electronic absorption spectroscopy, using chemometric analysis to separate enzyme-catalyzed MnO2 formation from MnO2 nanoparticle aging. The nanoparticle aging time course is characteristic of nucleation and particle growth; rates for these processes followed expected dependencies on Mn(II) concentration and temperature, but exhibited different pH optima. The enzymatic time course is sigmoidal, signaling an activation step, prior to turnover. The Mn(II) concentration and pH dependence of a preceding lag phase indicates weak Mn(II) binding. The activation step is enabled by a pKa > 8.6 deprotonation, which is assigned to Mn(II)-H2O; it induces a conformation change (consistent with a high activation energy, 106 kJ/mol) that increases Mn(II) affinity. Mnx activation is proposed to decrease the Mn(III/II) reduction potential below that of type 1 Cu(II/I) by formation of a hydroxide-bridged binuclear complex, Mn(II)(μ-OH)Mn(II), at the substrate site. Turnover is found to depend cooperatively on two Mn(II) and is enabled by a pKa 7.6 double deprotonation. It is proposed that turnover produces a Mn(III)(μ-OH)2Mn(III) intermediate that proceeds to the enzyme product, likely Mn(IV)(μ-O)2Mn(IV) or an oligomer, which subsequently nucleates MnO2 nanoparticles. We conclude that Mnx exploits manganese polynuclear chemistry in order to facilitate an otherwise difficult oxidation reaction, as well as biomineralization. The mechanism of the Mn(III/IV) conversion step is elucidated in an accompanying paper. © 2017 American Chemical Society.


OBJECTIVES: Mucuna pruriens (MP) seeds contain levodopa (up to 2% by weight) and have been used in traditional Indian medicine to treat an illness named “Kampavata,” now understood to be Parkinson’s disease (PD). Studies have shown MP to be beneficial, and even superior, to levodopa alone in treating PD symptoms. Commercial products containing MP are readily available from online and retail sources to patients and physicians. Products often contain extracts of MP seeds, with significantly higher levodopa content than the seeds. However, MP products have limited regulatory controls with respect to quality and content of active ingredient. The aim of this study was to apply a quantitative method to determine levodopa content in readily available MP products that might be used by patients or in research studies. DESIGN: Levodopa present in six commercial MP products was quantified by solvent extraction followed by reversed-phase
high-performance liquid chromatography (HPLC) coupled to fluorescence detection (FD). Certificates of analysis (COA) were obtained, from manufacturers of MP products, to assess the existence and implementation of specifications for levodopa content. RESULTS: HPLC-FD analysis revealed that the levodopa content of the six commercial MP products varied from 6% to 141% of individual label claims. No product contained levodopa within normal pharmacopeial limits of 90%-110% label claim. The maximum daily dose of levodopa delivered by the products varied from 14.4 to 720 mg/day. COAs were inconsistent in specifications for and verification of levodopa content. CONCLUSIONS: The commercial products tested varied widely in levodopa content, sometimes deviating widely from the label claim. These deficiencies could impact efficacy and safety of MP products used by PD patients and compromise the results of scientific studies on MP products. The HPLC-FD method described in this study could be utilized by both manufacturers and scientific researchers to verify levodopa content of MP products.


STUDY OBJECTIVE: To identify guidelines for anesthesia management and determine whether general anesthesia is safe for pediatric patients on ketogenic diet (KD). DESIGN: Retrospective medical record review. SETTING: Postoperative recovery area. PATIENTS: All pediatric patients who underwent general anesthesia while on KD between 2009 and 2014 were reviewed. We identified 24 patients who underwent a total of 33 procedures. All children were on KD due to intractable epilepsy. The age of patients ranged from 1 to 15 years. INTERVENTION: General anesthesia for the scheduled procedures. MEASUREMENTS: Patients’ demographics, seizure history, type of procedure; perioperative blood chemistry, medications including the anesthesia administered, and postoperative complications. MAIN RESULTS: Twenty-four patients underwent a total of 33 procedures. The duration of KD treatment at the time of general anesthesia ranged from 4 days to 8 years. Among the 33 procedures, 3 patients had complications that could be attributable to KD and general anesthesia. A 9-year-old patient experienced increased seizures on postoperative day 0. An 8-year-old patient with hydrocephalus developed metabolic acidosis on postoperative day 1, and a 7-year-old patient’s procedure was complicated by respiratory distress and increased seizure activity in the postanesthesia care unit. CONCLUSION: This study showed that it is relatively safe for children on KD to undergo general anesthesia. The 3 complications attributable to general anesthesia were mild, and the increased seizure frequencies in 2 patients returned back to baseline in 24 hours. Although normal saline is considered more beneficial than lactated Ringer’s solution in patients on KD, normal saline should also be administered carefully because of the risk of exacerbating patients’ metabolic acidosis. One should be aware of the potential change of the ketogenic status due to drugs given intraoperatively.


PURPOSE: Incident learning systems (ILSs) are a popular strategy for improving safety in radiation oncology (RO) clinics, but few reports focus on the causes of errors in RO. The goal of this study was to test a causal factor taxonomy developed in 2012 by the American Association of Physicists in Medicine and adopted for use in the RO: Incident Learning System (RO-ILS). METHODS AND MATERIALS: Three hundred event reports were randomly selected from an institutional ILS database and Safety in Radiation Oncology (SAFRON), an international ILS. The reports were split into 3 groups of 100 events each: low-risk institutional, high-risk institutional, and SAFRON. Three raters retrospectively analyzed each event for contributing factors using the American Association of Physicists in Medicine taxonomy. RESULTS: No events were described by a single causal factor (median, 7). The causal factor taxonomy was found to be applicable for all events, but 4 causal factors were not described in the taxonomy: linear accelerator failure (n = 3), hardware/equipment failure (n = 2), failure to follow through with a quality improvement intervention (n = 1), and workflow documentation was misleading (n = 1). The most common causal factor categories contributing to events were similar in all event types. The most common specific causal factor to contribute to events was a “slip causing physical
Poor human factors engineering was the only causal factor found to contribute more frequently to high-risk institutional versus low-risk institutional events. CONCLUSIONS: The taxonomy in the study was found to be applicable for all events and may be useful in root cause analyses and future studies. Communication and human behaviors were the most common errors affecting all types of events. Poor human factors engineering was found to specifically contribute to high-risk more than low-risk institutional events, and may represent a strategy for reducing errors in all types of events.


BACKGROUND: Despite increases in imaging guidelines for other body-regions during initial trauma assessment and the demonstrated utility of chest radiographs (CXR), guidelines for use of thoracic computed-tomography (TCT) are lacking. We hypothesized that TCT utilization had not decreased relative to other protocolized CT, and mechanism and CXR could together predict significant injury independent of TCT. METHODS: We performed a retrospective review of blunt trauma patients $<=$18 y.o. (2007-2015) at two level-1 trauma centers who received chest imaging. Baseline characteristics and incidences of body region-specific CT were compared. Injury mechanism, intrathoracic pathology, and interventions among other data were examined (significance: $p<0.05$). RESULTS: Although other body-region CT incidence decreased ($p<0.05$), TCT incidence did not change ($p=0.65$). Of the 2951 patients, 567 had both CXR and TCT, 933 received TCT-only, and 1451 had CXR-only. TCT altered management in 17 patients: 2 operations, 1 stent-placement, 1 medical management, 9 thoracostomy tube placements, and 4 negative diagnostic workups. All clinically significant changes were predicted by vehicle-related mechanism and abnormal CXR findings. CONCLUSIONS: TCT utilization has not decreased over time. All meaningful interventions were predicted by CXR and mechanism of injury. We propose a rule, for prospective validation, reserving TCT for patients with abnormal CXR findings and severe vehicle-related trauma. LEVEL OF EVIDENCE: Diagnostic study, Level III.


The deployment of molecular to microscale carriers for intracellular delivery has tremendous potential for biology and medicine, especially for in vivo therapies. The field remains limited, however, by a poor understanding of how carriers gain access to the cell interior. In this review, we provide an overview of the different types of carriers, their speculated modes of entry, putative pathways of vesicular transport, and sites of endosomal escape. We compare this alongside pertinent examples from the cell biology of how viruses, bacteria, and their effectors enter cells and escape endosomal confinement. We anticipate insights into the mechanisms of cellular entry and endosomal escape will benefit future research efforts on effective carrier-mediated intracellular delivery. WIREs Nanomed Nanobiotechnol 2016, 8:465-478. doi: 10.1002/wnan.1377 For further resources related to this article, please visit the WIREs website.

