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Henry Ford Health System Publication List – February 2017

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health System personnel. Searches were conducted in PubMed, Embase, Web of Science, and Google Scholar during the beginning of February, and then imported into EndNote for formatting. There are 83 unique citations listed this month. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

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Administration

Coticchia ME. Taking a broader approach to innovation *Front Health Serv Manage* 2016; 33(2):27-32. PMID: 28199288. Article request form

Mark E. Coticchia is vice president and chief innovation officer of the Henry Ford Health System in Detroit, Michigan.

Allergy

Hoch HE, Calatroni A, West JB, Liu AH, Gergen PJ, Gruchalla RS, Hershey KG, Kercsmar CM, **Kim H**, Lamm CI, Makhija MM, Mitchell HE, Teach SJ, Wildfire JJ, Busse WW, and Szefler SJ. Can we predict fall asthma exacerbations? Validation of the seasonal asthma exacerbation index *J Allergy Clin Immunol* 2017;PMID: 28238748. Full text

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Boston University School of Medicine, Boston, MA.
Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, CO.
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University of Texas Southwestern Medical Center, Dallas, TX.
Cincinnati Children's Hospital, Cincinnati, OH.
Henry Ford Health System, Detroit, MI.
Columbia University College of Physicians and Surgeons, New York, NY.
Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.
Children's National Health System, Washington, DC.
University of Wisconsin School of Medicine and Public Health, Madison, WI.

BACKGROUND: A Seasonal Asthma Exacerbation Predictive Index (saEPI) was previously reported based on two prior NIAID Inner City Asthma Consortium trials. OBJECTIVE: We sought to validate the saEPI in a separate trial designed to prevent fall exacerbations with omalizumab therapy. METHODS: The saEPI and its components were analyzed to characterize those who had an asthma exacerbation during the PROSE (Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations) study. We characterized those inner-city children with and without asthma exacerbations in the fall periods treated with guidelines based therapy (GBT) in the absence and presence of omalizumab. RESULTS: A higher saEPI was associated with an exacerbation in both the GBT alone ($p<0.001$, AUC 0.76) and the GBT + omalizumab group ($p<0.01$, AUC 0.65). In the GBT group, younger age at recruitment, higher total IgE, higher blood eosinophil percent and number, and higher treatment step were associated with those who had an exacerbation compared to those who did not. In the GBT + omalizumab group, younger age at recruitment, increased eosinophil number, recent exacerbation, and higher treatment step were also associated with those who had an exacerbation. The saEPI was associated with a high negative predictive value in both groups. CONCLUSIONS: An exacerbation in children treated with GBT with or without omalizumab was associated with a higher saEPI along with higher markers of allergic inflammation, treatment step, and a recent exacerbation. Those that exacerbated on omalizumab had similar features, indicating a need to develop better markers to predict poor

response to omalizumab therapy and alternative treatment strategies for children with these risk factors. The saEPI was able to reliably predict those children unlikely to have an asthma exacerbation in both groups.

Allergy

Liu AH, **Zoratti EM**, Pongracic JA, Babineau DC, Visness CM, Gergen PJ, Togias A, and Busse WW. Reply *J Allergy Clin Immunol* 2017;PMID: 28237730. Full text

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Behavioral Health

Jesse MT, **Abouljoud M**, **Eshelman A**, De Reyck C, and Lerut J. Professional interpersonal dynamics and burnout in european transplant surgeons *Clin Transplant* 2017;PMID: 28185307. Full text

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Burnout within the health professions has become an increasingly important topic. Evidence suggests there are differences in burnout across different countries. Research has yet to examine burnout in transplant surgeons throughout Europe. METHODS: A cross-sectional survey of transplant surgeons across Europe. Survey included sociodemographics, professional characteristics, frequency and discomfort with difficult patient interactions, decisional autonomy, psychological job demands, support (coworker, supervisor, and hospital administration), and burnout including emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA). RESULTS: 108 transplant surgeons provided data; 33 (30.6%) reported high EE, 19 (17.6%) reported high DP, and 29 (26.9%) reported low PA. Three hierarchical multiple linear regressions examined the burnout subscales as outcomes (EE, DP, and PA) and predictors selected based upon theoretical relationships with the outcomes. Greater psychological job demands, greater discomfort in managing difficult patient interactions, and lower levels of perceived supervisor support predicting greater EE. Only decisional autonomy significantly predicted DP, accounting for a small proportion of the variance. None of the steps for PA were significant. CONCLUSIONS: Given prior research on burnout, there were several surprising findings from this study. For example, the relatively low levels of emotional exhaustion compared to U.S. physicians and surgeons. At this time, we can only hypothesize why this finding occurred but there are multiple possible explanations including cultural effects, response bias, or other factors unknown at this time. Research is needed to attempt to clarify these findings.

Behavioral Health

Ketterer MW, **Chawa M**, and **Paone G**. Prospective correlates of early (30 day) readmissions on a cardiothoracic surgery service *Psychol Health Med* 2017:1-8. PMID: 28161983. Article request form

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Known to vary widely among hospitals for unclear reasons, early readmissions are associated with higher mortality and are suspected to frequently be due to inadequate discharge preparation/planning. It has been previously documented that the strongest and most consistent predictor of early readmissions in CHF patients is chronic cognitive impairment, and compensatory assistance with adherence on discharge improves early readmission rates. Prospective observational study. The present investigation examined multiple putative perioperative predictors of early readmission in a hospitalized Cardiothoracic Surgery Service. A subtest of the Mini-Cog, Short Term Memory, was the strongestunivariate predictor of early readmissions ($p < .001$), but the overall Mini-Cog ($p = .024$), Age ($p = .045$), Number of Admissions over the Preceding Year ($p = .036$), an Anxiety Scale ($p = .035$), Years of Education (p

= .055) and a Depression Scale (p = .056) also demonstrated covariation. In a Logistic Regression, only Short Term Memory survived as a predictor variable (p = .007), correctly classifying 76% of patients. Chronic cognitive impairment is a predictor of early readmissions in Cardiothoracic patients. A brief bedside exam interpreted in medical context may permit identification of patients requiring familial assistance for adherence on discharge.

Bone and Joint Center
Gibson GJ, and **Yang M**. What rheumatologists need to know about CRISPR/Cas9 *Nat Rev Rheumatol* 2017;PMID: 28202911. Article request form

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CRISPR/Cas9 genome editing technology has taken the research world by storm since its use in eukaryotes was first proposed in 2012. Publications describing advances in technology and new applications have continued at an unrelenting pace since that time. In this Review, we discuss the application of CRISPR/Cas9 for creating gene mutations - the application that initiated the current avalanche of interest - and new developments that have largely answered initial concerns about its specificity and ability to introduce new gene sequences. We discuss the new, diverse and rapidly growing adaptations of the CRISPR/Cas9 technique that enable activation, repression, multiplexing and gene screening. These developments have enabled researchers to create sophisticated tools for dissecting the function and inter-relatedness of genes, as well as noncoding regions of the genome, and to identify gene networks and noncoding regions that promote disease or confer disease susceptibility. These approaches are beginning to be used to interrogate complex and multilayered biological systems and to produce complex animal models of disease. CRISPR/Cas9 technology has enabled the application of new therapeutic approaches to treating disease in animal models, some of which are beginning to be seen in the first human clinical trials. We discuss the direct application of these techniques to rheumatic diseases, which are currently limited but are sure to increase rapidly in the near future.

Cardiology
Brawner CA, **Al-Mallah MH**, **Ehrman JK**, Qureshi WT, Blaha MJ, and **Keteyian SJ**. Change in maximal exercise capacity is associated with survival in men and women *Mayo Clin Proc* 2017;PMID: 28185659. Full text

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OBJECTIVE: To describe the relationship between change in maximal exercise capacity (MEC) over time and risk of all-cause mortality separately in men and women. PATIENTS AND METHODS: Consecutive patients (n=10,854; mean +/- SD age, 54+/-11 years; 43% women; 30% nonwhite) who completed 2 physician-referred exercise tests between January 2, 1991, and May 28, 2009, were identified from the Henry Ford Exercise Testing (FIT) Project. The MEC was quantified in metabolic equivalents of task (METs) calculated from peak workload on a treadmill and adjusted to the equivalent for a 50-year-old man. Multivariable Cox proportional hazards regression was performed to assess risk of all-cause mortality associated with change in MEC based on (1) change from age-/sex-adjusted low fitness (<8 METs) to intermediate or high fitness and (2) an absolute change in METs. RESULTS: Relative to patients with low fitness at both tests, increasing from low to intermediate or high fitness was associated with lower risk of all-cause mortality (adjusted hazard ratio [aHR] = 0.63 [95% CI, 0.45-0.87] in men and 0.56 [95% CI, 0.34-0.91] in women). Each 1-MET increase in age-/sex-adjusted MEC between baseline and follow-up was associated with an aHR of 0.87 (95% CI, 0.84-0.91) in men and 0.84 (95% CI, 0.79-0.89) in women, with no significant interaction by sex (P=.995). Similar aHRs were observed in a subgroup with intermediate fitness at baseline. CONCLUSION: In men and women referred for an exercise stress test, change in MEC over time is inversely related to risk of all-cause mortality.

Cardiology
Christakopoulos GE, Christopoulos G, Karmpaliotis D, **Alaswad K**, Yeh RW, Jaffer FA, Wyman MR, Lombardi WL, Tarar MN, Grantham JA, Kandzari DE, Lembo N, Moses JW, Kirtane AJ, Parikh M, Green P, Finn M, Garcia S, Doing AH, Hatem R, Thompson CA, Banerjee S, and Brilakis ES. Predictors of excess patient radiation exposure during

chronic total occlusion coronary intervention: Insights from a contemporary multicentre registry *Can J Cardiol* 2016;PMID: 28169091. Full text

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BACKGROUND: High patient radiation dose during chronic total occlusion (CTO) percutaneous coronary intervention (PCI) might lead to procedural failure and radiation skin injury. METHODS: We examined the association between several clinical and angiographic variables on patient air kerma (AK) radiation dose among 748 consecutive CTO PCIs performed at 9 experienced US centres between May 2012 and May 2015. RESULTS: The mean age was 65 +/- 10 years, 87% of patients were men, and 35% had previous coronary artery bypass graft surgery (CABG). Technical and procedural success was 92% and 90%, respectively. The median patient AK dose was 3.40 (interquartile range, 2.00-5.40) Gy and 34% of the patients received > 4.8 Gy (high radiation exposure). In univariable analysis male sex (P = 0.016), high body mass index (P < 0.001), history of hyperlipidemia (P = 0.023), previous CABG (P < 0.001), moderate or severe calcification (P < 0.001), tortuosity (P < 0.001), proximal cap ambiguity (P = 0.001), distal cap at a bifurcation (P = 0.006), longer CTO occlusion length (P < 0.001), blunt/no blunt stump (P < 0.001), and centre (P < 0.001) were associated with higher patient AK dose. In multivariable analysis high body mass index (P < 0.001), previous CABG (P = 0.005), moderate or severe calcification (P = 0.005), longer CTO occlusion length (P < 0.001), and centre (P < 0.001) were independently associated with higher patient AK dose. CONCLUSIONS: Approximately 1 in 3 patients who undergo CTO PCI receive high AK radiation dose (> 4.8 Gy). Several baseline clinical and angiographic characteristics can help predict the likelihood of high radiation dose and assist with intensifying efforts to reduce radiation exposure for the patient and the operator.

Cardiology

de Ronde MW, Ruijter JM, **Lanfear D**, Bayes-Genis A, Kok M, Creemers E, Pinto YM, and Pinto-Sietsma SJ. Practical data handling pipeline improves performance of qPCR-based circulating miRNA measurements *Rna* 2017;PMID: 28202710. Article request form

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BACKGROUND: Since numerous miRNAs have been shown to be present in the circulation, these so-called circulating miRNAs have emerged as potential biomarkers for disease. However, results of qPCR studies on circulating miRNA biomarkers vary greatly and many experiments cannot be reproduced. Missing data in qPCR experiments often occur due to off-target amplification, non-analyzable qPCR curves and discordance between replicates. The low concentration of most miRNAs leads to most, but not all missing data. Therefore, failure to distinguish between missing data due to a low concentration and missing data due to randomly occurring technical errors partly explains the variation within and between otherwise similar studies. METHODS&RESULTS: Based on qPCR kinetics, an analysis pipeline was developed to distinguish missing data due to technical errors from missing data due to a low concentration of the miRNA-equivalent cDNA in the PCR reaction. Furthermore, this pipeline incorporates a method to statistically decide if concentrations from replicates are sufficiently concordant, which improves stability of results and avoids unnecessary data loss. By going through the pipeline's steps, the result of each measurement is categorized as either valid, invalid or undetectable. Together with a set of imputation rules, the pipeline leads to more robust and reproducible data as was confirmed experimentally. Using two validation approaches, in two cohorts totalling 2214 heart failure patients, we showed that this pipeline increases both accuracy and precision of qPCR measurements. CONCLUSION: This statistical data handling pipeline improves the performance of qPCR studies on low expressed targets such as circulating miRNAs.

Cardiology

Eng MH, **Greenbaum A**, **Dee Wang D**, **Wyman J**, **Dnp**, **Arjomand H**, **Yadav P**, **Nemeh H**, **Paone G**, Guerrero M, and **O'Neill W**. Thrombotic valvular dysfunction with transcatheter mitral interventions for postsurgical failures *Catheter Cardiovasc Interv* 2017;PMID: 28185392. Full text

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BACKGROUND: Degenerated surgical mitral valve repairs or surgical prostheses are currently being treated with transcatheter mitral valve replacement (TMVR). We report the procedural and mid-term assessment of thirteen cases. METHODS: From 12/2013 to 12/2015, 13 consecutive patients with degenerated mitral valve repair or valve replacement were treated. Patients were assessed for mitral valve academic valve consortium (MVARC) defined outcomes. RESULTS: Immediate procedural MVARC defined technical success was 92%. At 30 days MVARC device and procedure success were 61% and 84%, respectively. Mean follow-up was 150 days [IQR 40-123 days]. There were 2 late major adverse outcomes, a noncardiac related death (628 days) and a stroke (382 days). The mean mitral gradient decreased from 9.5 +/- 3.4 to 5.5 +/- 2.6 mm Hg ($P < 0.01$). Three patients were found to have high gradients, two presented with heart failure while another patient was found to have reduced leaflet motion and abnormal thickening postprocedure. The two patients with heart failure were treated with enoxaparin, which caused subsequent resolution of increased valve gradients in one patient. The other patient could not tolerate prolonged treatment from anticoagulation due to gastrointestinal bleeding. Three of 13 patients were treated with dual-antiplatelet therapy and were suspected to have valve thrombosis. CONCLUSION: Thrombotic related dysfunction post-TMVR occurred in 15% (2/13) of patients and one patient had abnormal leaflet thickening that may have been thrombus related. Dual-antiplatelet therapy was used in all 3 cases suggesting the possible need for oral anticoagulation postmitral valve-in-valve therapy. (c) 2017 Wiley Periodicals, Inc.

Cardiology

Kolte D, Khera S, Sardar MR, **Gheewala N**, Gupta T, Chatterjee S, Goldsweig A, Aronow WS, Fonarow GC, Bhatt DL, **Greenbaum AB**, Gordon PC, Sharaf B, and Abbott JD. Thirty-day readmissions after transcatheter aortic valve replacement in the United States: Insights from the nationwide readmissions database *Circ Cardiovasc Interv* 2017; 10(1)PMID: 28034845. Full text

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BACKGROUND: Readmissions after cardiac procedures are common and contribute to increased healthcare utilization and costs. Data on 30-day readmissions after transcatheter aortic valve replacement (TAVR) are limited. METHODS AND RESULTS: Patients undergoing TAVR (International Classification of Diseases-Ninth Revision-CM codes 35.05 and 35.06) between January and November 2013 who survived the index hospitalization were identified in the Nationwide Readmissions Database. Incidence, predictors, causes, and costs of 30-day readmissions were analyzed. Of 12 221 TAVR patients, 2188 (17.9%) were readmitted within 30 days. Length of stay >5 days during index hospitalization (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.24-1.73), acute kidney injury (HR, 1.23; 95% CI, 1.05-1.44), >4 Elixhauser comorbidities (HR, 1.22; 95% CI, 1.03-1.46), transapical TAVR (HR, 1.21; 95% CI, 1.05-1.39), chronic kidney disease (HR, 1.20; 95% CI, 1.04-1.39), chronic lung disease (HR, 1.16; 95% CI, 1.01-1.34), and discharge to skilled nursing facility (HR, 1.16; 95% CI, 1.01-1.34) were independent predictors of 30-day readmission. Readmissions were because of noncardiac causes in 61.8% of cases and because of cardiac causes in 38.2% of cases. Respiratory (14.7%), infections (12.8%), bleeding (7.6%), and peripheral vascular disease (4.3%) were the most common noncardiac causes, whereas heart failure (22.5%) and arrhythmias (6.6%) were the most common cardiac causes of readmission. Median length of stay and cost of readmissions were 4 days (interquartile

range, 2-7 days) and $8302 (interquartile range, $5229-16 021), respectively. CONCLUSIONS: Thirty-day readmissions after TAVR are frequent and are related to baseline comorbidities, TAVR access site, and post-procedure complications. Awareness of these predictors can help identify and target high-risk patients for interventions to reduce readmissions and costs.

Cardiology

McCord J, **Cabrera R**, Lindahl B, Giannitsis E, **Evans K**, **Nowak R**, **Frisoli T**, Body R, Christ M, deFilippi CR, Christenson RH, **Jacobsen G**, Alquezar A, Panteghini M, Melki D, Plebani M, Verschuren F, French J, Bendig G, Weiser S, and Mueller C. Prognostic utility of a modified HEART score in chest pain patients in the emergency department *Circ Cardiovasc Qual Outcomes* 2017; 10(2)PMID: 28167641. Full text

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BACKGROUND: The TRAPID-AMI trial study (High-Sensitivity Troponin-T Assay for Rapid Rule-Out of Acute Myocardial Infarction) evaluated high-sensitivity cardiac troponin-T (hs-cTnT) in a 1-hour acute myocardial infarction (AMI) exclusion algorithm. Our study objective was to evaluate the prognostic utility of a modified HEART score (m-HS) within this trial. METHODS AND RESULTS: Twelve centers evaluated 1282 patients in the emergency department for possible AMI from 2011 to 2013. Measurements of hs-cTnT (99th percentile, 14 ng/L) were performed at 0, 1, 2, and 4 to 14 hours. Evaluation for major adverse cardiac events (MACEs) occurred at 30 days (death or AMI). Low-risk patients had an m-HS</=3 and had either hs-cTnT<14 ng/L over serial testing or had AMI excluded by the 1-hour protocol. By the 1-hour protocol, 777 (60%) patients had an AMI excluded. Of those 777 patients, 515 (66.3%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 262 (33.7%) patients had an m-HS>/=4, with 6 (2.3%) patients having MACEs (P=0.007). Over 4 to 14 hours, 661 patients had a hs-cTnT<14 ng/L. Of those 661 patients, 413 (62.5%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 248 (37.5%) patients had an m-HS>/=4, with 5 (2.0%) patients having MACEs (P=0.03). CONCLUSIONS: Serial testing of hs-cTnT over 1 hour along with application of an m-HS identified a low-risk population that might be able to be directly discharged from the emergency department.

Cardiology

Thomas GS, Cullom SJ, Kitt TM, Feaheny KM, **Ananthasubramaniam K**, Gropler RJ, Jain D, and Thompson RC. The EXERRT trial: "EXErcise to Regadenoson in Recovery Trial": A phase 3b, open-label, parallel group, randomized, multicenter study to assess regadenoson administration following an inadequate exercise stress test as compared to regadenoson without exercise for myocardial perfusion imaging using a SPECT protocol *J Nucl Cardiol* 2017;PMID: 28224449. Article request form

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Cardiovascular Nuclear Imaging Laboratory, New York Medical College, Westchester Medical Center, Valhalla, NY, USA.
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University of Missouri-Kansas City, Kansas City, MO, USA.

BACKGROUND: This study assessed the non-inferiority and safety of regadenoson administration during recovery from inadequate exercise compared with administration without exercise. METHODS: Patients unable to achieve adequate exercise stress were randomized to regadenoson 0.4 mg either during recovery (Ex-Reg) or 1 hour after inadequate exercise (Regadenoson) (MPI1). All patients also underwent non-exercise regadenoson MPI 1-14 days later (MPI2). The number of segments with reversible perfusion defects (RPDs) detected using single photon emission computerized tomography imaging was categorized. The primary analysis evaluated the majority agreement rate between Ex-Reg and Regadenoson groups. RESULTS: 1,147 patients were randomized. The lower bound of the 95% confidence interval of the difference in agreement rates (-6%) was above the -7.5% non-inferiority margin, demonstrating non-inferiority of Ex-Reg to Regadenoson. Adverse events were numerically less with Ex-Reg (MPI1). In the Ex-Reg group, one patient developed an acute coronary syndrome and another had a myocardial infarction following regadenoson after exercise. Upon review, both had electrocardiographic changes consistent with ischemia prior to regadenoson. CONCLUSIONS: Administering regadenoson during recovery from inadequate exercise results in comparable categorization of segments with RPDs and with careful monitoring appears to be well tolerated in patients without signs/symptoms of ischemia during exercise and recovery.

Center for Health Policy and Health Services Research

Gold LS, Bryan M, Comstock BA, Bresnahan BW, Deyo RA, Nedeljkovic SS, **Nerenz DR**, Heagerty P, and Jarvik JG. Associations between relative value units and patient-reported back pain and disability *Gerontol Geriatr Med* 2017; 3PMID: Not assigned. Full text

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Objective: To describe associations between health care utilization measures and patient-reported outcomes (PROs). Method: Primary data were collected from patients ≥65 years with low back pain visits from 2011 to 2013. Six PROs of pain and functionality were collected 12 and 24 months after the index visits and total and spine-specific relative value units (RVUs) from electronic health records were tabulated over 1 year. We calculated correlation coefficients between RVUs and 12-and 24-month PROs and conducted linear regressions with each 12-and 24-month PRO as the outcome variables and RVUs as predictors of interest. Results: We observed very weak correlations between worse PROs at 12 and 24 months and greater 12-month utilization. In regression analyses, we observed slight associations between greater utilization and worse 12-and 24-month PROs. Discussion: We found that 12-month health care utilization is not strongly associated with PROs at 12 or 24 months.

Center for Health Policy and Health Services Research

Jesse MT, **Abouljoud M**, **Eshelman A**, De Reyck C, and Lerut J. Professional interpersonal dynamics and burnout in european transplant surgeons *Clin Transplant* 2017;PMID: 28185307. Full text

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Burnout within the health professions has become an increasingly important topic. Evidence suggests there are differences in burnout across different countries. Research has yet to examine burnout in transplant surgeons throughout Europe. METHODS: A cross-sectional survey of transplant surgeons across Europe. Survey included sociodemographics, professional characteristics, frequency and discomfort with difficult patient interactions, decisional autonomy, psychological job demands, support (coworker, supervisor, and hospital administration), and burnout including emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA). RESULTS: 108 transplant surgeons provided data; 33 (30.6%) reported high EE, 19 (17.6%) reported high DP, and 29 (26.9%) reported low PA. Three hierarchical multiple linear regressions examined the burnout subscales as outcomes (EE, DP, and PA) and predictors selected based upon theoretical relationships with the outcomes. Greater psychological job demands, greater discomfort in managing difficult patient interactions, and lower levels of perceived supervisor support predicting greater EE. Only decisional autonomy significantly predicted DP, accounting for a small proportion of the variance. None of the steps for PA were significant. CONCLUSIONS: Given prior research on burnout, there were several surprising findings from this study. For example, the relatively low levels of emotional exhaustion compared to U.S. physicians and surgeons. At this time, we can only hypothesize why this finding occurred but there are multiple possible explanations including cultural effects, response bias, or other factors unknown at this time. Research is needed to attempt to clarify these findings.

Center for Health Policy and Health Services Research
Lim HW, Collins SA, Resneck JS, Jr., Bolognia JL, Hodge JA, Rohrer TA, Van Beek MJ, Margolis DJ, Sober AJ, Weinstock MA, **Nerenz DR**, Smith Begolka W, and Moyano JV. The burden of skin disease in the United States *J Am Acad Dermatol* 2017;PMID: 28259441. Full text

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Since the publication of the last US national burden of skin disease report in 2006, there have been substantial changes in the practice of dermatology and the US health care system. These include the development of new treatment modalities, marked increases in the cost of medications, increasingly complex payer rules and regulations, and an aging of the US population. Recognizing the need for up-to-date data to inform researchers, policy makers, public stakeholders, and health care providers about the impact of skin disease on patients and US society, the American Academy of Dermatology produced a new national burden of skin disease report. Using 2013 claims data from private and governmental insurance providers, this report analyzed the prevalence, cost, and mortality attributable to 24 skin disease categories in the US population. In this first of 3 articles, the presented data demonstrate that nearly 85 million Americans were seen by a physician for at least 1 skin disease in 2013. This led to an estimated direct health care cost of $75 billion and an indirect lost opportunity cost of $11 billion. Further, mortality was noted in half of the 24 skin disease categories.

Dermatology
Lim HW, Collins SA, Resneck JS, Jr., Bolognia JL, Hodge JA, Rohrer TA, Van Beek MJ, Margolis DJ, Sober AJ, Weinstock MA, **Nerenz DR**, Smith Begolka W, and Moyano JV. The burden of skin disease in the United States *J Am Acad Dermatol* 2017;PMID: 28259441. Full text

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Dermatology
Lim HW, and **Schneider SL**. Sun safety practices-progress made, more to go *JAMA Dermatol* 2017;PMID: 28257532. Full text

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Dermatology
Liu Q, **Zhang X**, **Yin C**, **Chen X**, **Zhang Z**, **Brown S**, **Xie H**, **Zhou L**, and **Mi QS**. HDAC4 is expressed on multiple T cell lineages but dispensable for their development and function *Oncotarget* 2017;PMID: 28177888. Full text

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Histone deacetylation, reciprocally mediated by histone deacetylases (HDAC) and acetyltransferases, represents one major form of post-translational modification. Previous research indicates that HDACs play an essential regulatory role in the development of various immune cells. However, the specific function of individual HDACs remains largely unexplored. HDAC4, a member of class II HDACs, profoundly investigated in the nervous system, while the expression profile and function of HDAC4 in T cells are barely known. For the first time, we report here that HDAC4 is expressed in the multiple T cell lineages. Using T-cell-specific HDAC4-deficient mice, we discovered that lack of HDAC4 did not alter the frequencies of conventional T cells, invariant NKT (iNKT) cells or regulatory T cells within both the thymus and secondary lymphoid organs. Moreover, conventional T cells and iNKT cells from wild-type and HDAC4-deficient mice displayed no significant difference in cytokine production. In conclusion, our results imply that under steady stage, HDAC4 is not required for the development and function of multiple T cell lineages, including conventional T cells and iNKT cells.

Dermatology

Mohammad TF, Al-Jamal M, **Hamzavi IH**, Harris JE, Leone G, Cabrera R, **Lim HW**, Pandya AG, and Esmat SM. The Vitiligo Working Group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo *J Am Acad Dermatol* 2017;PMID: 28216034. Full text

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BACKGROUND: Treatment of vitiligo with narrowband ultraviolet B light (NBUVB) is an important component of the current standard of care. However, there are no consistent guidelines regarding the dosing and administration of NBUVB in vitiligo, reflected by varied treatment practices around the world. OBJECTIVE: To create phototherapy recommendations to facilitate clinical management and identify areas requiring future research. METHODS: The Vitiligo Working Group (VWG) Phototherapy Committee addressed 19 questions regarding the administration of phototherapy over 3 conference calls. Members of the Photomedicine Society and a group of phototherapy experts were surveyed regarding their phototherapy practices. RESULTS: Based on comparison and analysis of survey results, expert opinion, and discussion held during conference calls, expert recommendations for the administration of NBUVB phototherapy in vitiligo were created. LIMITATIONS: There were several areas that required further research before final recommendations could be made. In addition, no standardized methodology was used during literature review and to assess the strength of evidence during the development of these recommendations. CONCLUSION: This set of expert recommendations by the VWG is based on the prescribing practices of phototherapy experts from around the world to create a unified, broadly applicable set of recommendations on the use of NBUVB in vitiligo.

Dermatology

Paul C, Leonardi C, Menter A, Reich K, **Gold LS**, Warren RB, Moller A, and Lebwohl M. Calcipotriol plus betamethasone dipropionate aerosol foam in patients with moderate-to-severe psoriasis: Sub-group analysis of the pso-able study *Am J Clin Dermatol* 2017;PMID: 28236223. Article request form

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BACKGROUND: Fixed-combination calcipotriol 50 mug/g plus betamethasone 0.5 mg/g (Cal/BD) aerosol foam is a new topical treatment for psoriasis. Although moderate-to-severe psoriasis is typically treated with systemic/biologic therapies, a topical treatment that is efficacious in these patients may be a significant cost-saving alternative to systemic therapy. OBJECTIVE: The objective of this study was to assess the response to Cal/BD foam and gel in patients with moderate-to-severe psoriasis enrolled in the phase III, 12-week PSO-ABLE study. METHODS: Patients eligible for this analysis had moderate-to-severe psoriasis, defined by the 'Rule of Tens': body surface area >/=10% or Psoriasis Area and Severity Index (PASI) [excluding head; modified PASI (mPASI)] >10 or Dermatology Life-Quality Index >10. Endpoints included: proportion of patients achieving mPASI75 or mPASI90; change in body surface area; proportion of patients clear/almost clear with a >/=2 grade improvement (i.e., treatment success); change in Dermatology Life-Quality Index. RESULTS: Seventy-seven Cal/BD foam patients and 82 gel patients had moderate-to-severe psoriasis. A greater proportion achieved mPASI75 and mPASI90 with Cal/BD foam than gel at weeks 4, 8, and 12 (57.1 vs. 35.4%; p = 0.006 and 15.6 vs. 12.2% at week 12, respectively); overall reduction in mPASI from baseline to week 12 was 64% with the foam vs. 51% with the gel. Overall reduction in body surface area at week 12 was 50% with the foam and 39% with the gel. Treatment success rates were higher with the Cal/BD foam than the gel at weeks 1, 2, 4, 8 (p = 0.0089), and 12, and a greater proportion of foam patients achieved a Dermatology Life-Quality Index score of 0/1 at weeks 4 (p = 0.004), 8, and 12 (p = 0.001). CONCLUSION: Cal/BD

foam can be considered as a treatment option in some patients with moderate-to-severe psoriasis who are potential candidates for systemic therapy. CLINICALTRIALS. GOV IDENTIFIER: NCT02132936.