Antimalarial combination therapies play a crucial role in preventing the emergence of drug-resistant Plasmodium parasites. Although artemisinin-based combination therapies (ACTs) comprise the majority of these formulations, inhibitors of the mitochondrial cytochrome bc1 complex (cyt bc1) are among the few compounds that are effective for both acute antimalarial treatment and prophylaxis. There are two known sites for inhibition within cyt bc1: atovaquone (ATV) blocks the quinol oxidase (Qo) site of cyt bc1, while some members of the endochin-like quinolone (ELQ) family, including preclinical candidate ELQ-300, inhibit the quinone reductase (Qi) site and retain full potency against ATV-resistant Plasmodium falciparum strains with Qo site mutations. Here, we provide the first in vivo comparison of ATV, ELQ-300, and combination therapy consisting of ATV plus ELQ-300 (ATV:ELQ-300), using P. yoelii murine models of malaria. In our monotherapy assessments, we found that ATV functioned as a single-dose curative compound in suppressive tests whereas ELQ-300 demonstrated a unique cumulative dosing effect that successfully blocked recrudescence even in a high-parasitemia acute infection model. ATV:ELQ-300 therapy was highly synergistic, and the combination was curative with a single combined dose of 1 mg/kg of body weight. Compared to the ATV:proguanil (Malarone) formulation, ATV:ELQ-300 was more efficacious in multiday, acute infection models and was equally effective at blocking the emergence of ATV-resistant parasites. Ultimately, our data suggest that dual-site inhibition of cyt bc1 is a valuable strategy for antimalarial combination therapy and that Qi site inhibitors such as ELQ-300 represent valuable partner drugs for the clinically successful Qo site inhibitor ATV.


**KEY POINTS:** Direction selectivity has been widely studied as an example of a complex neural computation. Directional GABA release from starburst amacrine cells (SBACs) is critical for generating directional signals in direction-selective ganglion cells. The mechanisms producing the directional release remain unclear. For SBACs, ordered distribution of sustained and transient bipolar cell inputs along the dendrites is proposed to generate directional GABA release. This study tests whether this hypothesis applies to ON-type SBACs. EPSCs activated at proximal and distal dendritic locations have the same time course. Therefore, the ordered arrangement of inputs from bipolar cells with different kinetic properties cannot be responsible for generating directional GABA release from ON-type SBACs. **ABSTRACT:** Direction selectivity in the retina relies critically on directionally asymmetric GABA release from the dendritic tips of starburst amacrine cells (SBACs). GABA release from each radially directed dendrite is larger for motion outward from the soma toward the dendritic tips than for motion inwards toward the soma. The biophysical mechanisms generating these directional signals remain controversial. A model based on electron-microscopic reconstructions of the mouse retina proposed that an ordered arrangement of kinetically distinct bipolar cell inputs to ON- and OFF-type SBACs could produce directional GABA release. We tested this prediction by measuring the time course of EPSCs in ON-type SBACs in the mouse retina, activated by proximal and distal light stimulation. Contrary to the prediction, the kinetics of the excitatory inputs were independent of dendritic location. Computer simulations based on 3D reconstructions of SBAC dendrites demonstrated that the response kinetics of distal inputs were not significantly altered by dendritic filtering. These direct physiological measurements, do not support the hypothesis that directional signals in SBACs arise from the ordered arrangement of kinetically distinct bipolar cell inputs.


**BACKGROUND:** Through development of Coordinated Care Organizations (CCOs), Oregon’s version of the Accountable Care Organization (ACO) for Medicaid beneficiaries, Oregon is redesigning the healthcare system delivering care to some of its most vulnerable citizens. While clinicians are central to healthcare transformation, little is known about the impact on their role. The aim of this study was to understand the current and perceived effect CCO-related changes have on Oregon physicians’ professional and personal lives. **METHODS:** This qualitative observational study involved semi-structured interviews, conducted
between March and October, 2013, of twenty-two purposively selected physicians who varied in years of practice, gender, employment status, specialty, and geographic location from three different CCOs. A grounded theory approach was used to analyze data. RESULTS: Physicians expressed uncertainty and ambiguity about the CCO model, reporting minor financial changes in the first year, but anticipating future reimbursement changes; new team-based care roles and responsibilities, accountability for quality incentive measures; and effects of CCO implementation on their personal lives. To meet CCO model changes and requirements, physicians requested collegial networking, team-based care training, and data system and information technology support for undergoing health system transformation. CONCLUSIONS: Although perhaps not immediate, healthcare reform can have a real and perceived impact on physicians' professional and personal lives. IMPLICATIONS: Attention to the impact of healthcare reform on physicians' personal and professional lives is important to ensure strategies are implemented to maintain a viable workforce, professional satisfaction, financial sustainability, and quality of care.


BACKGROUND: Evidence supports the benefits of exercise for patients with cancer; however, specific guidance for clinical decision making regarding exercise timing, frequency, duration, and intensity is lacking. Efforts are needed to optimize clinical recommendations for exercise in the cancer population. OBJECTIVES: To aggregate information regarding the benefit of exercise through a systematic review of existing systematic reviews in the cancer exercise literature. DATA SOURCES: PubMed, CINAHL Plus, Scopus, Web of Science, and EMBASE. STUDY ELIGIBILITY CRITERIA: Systematic reviews and meta-analyses of the impact of movement-based exercise on the adult cancer population. METHODS: Two author teams reviewed 302 abstracts for inclusion with 93 selected for full-text review. A total of 53 studies were analyzed. A Measurement Tool to Assess Systematic Reviews (AMSTAR) was used as a quality measure of the reviews. Descriptive findings are reported. RESULTS: Mean AMSTAR score = 7.66/11 (+/-2.04) suggests moderate quality of the systematic reviews. Exercise is beneficial before, during, and after cancer treatment, across all cancer types, and for a variety of cancer-related impairments. Moderate-to-vigorous exercise is the best level of exercise intensity to improve physical function and mitigate cancer-related impairments. Therapeutic exercises are beneficial to manage treatment side effects, may enhance tolerance to cancer treatments, and improve functional outcomes. Supervised exercise yielded superior benefits versus unsupervised. Serious adverse events were not common. LIMITATIONS: Movement-based exercise intervention outcomes are reported. No analysis of pooled effects was calculated across reviews due to significant heterogeneity within the systematic reviews. Findings do not consider exercise in advanced cancers or pediatric populations. CONCLUSIONS: Exercise promotes significant improvements in clinical, functional, and in some populations, survival outcomes and can be recommended regardless of the type of cancer. Although generally safe, patients should be screened and appropriate precautions taken. Efforts to strengthen uniformity in clinical trial reporting, develop clinical practice guidelines, and integrate exercise and rehabilitation services into the cancer delivery system are needed.


Prepregnancy maternal obesity is associated with adverse outcomes for the offspring, including increased incidence of neonatal bacterial sepsis and necrotizing enterocolitis. We recently reported that umbilical cord blood (UCB) monocytes from babies born to obese mothers generate a reduced IL-6/TNF-alpha response to TLR 1/2 and 4 ligands compared to those collected from lean mothers. These observations suggest altered development of the offspring’s immune system, which in turn results in dysregulated function. We therefore investigated transcriptional and epigenetic differences within UCB monocytes stratified by prepregnancy
Maternal body mass index. We show that UCB monocytes from babies born to obese mothers generate a dampened response to LPS stimulation compared with those born to lean mothers, at the level of secreted immune mediators and transcription. Because gene expression profiles of resting UCB monocytes from both groups were comparable, we next investigated the role of epigenetic differences. Indeed, we detected stark differences in methylation levels within promoters and regulatory regions of genes involved in TLR signaling in resting UCB monocytes. Interestingly, the DNA methylation status of resting cells was highly predictive of transcriptional changes post-LPS stimulation, suggesting that cytosine methylation is one of the dominant mechanisms driving functional inadequacy in UCB monocytes obtained from babies born to obese mothers. These data highlight a potentially critical role of maternal pregravid obesity-associated epigenetic changes in influencing the function of an offspring’s monocytes at birth. These findings further our understanding of mechanisms that explain the increased risk of infection in neonates born to mothers with high prepregnancy body mass index.


Engaging primary care practices in initiatives designed to enhance quality, reduce costs, and promote safety is challenging as practices are already participating in numerous projects and mandated programs designed to improve care delivery and quality. Recruiters must expand their recruitment tools to engage today’s practices in quality improvement. Using grant proposals, online diaries, observational site visits, and interviews with key stakeholders, the authors identify successful practice recruitment strategies in the EvidenceNOW initiative, which aimed to recruit approximately 1500 small- to medium-sized primary care practices. Recruiters learned they needed to articulate how participation in EvidenceNOW aligned with other initiatives and could help practices succeed with federal and state initiatives, recognition programs, and existing or future payment requirements. Recruiters, initiative leaders, and funders must now consider how their efforts align with ongoing initiatives to successfully recruit and engage practices, ease practice burden, and encourage participation in efforts that support practice transformation.


Coordinated development of excitatory and inhibitory synapses is essential for higher brain function, and impairment in this development is associated with neuropsychiatric disorders. In contrast to the large body of accumulated evidence regarding excitatory synapse development, little is known about synaptic adhesion and organization mechanisms underlying inhibitory synapse development. Through unbiased expression screens and proteomics, we identified immunoglobulin superfamily member 21 (IgSF21) as a neurexin2alpha-interacting membrane protein that selectively induces inhibitory presynaptic differentiation. IgSF21 localizes postsynaptically and recruits axonal neurexin2alpha in a trans-interaction manner. Deleting IgSF21 in mice impairs inhibitory presynaptic organization, especially in the hippocampal CA1 stratum radiatum, and also diminishes GABA-mediated synaptic transmission in hippocampal CA1 neurons without affecting their excitatory synapses. Finally, mice lacking IgSF21 show a sensorimotor gating deficit. These findings suggest that IgSF21 selectively regulates inhibitory presynaptic differentiation through interacting with presynaptic neurexin2alpha and plays a crucial role in synaptic inhibition in the brain. Molecular mechanisms regulating the development of inhibitory synapses are poorly understood. Here the authors show that IgSF21 interacts with neurexin2alpha to induce presynaptic differentiation of inhibitory synapses, and that mice lacking IgSF21 exhibit deficits in inhibitory synaptic transmission.