Dermatology

Powers MC, **Mehta D**, and **Ozog D**. Cutting out the tracts: Staged excisions for dissecting cellulitis of the scalp *Dermatol Surg* 2017;PMID: 28221182. Full text

Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.

Emergency Medicine

Anderson EL, Nordstrom K, Wilson MP, **Peltzer-Jones JM**, Zun L, Ng A, and Allen MH. American association for emergency psychiatry task force on medical clearance of adults part i: Introduction, review and evidence-based guidelines *West J Emerg Med* 2017; 18(2):235-242. PMID: 28210358. Full text

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INTRODUCTION: In the United States, the number of patients presenting to the emergency department (ED) for a mental health concern is significant and expected to grow. The breadth of the medical evaluation of these patients is controversial. Attempts have been made to establish a standard evaluation for these patients, but to date no nationally accepted standards exist. A task force of the American Association of Emergency Psychiatry, consisting of physicians from emergency medicine and psychiatry, and a psychologist was convened to form consensus recommendations on the medical evaluation of psychiatric patients presenting to EDs. METHODS: The task force reviewed existing literature on the topic of medical evaluation of psychiatric patients in the ED (Part I) and then combined this with expert consensus (Part II). RESULTS: In Part I, we discuss terminological issues and existing evidence on medical exams and laboratory studies of psychiatric patients in the ED. CONCLUSION: Emergency physicians should work cooperatively with psychiatric receiving facilities to decrease unnecessary testing while increasing the quality of medical screening exams for psychiatric patients who present to EDs.

Emergency Medicine

McCord J, **Cabrera R**, Lindahl B, Giannitsis E, **Evans K**, **Nowak R**, **Frisoli T**, Body R, Christ M, deFilippi CR, Christenson RH, **Jacobsen G**, Alquezar A, Panteghini M, Melki D, Plebani M, Verschuren F, French J, Bendig G, Weiser S, and Mueller C. Prognostic utility of a modified HEART score in chest pain patients in the emergency department *Circ Cardiovasc Qual Outcomes* 2017; 10(2)PMID: 28167641. Full text

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BACKGROUND: The TRAPID-AMI trial study (High-Sensitivity Troponin-T Assay for Rapid Rule-Out of Acute Myocardial Infarction) evaluated high-sensitivity cardiac troponin-T (hs-cTnT) in a 1-hour acute myocardial infarction (AMI) exclusion algorithm. Our study objective was to evaluate the prognostic utility of a modified HEART score (m-HS) within this trial. METHODS AND RESULTS: Twelve centers evaluated 1282 patients in the emergency department for possible AMI from 2011 to 2013. Measurements of hs-cTnT (99th percentile, 14 ng/L) were performed at 0, 1, 2, and 4 to 14 hours. Evaluation for major adverse cardiac events (MACEs) occurred at 30 days (death or AMI). Low-risk patients had an m-HS</=3 and had either hs-cTnT<14 ng/L over serial testing or had AMI excluded by the 1-hour protocol. By the 1-hour protocol, 777 (60%) patients had an AMI excluded. Of those 777 patients, 515 (66.3%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 262 (33.7%) patients had an m-HS>/=4, with 6 (2.3%) patients having MACEs (P=0.007). Over 4 to 14 hours, 661 patients had a hs-cTnT<14 ng/L. Of those 661 patients, 413 (62.5%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 248 (37.5%) patients had an m-HS>/=4, with 5 (2.0%) patients having MACEs (P=0.03). CONCLUSIONS: Serial testing of hs-cTnT over 1 hour along with application of an m-HS identified a low-risk population that might be able to be directly discharged from the emergency department.

Emergency Medicine

Peacock WF, Diercks D, Birkhahn R, Singer AJ, Hollander JE, **Nowak R**, Safdar B, Miller CD, Peberdy M, Counselman F, Chandra A, Kosowsky J, Neuenschwander J, Schrock J, Lee-Lewandrowski E, Arnold W, and Nagurney J. Can a point-of-care troponin I assay be as good as a central laboratory assay? A MIDAS investigation *Ann Lab Med* 2016; 36(5):405-412. PMID: 27374704. Full text

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Metrohealth Medical Center, Cleveland, OH, USA.
Alere, Inc., San Diego, CA, USA.

BACKGROUND: We aimed to compare the diagnostic accuracy of the Alere Triage Cardio3 Tropinin I (TnI) assay (Alere, Inc., USA) and the PathFast cTnI-II (Mitsubishi Chemical Medience Corporation, Japan) against the central laboratory assay Singulex Erenna TnI assay (Singulex, USA). METHODS: Using the Markers in the Diagnosis of Acute Coronary Syndromes (MIDAS) study population, we evaluated the ability of three different assays to identify patients with acute myocardial infarction (AMI). The MIDAS dataset, described elsewhere, is a prospective multicenter dataset of emergency department (ED) patients with suspected acute coronary syndrome (ACS) and a planned objective myocardial perfusion evaluation. Myocardial infarction (MI) was diagnosed by central adjudication.

RESULTS: The C-statistic with 95% confidence intervals (CI) for diagnosing MI by using a common population (n=241) was 0.95 (0.91-0.99), 0.95 (0.91-0.99), and 0.93 (0.89-0.97) for the Triage, Singulex, and PathFast assays, respectively. Of samples with detectable troponin, the absolute values had high Pearson (R(P)) and Spearman (R(S)) correlations and were R(P)=0.94 and R(S)=0.94 for Triage vs Singulex, R(P)=0.93 and R(S)=0.85 for Triage vs PathFast, and R(P)=0.89 and R(S)=0.73 for PathFast vs Singulex. CONCLUSIONS: In a single comparative population of ED patients with suspected ACS, the Triage Cardio3 TnI, PathFast, and Singulex TnI assays provided similar diagnostic performance for MI.

Emergency Medicine

Schuetz P, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, Runyon MS, Self WH, Courtney DM, **Nowak RM**, Gaieski DF, Ebmeyer S, Johannes S, Wiemer JC, Schwabe A, and Shapiro NI. Serial procalcitonin predicts mortality in severe sepsis patients: Results from the multicenter procalcitonin monitoring sepsis (MOSES) study *Crit Care Med* 2017;PMID: 28257335. Full text

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OBJECTIVES: To prospectively validate that the inability to decrease procalcitonin levels by more than 80% between baseline and day 4 is associated with increased 28-day all-cause mortality in a large sepsis patient population recruited across the United States. DESIGN: Blinded, prospective multicenter observational clinical trial following an Food and Drug Administration-approved protocol. SETTING: Thirteen U.S.-based emergency departments and ICUs. PATIENTS: Consecutive patients meeting criteria for severe sepsis or septic shock who were admitted to the ICU from the emergency department, other wards, or directly from out of hospital were included. INTERVENTIONS: Procalcitonin was measured daily over the first 5 days. MEASUREMENTS AND MAIN RESULTS: The primary analysis of interest was the relationship between a procalcitonin decrease of more than 80% from baseline to day 4 and 28-day mortality using Cox proportional hazards regression. Among 858 enrolled patients, 646 patients were alive and in the hospital on day 4 and included in the main intention-to-diagnose analysis. The 28-day all-cause mortality was two-fold higher when procalcitonin did not show a decrease of more than 80% from baseline to day 4 (20% vs 10%; p = 0.001). This was confirmed as an independent predictor in Cox regression analysis (hazard ratio, 1.97 [95% CI, 1.18-3.30; p < 0.009]) after adjusting for demographics, Acute Physiology and Chronic Health Evaluation II, ICU residence on day 4, sepsis syndrome severity, antibiotic administration time, and other relevant confounders. CONCLUSIONS: Results of this large, prospective multicenter U.S. study indicate that inability to decrease procalcitonin by more than 80% is a significant independent predictor of mortality and may aid in sepsis care.

Emergency Medicine

Xin H, **Wang F**, **Li Y**, **Lu QE**, **Cheung WL**, **Zhang Y**, **Zhang ZG**, and **Chopp M**. Secondary release of exosomes from astrocytes contributes to the increase in neural plasticity and improvement of functional recovery after stroke in rats treated with exosomes harvested from microrna 133b-overexpressing multipotent mesenchymal stromal cells *Cell Transplant* 2017; 26(2):243-257. PMID: 27677799. Full text

We previously demonstrated that multipotent mesenchymal stromal cells (MSCs) that overexpress microRNA 133b (miR-133b) significantly improve functional recovery in rats subjected to middle cerebral artery occlusion (MCAO) compared with naive MSCs and that exosomes generated from naive MSCs mediate the therapeutic benefits of MSC therapy for stroke. Here we investigated whether exosomes isolated from miR-133b-overexpressing MSCs (Ex-miR-133b+) exert amplified therapeutic effects. Rats subjected to 2 h of MCAO were intra-arterially injected with Ex-miR-133b+, exosomes from MSCs infected by blank vector (Ex-Con), or phosphate-buffered saline (PBS) and were sacrificed 28 days after MCAO. Compared with the PBS treatment, both exosome treatment groups exhibited significant improvement of functional recovery. Ex-miR-133b+ treatment significantly increased functional

improvement and neurite remodeling/brain plasticity in the ischemic boundary area compared with the Ex-Con treatment. Treatment with Ex-miR-133b+ also significantly increased brain exosome content compared with Ex-Con treatment. To elucidate mechanisms underlying the enhanced therapeutic effects of Ex-miR-133b+, astrocytes cultured under oxygen- and glucose-deprived (OGD) conditions were incubated with exosomes harvested from naive MSCs (Ex-Naive), miR-133b downregulated MSCs (Ex-miR-133b-), and Ex-miR-133b+. Compared with the Ex-Naive treatment, Ex-miR-133b+ significantly increased exosomes released by OGD astrocytes, whereas Ex-miR-133b- significantly decreased the release. Also, exosomes harvested from OGD astrocytes treated with Ex-miR-133b+ significantly increased neurite branching and elongation of cultured cortical embryonic rat neurons compared with the exosomes from OGD astrocytes subjected to Ex-Con. Our data suggest that exosomes harvested from miR-133b-overexpressing MSCs improve neural plasticity and functional recovery after stroke with a contribution from a stimulated secondary release of neurite-promoting exosomes from astrocytes.

Endocrinology

Aleppo G, Ruedy KJ, Riddlesworth TD, **Kruger DF**, Peters AL, Hirsch I, Bergenstal RM, Toschi E, Ahmann AJ, Shah VN, Rickels MR, Bode BW, Philis-Tsimikas A, Pop-Busui R, Rodriguez H, Eyth E, Bhargava A, Kollman C, and Beck RW. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in well-controlled adults with type 1 diabetes *Diabetes Care* 2017;PMID: 28209654. Full text

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OBJECTIVE: To determine whether the use of continuous glucose monitoring (CGM) without confirmatory blood glucose monitoring (BGM) measurements is as safe and effective as using CGM adjunctive to BGM in well-controlled adults with type 1 diabetes (T1D). RESEARCH DESIGN AND METHODS: A randomized noninferiority clinical trial was conducted at 14 sites in the T1D Exchange Clinic Network. Participants were >/=18 years of age (mean 44 +/- 14 years), had T1D for >/=1 year (mean duration 24 +/- 12 years), used an insulin pump, and had an HbA1c </=9.0% (</=75 mmol/mL) (mean 7.0 +/- 0.7% [53 +/- 7.7 mmol/mol]); prestudy, 47% were CGM users. Participants were randomly assigned 2:1 to the CGM-only (n = 149) or CGM+BGM (n = 77) group. The primary outcome was time in range (70-180 mg/dL) over the 26-week trial, with a prespecified noninferiority limit of 7.5%. RESULTS: CGM use averaged 6.7 +/- 0.5 and 6.8 +/- 0.4 days/week in the CGM-only and CGM+BGM groups, respectively, over the 26-week trial. BGM tests per day (including the two required daily for CGM calibration) averaged 2.8 +/- 0.9 and 5.4 +/- 1.4 in the two groups, respectively (P < 0.001). Mean time in 70-180 mg/dL was 63 +/- 13% at both baseline and 26 weeks in the CGM-only group and 65 +/- 13% and 65 +/- 11% in the CGM+BGM group (adjusted difference 0%; one-sided 95% CI -2%). No severe hypoglycemic events occurred in the CGM-only group, and one occurred in the CGM+BGM group. CONCLUSIONS: Use of CGM without regular use of confirmatory BGM is as safe and effective as using CGM with BGM in well-controlled adults with T1D at low risk for severe hypoglycemia.

Endocrinology

Gopalaswamy V, Dhibar DP, Gupta V, Arya AK, Khandelwal N, Bhansali A, Garg SK, Agarwal N, **Rao SD**, and Bhadada SK. Anabolic bone window with weekly teriparatide therapy in post menopausal osteoporosis: A pilot study *Endocr Pract* 2017;PMID: 28225309. Article request form

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BACKGROUND: Osteoporosis is a major public health problem, which reduces bone strength and increases risk of fracture. Teriparatide is an established and the only currently available anabolic therapy for the treatment of postmenopausal osteoporosis (PMO) with recommended daily dose of 20 mug subcutaneously. However data regarding the long term effect of once-weekly teriparatide therapy on bone mineral density (BMD), bone turnover markers (BTMs) and anabolic bone window is limited. METHODS: In this prospective observational study, 26 patients with PMO were treated with weekly teriparatide therapy (60 mug) for 2 years. BMD was measured at baseline, 12 months and 24 months. The bone formation marker, type 1 collagen C-terminal propeptide (P1NP) and the bone resorption marker, C-terminal telopeptide of type 1 collagen (CTx) were measured at baseline, 6 weeks, and at 6, 12, 18 and 24 months. RESULTS: BMD at the lumbar spine increased by 3.1% and 10.8% respectively after 1 year and 2 years of weekly teriparatide therapy. The T-score increased significantly at the lumbar spine as compared to baseline after 2 years of therapy (p=0.015). Serum P1NP levels increased significantly at 6 months (p=0.024), peaked at one year and remained above the baseline even after 2 years. Serum CTx levels decreased significantly at 6 months (p=0.025) and remained below the baseline at the end of 2 years of teriparatide therapy. CONCLUSION: Weekly teriparatide therapy (60 mug) appears to be as effective as daily teriparatide for the treatment of PMO by achieving an extendable anabolic bone window.

Gastroenterology
DuBrock HM, Goldberg DS, Sussman NL, Bartolome SD, Kadry Z, **Salgia RJ**, Mulligan DC, Kremers WK, Kawut SM, Krowka MJ, and Channick RN. Predictors of waitlist mortality in portopulmonary hypertension *Transplantation* 2017;PMID: 28207639. Full text

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BACKGROUND: The current Organ Procurement Transplantation Network (OPTN) policy grants Model for End Stage Liver Disease (MELD) exception points to patients with portopulmonary hypertension (POPH), but potentially important factors, such as severity of liver disease and pulmonary hypertension, are not included in the exception score, and may affect survival. The purpose of this study was to identify significant predictors of waitlist mortality in patients with POPH. METHODS: We performed a retrospective cohort study of patients in the OPTN database with hemodynamics consistent with POPH [defined as mean pulmonary arterial pressure (mPAP) >25mmHg and pulmonary vascular resistance (PVR) >/=240 dynes-s-cm] who were approved for a POPH MELD exception between 2006 and 2014. Using a Cox proportional hazards model, we identified predictors of waitlist mortality (or removal for clinical deterioration). RESULTS: One hundred ninety adults were included. Age (HR 1.04, 95% CI 1.00-1.08, P=0.0499), initial native MELD score (HR 1.11, 95% CI 1.05-1.17, P<0.001), and initial PVR (HR 1.12 per 100 dynes-s-cm, 95% CI 1.02-1.23, P=0.02) were the only significant univariate predictors of waitlist mortality and remained significant predictors in a multivariate model, which had a c-statistic of 0.71. PVR and mPAP were not significant predictors of posttransplant mortality. CONCLUSIONS: Both the severity of liver disease and POPH (as assessed by MELD and PVR, respectively) were significantly associated with waitlist, but not posttransplant, mortality in patients with approved MELD exceptions for POPH. Both factors should potentially be included in the POPH MELD exception score to more accurately reflect waitlist mortality risk.

Gastroenterology
Terrault N, Berenguer M, Strasser S, Gadano A, Lilly L, Samuel D, Kwo PY, Agarwal K, Curry M, Fagiuoli S, Fung JY, Gane E, **Brown KA**, Burra P, Charlton M, Pessoa M, and McCaughan GW. International liver transplant society consensus statement on hepatitis c management in liver transplant recipients *Transplantation* 2017;PMID: 28252566. Full text

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Gastroenterology
Terrault NA, McCaughan GW, Curry MP, Gane E, Fagiuoli S, Fung J, Agarwal K, Lilly L, Strasser SI, **Brown K**, Gadano A, Kwo PY, Burra P, Samuel D, Charlton M, Pessoa MG, and Berenguer M. International liver transplant society consensus statement on hepatitis c management in liver transplant candidates *Transplantation* 2017;PMID: 28252565. Full text

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Hematology / Oncology
Bazhenova L, Mehra R, Nagy T, Cavanna L, Lee JS, Han JY, Kim HK, Halmos B, Shum M, Schreeder M, **Rybkin I**, Badin F, Mena R, Janne PA, Christensen J, Tassell V, Chao R, Faltaos D, and Kim DW. Amethyst nsclc trial: Phase 2, parallel-arm study of receptor tyrosine kinase (rtk) inhibitor, mgcd265 in patients with advanced or metastatic non-small cell lung cancer (nsclc) with activating genetic alterations in mesenchymal-epithelial transition factor (met) *Ann Oncol* 2016; 27:1. PMID: Not assigned. Abstract

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Hematology / Oncology
Gajra A, **Ali H**, Amiri KI, Karim NA, Matrana MR, Mulford D, Ong TJ, Sanford A, Santos E, Socinski M, Spigel DR, and Lilenbaum RC. Interim safety results from the phase 2 abound.Ps2 study evaluating nab-paclitaxel (nab-p) plus

carboplatin (c) followed by nab-p monotherapy in patients (pts) with nsclc and an eastern cooperative oncology group (ecog) performance status (ps) 2 *Ann Oncol* 2016; 27:1. PMID: Not assigned. Abstract

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Hematology / Oncology

Patel D, Sohrawardy S, Sedhai YR, Basnyat S, Daxini A, **Basu A**, Mehta VR, Mohammed A, and Lichtenstein S. Metastatic cutaneous melanoma of the gallbladder *Case Rep Gastrointest Med* 2017; 2017:8532379. PMID: 28251000. Full text

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Metastatic melanoma is an aggressive disease that can spread to many organs of the body. In rare cases, it can spread to the gallbladder causing secondary lesions, yet presenting with little to no symptoms. Therefore, most cases of metastatic melanoma lesions to the gallbladder go undiagnosed. Here, we present the case of a 41-year-old male with a four-month history of melanoma of the face, with a postresection status, who presented with right upper quadrant abdominal pain. Doppler ultrasound and computed tomography confirmed the presence of a mass on the gallbladder. Laparoscopic excision along with liver wedge resection was performed. Pathology staining revealed the presence of a malignant metastatic melanoma lesion of the gallbladder.

Hematology / Oncology

Pilling AB, **Hwang O**, Boudreault A, Laurent A, and **Hwang C**. Iap antagonists enhance apoptotic response to enzalutamide in castration-resistant prostate cancer cells via autocrine tnf-alpha signaling *Prostate* 2017;PMID: 28240376. Full text

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Pharmascience Inc. Montreal, Quebec, Canada.

BACKGROUND: Castration-resistant prostate cancer (CRPC) remains incurable and identifying effective treatments continues to present a clinical challenge. Although treatment with enzalutamide, a second generation androgen receptor (AR) antagonist, prolongs survival in prostate cancer patients, responses can be limited by intrinsic resistance or acquired resistance. A potential mechanism of resistance to androgen axis inhibition is evasion of apoptosis. Inhibitor of apoptosis proteins (IAPs) are found to be overexpressed in prostate cancer and function to block apoptosis and promote survival signaling. Novel, small-molecule IAP antagonists, such as AEG40995, are emerging as a strategy to induce apoptosis and increase therapeutic response in cancer. METHODS: Human prostate cancer cell lines LNCaP and C4-2 were treated with enzalutamide with or without addition of IAP antagonist AEG40995 and proliferation and survival were determined by MTS and clonogenic assay. Western blot was used to evaluate IAP protein expression changes and PARP-1 cleavage was assessed as indication of apoptosis. Flow cytometry was performed to analyze apoptosis in treated cells. Caspase activity was determined by luminescence assay. Quantitative real-time PCR and immunometric ELISA was used to assess TNF-alpha (transcript and protein levels, respectively) in response to treatment. RESULTS: In this study, we demonstrate that IAP antagonist AEG40995 exhibits minimal effects on prostate cancer cell proliferation or survival, but rapidly degrades cIAP1 protein. Combination treatment with enzalutamide demonstrates that AEG40995 increases apoptosis and reduces proliferation and clonogenic survival in cell line models of prostate cancer. Mechanistically, we demonstrate that apoptosis in response to enzalutamide and IAP antagonist requires activation of caspase-8, suggesting extrinsic/death receptor apoptosis signaling. Assessment of TNF-alpha in response to combination treatment with enzalutamide and AEG40995 reveals increased mRNA expression and autocrine protein secretion. Blocking TNF-alpha signaling abrogates the apoptotic response demonstrating that TNF-alpha plays a critical role in executing cell

death in response to this drug combination. CONCLUSIONS: These findings suggest that IAP antagonists can increase sensitivity and amplify the caspase-mediated apoptotic response to enzalutamide through TNF-alpha signaling mechanisms. Combination with an IAP antagonist increases enzalutamide sensitivity, lowers the apoptotic threshold and may combat drug resistance in patients with prostate cancer. Prostate (c) 2017 Wiley Periodicals, Inc.

Hematology / Oncology

Sachdev JC, Edelman M, Harb W, Armour A, **Wang D**, and Starodub AN. Phase 1 dose-escalation study of the folic acid-tubulysin small-molecule drug conjugate (smdc) folate-tubulysin ec1456: Study update *Ann Oncol* 2016; 27:1. PMID: Not assigned. Abstract

[Sachdev, J. C.] HonorHlth Res Inst, Oncol, Scottsdale, AZ USA. [Edelman, M.] Univ Maryland, Ctr Canc, Greenebaum Canc Ctr, Baltimore, MD 21201 USA. [Harb, W.] Horizon Oncol Ctr, Unity Campus, Lafayette, IN USA. [Armour, A.] Clin Endocyte Inc, Indianapolis, IN USA. [Wang, D.] Henry Ford Hosp, Oncol Hematol, Detroit, MI 48202 USA. [Starodub, A. N.] IU Goshen Ctr Canc Care, Oncol Hematol, Goshen, IN USA.

Hematology / Oncology Research

Deeb D, **Gao X**, **Bo Liu Y**, **Zhang Y**, **Shaw J**, **Valeriote FA**, and **Gautam SC**. Inhibition of hTERT in pancreatic cancer cells by pristimerin involves suppression of epigenetic regulators of gene transcription *Oncology Reports* 2017; 37(3):1914-1920. PMID: Not yet assigned. Article request form

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Previously we have shown that the inhibition of proliferation and induction of apoptosis in pancreatic ductal adenocarcinoma (PDA) cells by pristimerin (PM), a quinonemethide triterpenoid, was associated with the inhibition of human telomerase reverse transcriptase (hTERT) mRNA and hTERT protein. Herein we show that PM inhibits transcription factors and epigenetic processes that regulate hTERT expression. Treatment with PM inhibited transcription factors c-Myc, Sp1, NF-κB and kinases p-Akt and p-mTOR that regulate hTERT post-translationally. PM also downregulated DNA methyl transferases DNMT1 and DNMT3a and transcriptionally active chromatin markers, such as acetylated histone H3 (Lys9), acetylated histone H4, di-methyl H3 (Lys4) and trimethyl H3 (Lys9). In addition, chromatin immunoprecipitation (ChIP) analysis showed decrease in c-Myc and Sp1 transcription factors, but not repressive factors CTCF, E2F or Mad1 in the regulatory region of the hTERT promoter after treatment with PM. PM also reduced acetylated histone 3 and 4 and methylated H3 at hTERT promoter. Collectively, these results indicated that PM downregulates hTERT/telomerase through the inhibition of the genetic and epigenetic regulators of hTERT gene expression.

Hospital Medicine

Gunasekaran K, Rudd KM, Murthi S, **Kaatz S**, and Lone N. Spontaneous thyroid hemorrhage on chronic anticoagulation therapy *Clin Pract* 2017; 7(1):932. PMID: 28243434. Full text

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Even though highly vascularized, the thyroid gland rarely has spontaneous bleeding. Bleeding into the thyroid gland can result in potentially lethal acute airway compromise. This case report describes an elderly patient on warfarin for atrial fibrillation, who presented with swelling on the right side of her neck causing acute airway obstruction. An urgent computed tomography of the neck showed an enlarging hemorrhage into the right lobe of the thyroid gland. She was initially intubated for airway protection and her anticoagulation was reversed to stop the bleeding. She was closely monitored in the intensive care unit. After an uncomplicated tracheal extubation and recovery, she was discharged and scheduled for an elective total thyroidectomy. We desire that physicians be aware of this rare, potentially lethal bleeding complication.

Infectious Diseases
Linder KA, **Alkhouli L**, **Ramesh M**, **Alangaden GA**, Kauffman CA, and Miceli MH. Effect of underlying immune compromise on the manifestations and outcomes of group A streptococcal bacteremia *J Infect* 2017;PMID: 28237623. Full text

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Henry Ford Health System.
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BACKGROUND: Group A streptococcal bloodstream infection is the most common presentation of invasive group A streptococcal disease. We sought to determine the impact of immunosuppression on severity of disease and clinical outcomes. METHODS: This retrospective review of 148 patients with at least one positive blood culture for Streptococcus pyogenes from 1/2003 to 3/2013 compared immunocompromised patients with those with no immunocompromise in regards to development of severe complications and mortality. RESULTS: Twenty-five patients (17%) were immunocompromised; 123 were not. Skin and soft tissue infection occurred in 60% of immunocompromised vs. 38% of non-immunocompromised patients, p=.04. Necrotizing fasciitis and septic shock were significantly more common in immunocompromised patients, p<.0001 and .028, respectively. Mortality at 30 days was 32% in immunocompromised patients vs. 16% in non-immunocompromised patients, p=.05. CONCLUSION: Patients who are immunocompromised are more likely to develop necrotizing fasciitis and septic shock as complications of group A streptococcal bacteremia and have a higher mortality rate than patients who are not immunocompromised.

Internal Medicine
Khan U, Ali F, Khurram MS, **Zaka A**, and Hadid T. Immunotherapy-associated autoimmune hemolytic anemia *J Immunother Cancer* 2017; 5(1)PMID: 28239468. Full text

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Background: Immunotherapy has been widely used in the treatment of several solid and hematologic malignancies. Checkpoint inhibitors have been the forefront of cancer immunotherapy in recent years. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) pathway are the prototypic checkpoint targets for immunotherapy. When combined, CTLA-4 and PD-1 checkpoint inhibitors work synergistically, but with increased probability of toxicity. The following case represents an unusual adverse effect of combined treatment with ipilimumab and nivolumab used for treatment of metastatic melanoma. Case presentation: A 43-year-old woman with metastatic melanoma presented with severe generalized weakness and fatigue. She has received two cycles of ipilimumab and nivolumab, last administered 3 weeks prior to her presentation. Initial investigations revealed severe anemia with appropriate reticulocytosis, severely elevated lactate dehydrogenase, undetectable haptoglobin level and positive direct coombs test. Patient was diagnosed with severe autoimmune hemolytic anemia secondary to ipilimumab and nivolumab. She was successfully treated with high dose steroids and rituximab. Conclusions: In our case, we present a rare but serious adverse effect of immunotherapy. We illustrate the clinical presentation and management of immunotherapy associated autoimmune hemolytic anemia. Immunotherapy has revolutionized the treatment of many malignant conditions; therefore, it is imperative for health care professionals caring for cancer patient to be familiar with the adverse effects of immunotherapy, which allow for early recognition and management of these potentially lethal side effects.

Internal Medicine
Liu Q, **Zhang X**, **Yin C**, **Chen X**, **Zhang Z**, **Brown S**, **Xie H**, **Zhou L**, and **Mi QS**. HDAC4 is expressed on multiple T cell lineages but dispensable for their development and function *Oncotarget* 2017;PMID: 28177888. Full text

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Histone deacetylation, reciprocally mediated by histone deacetylases (HDAC) and acetyltransferases, represents one major form of post-translational modification. Previous research indicates that HDACs play an essential regulatory role in the development of various immune cells. However, the specific function of individual HDACs remains largely unexplored. HDAC4, a member of class II HDACs, profoundly investigated in the nervous system, while the expression profile and function of HDAC4 in T cells are barely known. For the first time, we report here that HDAC4 is expressed in the multiple T cell lineages. Using T-cell-specific HDAC4-deficient mice, we discovered that lack of HDAC4 did not alter the frequencies of conventional T cells, invariant NKT (iNKT) cells or regulatory T cells within both the thymus and secondary lymphoid organs. Moreover, conventional T cells and iNKT cells from wild-type and HDAC4-deficient mice displayed no significant difference in cytokine production. In conclusion, our results imply that under steady stage, HDAC4 is not required for the development and function of multiple T cell lineages, including conventional T cells and iNKT cells.

Internal Medicine

McCord J, **Cabrera R**, Lindahl B, Giannitsis E, **Evans K**, **Nowak R**, **Frisoli T**, Body R, Christ M, deFilippi CR, Christenson RH, **Jacobsen G**, Alquezar A, Panteghini M, Melki D, Plebani M, Verschuren F, French J, Bendig G, Weiser S, and Mueller C. Prognostic utility of a modified HEART score in chest pain patients in the emergency department *Circ Cardiovasc Qual Outcomes* 2017; 10(2)PMID: 28167641. Full text

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BACKGROUND: The TRAPID-AMI trial study (High-Sensitivity Troponin-T Assay for Rapid Rule-Out of Acute Myocardial Infarction) evaluated high-sensitivity cardiac troponin-T (hs-cTnT) in a 1-hour acute myocardial infarction (AMI) exclusion algorithm. Our study objective was to evaluate the prognostic utility of a modified HEART score (m-HS) within this trial. METHODS AND RESULTS: Twelve centers evaluated 1282 patients in the emergency department for possible AMI from 2011 to 2013. Measurements of hs-cTnT (99th percentile, 14 ng/L) were performed at 0, 1, 2, and 4 to 14 hours. Evaluation for major adverse cardiac events (MACEs) occurred at 30 days (death or AMI). Low-risk patients had an m-HS</=3 and had either hs-cTnT<14 ng/L over serial testing or had AMI excluded by the 1-hour protocol. By the 1-hour protocol, 777 (60%) patients had an AMI excluded. Of those 777 patients, 515 (66.3%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 262 (33.7%) patients had an m-HS>/=4, with 6 (2.3%) patients having MACEs (P=0.007). Over 4 to 14 hours, 661 patients had a hs-cTnT<14 ng/L.