Teeter, A. E., Griffin, K., Howard, L. E., Aronson, W. J., Terris, M. K., Kane, C. J.,... Freedland, S. J. (2017). Does early PSADT (ePSADT) after Radical Prostatectomy, Calculated prior to PSA Recurrence, Correlate with...
PURPOSE: Short PSA doubling time (PSADT) following recurrence after radical prostatectomy (RP) portends a poor prognosis. PSADT is traditionally calculated using PSA values >0.2ng/ml. We determined if early PSADT (ePSADT), calculated from the first detectable post-operative PSA up to and including the first recurrence value, correlates with prostate cancer outcomes. METHODS: Cox models were used to examine the association between ePSADT and castration-resistant prostate cancer (CRPC), metastases, all-cause mortality (ACM), and prostate-cancer specific mortality (PCSM) in 674 men who underwent RP between 1988 and 2014. ePSADT was examined as both a log-transformed continuous and categorical variable. RESULTS: After adjusting for multiple clinicopathological characteristics, log-transformed ePSADT was not associated with any outcomes. However, when ePSADT was categorized as >/=15, 9-14.9, 3-8.9, and <3 months, on multivariable analysis, those with ePSADT <3 months had increased risk of CRPC (HR 6.20, p=0.004), metastases (HR 5.26, p=0.001), and PCSM (HR 5.06, p=0.026) and ACM (HR 1.63, p=0.065) compared to those with ePSADT >/=15 months, though the association with ACM was not significant. Those with ePSADT 3-8.9 months were at increased risk of CRPC (HR 3.56, p=0.015), ACM (HR 1.67, p=0.006), and PCSM (HR 3.17, p=0.044), but not metastases (p=0.13). CONCLUSIONS: ePSADT <9 months, calculated using PSA values before and up to BCR, is associated with increased risk of CRPC, metastases, PCSM, and ACM among men with BCR after RP. ePSADT allows for risk-stratification at BCR and before PSADT is calculable allowing these men to be referred for early aggressive secondary treatment and/or clinical trials.
CONCLUSIONS: IL-6R CC was associated with a three times greater concussion risk and APOE4 with a 40% lower risk.

INTRODUCTION: To assess the outcomes of immediate LDT versus observation strategies for T1 hepatocellular carcinoma (HCC) with respect to progression beyond Milan and survival. METHOD: T1 HCCs were retrospectively reviewed from a multidisciplinary tumour board database between September 2007 and May 2015. In the observation group, T1 lesions were observed until the tumour grew to meet T2 criteria (=2 cm). The treatment group consisted of T1 lesions treated at diagnosis with liver directed therapy (LDT). Kaplan-Meier plots were constructed for tumour progression beyond Milan and overall survival. RESULTS: 87 patients (observation n=56; LDT n=31) were included in the study. A total of 22% (n=19) of patients progressed beyond Milan with no difference in progression between treatment and observation groups (19% vs 23%, p=0.49). Median time to progression beyond Milan was 16 months. Overall transplantation rate was 22% (observation n=16; treatment group n=3, p=0.04). Median survival was 55 months with LDT versus 36 months in the observation group (p=0.22). In patients who progressed to T2 (n=60), longer time to T2 progression was a predictor of improved survival (HR=0.94, 95% CI 0.88 to 0.99, p=0.03). CONCLUSIONS: Immediate LDT of T1 lesions was not associated with increased risk of progression beyond Milan criteria when compared with an observation approach. Longer time to T2 progression was associated with increased survival and may be a surrogate for favourable tumour biology.


Functional reconstruction of craniofacial defects is a major clinical challenge in craniofacial sciences. The advent of biomaterials is a potential alternative to standard autologous/allogenic grafting procedures to achieve clinically successful bone regeneration. This article discusses various classes of biomaterials currently used in craniofacial reconstruction. Also reviewed are clinical applications of biomaterials as delivery agents for sustained release of stem cells, genes, and growth factors. Recent promising advancements in 3D printing and bioprinting techniques that seem to be promising for future clinical treatments for craniofacial reconstruction are covered. Relevant topics in the bone regeneration literature exemplifying the potential of biomaterials to repair bone defects are highlighted.


The mechanistic target of rapamycin (mTOR), a protein kinase, is a central regulator of mammalian metabolism and physiology. Protein mTOR complex 1 (mTORC1) functions as a major sensor for the nutrient, energy, and redox state of a cell and is activated by ras homolog enriched in brain (RHEB1), a GTP-binding protein. Increased activation of mTORC1 pathway has been associated with developmental abnormalities, certain form of epilepsy (tuberous sclerosis), and cancer. Clinically, those mTOR-related disorders are treated with the mTOR inhibitor rapamycin and its rapalogs. Because the effects of chronic interference with mTOR signaling in the aged brain are yet unknown, we used a genetic strategy to interfere with mTORC1 signaling selectively by introducing mutations of Rheb1 into the mouse. We created conventional knockout (Rheb1 +/-) and gene trap (Rheb1 Delta/+ ) mutant mouse lines. Rheb1-insufficient mice with different combinations of mutant alleles were monitored over a time span of 2 years. The mice did not show any behavioral/neurological changes during the first 18 months of age. However, after aging (> 18 months of age), both the Rheb1 +/- and Rheb1 Delta/- hybrid males developed rare stress-induced seizures, whereas Rheb1 +/- and Rheb1 Delta/- females and Rheb1 Delta/+ and Rheb1 Delta/Delta mice of both genders did
not show any abnormality. Our findings suggest that chronic intervention with mTORC1 signaling in the aged brain might be associated with major adverse events.


Introduction: Recurrent joint hemarthroses due to hemophilia (Factor VIII and Factor IX deficiency) often lead to invasive orthopedic interventions to decrease frequency of bleeding and/or to alleviate pain associated with end-stage hemophilic arthropathy. Aim: Identify trends in invasive orthopedic interventions among people with hemophilia who were enrolled in the Universal Data Collection (UDC) program during the period 2000–2010. Methods: Data were collected from 130 hemophilia treatment centers in the United States annually during the period 2000–2010, in collaboration with the Centers for Disease Control and Prevention (CDC). The number of visits in which an invasive orthopedic intervention was reported was expressed as a proportion of the total visits in each year of the program. Invasive orthopedic interventions consisted of arthroplasty, arthrodesis, and synovectomy. Joints included in this study were the shoulder, elbow, hip, knee, and ankle. Results: A 5.6% decrease in all invasive orthopedic interventions in all joints of people with hemophilia enrolled in the UDC program over the 11-year study period was observed. Conclusions: These data reflect a declining trend in invasive orthopedic interventions in people with hemophilia. Further research is needed to understand the characteristics that may influence invasive orthopedic interventions. © 2016 John Wiley & Sons Ltd


PURPOSE: To estimate the potential near-term population impact of alternative second opinion breast biopsy pathology interpretation strategies. METHODS: Decision analysis examining 12-month outcomes of breast biopsy for nine breast pathology interpretation strategies in the U.S. health system. Diagnoses of 115 practicing pathologists in the Breast Pathology Study were compared to reference-standard-consensus diagnoses with and without second opinions. Interpretation strategies were defined by whether a second opinion was sought universally or selectively (e.g., 2nd opinion if invasive). Main outcomes were the expected proportion of concordant breast biopsy diagnoses, the proportion involving over- or under-interpretation, and cost of care in U.S. dollars within one-year of biopsy. RESULTS: Without a second opinion, 92.2% of biopsies received a concordant diagnosis. Concordance rates increased under all second opinion strategies, and the rate was highest (95.1%) and under-treatment lowest (2.6%) when all biopsies had second opinions. However, over-treatment was lowest when second opinions were sought selectively for initial diagnoses of invasive cancer, DCIS, or atypia (1.8 vs. 4.7% with no 2nd opinions). This strategy also had the lowest projected 12-month care costs ($5.907 billion vs. $6.049 billion with no 2nd opinions). CONCLUSIONS: Second opinion strategies could lower overall care costs while reducing both over- and under-treatment. The most accurate cost-saving strategy required second opinions for initial diagnoses of invasive cancer, DCIS, or atypia.


Potent FLT3 inhibitors, such as quizartinib (AC220), have shown promise in treating acute myeloid leukemia (AML) containing FLT3 internal tandem duplication (ITD) mutations. However, responses are not durable and resistance develops within months. In this study, we outline a two-step model of resistance whereby extrinsic
microenvironmental proteins FLT3 ligand (FL) and fibroblast growth factor 2 (FGF2) protect FLT3-ITD+ MOLM14 cells from AC220, providing time for subsequent accumulation of ligand-independent resistance mechanisms. FL directly attenuated AC220 inhibition of FLT3, consistent with previous reports. Conversely, FGF2 promoted resistance through activation of FGFR1 and downstream MAPK effectors; these resistant cells responded synergistically to combinatorial inhibition of FGFR1 and FLT3. Removing FL or FGF2 from ligand-dependent resistant cultures transiently restored sensitivity to AC220, but accelerated acquisition of secondary resistance via reactivation of FLT3 and RAS/MAPK signaling. FLT3-ITD AML patients treated with AC220 developed increased FGF2 expression in marrow stromal cells, which peaked prior to overt clinical relapse and detection of resistance mutations. Overall, these results support a strategy of early combination therapy to target early survival signals from the bone marrow microenvironment, in particular FGF2, to improve the depth of response in FLT3-ITD AML. Cancer Res; 76(22); 6471-82. (c)2016 AACR.