Of those 661 patients, 413 (62.5%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 248 (37.5%) patients had an m-HS>/=4, with 5 (2.0%) patients having MACEs (P=0.03). CONCLUSIONS: Serial testing of hs-cTnT over 1 hour along with application of an m-HS identified a low-risk population that might be able to be directly discharged from the emergency department.

Nephrology

Bress AP, Kramer H, Khatib R, Beddhu S, Cheung AK, Hess R, Bansal VK, Cao G, **Yee J**, Moran AE, Durazo-Arvizu RA, Muntner P, and Cooper RS. Potential deaths averted and serious adverse events incurred from adoption of the sprint intensive blood pressure regimen in the u.S.: Projections from nhanes *Circulation* 2017;PMID: 28193605. Full text

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Background -The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated a 27% reduction in all-cause mortality with a systolic blood-pressure (SBP) goal of <120 mmHg versus <140 mmHg among U.S. adults at high cardiovascular disease (CVD) risk but without diabetes, stroke, or heart failure. To quantify the potential benefits and risks of SPRINT intensive goal implementation, we estimated the deaths prevented and excess serious adverse events (SAEs) incurred if the SPRINT intensive SBP treatment goal was implemented in all eligible U.S. adults. Methods -SPRINT eligibility criteria were applied to the 1999-2006 National Health and Nutrition Examination Survey and linked with the National Death Index through December 2011. SPRINT eligibility included age >/= 50 years, SBP of 130-180 mmHg (depending on the number of antihypertensive medications being taken), and high CVD risk. Exclusion criteria were diabetes, history of stroke, >1 gram of proteinuria, heart failure, estimated glomerular filtration rate < 20 ml/min/1.73m2, or dialysis. Annual mortality rates were calculated by dividing the Kaplan-Meier 5-year mortality by 5. Hazard ratios for all-cause mortality and heart failure and absolute risks for SAEs in SPRINT were used to estimate the number of potential deaths and heart failure cases prevented and SAEs incurred with intensive SBP treatment. Results -The mean age was 68.6 years and 83.2% and 7.4% were non-Hispanic white and non-Hispanic black, respectively. The annual mortality rate was 2.20% (95%CI 1.91%-2.48%) and intensive SBP treatment was projected to prevent about 107,500 deaths per year (95%CI 93,300-121,200) and give rise to 56,100 (95%CI 50,800-61,400) episodes of hypotension, 34,400 (95%CI 31,200-37,600) episodes of syncope, 43,400 (95%CI 39,400-47,500) serious electrolyte disorders, and 88,700 (95%CI 80,400-97,000) cases of acute kidney injury per year. The analysis of extremes approach indicated that the range of estimated lower and upper bound number of deaths prevented per year with intensive SBP control was 34,600 to 179,600. Intensive SBP control was projected to prevent 46,100 (95%CI 41,800-50,400) cases of heart failure annually. Conclusions -If fully implemented in eligible U.S. adults, intensive SBP treatment could prevent about 107,500 deaths per year. A consequence of this treatment strategy, however, could be an increase in SAEs.

Nephrology

Soman SS, and **Yee J**. Nephrology and telehealth: Now? Or now! *Adv Chronic Kidney Dis* 2017; 24(1):1-3. PMID: 28224936. Full text

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Neurology

Dehkordi AN, Kamali-Asl A, **Ewing JR**, **Wen N**, **Chetty IJ**, and **Bagher-Ebadian H**. An adaptive model for rapid and direct estimation of extravascular extracellular space in dynamic contrast enhanced MRI studies *NMR Biomed* 2017;PMID: 28195664. Full text

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Extravascular extracellular space (ve) is a key parameter to characterize the tissue of cerebral tumors. This study introduces an artificial neural network (ANN) as a fast, direct, and accurate estimator of ve from a time trace of the longitudinal relaxation rate, DeltaR1 (R1 = 1/T1), in DCE-MRI studies. Using the extended Tofts equation, a set of DeltaR1 profiles was simulated in the presence of eight different signal to noise ratios. A set of gain- and noise-insensitive features was generated from the simulated DeltaR1 profiles and used as the ANN training set. A K-fold cross-validation method was employed for training, testing, and optimization of the ANN. The performance of the optimal ANN (12:6:1, 12 features as input vector, six neurons in hidden layer, and one output) in estimating ve at a resolution of 10% (error of +/-5%) was 82%. The ANN was applied on DCE-MRI data of 26 glioblastoma patients to estimate ve in tumor regions. Its results were compared with the maximum likelihood estimation (MLE) of ve . The two techniques showed a strong agreement ($r = 0.82$, $p < 0.0001$). Results implied that the perfected ANN was less sensitive to noise and outperformed the MLE method in estimation of ve .

Neurology
Kelley BP, **Patel SC**, **Marin HL**, **Corrigan JJ**, **Mitsias PD**, and **Griffith B**. Autoimmune encephalitis: Pathophysiology and imaging review of an overlooked diagnosis *AJNR Am J Neuroradiol* 2017;PMID: 28183838. Full text

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Autoimmune encephalitis is a relatively new category of immune-mediated disease involving the central nervous system that demonstrates a widely variable spectrum of clinical presentations, ranging from the relatively mild or insidious onset of cognitive impairment to more complex forms of encephalopathy with refractory seizure. Due to its diverse clinical features, which can mimic a variety of other pathologic processes, autoimmune encephalitis presents a diagnostic challenge to clinicians. Imaging findings in patients with these disorders can also be quite variable, but recognizing characteristic findings within limbic structures suggestive of autoimmune encephalitis can be a key step in alerting clinicians to the potential diagnosis and ensuring a prompt and appropriate clinical work-up. In this article, we review antibody-mediated encephalitis and its various subtypes with a specific emphasis on the role of neuroimaging in the diagnostic work-up.

Neurology
LeWitt PA, **Li J**, **Lu M**, Guo L, and Auinger P. Metabolomic biomarkers as strong correlates of Parkinson disease progression *Neurology* 2017;PMID: 28179471. Full text

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OBJECTIVE: To determine whether a Parkinson disease (PD)-specific biochemical signature might be found in the total body metabolic milieu or in the CSF compartment, especially since this disorder has systemic manifestations beyond the progressive loss of dopaminergic nigrostriatal neurons. METHODS: Our goal was to discover biomarkers of PD progression. Using ultra-high-performance liquid chromatography linked to gas chromatography and tandem mass spectrometry, we measured concentrations of small-molecule (</=1.5 kDa) constituents of plasma and CSF from 49 unmedicated, mildly affected patients with PD (mean age 61.4 years; mean duration of PD 11.4 months). Specimens were collected twice (baseline and final) at intervals up to 24 months. During this time, mean Unified Parkinson's Disease Rating Scale (UPDRS) parts 2 + 3 scores increased 47% (from 28.8 to 42.2). Measured compounds underwent unbiased univariate and multivariate analyses, including fitting data into multiple linear regression with variable selection using least absolute shrinkage and selection operator (LASSO). RESULTS: Of 575 identified plasma and 383 CSF biochemicals, LASSO led to selection of 15 baseline plasma constituents with high positive correlation (0.87, p = 2.2e-16) to baseline-to-final change in UPDRS parts 2 + 3 scores. Three of the compounds had xanthine structures, and 4 were either medium- or long-chain fatty acids. For the 15 LASSO-selected

biomarkers, pathway enrichment software found no overrepresentation among metabolic pathways. CSF concentrations of the dopamine metabolite homovanillate showed little change between baseline and final collections and minimal correlation with worsening UPDRS parts 2 + 3 scores (0.29, p = 0.041). CONCLUSIONS: Metabolomic profiling of plasma yielded strong prediction of PD progression and offered biomarkers that may provide new insights into PD pathogenesis.

Neurology

Lin Y, Luo LL, Sun J, Gao W, Tian Y, Park E, Baker A, **Chen J**, Jiang R, and Zhang J. Relationship of circulating cxcr4+ epc with prognosis of mild traumatic brain injury patients *Aging Dis* 2017; 8(1):115-127. PMID: 28203485. Full text

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To investigate the changes of circulating endothelial progenitor cells (EPCs) and stromal cell-derived factor-1alpha (SDF-1alpha)/CXCR4 expression in patients with mild traumatic brain injury (TBI) and the correlation between EPC level and the prognosis of mild TBI. 72 TBI patients (57 mild TBI, 15 moderate TBI patients) and 25 healthy subjects (control) were included. The number of circulating EPCs, CD34+, and CD133+ cells and the percentage of CXCR4+ cells in each cell population at 1,4,7,14,21 days after TBI were counted by flow cytometer. SDF-1alpha levels in serum were detected by ELISA assay. The patients were divided into poor and good prognosis groups based on Extended Glasgow Outcome Scale and Activity of Daily Living Scale at 3 months after TBI. Correlation analysis between each detected index and prognosis of mild TBI was performed. Moderate TBI patients have higher levels of SDF-1alpha and CXCR4 expression than mild TBI patients ($P < 0.05$). The percentage of CXCR4+ EPCs at day 7 post-TBI was significantly higher in mild TBI patients with poor prognosis than the ones with good prognosis ($P < 0.05$). HAMA and HAMD scores in mild TBI patients were significantly lower than moderate TBI patients ($P < 0.05$) in early term. The percentage of CXCR4+ EPCs at day 7 after TBI was significantly correlated with the prognosis outcome at 3 months. The mobilization of circulating EPCs can be induced in mild TBI. The expression of CXCR4+ in EPCs at 7 days after TBI reflects the short-term prognosis of brain injury, and could be a potential biological marker for prognosis prediction of mild TBI.

Neurology

Liu Q, **Zhang X**, **Yin C**, **Chen X**, **Zhang Z**, **Brown S**, **Xie H**, **Zhou L**, and **Mi QS**. HDAC4 is expressed on multiple T cell lineages but dispensable for their development and function *Oncotarget* 2017;PMID: 28177888. http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path[]=15077&pubmed-linkout=1

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Histone deacetylation, reciprocally mediated by histone deacetylases (HDAC) and acetyltransferases, represents one major form of post-translational modification. Previous research indicates that HDACs play an essential regulatory role in the development of various immune cells. However, the specific function of individual HDACs remains largely unexplored. HDAC4, a member of class II HDACs, profoundly investigated in the nervous system, while the expression profile and function of HDAC4 in T cells are barely known. For the first time, we report here that HDAC4 is expressed in the multiple T cell lineages. Using T-cell-specific HDAC4-deficient mice, we discovered that lack of HDAC4 did not alter the frequencies of conventional T cells, invariant NKT (iNKT) cells or regulatory T cells within both the thymus and secondary lymphoid organs. Moreover, conventional T cells and iNKT cells from wild-type and HDAC4-deficient mice displayed no significant difference in cytokine production. In conclusion, our results imply that under steady stage, HDAC4 is not required for the development and function of multiple T cell lineages, including conventional T cells and iNKT cells.

Neurology
Nejad-Davarani SP, **Bagher-Ebadian H**, **Ewing JR**, Noll DC, **Mikkelsen T**, **Chopp M**, and **Jiang Q**. A parametric model of the brain vascular system for estimation of the arterial input function (AIF) at the tissue level *NMR Biomed* 2017;PMID: 28211963. Full text

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In this paper, we introduce a novel model of the brain vascular system, which is developed based on laws of fluid dynamics and vascular morphology. This model is used to address dispersion and delay of the arterial input function (AIF) at different levels of the vascular structure and to estimate the local AIF in DCE images. We developed a method based on the simplex algorithm and Akaike information criterion to estimate the likelihood of the contrast agent concentration signal sampled in DCE images belonging to different layers of the vascular tree or being a combination of different signal levels from different nodes of this structure. To evaluate this method, we tested the method on simulated local AIF signals at different levels of this structure. Even down to a signal to noise ratio of 5.5 our method was able to accurately detect the branching level of the simulated signals. When two signals with the same power level were combined, our method was able to separate the base signals of the composite AIF at the 50% threshold. We applied this method to dynamic contrast enhanced computed tomography (DCE-CT) data, and using the parameters estimated by our method we created an arrival time map of the brain. Our model corrected AIF can be used for solving the pharmacokinetic equations for more accurate estimation of vascular permeability parameters in DCE imaging studies.

Neurology
Nejad-Davarani SP, **Bagher-Ebadian H**, **Ewing JR**, Noll DC, **Mikkelsen T**, **Chopp M**, and **Jiang Q**. An extended vascular model for less biased estimation of permeability parameters in DCE-T1 images *NMR Biomed* 2017;PMID: 28211961. Full text

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One of the key elements in dynamic contrast enhanced (DCE) image analysis is the arterial input function (AIF). Traditionally, in DCE studies a global AIF sampled from a major artery or vein is used to estimate the vascular permeability parameters; however, not addressing dispersion and delay of the AIF at the tissue level can lead to biased estimates of these parameters. To find less biased estimates of vascular permeability parameters, a vascular model of the cerebral vascular system is proposed that considers effects of dispersion of the AIF in the vessel branches, as well as extravasation of the contrast agent (CA) to the extravascular-extracellular space. Profiles of the CA concentration were simulated for different branching levels of the vascular structure, combined with the effects of vascular leakage. To estimate the permeability parameters, the extended model was applied to these simulated signals and also to DCE-T1 (dynamic contrast enhanced T1) images of patients with glioblastoma multiforme tumors. The simulation study showed that, compared with the case of solving the pharmacokinetic equation with a global AIF, using the local AIF that is corrected by the vascular model can give less biased estimates of the permeability parameters (Ktrans , vp and Kb). Applying the extended model to signals sampled from different areas of the DCE-T1 image showed that it is able to explain the CA concentration profile in both the normal areas and the tumor area, where effects of vascular leakage exist. Differences in the values of the permeability parameters estimated in these images using the local and global AIFs followed the same trend as the simulation study. These results demonstrate that the vascular model can be a useful tool for obtaining more accurate estimation of parameters in DCE studies.

Neurology
Sivakumar S, Taccone FS, **Rehman M**, Hinson H, Naval N, and Lazaridis C. Hemodynamic and neuro-monitoring for neurocritically ill patients: An international survey of intensivists *J Crit Care* 2017; 39:40-47. PMID: 28171804. Full text

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PURPOSE: To investigate multimodality systemic and neuro-monitoring practices in acute brain injury (ABI) and to analyze differences among "neurointensivists" (NI; clinical practice comprised >1/3 by neurocritical care), and other intensivists (OI). METHODS: Anonymous 22-question Web-based survey among physician members of SCCM and ESICM. RESULTS: Six hundred fifty-five responded (66% completion rate); 422 (65%) were OI, and 226 (35%) were NI. More NI follow hemodynamic protocols for TBI (44.5% vs 33%, P=.007) and SAH (38% vs 21%, P<.001). For CPP optimization, NI use more arterial-waveform-analysis (AWA) (45% vs 35%, P=.019), and ultrasound (37.5% vs 28%, P=.023); NI use more PbtO2 (28% vs 10%, P<.001). In the case scenario of raised ICP/low PbtO2, most employ analgesia and/or sedation (47%) and osmotherapy (38%). More NI use pressure reactivity (vasopressor use OI 23% vs NI 34.5%, P=.014). For DCI, more NI target cardiac index (CI) (35% vs 21%, P<.001), and fluid responsiveness (62.5% vs 53%, P=.03). Also, NI use more angiography (57% vs 43.5%, P=.004), TCD (56.5% vs 38%, P<.001), CTP (32% vs16%, P<.001), and PbtO2 (18% vs 7.5%, P=.001). CONCLUSIONS: Intensivists with exposure to ABI patients employ more neuro- and hemodynamic monitoring. We found large heterogeneity and low overall use of advanced brain-physiology parameters.

Neurology
Xin H, **Katakowski M**, **Wang F**, **Qian JY**, **Liu XS**, **Ali MM**, **Buller B**, **Zhang ZG**, and **Chopp M**. Microrna cluster mir-17-92 cluster in exosomes enhance neuroplasticity and functional recovery after stroke in rats *Stroke* 2017;PMID: 28232590. Full text

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BACKGROUND AND PURPOSE: Multipotent mesenchymal stromal cell (MSC) harvested exosomes are hypothesized as the major paracrine effectors of MSCs. In vitro, the miR-17-92 cluster promotes oligodendrogenesis, neurogenesis, and axonal outgrowth. We, therefore, investigated whether the miR-17-92 cluster-enriched exosomes harvested from MSCs transfected with an miR-17-92 cluster plasmid enhance neurological recovery compared with control MSC-derived exosomes. METHODS: Rats subjected to 2 hours of transient middle cerebral artery occlusion were intravenously administered miR-17-92 cluster-enriched exosomes, control MSC exosomes, or liposomes and were euthanized 28 days post-middle cerebral artery occlusion. Histochemistry, immunohistochemistry, and Golgi-Cox staining were used to assess dendritic, axonal, synaptic, and myelin remodeling. Expression of phosphatase and tensin homolog and activation of its downstream proteins, protein kinase B, mechanistic target of rapamycin, and glycogen synthase kinase 3beta in the peri-infarct region were measured by means of Western blots. RESULTS: Compared with the liposome treatment, both exosome treatment groups exhibited significant improvement of functional recovery, but miR-17-92 cluster-enriched exosome treatment had significantly more robust effects on improvement of neurological function and enhancements of oligodendrogenesis, neurogenesis, and neurite remodeling/neuronal dendrite plasticity in the ischemic boundary zone (IBZ) than the control MSC exosome treatment. Moreover, miR-17-92 cluster-enriched exosome treatment substantially inhibited phosphatase and tensin homolog, a validated miR-17-92 cluster target gene, and subsequently increased the phosphorylation of phosphatase and tensin homolog downstream proteins, protein kinase B, mechanistic target of rapamycin, and glycogen synthase kinase 3beta compared with control MSC exosome treatment. CONCLUSIONS: Our data suggest that treatment of stroke with tailored exosomes enriched with the miR-17-92 cluster increases neural plasticity and functional recovery after stroke, possibly via targeting phosphatase and tensin homolog to activate the PI3K/protein kinase B/mechanistic target of rapamycin/glycogen synthase kinase 3beta signaling pathway.

Neurology
Xin H, **Wang F**, **Li Y**, **Lu QE**, **Cheung WL**, **Zhang Y**, **Zhang ZG**, and **Chopp M**. Secondary release of exosomes from astrocytes contributes to the increase in neural plasticity and improvement of functional recovery after stroke in rats treated with exosomes harvested from microrna 133b-overexpressing multipotent mesenchymal stromal cells *Cell Transplant* 2017; 26(2):243-257. PMID: 27677799. Full text

We previously demonstrated that multipotent mesenchymal stromal cells (MSCs) that overexpress microRNA 133b (miR-133b) significantly improve functional recovery in rats subjected to middle cerebral artery occlusion (MCAO) compared with naive MSCs and that exosomes generated from naive MSCs mediate the therapeutic benefits of MSC therapy for stroke. Here we investigated whether exosomes isolated from miR-133b-overexpressing MSCs (Ex-miR-133b+) exert amplified therapeutic effects. Rats subjected to 2 h of MCAO were intra-arterially injected with Ex-miR-133b+, exosomes from MSCs infected by blank vector (Ex-Con), or phosphate-buffered saline (PBS) and were sacrificed 28 days after MCAO. Compared with the PBS treatment, both exosome treatment groups exhibited significant improvement of functional recovery. Ex-miR-133b+ treatment significantly increased functional improvement and neurite remodeling/brain plasticity in the ischemic boundary area compared with the Ex-Con treatment. Treatment with Ex-miR-133b+ also significantly increased brain exosome content compared with Ex-Con treatment. To elucidate mechanisms underlying the enhanced therapeutic effects of Ex-miR-133b+, astrocytes cultured under oxygen- and glucose-deprived (OGD) conditions were incubated with exosomes harvested from naive MSCs (Ex-Naive), miR-133b downregulated MSCs (Ex-miR-133b-), and Ex-miR-133b+. Compared with the Ex-Naive treatment, Ex-miR-133b+ significantly increased exosomes released by OGD astrocytes, whereas Ex-miR-133b- significantly decreased the release. Also, exosomes harvested from OGD astrocytes treated with Ex-miR-133b+ significantly increased neurite branching and elongation of cultured cortical embryonic rat neurons compared with the exosomes from OGD astrocytes subjected to Ex-Con. Our data suggest that exosomes harvested from miR-133b-overexpressing MSCs improve neural plasticity and functional recovery after stroke with a contribution from a stimulated secondary release of neurite-promoting exosomes from astrocytes.

Neurology

Xiong Y, **Mahmood A**, and **Chopp M**. Emerging potential of exosomes for treatment of traumatic brain injury *Neural Regen Res* 2017; 12(1):19-22. PMID: 28250732. Full text

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Traumatic brain injury (TBI) is one of the major causes of death and disability worldwide. No effective treatment has been identified from clinical trials. Compelling evidence exists that treatment with mesenchymal stem cells (MSCs) exerts a substantial therapeutic effect after experimental brain injury. In addition to their soluble factors, therapeutic effects of MSCs may be attributed to their generation and release of exosomes. Exosomes are endosomal origin small-membrane nano-sized vesicles generated by almost all cell types. Exosomes play a pivotal role in intercellular communication. Intravenous delivery of MSC-derived exosomes improves functional recovery and promotes neuroplasticity in rats after TBI. Therapeutic effects of exosomes derive from the exosome content, especially microRNAs (miRNAs). miRNAs are small non-coding regulatory RNAs and play an important role in posttranscriptional regulation of genes. Compared with their parent cells, exosomes are more stable and can cross the blood-brain barrier. They have reduced the safety risks inherent in administering viable cells such as the risk of occlusion in microvasculature or unregulated growth of transplanted cells. Developing a cell-free exosome-based therapy may open up a novel approach to enhancing multifaceted aspects of neuroplasticity and to amplifying neurological recovery, potentially for a variety of neural injuries and neurodegenerative diseases. This review discusses the most recent knowledge of exosome therapies for TBI, their associated challenges and opportunities.

Neurology

Zhang Y, **Zhang ZG**, **Chopp M**, **Meng Y**, **Zhang L**, **Mahmood A**, and **Xiong Y**. Treatment of traumatic brain injury in rats with N-acetyl-seryl-aspartyl-lysyl-proline *J Neurosurg* 2017; 126(3):782-795. PMID: 28245754. Full text

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OBJECTIVE The authors' previous studies have suggested that thymosin beta 4 (Tbeta4), a major actin-sequestering protein, improves functional recovery after neural injury. N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is an active peptide fragment of Tbeta4. Its effect as a treatment of traumatic brain injury (TBI) has not been investigated. Thus, this study was designed to determine whether AcSDKP treatment improves functional recovery in rats after TBI. METHODS Young adult male Wistar rats were randomly divided into the following groups: 1) sham group (no injury); 2) TBI + vehicle group (0.01 N acetic acid); and 3) TBI + AcSDKP (0.8 mg/kg/day). TBI was induced by controlled cortical impact over the left parietal cortex. AcSDKP or vehicle was administered subcutaneously starting 1 hour postinjury and continuously for 3 days using an osmotic minipump. Sensorimotor function and spatial learning were assessed using a modified Neurological Severity Score and Morris water maze tests, respectively. Some of the

animals were euthanized 1 day after injury, and their brains were processed for measurement of fibrin accumulation and neuroinflammation signaling pathways. The remaining animals were euthanized 35 days after injury, and brain sections were processed for measurement of lesion volume, hippocampal cell loss, angiogenesis, neurogenesis, and dendritic spine remodeling. RESULTS Compared with vehicle treatment, AcSDKP treatment initiated 1 hour postinjury significantly improved sensorimotor functional recovery (Days 7-35, $p < 0.05$) and spatial learning (Days 33-35, $p < 0.05$), reduced cortical lesion volume, and hippocampal neuronal cell loss, reduced fibrin accumulation and activation of microglia/macrophages, enhanced angiogenesis and neurogenesis, and increased the number of dendritic spines in the injured brain ($p < 0.05$). AcSDKP treatment also significantly inhibited the transforming growth factor-beta1/nuclear factor-kappaB signaling pathway. CONCLUSIONS AcSDKP treatment initiated 1 hour postinjury provides neuroprotection and neurorestoration after TBI, indicating that this small tetrapeptide has promising therapeutic potential for treatment of TBI. Further investigation of the optimal dose and therapeutic window of AcSDKP treatment for TBI and the associated underlying mechanisms is therefore warranted.

Neuroradiology

Kelley BP, **Patel SC**, **Marin HL**, **Corrigan JJ**, **Mitsias PD**, and **Griffith B**. Autoimmune encephalitis: Pathophysiology and imaging review of an overlooked diagnosis *AJNR Am J Neuroradiol* 2017;PMID: 28183838. Full text

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Autoimmune encephalitis is a relatively new category of immune-mediated disease involving the central nervous system that demonstrates a widely variable spectrum of clinical presentations, ranging from the relatively mild or insidious onset of cognitive impairment to more complex forms of encephalopathy with refractory seizure. Due to its diverse clinical features, which can mimic a variety of other pathologic processes, autoimmune encephalitis presents a diagnostic challenge to clinicians. Imaging findings in patients with these disorders can also be quite variable, but recognizing characteristic findings within limbic structures suggestive of autoimmune encephalitis can be a key step in alerting clinicians to the potential diagnosis and ensuring a prompt and appropriate clinical work-up. In this article, we review antibody-mediated encephalitis and its various subtypes with a specific emphasis on the role of neuroimaging in the diagnostic work-up.

Neuroradiology

Tahir RA, **Asmaro K**, **Pabaney A**, **Kole M**, **Nypaver T**, and **Marin H**. Separate origins of the left internal and external carotid arteries from the aortic arch and cervical internal carotid artery aneurysm in a patient with Noonan syndrome *BMJ Case Rep* 2016; 2016PMID: 27440846. Full text

Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA.
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Distinct origins of the external carotid artery and the internal carotid artery (ICA) from the aortic arch have been rarely described, and represent an aberrant development of the aortic arches during fetal life. This anatomical variation is usually discovered incidentally; infrequently, an aneurysm of the cervical ICA might accompany this rare configuration. We describe one such case in a patient with Noonan syndrome who presented with pulsatile neck mass. The diagnostic features and management of the aneurysm and a review of the literature are presented.

Neurosurgery

Basheer A, **Rammo R**, **Kalkanis S**, **Felicella MM**, and **Chedid M**. Multifocal intradural extramedullary pilocytic astrocytomas of the spinal cord: A case report and review of the literature *Neurosurgery* 2017; 80(2):E178-e184. PMID: 28173580. Full text

Departments of Neurosurgery, Henry Ford Hospital, Detroit, Michigan.

Neurosurgery
Henning PT, Wilson TJ, Willsey M, **John JK**, Popadich M, and Yang LJ. Pilot study of intraoperative ultrasound-guided instrument placement in nerve transection surgery for peripheral nerve pain syndromes *Neurosurg Focus* 2017; 42(3):E6. PMID: 28245671. Full text

Departments of 1 Physical Medicine & Rehabilitation and.
Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota; and.
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Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan.

Surgical transection of sensory nerves in the treatment of intractable neuropathic pain is a commonly performed procedure. At times these cases can be particularly challenging when encountering obese patients, when targeting deeper nerves or those with a variable branching pattern, or in the case of repeat operations. In this case series, the authors describe their experience with ultrasound-guided surgical instrument placement during transection of a saphenous nerve in the region of prior vascular surgery in 1 patient and in the lateral femoral cutaneous nerve in 2 obese patients. The authors also describe this novel technique and provide pilot data that suggests ultrasound-assisted surgery may allow for complex cases to be completed in an expedited fashion through smaller incisions.

Neurosurgery
Lassman AB, van den Bent M, Gan HK, Reardon DA, Kumthekar P, Butowski N, Lwin Z, **Mikkelsen T**, Nabors LB, Papadopoulos KP, Penas-Prado M, Simes J, Wheeler H, Gomez E, Lee HJ, Roberts-Rapp L, Xiong H, Bain E, Holen K, and Merrell R. Efficacy of a novel antibody-drug conjugate (ADC), ABT-414, with temozolomide (TMZ) in recurrent glioblastoma (rGBM) *Ann Oncol* 2016; 27:1. PMID: Not assigned. Abstract

[Lassman, A. B.] Columbia Univ, Dept Neurol, New York, NY USA. [Lassman, A. B.] Columbia Univ, Herbert Irving Comprehens Canc Ctr, New York, NY USA. [van den Bent, M.] Erasmus MC Canc Inst, Dept Neurooncol, Rotterdam, Netherlands. [Gan, H. K.] Austin Hlth, Dept Med Oncol, Melbourne, Vic, Australia. [Gan, H. K.] Olivia Newton John Canc Res Inst, Melbourne, Vic, Australia. [Reardon, D. A.] Dana Farber Canc Inst, Ctr Neurooncol, Boston, MA 02115 USA. [Kumthekar, P.] Northwestern Univ, Dept Neurol, Chicago, IL 60611 USA. [Butowski, N.] Univ Calif San Francisco, Dept Neurol Surg, San Francisco, CA USA. [Lwin, Z.] Univ Queensland, Sch Med, Dept Med Oncol, Brisbane, Qld, Australia. [Mikkelsen, T.] Henry Ford Hlth Syst, Neurosurg & Neurosci Res, Detroit, MI USA. [Nabors, L. B.] Univ Alabama Birmingham, Dept Neurobiol, Birmingham, AL USA. [Papadopoulos, K. P.] START, Dept Clin Res, San Antonio, TX USA. [Penas-Prado, M.] Univ Texas MD Anderson Canc Ctr, Dept Neurooncol, Houston, TX 77030 USA. [Simes, J.] Univ Sydney, NHMRC Clin Trials Ctr, Sydney, NSW, Australia. [Wheeler, H.] Royal North Shore Hosp, Med Oncol, Sydney, NSW, Australia. [Gomez, E.; Lee, H-J.; Roberts-Rapp, L.; Xiong, H.; Bain, E.; Holen, K.] AbbVie, Global Pharmaceut R&D, N Chicago, IL USA. [Merrell, R.] NorthShore Univ HealthSyst, Dept Neurol, Evanston, IL USA.