RATIONALE: Lung cancer screening (LCS) has a mortality benefit to high-risk smokers, but implementation remains suboptimal. Providers represent the key entry point to screening, and an understanding of provider perspectives on lung cancer screening is necessary to improve referral and overall implementation. OBJECTIVES: The objective of this study was to understand knowledge, beliefs, attitudes, barriers, and facilitators to screening in a diverse group of referring pulmonologists and primary care providers. METHODS: We conducted an electronic survey of primary care and pulmonary providers within a tertiary care medical center across different practice sites. The survey covered the following domains: 1) Beliefs and assessment of evidence; 2) Knowledge of LCS and guidelines; 3) Current screening practices; 4) Barriers and facilitators; and 5) Demographic and practice characteristics. RESULTS: The 196 participants included 80% primary care clinicians and 19% pulmonologists (1% others). 41% practiced at university-based or affiliated clinics, 47% at county hospital-based clinics, and 12% at other or unidentified sites. The majority endorsed LCS effectiveness (74%); however performance on knowledge-based assessments of screening eligibility, documentation and nodule management was suboptimal. Key barriers included inadequate time (36%), inadequate staffing (36%) and patients having too many other illnesses to address screening (38%). Decision aids, which are used at the point-of-referral, were commonly identified both as important LCS clinical facilitators (51%) and as provider knowledge facilitators (59%). There were several differences by provider specialty including primary care providers more frequently reporting time constraints and their patients having too many other illnesses to address screening as significant barriers to LCS. CONCLUSIONS: Providers endorsed the benefits of LCS, but there are limitations in provider knowledge of key screening components. The most frequently reported barriers to screening represent a lack of clinical time or resources to address lung cancer screening in clinical practice. Facilitators for nodule management as well as point-of-care referral materials may be helpful in reducing knowledge gaps and the clinical burden of referral. These are all modifiable factors, which could be addressed to increase screening referral. Differences in attitudes and barriers by specialty should also be considered to optimize screening implementation.


STUDY QUESTION: Does developmental exposure to the combination of hyperandrogenemia and western-style diet (WSD) worsen adult metabolic function compared to either treatment alone? SUMMARY ANSWER: Young female rhesus macaques treated for 3 years, beginning at menarche, with combined testosterone (T) and WSD have increased weight gain and insulin resistance compared to controls and animals treated with either T or WSD alone. WHAT IS KNOWN ALREADY: Hyperandrogenemia is a well-established component of polycystic ovary syndrome (PCOS) and can be observed in peripubertal girls, indicating a potential pubertal
onset of the disease. Obesity is often associated with hyperandrogenemia in peripubertal girls, and overweight girls appear to be at higher risk for the development of PCOS later in life. STUDY DESIGN, SIZE, DURATION: Juvenile (2.5- year old) female rhesus macaques were divided into four groups (n = 10/group): control animals receiving cholesterol implants and a control diet with 15% of calories derived from fat (C), animals receiving T implants (mean serum levels: 1.35 +/- 0.01 ng/ml) and a control diet (T), animals receiving a cholesterol implant and a WSD with 36% of calories derived from fat (WSD) and animals receiving a T implant and a WSD (T + WSD). Animals were maintained on the treatments for 36 months and were 5.5 years old at study completion. PARTICIPANTS/MATERIALS, SETTING, METHODS: Metabolic testing consisted of body measurements including weight, dual-energy X-ray absorptiometry scans, activity monitoring, and glucose tolerance testing at zero months and at least once every 12 months for the remainder of the study. Indirect calorimetry and serum hormone assays were performed following 36 months of treatment. MAIN RESULTS AND THE ROLE OF CHANCE: Body weight and fat mass gain were significantly increased in T + WSD at 24 and 36 months of treatment compared to the other three groups. Log transformed fasting insulin and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were significantly increased in T + WSD animals at 3 years of treatment compared to all other groups. T-treatment caused a greater rate of decline in activity after 18 months, while food intake and metabolic rate were largely unaffected by treatments. LIMITATIONS REASONS FOR CAUTION: Variability was present in the metabolic parameters measured; however, this is similar to the heterogeneity observed in human populations. WIDER IMPLICATIONS OF THE FINDINGS: Chronic hyperandrogenemia beginning at puberty may exacerbate metabolic dysfunction in women consuming a WSD and account for the increased rates of obesity and insulin resistance observed in PCOS patients. Counseling of female patient populations with elevated androgens about the potential benefit of consuming a lower fat diet could improve long-term metabolic health outcomes. STUDY FUNDING/COMPETING INTEREST(S): Eunice Kennedy Shriver National Institute of Child Health & Human Development P50HD071836 and Oregon National Primate Center Grant P51 OD011092. The authors have no competing conflict of interests to disclose.


OBJECTIVE: Describe blood loss with surgical abortion >/=16weeks of gestation in anticoagulated patients. STUDY DESIGN: Clinicians involved in a professional listserv (2011-2013) reported cases of abortion >/=16weeks of gestation in anticoagulated women. RESULTS: All 7 patients were using or had recently discontinued low molecular weight heparin (LMWH). One patient was reported to have greater than anticipated blood loss for gestational age. No patients required transfusion and no complications were reported. CONCLUSIONS: Our limited case series suggests D&E may not always be contraindicated in women with recent or current LMWH use.


Amplification and overexpression of erbB2/neu proto-oncogene is observed in 20-30% human breast cancer and is inversely correlated with the survival of the patient. Despite this, somatic activating mutations within erbB2 in human breast cancers are rare. However, we have previously reported that a splice isoform of erbB2, containing an in-frame deletion of exon 16 (herein referred to as ErbB2DeltaEx16), results in oncogenic activation of erbB2 because of constitutive dimerization of the ErbB2 receptor. Here, we demonstrate that the ErbB2DeltaEx16 is a major oncogenic driver in breast cancer that constitutively signals from the cell surface. We further show that inducible expression of the ErbB2DeltaEx16 variant in mammary gland of transgenic mice results in the rapid development of metastatic multifocal mammary tumors. Genetic and biochemical characterization of the ErbB2DeltaEx16-derived mammary tumors exhibit several unique features that distinguish this model from the conventional ErbB2 ones expressing the erbB2 proto-oncogene.
in mammary epithelium. Unlike the wild-type ErbB2-derived tumors that express luminal keratins, ErbB2DeltaEx16-derived tumors exhibit high degree of intratumoral heterogeneity co-expressing both basal and luminal keratins. Consistent with these distinct pathological features, the ErbB2DeltaEx16 tumors exhibit distinct signaling and gene expression profiles that correlate with activation of number of key transcription factors implicated in breast cancer metastasis and cancer stem cell renewal.


BACKGROUND: Pelvic tilt (PT) is a compensatory mechanism for adult spinal deformity patients to mitigate sagittal imbalance. The association between preop PT and postop clinical and radiographic outcomes has not been well studied in patients undergoing minimally invasive adult deformity surgery. OBJECTIVE: To evaluate clinical and radiographic outcomes in adult spinal deformity patients with high and low preoperative PT treated surgically using less invasive techniques. METHODS: Retrospective case-control, institutional review board-approved study. A multicenter, minimally invasive surgery spinal deformity patient database was queried for 2-yr follow-up with complete radiographic and health-related quality of life (HRQOL) data. Hybrid surgery patients were excluded. Inclusion criteria were as follows: age > 18 and either coronal Cobb angle > 20, sagittal vertical axis > 5 cm, pelvic incidence-lumbar lordosis (PI-LL) > 10 or PT > 20. Patients were stratified by preop PT as per Schwab classification: low (PT < 20), mid (PT 20-30), or high (>30). Postoperative radiographic alignment parameters (PT, PI, LL, Cobb angle, sagittal vertical axis) and HRQOL data (Visual Analog Scale Back/Leg, Oswestry Disability Index) were evaluated and analyzed. RESULTS: One hundred sixty-five patients had complete 2-yr outcomes data, and 64 patients met inclusion criteria (25 low, 21 mid, 18 high PT). High PT group had higher preop PI-LL mismatch (32.1 vs 4.7; P < .001). At last follow-up, 76.5% of patients in the high PT group had continued PI-LL mismatch compared to 34.8% in the low PT group (P < .006). There was a difference between groups in terms of postop changes of PT (-3.9 vs 1.9), LL (8.7 vs 0.5), and PI-LL (-9.5 vs 0.1). Postoperatively, HRQOL data (Oswestry Disability Index and Visual Analog Scale) were significantly improved in both groups (P < .001). CONCLUSION: Adult deformity patients with high preoperative PT treated with minimally invasive surgical techniques had less radiographic success but equivalent clinical outcomes as patients with low PT.


Introduction: Duodenal polyps and especially duodenal adenomas are a rare and mostly coincidental finding in patients undergoing upper gastrointestinal endoscopy. Due to their malignant potential, duodenal adenomas should be removed upon diagnosis. So far, the limited available data on the performance of endoscopic polypectomy show conflicting results with regard to adverse events and the adenoma recurrence rate. Patients and Methods: After summarizing the currently available data, we retrospectively analyzed all patients undergoing endoscopic resection of nonampullary duodenal adenomas (NAD) at our institution between 2006 and 2016. Results: A total of 78 patients underwent endoscopic polypectomy for NAD adenoma. End-of-treatment success with complete resection requiring a mean of 1.2 interventions was achieved in 91% (n = 71). Procedural hemorrhage occurred in 12.8% (n = 10), whereas delayed bleeding was noted in 9% (n = 7). Duodenal perforation was registered and successfully treated in 2 cases (2.6%). No adenoma recurrence was noted following primary complete adenoma resection after a mean follow-up time of 33 months. Acute post-polypectomy bleeding was statistically significantly associated with large polyp size (p = 0.003) and lack of endoscopic prophylaxis (p = 0.0008). Delayed post-polypectomy bleeding
showed a trend in the occurrence of large polyps (p = 0.064), and was statistically significantly associated with familial cancer syndrome (p = 0.019) and advanced histopathology (p = 0.013). Conclusion: Our data suggest that endoscopic polypectomy of NAD is well feasible with high success rates. Procedural and delayed hemorrhage seems to be the primary issue rather than adenoma recurrence. We therefore advocate referral of patients with large NAD to experienced centers for endoscopic resection. © 2017 S. Karger AG, Basel


PURPOSE OF REVIEW: Traumatic injuries are a major cause of mortality worldwide. Damage control resuscitation or balanced transfusion of plasma, platelets, and red blood cells for the management of exsanguinating hemorrhage after trauma has become the standard of care. We review the literature regarding the use of alternatives to achieve the desired 1:1:1 ratio as availability of plasma and platelets can be problematic in some environments. RECENT FINDINGS: Liquid and freeze dried plasma (FDP) are logistical easier to use and may be superior to fresh frozen plasma. Cold storage platelets (CSPs) have improved hemostatic properties and resistance to bacterial contamination. Low titer type O whole blood can be transfused safely in civilian patients. SUMMARY: In the face of hemorrhagic shock from traumatic injury, resuscitation should be initiated with 1:1:1 transfusion of plasma, platelets, and red blood cells with limited to no use of crystalloids. Availability of plasma and platelets is limited in some environments. In these situations, the use of low titer type O whole blood, thawed or liquid plasma, cold stored platelets or reconstituted FDP can be used as substitutes to achieve optimal transfusion ratios. The hemostatic properties of CSPs may be superior to room temperature platelets.


BACKGROUND AND AIMS: Sedation for GI endoscopy directed by anesthesia professionals (ADS) is used with the intention of improving throughput and patient satisfaction. However, data on its safety are sparse because of the lack of adequately powered, randomized controlled trials comparing it with endoscopist-directed sedation (EDS). This study was intended to determine whether ADS provides a safety advantage when compared with EDS for EGD and colonoscopy. METHODS: This retrospective, nonrandomized, observational cohort study used the Clinical Outcomes Research Initiative National Endoscopic Database, a network of 84 sites in the United States composed of academic, community, health maintenance organization, military, and Veterans Affairs practices. Serious adverse events (SAEs) were defined as any event requiring administration of cardiopulmonary resuscitation, hospital or emergency department admission, administration of rescue/reversal medication, emergency surgery, procedure termination because of an adverse event, intraprocedural adverse events requiring intervention, or blood transfusion. RESULTS: There were 1,388,235 patients in this study that included 880,182 colonoscopy procedures (21% ADS) and 508,053 EGD procedures (23% ADS) between 2002 and 2013. When compared with EDS, the propensity-adjusted SAE risk for patients receiving ADS was similar for colonoscopy (OR, .93; 95% CI, .82-1.06) but higher for EGD (OR, 1.33; 95% CI, 1.18-1.50). Additionally, with further stratification by American Society of Anesthesiologists (ASA) class, the use of ADS was associated with a higher SAE risk for ASA I/II and ASA III subjects undergoing EGD and showed no difference for either group undergoing colonoscopy. The sample size was not sufficient to make a conclusion regarding ASA IV/V patients. CONCLUSIONS: Within the confines of the SAE definitions used, use of anesthesia professionals does not appear to bring a safety benefit to patients receiving colonoscopy and is associated with an increased SAE risk for ASA I, II, and III patients undergoing EGD.
STUDY QUESTION: What are the separate and combined effects of mild hyperandrogenemia and consumption of a high-fat Western-style diet on white adipose tissue (WAT) morphology and function in young adult female nonhuman primates? SUMMARY ANSWER: Combined exposure to mild hyperandrogenemia and WSD induces visceral omental (OM-WAT) but not subcutaneous (SC-WAT) adipocyte hypertrophy that is associated with increased uptake and reduced mobilization of free fatty acids. WHAT IS KNOWN ALREADY: Mild hyperandrogenemia in females, principally in the context of polycystic ovary syndrome, is often associated with adipocyte hypertrophy, but the mechanisms of associated WAT dysfunction and depot specificity remain poorly understood. STUDY DESIGN, SIZE AND DURATION: Female rhesus macaques were randomly assigned at 2.5 years of age (near menarche) to receive either cholesterol (C; n = 20) or testosterone (T; n = 20)-containing silastic implants to elevate T levels 5-fold above baseline. Half of each of these groups was then fed either a low-fat monkey chow diet or WSD, resulting in four treatment groups (C, control diet; T alone; WSD alone; T + WSD; n = 10/group) that were maintained until the current analyses were performed at 5.5 years of age (3 years of treatment, young adults). PARTICIPANTS/MATERIALS, SETTING AND METHODS: OM and SC-WAT biopsies were collected and analyzed longitudinally for in vivo changes in adipocyte area and blood vessel density, and ex vivo basal and insulin-stimulated fatty acid uptake and basal and isoproterenol-stimulated lipolysis. MAIN RESULTS AND THE ROLE OF CHANCE: In years 2 and 3 of treatment, the T + WSD group exhibited a significantly greater increase in OM adipocyte size compared to all other groups (P < 0.05), while the size of SC adipocytes measured at the end of the study was not significantly different between groups. In year 3, both WAT depots from the WSD and T + WSD groups displayed a significant reduction in local capillary length and vessel junction density (P < 0.05). In year 3, insulin-stimulated fatty acid uptake in OM-WAT was increased in the T + WSD group compared to year 2 (P < 0.05). In year 3, basal lipolysis was blunted in the T and T + WSD groups in both WAT depots (P < 0.01), while isoproterenol-stimulated lipolysis was significantly blunted in the T and T + WSD groups only in SC-WAT (P < 0.01). LIMITATIONS, REASONS FOR CAUTION: At this stage of the study, subjects were still relatively young adults, so that the effects of mild hyperandrogenemia and WSD may become more apparent with increasing age. WIDER IMPLICATIONS OF THE FINDINGS: The combination of mild hyperandrogenemia and WSD accelerates the development of WAT dysfunction through T-specific (suppression of lipolytic response by T), WSD-dependent (reduced capillary density) and combined T + WSD (increased fatty acid uptake) mechanisms. These data support the idea that combined hyperandrogenemia and WSD increases the risk of developing obesity in females. STUDY FUNDING/COMPETING INTEREST(S): Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under award number P50 HD071836 to C.T.R. and award number OD 011092 from the Office of the Director, National Institutes of Health, for operation of the Oregon National Primate Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
(95% confidence intervals) were determined for colon histology prediction. RESULTS: Phase I (criteria development/internal testing): 8 criteria were assessed by 4 pCLE experts using 28 videos (14 HP/14 TA). Five of 8 pCLE criteria met selection for phase II (accuracy >75%). Phase II (external validation): 36 pCLE colon polyp videos (HP 16/TA 20) were evaluated by 8 external assessors. Overall accuracy in diagnosis of colon polyp histology was 84.9% (95% confidence interval, 81.7-87.7). Of predictions made with high confidence (75%), histology was predicted with an accuracy of 91%, sensitivity 83%, specificity 100%, negative predictive value 87% and positive predictive value 98%. Interobserver agreement was substantial (kappa=0.73).

CONCLUSIONS: We demonstrate the development and validation of pCLE criteria for prediction of colon polyp histology. Using these criteria, overall accuracy in differentiating TA from HP was high with substantial interobserver agreement.


BACKGROUND: Idiopathic intracranial hypertension (IIH) in patients with Cushing disease (CD), after treatment, is rarely described, in adults. The cause is believed to be multifactorial, potentially related to a relative decrease in cortisol after surgical resection or medical treatment of a corticotroph pituitary adenoma. We investigate our center's CD database (140 surgically and 60 medically [primary or adjunct] treated patients) for cases of IIH, describe our center’s experience with symptomatic IIH, and review treatment strategies in adults with CD after transsphenoidal resection. CASE DESCRIPTION: We present the case of a 22-year-old woman who presented with worsening headache, nausea, vomiting, blurry vision, diplopia, visual loss, and facial numbness 14 weeks after surgical resection of adrenocorticotropic hormone-positive pituitary adenoma. Her CD had been in remission since surgery, with subsequent adrenal insufficiency (AI), which was initially treated with supraphysiologic glucocorticoid replacement, tapered down to physiologic doses at the time the IIH symptoms developed. CONCLUSIONS: Symptomatic IIH is rare in adult patients but can be severe and result in permanent vision loss. A high index of suspicion should be maintained and a fundus examination is necessary to exclude papilledema, whenever there are suggestive symptoms that initially may overlap with AI. It is possible that some cases of mild IIH are misdiagnosed as GC withdrawal or AI; however, further studies are needed. Treatment consists of reinitiation of higher steroid doses together with acetazolamide with or without cerebrospinal fluid diversion and the priority is to preserve vision and reverse any visual loss.