Neurosurgery
Nejad-Davarani SP, **Bagher-Ebadian H**, **Ewing JR**, Noll DC, **Mikkelsen T**, **Chopp M**, and **Jiang Q**. A parametric model of the brain vascular system for estimation of the arterial input function (AIF) at the tissue level *NMR Biomed* 2017;PMID: 28211963. Full text

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In this paper, we introduce a novel model of the brain vascular system, which is developed based on laws of fluid dynamics and vascular morphology. This model is used to address dispersion and delay of the arterial input function (AIF) at different levels of the vascular structure and to estimate the local AIF in DCE images. We developed a method based on the simplex algorithm and Akaike information criterion to estimate the likelihood of the contrast agent concentration signal sampled in DCE images belonging to different layers of the vascular tree or being a combination of different signal levels from different nodes of this structure. To evaluate this method, we tested the method on simulated local AIF signals at different levels of this structure. Even down to a signal to noise ratio of 5.5 our method was able to accurately detect the branching level of the simulated signals. When two signals with the same power level were combined, our method was able to separate the base signals of the composite AIF at the 50% threshold. We applied this method to dynamic contrast enhanced computed tomography (DCE-CT) data, and using the parameters estimated by our method we created an arrival time map of the brain. Our model corrected AIF can

be used for solving the pharmacokinetic equations for more accurate estimation of vascular permeability parameters in DCE imaging studies.

Neurosurgery
Nejad-Davarani SP, **Bagher-Ebadian H**, **Ewing JR**, Noll DC, **Mikkelsen T**, **Chopp M**, and **Jiang Q**. An extended vascular model for less biased estimation of permeability parameters in DCE-T1 images *NMR Biomed* 2017;PMID: 28211961. Full text

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA.
Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA.
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One of the key elements in dynamic contrast enhanced (DCE) image analysis is the arterial input function (AIF). Traditionally, in DCE studies a global AIF sampled from a major artery or vein is used to estimate the vascular permeability parameters; however, not addressing dispersion and delay of the AIF at the tissue level can lead to biased estimates of these parameters. To find less biased estimates of vascular permeability parameters, a vascular model of the cerebral vascular system is proposed that considers effects of dispersion of the AIF in the vessel branches, as well as extravasation of the contrast agent (CA) to the extravascular-extracellular space. Profiles of the CA concentration were simulated for different branching levels of the vascular structure, combined with the effects of vascular leakage. To estimate the permeability parameters, the extended model was applied to these simulated signals and also to DCE-T1 (dynamic contrast enhanced T1) images of patients with glioblastoma multiforme tumors. The simulation study showed that, compared with the case of solving the pharmacokinetic equation with a global AIF, using the local AIF that is corrected by the vascular model can give less biased estimates of the permeability parameters (Ktrans , vp and Kb). Applying the extended model to signals sampled from different areas of the DCE-T1 image showed that it is able to explain the CA concentration profile in both the normal areas and the tumor area, where effects of vascular leakage exist. Differences in the values of the permeability parameters estimated in these images using the local and global AIFs followed the same trend as the simulation study. These results demonstrate that the vascular model can be a useful tool for obtaining more accurate estimation of parameters in DCE studies.

Neurosurgery
Silva TC, Colaprico A, Olsen C, D'Angelo F, Bontempi G, Ceccarelli M, and **Noushmehr H**. TCGA Workflow: Analyze cancer genomics and epigenomics data using Bioconductor packages *F1000Res* 2016; 5:1542. PMID: 28232861. Full text

Department of Genetics, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Brazil; Department of Biomedical Sciences, Cedars-Sinai, Los Angeles, CA, USA.
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Interuniversity Institute of Bioinformatics in Brussels, Brussels, Belgium; Machine Learning Group, ULB, Brussels, Belgium; Department of Science and Technology, University of Sannio, Benevento, Italy.
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Biotechnological advances in sequencing have led to an explosion of publicly available data via large international consortia such as The Cancer Genome Atlas (TCGA), The Encyclopedia of DNA Elements (ENCODE), and The NIH Roadmap Epigenomics Mapping Consortium (Roadmap). These projects have provided unprecedented opportunities to interrogate the epigenome of cultured cancer cell lines as well as normal and tumor tissues with high genomic resolution. The Bioconductor project offers more than 1,000 open-source software and statistical packages to analyze high-throughput genomic data. However, most packages are designed for specific data types (e.g. expression, epigenetics, genomics) and there is no one comprehensive tool that provides a complete integrative analysis of the resources and data provided by all three public projects. A need to create an integration of these different analyses was recently proposed. In this workflow, we provide a series of biologically focused integrative analyses of different molecular data. We describe how to download, process and prepare TCGA data and by harnessing several key Bioconductor packages, we describe how to extract biologically meaningful genomic and epigenomic data. Using Roadmap and ENCODE data, we provide a work plan to identify biologically relevant functional epigenomic elements

associated with cancer. To illustrate our workflow, we analyzed two types of brain tumors: low-grade glioma (LGG) versus high-grade glioma (glioblastoma multiform or GBM). This workflow introduces the following Bioconductor packages: AnnotationHub, ChIPSeeker, ComplexHeatmap, pathview, ELMER, GAIA, MINET, RTCGAToolbox, TCGAbiolinks.

Neurosurgery
Tahir RA, **Asmaro K**, **Pabaney A**, **Kole M**, **Nypaver T**, and **Marin H**. Separate origins of the left internal and external carotid arteries from the aortic arch and cervical internal carotid artery aneurysm in a patient with Noonan syndrome *BMJ Case Rep* 2016; 2016PMID: 27440846. Full text

Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA.
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Distinct origins of the external carotid artery and the internal carotid artery (ICA) from the aortic arch have been rarely described, and represent an aberrant development of the aortic arches during fetal life. This anatomical variation is usually discovered incidentally; infrequently, an aneurysm of the cervical ICA might accompany this rare configuration. We describe one such case in a patient with Noonan syndrome who presented with pulsatile neck mass. The diagnostic features and management of the aneurysm and a review of the literature are presented.

Neurosurgery
Xiong Y, **Mahmood A**, and **Chopp M**. Emerging potential of exosomes for treatment of traumatic brain injury *Neural Regen Res* 2017; 12(1):19-22. PMID: 28250732. Full text

Department of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA.
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Traumatic brain injury (TBI) is one of the major causes of death and disability worldwide. No effective treatment has been identified from clinical trials. Compelling evidence exists that treatment with mesenchymal stem cells (MSCs) exerts a substantial therapeutic effect after experimental brain injury. In addition to their soluble factors, therapeutic effects of MSCs may be attributed to their generation and release of exosomes. Exosomes are endosomal origin small-membrane nano-sized vesicles generated by almost all cell types. Exosomes play a pivotal role in intercellular communication. Intravenous delivery of MSC-derived exosomes improves functional recovery and promotes neuroplasticity in rats after TBI. Therapeutic effects of exosomes derive from the exosome content, especially microRNAs (miRNAs). miRNAs are small non-coding regulatory RNAs and play an important role in posttranscriptional regulation of genes. Compared with their parent cells, exosomes are more stable and can cross the blood-brain barrier. They have reduced the safety risks inherent in administering viable cells such as the risk of occlusion in microvasculature or unregulated growth of transplanted cells. Developing a cell-free exosome-based therapy may open up a novel approach to enhancing multifaceted aspects of neuroplasticity and to amplifying neurological recovery, potentially for a variety of neural injuries and neurodegenerative diseases. This review discusses the most recent knowledge of exosome therapies for TBI, their associated challenges and opportunities.

Neurosurgery
Zakaria HM, **Basheer A**, **Boyce-Fappiano D**, **Elibe E**, **Schultz L**, **Lee I**, **Siddiqui F**, **Griffith B**, and **Chang V**. Application of morphometric analysis to patients with lung cancer metastasis to the spine: a clinical study *Neurosurg Focus* 2016; 41(2):E12. PMID: 27476836. Full text

Departments of 1 Neurosurgery.
Radiation Oncology.
Public Health Sciences, and.
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OBJECTIVE Predicting the survival rate for patients with cancer is currently performed using the TNM Classification of Malignant Tumors (TNM). Identifying accurate prognostic markers of survival would allow better treatment stratification between more aggressive treatment strategies or palliation. This is especially relevant for patients with spinal metastases, who all have identical TNM staging and whose surgical decision-making is potentially complex. Analytical morphometrics quantifies patient frailty by measuring lean muscle mass and can predict risk for

postoperative morbidity after lumbar spine surgery. This study evaluates whether morphometrics can be predictive of survival in patients with spinal metastases. METHODS Utilizing a retrospective registry of patients with spinal metastases who had undergone stereotactic body radiation therapy, the authors identified patients with primary lung cancer. Morphometric measurements were taken of the psoas muscle using CT of the lumbar spine. Additional morphometrics were taken of the L-4 vertebral body. Patients were stratified into tertiles based on psoas muscle area. The primary outcome measure was overall survival, which was measured from the date of the patient's CT scan to date of death. RESULTS A total of 168 patients were identified, with 54% male and 54% having multiple-level metastases. The median survival for all patients was 185.5 days (95% confidence interval [CI] 146-228 days). Survival was not associated with age, sex, or the number of levels of metastasis. Patients in the smallest tertile for the left psoas area had significantly shorter survival compared with a combination of the other two tertiles: 139 days versus 222 days, respectively, hazard ratio (HR) 1.47, 95% CI 1.06-2.04, p = 0.007. Total psoas tertiles were not predictive of mortality, but patients whose total psoas size was below the median size had significantly shorter survival compared with those greater than the median size: 146 days versus 253.5 days, respectively, HR 1.43, 95% CI 1.05-1.94, p = 0.025. To try to differentiate small body habitus from frailty, the ratio of psoas muscle area to vertebral body area was calculated. Total psoas size became predictive of mortality when normalized to vertebral body ratio, with patients in the lowest tertile having significantly shorter survival (p = 0.017). Left psoas to vertebral body ratio was also predictive of mortality in patients within the lowest tertile (p = 0.021). Right psoas size was not predictive of mortality in any calculations. CONCLUSIONS In patients with lung cancer metastases to the spine, morphometric analysis of psoas muscle and vertebral body size can be used to identify patients who are at risk for shorter survival. This information should be used to select patients who are appropriate candidates for surgery and for the tailoring of oncological treatment regimens.

Neurosurgery

Zhang Y, **Zhang ZG**, **Chopp M**, **Meng Y**, **Zhang L**, **Mahmood A**, and **Xiong Y**. Treatment of traumatic brain injury in rats with N-acetyl-seryl-aspartyl-lysyl-proline *J Neurosurg* 2017; 126(3):782-795. PMID: 28245754. Full text

Departments of 1 Neurosurgery and.
Neurology, Henry Ford Hospital, Detroit; and.
Department of Physics, Oakland University, Rochester, Michigan.

OBJECTIVE The authors' previous studies have suggested that thymosin beta 4 (Tbeta4), a major actin-sequestering protein, improves functional recovery after neural injury. N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) is an active peptide fragment of Tbeta4. Its effect as a treatment of traumatic brain injury (TBI) has not been investigated. Thus, this study was designed to determine whether AcSDKP treatment improves functional recovery in rats after TBI. METHODS Young adult male Wistar rats were randomly divided into the following groups: 1) sham group (no injury); 2) TBI + vehicle group (0.01 N acetic acid); and 3) TBI + AcSDKP (0.8 mg/kg/day). TBI was induced by controlled cortical impact over the left parietal cortex. AcSDKP or vehicle was administered subcutaneously starting 1 hour postinjury and continuously for 3 days using an osmotic minipump. Sensorimotor function and spatial learning were assessed using a modified Neurological Severity Score and Morris water maze tests, respectively. Some of the animals were euthanized 1 day after injury, and their brains were processed for measurement of fibrin accumulation and neuroinflammation signaling pathways. The remaining animals were euthanized 35 days after injury, and brain sections were processed for measurement of lesion volume, hippocampal cell loss, angiogenesis, neurogenesis, and dendritic spine remodeling. RESULTS Compared with vehicle treatment, AcSDKP treatment initiated 1 hour postinjury significantly improved sensorimotor functional recovery (Days 7-35, p < 0.05) and spatial learning (Days 33-35, p < 0.05), reduced cortical lesion volume, and hippocampal neuronal cell loss, reduced fibrin accumulation and activation of microglia/macrophages, enhanced angiogenesis and neurogenesis, and increased the number of dendritic spines in the injured brain (p < 0.05). AcSDKP treatment also significantly inhibited the transforming growth factor-beta1/nuclear factor-kappaB signaling pathway. CONCLUSIONS AcSDKP treatment initiated 1 hour postinjury provides neuroprotection and neurorestoration after TBI, indicating that this small tetrapeptide has promising therapeutic potential for treatment of TBI. Further investigation of the optimal dose and therapeutic window of AcSDKP treatment for TBI and the associated underlying mechanisms is therefore warranted.

Obstetrics, Gynecology and Women's Health Services

Elshatanoufy S, Griffin M, **Wang Y**, **Jamil M**, **Matthews A**, **Yousif M**, **Richardson D**, **Atiemo HO**, and **Luck A**. Longterm follow up in patients with mid-urethral slings with BMI greater than 40 *Neurourol Urodyn* 2017; 36:S147. PMID: Not assigned. Abstract

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Introduction: Mid-urethral slings (MUS) are the most widely accepted and studied minimally invasive procedure for the management of stress urinary incontinence (SUI). However, studies have suggested decrease in efficacy of MUS procedures in the morbidly obese patients. In our urban population, we are encountering an increasing number of morbidly obese patients (BMI ≥ 40) with stress urinary incontinence interested in surgical options. The aim of our study was to assess the success rate of MUS in morbidly obese patients. Our secondary outcome was to assess difference in complication rates between patients with BMI ≥ 40 and <40. Methods: This is a retrospective chart review. Data was collected on all patients that have undergone a sling procedure between 2010 and 2015. Failure was defined as reported SUI symptoms or treatment for SUI. Variables collected were BMI, smoking status, comorbidities, perioperative complications(within 24 hours), short term (within 30 days) and long term complications (>30 days) and follow-up time. Analyses included ANOVA, Chi-square test, logistic, Kaplan Meier method and Cox regression. Results: We identified 382 patients, 80 were eliminated as they had a sling procedure other than MUS or, for follow-up time <6 months. Analysis included 302 patients, 36 were morbidly obese (mean = 44.8 +/- 5.6), 119 with BMI of 30-39 (mean = 33.7 +/- 2.52) and 69 with BMI ≤25 (mean = 23.1 +/- 1.69). Our mean follow-up time was 54 months. There was no difference in failure rate between all three groups (p = 0.6) even after controlling for potential confounders such as diabetes mellitus (DM), smoking status, or chronic obstructive pulmonary disease (COPD) (p = 0.61). COPD independently was associated with an increased risk of failure, odds ratio (OR) = 2.11 (1.07-4.06) p = 0.03. BMI category was not a significant predictor of peri-operative, short-term post-operative or long-term postoperative complications (p = 0.41, p = 0.19 and p = 0.18 respectively) and also after controlling for other comorbidities as potential confounders. However, active smoking status was linked to a significantly higher risk of long-term post-operative complications than nonsmokers OR = 4.14 (1.16-13.56) p = 0.02. Conclusion: BMI has no significant impact on the success of MUS in the morbidly obese patients. Smoking status was linked to an increased risk of long term postoperative complications. COPD independently and after stratification based on BMI category was associated with a higher failure rate and recurrence of stress urinary incontinence.