Systemic iron homeostasis is maintained by regulation of iron absorption in the duodenum, iron recycling from erythrocytes, and iron mobilization from the liver and is controlled by the hepatic hormone hepcidin. Hepcidin expression is induced via the bone morphogenetic protein (BMP) signaling pathway that preferentially uses two type-I (ALK2 and ALK3) and two type-II (ActRIIA and Bmpr2) BMP receptors. Hemojuvelin (HJV), HFE, and transferrin receptor-2 (TfR2) facilitate this process presumably by forming a plasma membrane complex with BMP receptors. Matriptase-2 (MT2) is a protease and key suppressor of hepcidin expression and cleaves HJV. Previous studies have therefore suggested that MT2 exerts its inhibitory effect by inactivating HJV. Here, we report that MT2 suppresses hepcidin expression independently of HJV. In Hjv−/− mice, increased expression of exogenous MT2 in the liver significantly reduced hepcidin expression similarly as observed in wild-type mice. Exogenous MT2 could fully correct abnormally high hepcidin expression and iron deficiency in MT2−/− mice. In contrast to MT2, increased Hjv expression caused no significant changes in wild-type mice, suggesting that Hjv is not a limiting factor for hepcidin expression. Further studies revealed that MT2 cleaves ALK2, ALK3, ActRIIA, Bmpr2, Hfe, and to a lesser extent Hjv and TfR2. MT2-mediated TfR2 cleavage was also observed in HepG2 cells endogenously expressing MT2 and TfR2. Moreover, iron-loaded transferrin blocked MT2-mediated TfR2 cleavage, providing further insights into the
mechanism of Tfr2 regulation by transferrin. Together, these observations indicate that MT2 suppresses hepcidin expression by cleaving multiple components of the hepcidin induction pathway.


The cause of PHACE syndrome is unknown. In a study of 218 patients, we examined potential prenatal risk factors for PHACE syndrome. Rates of pre-eclampsia and placenta previa in affected individuals were significantly greater than in the general population. No significant risk factor differences were detected between male and female subjects.


OBJECTIVE: To determine if arterial oxygen and carbon dioxide abnormalities in the first 24h after return of spontaneous circulation (ROSC) are associated with increased mortality in adult out-of-hospital cardiac arrest (OHCA). METHODS: We used data from the Resuscitation Outcomes Consortium (ROC), including adult OHCA with sustained ROSC >/=1h after Emergency Department arrival and at least one arterial blood gas (ABG) measurement. Among ABGs measured during the first 24h of hospitalization, we identified the presence of hyperoxemia (PaO2/= 300mmHg), hypoxemia (PaO2<60mmHg), hypercarbia (PaCO2>50mmHg) and hypocarbia (PaCO2<30mmHg). We evaluated the associations between oxygen and carbon dioxide abnormalities and hospital mortality, adjusting for confounders. RESULTS: Among 9186 OHCA included in the analysis, hospital mortality was 67.3%. Hyperoxemia, hypoxemia, hypercarbia, and hypocarbia occurred in 26.5%, 19.0%, 51.0% and 30.6%, respectively. Initial hyperoxemia only was not associated with hospital mortality (adjusted OR 1.10; 95% CI: 0.97-1.26). However, final and any hyperoxemia (1.25; 1.11-1.41) were associated with increased hospital mortality. Initial (1.58; 1.30-1.92), final (3.06; 2.42-3.86) and any (1.76; 1.54-2.02) hypoxemia (PaO2<60mmHg) were associated with increased hospital mortality. Initial (1.89; 1.70-2.10); final (2.57; 2.18-3.04) and any (1.85; 1.67-2.05) hypercarbia (PaCO2>50mmHg) were associated with increased hospital mortality. Initial (1.13; 0.90-1.41), final (1.19; 1.04-1.37) and any (1.01; 0.91-1.12) hypocarbia (PaCO2<30mmHg) were not associated with hospital mortality. CONCLUSIONS: In the first 24h after ROSC, abnormal post-arrest oxygen and carbon dioxide tensions are associated with increased out-of-hospital cardiac arrest mortality.


HYPOTHESIS: Auditory input in people with hearing impairment will improve balance while walking. BACKGROUND: Auditory input is increasingly recognized as an additional input for balance. Several studies have found auditory cues to improve static balance measured on a sway platform. The effect of audition on gait, a dynamic task also linked to fall risk, has not been fully examined. If a positive effect were shown between audition and balance, it would further indicate that improving hearing could also improve balance.

METHODS: Inertial sensors quantified gait parameters of 13 bilateral hearing aid users and 12 bilateral cochlear implant (CI) users with their hearing devices on and off. Outcome measures included gait velocity, stride length variability, swing time variability, and double support phase. RESULTS: Group analysis of each of the gait outcomes showed no significant differences between the aided and unaided conditions in both the hearing aid and CI groups. Gait velocity, an outcome most strongly linked to fall risk had 95% confidence interval differences of -2.16 to 1.52 and -1.45 to 4.17 cm/s in hearing aid and CI users, respectively (aided versus unaided condition). There was considerable variation among participants with some individuals improving in all four parameters. CONCLUSION: The overall findings were not statistically significant,
however, a small subset of our population improved clinically across several outcomes. This demonstrates that audition may have a clinically beneficial effect on balance in some patients.


INTRODUCTION: The over-the-scope-clip (OTSC) can potentially overcome limitations of standard clips and achieve more efficient and reliable hemostasis. Data on OTSC use for non-variceal upper gastrointestinal bleeding (NVUGIB) in patients with cardiovascular comorbidities are currently limited. PATIENTS AND METHODS: We prospectively collected and retrospectively analyzed our database from February 2009 to September 2015 from all patients who underwent emergency endoscopy for high-risk NVUGIB in 2 academic centers and were treated with OTSC as first-line (n = 81) or second-line therapy (n = 19). RESULTS: One hundred patients mean age 72 (range 27 - 97 years) were included in this study. Fifty-one percent (n = 51) had severe cardiovascular co-morbidity (ischemic heart disease, congestive heart failure, hypertension, valvular heart disease, peripheral arterial occlusive disease and atrial fibrillation) and 73 % (n = 73) were on antiplatelet or/and anticoagulation therapy. The median size of the treated ulcers was 3 cm (range 1 - 5 cm). In 94 % (n = 94) primary hemostasis with OTSC was achieved. Clinical long-term success during a mean 6-month follow-up without rebleeding was 86 % (n = 86). CONCLUSIONS: In this cohort OTSC was demonstrated to be a safe and effective first- or second-line treatment for NVUGIB in high-risk patients with cardiovascular disease and complex, large ulcers.


Enzyme immunoassays (EIAs) are widely used to measure salivary testosterone. However, little is known about how accurately different EIAs assess testosterone, partially because estimates across various EIAs differ considerably. We compared testosterone concentrations across EIAs of three commonly used manufacturers (DRG International, Salimetrics, and IBL International) to liquid chromatography tandem mass spectrometry (LC-MS/MS). Relative to EIAs from Salimetrics and IBL International, EIAs supplied by DRG International provided the closest approximation to LC-MS/MS testosterone concentrations, followed closely by EIAs from Salimetrics, and then IBL. Additionally, EIAs tended to inflate estimates of lower testosterone concentrations in women. Examining our results and comparing them to existing data revealed that testosterone EIAs had decreased linear correspondence with LC-MS/MS in comparison to cortisol EIAs. Overall, this paper provides researchers with information to better measure testosterone in their research and more accurately compare testosterone measurements across different methods.

PURPOSE: To determine global protein expression changes in the lens of the GSH-deficient LEGSKO mouse model of age-related cataract compared with recently published gene expression data obtained by RNA-Seq transcriptome analysis. METHODS: Lenses were separated into epithelial and cortical fiber sections, digested with trypsin, and labeled with isobaric tags (10-plex TMTTM). Peptides were analyzed by LC-MS/MS (Orbitrap Fusion) and mapped to the mouse proteome for relative protein quantification. RESULTS: 1871 proteins in lens epithelia and 870 proteins in lens fiber cells were quantified. 40 proteins in LEGSKO epithelia, 14 proteins in LEGSKO fiber cells, 22 proteins in buthionine sulfoximine (BSO)-treated LEGSKO epithelia, and 55 proteins in BSO-treated LEGSKO fiber cells had significantly (p<0.05, FDR<0.1) altered protein expression compared to WT controls. HSF4 and MAF transcription factors were the most common upstream regulators of the response to GSH-deficiency. Many detoxification proteins, including aldehyde dehydrogenases, peroxiredoxins, and quinone oxidoreductase, were upregulated but several glutathione S-transferases were downregulated. Several cellular stress response proteins showed regulation changes, including an upregulation of HERPUD1, downregulation of heme oxygenase, and mixed changes in heat shock proteins. NRF2-regulated proteins showed broad upregulation in BSO-treated LEGSKO fiber cells, but not in other groups. Strong trends were seen in downregulation of lens specific proteins, including beta- and gamma-crystallins, lenssin, and phakinin, and in epithelial-mesenchymal transition (EMT)-related changes. Western blot analysis of LEGSKO lens epithelia confirmed expression changes in several proteins. CONCLUSIONS: This dataset confirms at the proteomic level many findings from the recently determined GSH-deficient lens transcriptome and provides new insight into the roles of GSH in the lens, how the lens adapts to oxidative stress, and how GSH affects EMT in the lens.


Accurate retrospective reporting of activities and symptoms has been shown to be problematic for older adults, yet standard clinical care relies on self-reports to aid in assessment and management. Our aim was to examine the relationship between self-report and sensor-based measures of activity. We administered an online activity survey to participants in our ongoing longitudinal study of in-home ubiquitous monitoring. We found a wide range of accuracies when comparing self-report with time-stamped sensor-based data. Of the 95 participants who completed the 2-hr activity log, nearly one quarter did not complete the task in a way that could potentially be compared with sensor data. Where comparisons were possible, agreement between self-reported and sensor-based activity was achieved by a minority of participants. The findings suggest that capture of real-time events with unobtrusive activity monitoring may be a more reliable approach to describing behavioral patterns and meaningful changes in older adults.


Pediatric Neurocritical Care diagnoses account for a large proportion of intensive care admissions. Critical care survivors suffer high rates of long-term morbidity, including physical disability, cognitive impairment, and psychosocial dysfunction. To address these morbidities in Pediatric Neurocritical Care survivors, collaboration between Pediatric Neurology and Pediatric Critical Care created a multidisciplinary follow-up clinic providing specialized evaluations after discharge. Clinic referrals apply to all Pediatric Neurocritical Care patients regardless of admission severity of illness. Here, we report an initial case series, which revealed a population that is heterogenous in age, ranging from 1 month to 18 years, and in diagnoses. Traumatic brain injuries of
varying severity as well as neuroinfectious and inflammatory diseases accounted for the majority of referrals. Most patients (87%) seen in the clinic had morbidities identified, requiring ongoing evaluation and expansion of the clinic. Cognitive and psychological disturbance were seen in over half of patients at the initial clinic follow-up. Sleep disturbances, daytime fatigue, headache or chronic pain, and vision or hearing concerns were also common at initial follow-up. Data from this initial population of clinic patients reiterates the need for specialized follow-up care, but also highlights the difficulties related to providing this comprehensive care and evaluating interventions to improve outcomes.


Early diagnosis and treatment of melanoma improve survival. New technologies are emerging that may augment the diagnosis, assessment, and management of melanoma but penetrance into everyday practice is low. In the current health care climate, greater emphasis will be placed on the incorporation of technology for clinically suspicious pigmented lesions to facilitate better, more cost-effective management.


Purpose Chemotherapy-induced peripheral neuropathy (CIPN) may persist after treatment ends and may lead to functional decline and falls. This study compared objective and self-report measures of physical function, gait patterns, and falls between women cancer survivors with and without symptoms of CIPN to identify targets for functional rehabilitation. Methods A secondary data analysis of 512 women cancer survivors (age, 62 +/- 6 years; time since diagnosis, 5.8 +/- 4.1 years) categorized and compared women self-reporting symptoms of CIPN (CIPN+) with asymptomatic women (CIPN-) on the following: maximal leg strength, timed chair stand, physical function battery, gait characteristics (speed; step number, rate, and length; base of support), self-report physical function and disability, and falls in the past year. Results After an average of 6 years after treatment, 47% of women still reported symptoms of CIPN. CIPN+ had significantly worse self-report and objectively measured function than did CIPN-, with the exception of maximal leg strength and base of support during a usual walk. Gait was slower among CIPN+, with those women taking significantly more, but slower and shorter, steps than did CIPN- (all P < .05). CIPN+ reported significantly more disability and 1.8 times the risk of falls compared with CIPN- (P < .0001). Increasing symptom severity was linearly associated with worsening function, increasing disability, and higher fall risk (all P < .05). Conclusion This work makes a significant contribution toward understanding the functional impact of CIPN symptoms on cancer survivors. Remarkably, 47% of women in our sample had CIPN symptoms many years after treatment, together with worse function, greater disability, and more falls. CIPN must be assessed earlier in the clinical pathway, and strategies to limit symptom progression and to improve function must be included in clinical and survivorship care plans.


Objective: Patients with rheumatoid arthritis (RA) are at increased risk of herpes zoster, and vaccination is recommended for patients ages 50 years and older, prior to starting treatment with biologic agents or tofacitinib. Tofacitinib is an oral JAK inhibitor for the treatment of RA. We evaluated its effect on the immune response and safety of live zoster vaccine (LZV). Methods: In this phase II, 14-week, placebo-controlled trial, patients ages 50 years and older who had active RA and were receiving background methotrexate were given LZV and randomized to receive tofacitinib 5 mg twice daily or placebo 2-3 weeks postvaccination. We
measured humoral responses (varicella zoster virus [VZV]-specific IgG level as determined by glycoprotein enzyme-linked immunosorbent assay) and cell-mediated responses (VZV-specific T cell enumeration, as determined by enzyme-linked immunospot assay) at baseline and 2 weeks, 6 weeks, and 14 weeks postvaccination. End points included the geometric mean fold rise (GMFR) in VZV-specific IgG levels (primary end point) and T cells (number of spot-forming cells/106 peripheral blood mononuclear cells) at 6 weeks postvaccination. Results: One hundred twelve patients were randomized to receive tofacitinib (n=55) or placebo (n=57). Six weeks postvaccination, the GMFR in VZV-specific IgG levels was 2.11 in the tofacitinib group and 1.74 in the placebo group, and the VZV-specific T cell GMFR was similar in the tofacitinib group and the placebo group (1.50 and 1.29, respectively). Serious adverse events occurred in 3 patients in the tofacitinib group (5.5%) and 0 patients (0.0%) in the placebo group. One patient, who lacked preexisting VZV immunity, developed cutaneous vaccine dissemination 2 days after starting tofacitinib (16 days postvaccination). This resolved after tofacitinib was discontinued and the patient received antiviral treatment. Conclusion: Patients who began treatment with tofacitinib 2-3 weeks after receiving LZV had VZV-specific humoral and cell-mediated immune responses to LZV similar to those in placebo-treated patients. Vaccination appeared to be safe in all of the patients except 1 patient who lacked preexisting VZV immunity. © 2017 The Authors. Arthritis & Rheumatology published by Wiley Periodicals, Inc. on behalf of American College of Rheumatology.


Primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) has become recently more complex than ever, leaving the clinicians perplexed with outdated guidelines and emerging evidence about new LDL-C lowering therapies. 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines have focused on high intensity statin therapy for specific groups of patients, while abandoning long established LDL-C goals, a strategy which no longer seems valid. PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors have emerged as the add-on therapy on top of statins and/or ezetimibe for the treatment of hypercholesterolemia and ASCVD prevention. In several clinical trials, PCSK9 inhibitors have demonstrated their safety and robust LDL-C-lowering power. One completed cardiovascular (CV) outcomes trial (FOURIER; Further Cardiovascular Outcomes Research with PCSK9 Inhibitions in Subjects with Elevated Risk) has demonstrated that PCSK9 inhibition reduces rates of CV death as well as non-fatal stroke and MI, while another major CV outcome trial is under way (ODYSSEY-OUTCOMES). Several trials studying CV benefits of novel LDL-C-lowering therapies are also being conducted. Prompt revision of ACC/AHA guidelines is necessary. In the meantime, physicians need to use clinical judgment integrating the most recent evidence into their practice.


BACKGROUND AND OBJECTIVES: To examine the effectiveness of behavioral interventions for melanoma prevention targeted to individuals at elevated risk due to personal and/or family history. METHODS: Through literature searches in 5 search databases (through July 2014), 20 articles describing 14 unique interventions focused on melanoma prevention among individuals at elevated risk for the disease were identified. Interventions targeting only patients undergoing active treatment for melanoma were excluded. RESULTS: The average study quality was moderate. The majority of interventions (6 out of 9, 66% of studies) led to improvements in one or more photoprotective behaviors, particularly for improvements in use of protective clothing (3 out of 5, 60% of studies), and frequency and/or thoroughness of skin self-examinations (9 out of 12, 75%). Fewer interventions (5 out of 14, 36%) targeted uptake of total body skin examinations (60% led to improvements). Also, fewer interventions targeted all three preventive behaviors (5 out of 14, 36%). CONCLUSIONS: Findings suggest that future interventions should aim to improve adherence across multiple preventive behaviors, over a longer time period (past 8months post-intervention), and target high-risk children. Studies should include adequate sample sizes to investigate moderators and mediators of intervention effectiveness. Interventions may be strengthened by new techniques, such as incorporating family members (e.g., to improve thoroughness of skin self-examinations) and eHealth technology.


The mossy fiber-granule cell-parallel fiber system conveys proprioceptive and corollary discharge information to principal cells in cerebellum-like systems. In the dorsal cochlear nucleus (DCN), Golgi cells inhibit granule cells and thus regulate information transfer along the mossy fiber-granule cell-parallel fiber pathway. Whereas excitatory synaptic inputs to Golgi cells are well understood, inhibitory and electrical synaptic inputs to Golgi cells have not been examined. Using paired recordings in a mouse brain slice preparation, we find that Golgi cells of the cochlear nucleus reliably form electrical synapses onto one another. Golgi cells were only rarely electrically coupled to superficial stellate cells, which form a separate network of electrically coupled interneurons in the DCN. Spikelets had a biphasic effect on the excitability of postjunctional Golgi cells, with a brief excitatory phase and a prolonged inhibitory phase due to the propagation of the prejunctional afterhyperpolarization through gap junctions. Golgi cells and stellate cells made weak inhibitory chemical synapses onto Golgi cells with low probability. Electrical synapses are therefore the predominant form of synaptic communication between auditory Golgi cells. We propose that electrical synapses between Golgi cells may function to regulate the synchrony of Golgi cell firing when electrically coupled Golgi cells receive temporally correlated excitatory synaptic input.


INTRODUCTION: The risk of stillbirth associated with maternal obesity increases with gestational age; however, it is unclear if earlier delivery reduces the overall perinatal mortality rate. Our objective was to compare the risk of perinatal mortality associated with each additional week of expectant management to that of immediate delivery. METHODS: This was a retrospective cohort study of singleton non-anomalous births in Texas between 2006 and 2011. Analyses were stratified based on maternal pre-pregnancy BMI class. For each BMI class, we calculated the rate of neonatal death and stillbirth at each week of gestation from 34 to 41 weeks. A composite risk of perinatal mortality associated with 1 week of expectant management was estimated combining the stillbirth rate of the current week and the neonatal death rate of the following week. This was compared with the rate of neonatal death of the current week. RESULTS: After all exclusions, 2,149,771 births remained for analysis. In the normal weight group, stillbirth risk increased from 0.8 per 10,000 births at 34 weeks to 5.7 per 10,000 births at 42 weeks, whereas the neonatal death risk decreased from 76.5 per 10,000
births at 34 weeks to 30.4 per 10,000 births at 42 weeks, there were no differences between expectant management and delivery for any gestational week. In the obese group, stillbirth risk increased from 1.8 per 10,000 births at 34 weeks to 10.5 per 10,000 births at 42 weeks, whereas the neonatal death risk decreased from 67.7 per 10,000 births at 34 weeks to 26.2 per 10,000 births at 42 weeks, the perinatal mortality risk favored delivery at 39 weeks (RR: 1.17; 99% CI: 1.01-1.36) and not thereafter. In contrast, in the morbidly obese group, stillbirth risk increased from 8.8 per 10,000 births at 34 weeks to 83.7 per 10,000 births at 42 weeks, whereas the neonatal death risk decreased from 63.6 per 10,000 births at 34 weeks to 15.5 per 10,000 births at 42 weeks, the perinatal mortality risk favored delivery from 38 weeks (RR: 1.53; 99% CI: 1.16-2.02) through 41 weeks (RR: 5.39; 99% CI: 1.83-15.88). CONCLUSION: The findings reported here suggest that delivery by 38 weeks in gestation minimizes perinatal mortality in pregnancies complicated by maternal morbid obesity.


OBJECTIVE: To evaluate the potential role of low serum Ca levels in the occurrence of sudden cardiac arrest (SCA) in the community. PATIENTS AND METHODS: We compared 267 SCA cases [177 (66%) men] and 445 controls [314 (71%) men] from a large population-based study (catchment population approximately 1 million individuals) in the US Northwest from February 1, 2002, through December 31, 2015. Patients were included if their age was 18 years or older with available creatinine clearance (CrCl) and serum electrolyte levels for analyses to enable adjustment for renal function. For cases, creatinine clearance and electrolyte levels were required to be measured within 90 days of the SCA event. RESULTS: Cases of SCA had higher proportions of blacks [31 (12%) vs 14 (3%); P<.001], diabetes mellitus [122 (46%) vs 126 (28%); P<.001], and chronic kidney disease [102 (38%) vs 73 (16%); P<.001] than did controls. In multivariable logistic regression analysis, a 1-unit decrease in Ca levels was associated with a 1.6-fold increase in odds of SCA (odds ratio, 1.63; 95% CI, 1.06-2.51). Blood Ca levels lower than 8.95 mg/dL (to convert to mmol/L, multiply by 0.025) were associated with a 2.3-fold increase in odds of SCA as compared with levels higher than 9.55 mg/dL (odds ratio, 2.33; 95% CI, 1.17-4.61). Cases of SCA had significantly prolonged corrected QT intervals on the 12-lead electrocardiogram than did controls (465+/−37 ms vs 425+/−33 ms; P<.001). CONCLUSION: Lower serum Ca levels were independently associated with an increased risk of SCA in the community.


Medecins sans Frontiere, an international non-governmental organization, initiated a mental health program for Palestinian refugees living in Lebanon. To evaluate the impact of the program after its completion, focus groups were conducted with three target groups: (1) patients, (2) staff, and (3) local community stakeholders. Participants voiced overall satisfaction with the program. The program provided easy access, good quality care, decreased stigma, as perceived by participants, and revealed a sense of community contentedness. In addition, several short-term outcomes were achieved, such as increasing the numbers of patients visiting the center/ receiving mental health treatment. However, lack of planning for sustainability and proper procedures for hand-over of the program constituted a major downfall. Program discontinuation posed ethical dilemmas, common in provisional interventions in underprivileged refugee communities.

Nasopharyngeal carcinoma (NPC) is an invasive cancer with particularly high incidence in Southeast Asia and Southern China. The pathogenic mechanisms of NPC, particularly those involving epigenetic dysregulation, remain largely elusive, hampering clinical management of this malignancy. To identify novel druggable targets, we carried out an unbiased high-throughput chemical screening and observed that NPC cells were highly sensitive to inhibitors of cyclin-dependent kinases (CDK), especially THZ1, a covalent inhibitor of CDK7. THZ1 demonstrated pronounced anti-neoplastic activities both in vitro and vivo. An integrative analysis using both whole-transcriptome sequencing (RNA-Seq) and chromatin-immunoprecipitation sequencing (ChIP-Seq) pinpointed oncogenic transcriptional amplification mediated by super-enhancers (SE) as a key mechanism underlying the vulnerability of NPC cells to THZ1 treatment. Further characterization of SE-mediated networks identified many novel SE-associated oncogenic transcripts, such as BCAR1, F3, LDLR, TBC1D2 and the long non-coding RNA TP53TG1. These transcripts were highly and specifically expressed in NPC and functionally promoted NPC malignant phenotypes. Moreover, DNA-binding motif analysis within the SE segments suggest that several transcription factors (including ETS2, MAFK and TEAD1) may help establish and maintain SE activity across the genome. Taken together, our data establish the landscape of SE-associated oncogenic transcriptional network in NPC, which can be exploited for the development of more effective therapeutic regimens for this disease.


The rebound mechanism for alkane hydroxylation was invoked over 40 years ago to help explain reactivity patterns in cytochrome P450, and subsequently has been used to provide insight into a range of biological and synthetic systems. Efforts to model the rebound reaction in a synthetic system have been unsuccessful, in part because of the challenge in preparing a suitable metal-hydroxide complex at the correct oxidation level. Herein we report the synthesis of such a complex. The reaction of this species with a series of substituted radicals allows for the direct interrogation of the rebound process, providing insight into this uniformly invoked, but previously unobserved process.


As has been well established, the Diabetes Care journal’s most visible signature event is the Diabetes Care Symposium held each year during the American Diabetes Association’s Scientific Sessions. Held this past year on 10 June 2017 in San Diego, California, at the 77th Scientific Sessions, this event has become one of the most attended sessions during the Scientific Sessions. Each year, in order to continue to have the symposium generate interest, we revise the format and content of this event. For this past year, our 6th annual symposium, I felt it was time to provide a comprehensive overview of our efforts in diabetes care to determine, first and foremost, how we arrived at our current state of management. I also felt the narrative needed to include the current status of management, especially with a focus toward cardiovascular disease, and finally, we wanted to ask what the future holds. Toward this goal, I asked four of the most noted experts in the world to provide their opinion on this topic. The symposium started with a very thoughtful presentation by Dr. Jay Skyler entitled “A Look Back as to How We Got Here.” That was followed by two lectures on current concepts by Dr. Bernard Zinman entitled “Current Treatment Paradigms Today—How Well Are We Doing?” and by Dr. Matthew Riddle entitled “Evolving Concepts and Future Directions for Cardiovascular Outcomes Trials.” The final lecture for the symposium was delivered by Dr. Ele Ferrannini and was entitled “What Does the Future Hold?” As always, a well-attended and well-received symposium is now the norm for our signature event and our efforts were rewarded by the enthusiasm of the attendees. This

Understanding how murine models can elucidate the mechanisms underlying antitumor immune responses and advance immune-based drug development is essential to advancing the field of cancer immunotherapy. The Society for Immunotherapy of Cancer (SITC) convened a workshop titled, “Challenges, Insights, and Future Directions for Mouse and Humanized Models in Cancer Immunology and Immunotherapy” as part of the SITC 31st Annual Meeting and Associated Programs on November 10, 2016 in National Harbor, MD. The workshop focused on key issues in optimizing models for cancer immunotherapy research, with discussions on the strengths and weaknesses of current models, approaches to improve the predictive value of mouse models, and advances in cancer modeling that are anticipated in the near future. This full-day program provided an introduction to the most common immunocompetent and humanized models used in cancer immunology and immunotherapy research, and addressed the use of models to evaluate immune-targeting therapies. Here, we summarize the workshop presentations and subsequent panel discussion.