Obstetrics, Gynecology and Women's Health Services

Wahid M, Akhter N, Jawed A, **Dar SA**, Mandal RK, Lohani M, Areeshi MY, Khan S, and Haque S. Pembrolizumab's non-cross resistance mechanism of action successfully overthrown ipilimumab *Crit Rev Oncol Hematol* 2017; 111:1-6. PMID: 28259284. Full text

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The incidences of melanomas are increasing by leaps and bounds across the globe despite early detection and intervention. The numbers of patients dying from metastatic melanoma have been continually increased over the past thirty years. It has been considered as one of the most therapy-resistant malignancies due to the cross-resistant mechanism developed by the metastatic cells. With time, many new therapies came and they failed miserably. Ipilimumab, a monoclonal antibody that works to activate the immune system by targeting CTLA-4 proved to be a boon for advance melanoma very recently. But it could not stand firmly against the resistant metastatic skin cancer cells. Now, the new skin cancer drug named pembrolizumab proved as a new miraculous molecule. It's a humanized monoclonal antibody that blocks a biological pathway called programmed cell death-1 (PD-1), which melanoma cells activate to suppress the immune system. This antibody has surpassed ipilimumab at all the stages of clinical trials because of its non-cross resistant mechanism to malignant cells. The present review critically analyses the reasons of efficacy success of pembrolizumab over ipilizumab shown at various stages of clinical trials.

Ophthalmology and Eye Care Services

Peracha-Riyaz MH, **Peracha ZH**, **Spaulding J**, **Baciu P**, **Ahmed S**, **Imami NR**, **Darnley-Fisch D**, and **Desai U**. First described case of anterior and posterior segment crystals in phacolytic glaucoma *J Glaucoma* 2017;PMID: 28234682. Full text

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Phacolytic glaucoma is an open-angle glaucoma that occurs when lens proteins from hypermature cataracts seep through an intact anterior capsule and induce obstruction of the trabecular meshwork by inflammatory cells. We review the case of a 66-year-old man who presented with acute pain, a hypermature cataract, prominent anterior chamber crystals, and elevated intraocular pressure. After cataract surgery was performed, iridescent crystals were noted in the posterior chamber. Anterior chamber crystals have been associated with phacolytic glaucoma, but this is the first case demonstrating crystals in the posterior chamber as well.

Orthopaedics

Frisch NB, **Pepper AM**, **Rooney E**, and **Silverton C**. Intraoperative hypothermia in total hip and knee arthroplasty *Orthopedics* 2016:1-8. PMID: 27783839. Article request form

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are common and successful orthopedic procedures, and as their frequency continues to increase substantially, the focus on limiting perioperative complications heightens. Intraoperative normothermia is recommended to minimize additional complications, but limited evidence exists regarding the effect of hypothermia on orthopedic patients. The purpose of this retrospective study was to determine the incidence of perioperative hypothermia in the setting of TKA and THA, and to evaluate its impact on complications and outcomes. The clinical records of 2580 consecutive patients who underwent TKA or THA at a single institution between January 1, 2011, and December 31, 2013 were reviewed. After excluding patients with complex or revision procedures, a total of 2397 patients comprised the study population. Patient demographic data, surgery-specific data, postoperative complications, length of hospital stay, and 30-day readmission were recorded. Patients with a mean intraoperative temperature less than 36 degrees C were identified as hypothermic. Statistical analysis evaluated associations with hypothermia and the effect on complications and outcomes. The incidence of mean intraoperative hypothermia was 37%, 43.9%, and 32.6% for arthroplasty, THA, and TKA, respectively. General anesthesia was significantly associated with hypothermia (P<.001). Women and THA patients were at higher risk for hypothermia. In the arthroplasty and THA cohorts, longer operating room time and re-warmer use were associated with hypothermia (P=.010). Overall, hypothermia was associated with increased estimated blood loss, but no increase in associated transfusion was demonstrated (P=.006). Hypothermia was not associated with postoperative complications. [Orthopedics. 201x; xx(x):xx-xx.].

Orthopaedics

Frisch NB, **Wessell NM**, **Taliaferro K**, **Van Holsbeeck M**, and **Silverton CD**. Ultrasound findings in asymptomatic patients with modular metal on metal total hip arthroplasty *Skeletal Radiol* 2017;PMID: 28204856. Full text

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OBJECTIVE: The use of metal-on-metal and modular total hip arthroplasty is associated with potentially serious local and systemic complications. The primary aim of this study was to identify the prevalence of a pseudotumor in asymptomatic patients with a particular metal-on-metal hip prosthesis after a minimum follow-up of 5 years using ultrasound evaluation. A secondary purpose was to identify associations between the presence of pseudotumor and serum metal ion levels following implantation. METHODS: We prospectively evaluated data collected from 36 asymptomatic patients who underwent implantation of a Profemur Z metal-on-metal total hip arthroplasty from January 2004 to January 2010. Serum metal ion levels were collected in 2012 and 2015. Hip ultrasounds were performed in 2015. RESULTS: Pseudotumors were found in 7/36 patients (19.4%). The average pseudotumor size measured 38.2 cm3 (range 7.35 cm3-130.81 cm3). Elevated metal ion levels were found in all patients at all time points. No statistical correlation was found between the presence of pseudotumor and patient age, age of the implant, component design, and any of the serum metal ion levels or ratios. CONCLUSIONS: One in every five asymptomatic patients with metal-on-metal implants was found to have a periarticular pseudotumor. There was no dose-dependent relationship found between elevated serum metal ion levels and the development of a pseudotumor. Our findings

suggest that in patients with known elevated metal ion levels, continued monitoring of ion levels may not be a reliable predictor of pseudotumor formation, and ultrasound surveillance can and should be routinely used to document the presence and progression of pseudotumor.

Orthopaedics

Okoroha KR, **Keller RA**, **Jung EK**, Khalil L, **Marshall N**, **Kolowich PA**, and **Moutzouros V**. Pain assessment after anterior cruciate ligament reconstruction: Bone-patellar tendon-bone versus hamstring tendon autograft *Orthop J Sports Med* 2016; 4(12):2325967116674924. PMID: 28210646. Full text

Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Michigan, USA.
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BACKGROUND: Anterior cruciate ligament (ACL) reconstruction is a common outpatient procedure that is accompanied by significant postoperative pain. PURPOSE: To determine differences in acute pain levels between patients undergoing ACL reconstruction with bone-patellar tendon-bone (BTB) versus hamstring tendon (HS) autograft. STUDY DESIGN: Cohort study; Level of evidence, 2. METHODS: A total of 70 patients who underwent primary ACL reconstruction using either BTB or HS autografts consented to participate. The primary outcome of the study was postoperative pain levels (visual analog scale), which were collected immediately after surgery and for 3 days postoperatively. Secondary outcome measures included opioid consumption (intravenous morphine equivalents), hours slept, patient satisfaction, reported breakthrough pain, and calls to the physician. RESULTS: Patients treated with BTB had increased pain when compared with those treated with HS in the acute postoperative period (mean +/- SD: day 0, 6.0 +/- 1.7 vs 5.2 +/- 2.0 [P = .066]; day 1, 5.9 +/- 1.7 vs 4.9 +/-1.7 [P = .024]; day 2, 5.2 +/- 1.9 vs 4.1 +/- 2.0 [P = .032]; day 3, 4.8 +/- 2.1 vs 3.9 +/- 2.3 [P = .151]). There were also significant increases in reported breakthrough pain (day 0, 76% vs 43% [P = .009]; day 1, 64% vs 35% [P = .003]) and calls to the physician due to pain (day 1, 19% vs 0% [P = .041]) in the BTB group. There were no significant differences in narcotic requirements or sleep disturbances. Overall, the BTB group reported significantly less satisfaction with pain management on days 0 and 1 (P = .024 and .027, respectively). CONCLUSION: A significant increase in acute postoperative pain was found when performing ACL reconstruction with BTB compared with HS. Patients treated with BTB were more likely to have breakthrough pain, decreased satisfaction with their pain management, and to contact their physician due to pain. These findings suggest a difference in early postoperative pain between the 2 most common graft options for ACL reconstruction. Patients should be informed of the differences in acute postoperative pain when deciding on graft choice with their physician.

Orthopaedics

Okoroha KR, **Mehran N**, **Duncan J**, **Washington T**, **Spiering T**, **Bey MJ**, **Van Holsbeeck M**, and **Moutzouros V**. Characterization of rotator cuff tears: Ultrasound versus magnetic resonance imaging *Orthopedics* 2016:1-7. PMID: 27755645. Article request form

Ultrasound and magnetic resonance imaging (MRI) are both capable of diagnosing full-thickness rotator cuff tears. However, it is unknown which imaging modality is more accurate and precise in evaluating the characteristics of full-thickness rotator cuff tears in a surgical population. This study reviewed 114 patients who underwent arthroscopic repair of a full-thickness rotator cuff tear over a 1-year period. Of these patients, 61 had both preoperative MRI and ultrasound for review. Three musculoskeletal radiologists evaluated each ultrasound and MRI in a randomized and blinded fashion on 2 separate occasions. Tear size, retraction status, muscle atrophy, and fatty infiltration were analyzed and compared between the 2 modalities. Ultrasound measurements were statistically smaller in both tear size (P=.001) and retraction status (P=.001) compared with MRI. The 2 image modalities showed comparable intraobserver reliability in assessment of tear size and retraction status. However, MRI showed greater interobserver reliability in assessment of tear size, retraction status, and atrophy. Independent observers are more likely to agree on measurements of the characteristics of rotator cuff tears when using MRI compared with ultrasound. As tear size increases, the 2 image modalities show greater differences in measurement of tear size and retraction status. Additionally, compared with MRI, ultrasound shows consistently low reliability in detecting subtle, but clinically important, degeneration of the soft tissue envelope. Although it is inexpensive and convenient, ultrasound may be best used to identify a tear, and MRI is superior for use in surgical planning for larger tears.

Otolaryngology
Baskin JZ, Soenjaya Y, McMasters J, **Ko A**, Vasanji A, Morris N, and Eppell SJ. Nanophase bone substitute for craniofacial load bearing application: Pilot study in the rodent *J Biomed Mater Res B Appl Biomater* 2017;PMID: 28194875. Full text

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An exploratory pilot study shows that a rodent mandibular defect model is useful in determining the biological response to a nanophase collagen/apatite composite designed as a biomimetic load-bearing bone substitute. Using a critical size defect, eight groups of rats (n = 3) were implanted with four renditions of the nanophase bone substitute (NBS) biomaterial. Each rendition was tested with and without recombinant human bone morphogenetic protein 2 (BMP2). NBS biomaterial renditions were: baseline, hyper-densified, d-ribose crosslinked, and d-ribose crosslinked and hyper-densified. Biological outcomes were assessed surgically, radiologically, and histologically. With the limited power available due to the small N's involved, some interesting hypotheses were generated that will be more fully investigated in future studies. BMP2 loaded NBS, when uncrosslinked, resulted in robust bone formation in the entire defect volume (regardless of porosity). Unloaded NBS were well tolerated but did not cause significant new bone formation in the defect volume. Densification alone had little effect on in vivo performance. Crosslinking thwarted implant uptake of BMP2 and resulted in fibrous encapsulation. It is concluded that the nanophase bone substitute is well tolerated in this bone defect model. When loaded with BMP2, implantation resulted in complete bony healing and defect closure with implant density (porosity) having little effect on bone healing or remodeling. Without BMP2 the biomaterial did not result in defect closure. Crosslinking, necessary to increase mechanical properties in an aqueous environment, disrupts osteointegration and BMP2 uptake. Alternate implant fabrication strategies will be necessary to achieve an improved balance between material strength and osteointegration. (c) 2017 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2017.

Pathology
Samuel L, and Plebani M. Targeting errors in microbiology: the case of the Gram stain *Clin Chem Lab Med* 2017; 55(3):309-310. PMID: 27718489. Full text

Pharmacy
Lipari M, **Smith AL**, Kale-Pradhan P, and Wilhelm S. Adherence to gold guidelines in the inpatient COPD population *Pharmacotherapy* 2016; 36(12):E272-E272. PMID: Not assigned. Abstract

[Lipari, Melissa; Smith, Amber Lanae; Kale-Pradhan, Pramodini; Wilhelm, Sheila] Wayne State Univ, Eugene Applebaum Coll Pharm & Hlth Sci, Pharm Practice, Detroit, MI USA. [Lipari, Melissa; Kale-Pradhan, Pramodini] St John Hosp & Med Ctr, Detroit, MI USA. [Smith, Amber Lanae] Henry Ford Hosp, Detroit, MI 48202 USA. [Wilhelm, Sheila] Harper Univ Hosp, Detroit, MI USA.

Pharmacy
Walker E, **Jones M**, **Mlynarek M**, **Starosta K**, and **To L**. A comparison of the efficacy, safety, and costs of intravenous nitroprusside and nicardipine *Pharmacotherapy* 2016; 36(12):E216-E216. PMID: Not assigned. Abstract

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Psychiatry
Prabhakar D, and **Akinyemi E**. Concussion *J Am Acad Child Adolesc Psychiatry* 2017; 56(2):176-177. PMID: Not assigned. Full text

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Public Health Sciences

Jindal T, **Kachroo N**, **Sammon J**, **Dalela D**, **Sood A**, **Vetterlein MW**, **Karabon P**, **Jeong W**, **Menon M**, Trinh QD, and **Abdollah F**. Racial differences in prostate-specific antigen-based prostate cancer screening: State-by-state and region-by-region analyses *Urol Oncol* 2017;PMID: 28256311. Full text

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OBJECTIVE: Black men are more prone to harbor prostate cancer. They are more likely to succumb to this tumor than their White counterparts and may benefit from early detection and treatment. In this study, we assess the nationwide and regional disparity in prostate-specific antigen (PSA) screening for prostate cancer between Black men and non-Hispanic Whites (NHWs). METHODS: A total of 247,079 (weighted 55,185,102) men, aged 40 to 99 years, who responded to the 2012 and 2014 behavioral risk factor surveillance system surveys were used for our analysis. End points consisted of self-reported PSA screening and self-reported nonrecommended PSA screening within 12 months of the interview. The latter was defined as screening in men with <10-year life expectancy. Available sociodemographic variables were used to predict these end points. The independent predictors from multivariate models were used to calculate the adjusted prevalence of PSA screening and nonrecommended PSA screening on a nationwide and regional level. These numbers were calculated for Blacks and NHWs separately and were compared between the 2 groups. RESULTS: Prevalence of PSA screening was 30.7% in NHWs vs. 28.1% in Blacks (P<0.001). On a region-based analysis, New England, Middle Atlantic, South Atlantic, East North Central, East South Central, West South Central, and Mountain showed a significantly higher rate of PSA screening in NHWs as compared to Blacks (all P<0.001). Middle Atlantic had a significantly higher prevalence of nonrecommended screening in NHWs as compared to Blacks, whereas South Atlantic, West South Central, and Pacific had a significantly higher prevalence of nonrecommended screening in Blacks as compared to NHWs (all P<0.001). Overall, 43 states performed screening more frequently to NHWs, whereas only 8 states performed it more frequently to Black men. The nonrecommended screening was performed more frequently to NHWs in 19 states, whereas 24 states performed it more frequently to Black men. CONCLUSION: Our study demonstrates that on a regional-level (and state-level), there are significant racial differences in overall and nonrecommended PSA screening across the United States. Further research is necessary to identify the reasons for the differences and help overcoming it.

Public Health Sciences

LeWitt PA, **Li J**, **Lu M**, Guo L, and Auinger P. Metabolomic biomarkers as strong correlates of Parkinson disease progression *Neurology* 2017;PMID: 28179471. Full text

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From the Departments of Neurology (P.A.L.) and Public Health Science (J.L., M.L.), Henry Ford Health System; Wayne State University School of Medicine (P.A.L.), Detroit MI; Metabolon, Inc (L.G.), Durham, NC; and Center for Human Experimental Therapeutics (P.A.), University of Rochester, NY.

OBJECTIVE: To determine whether a Parkinson disease (PD)-specific biochemical signature might be found in the total body metabolic milieu or in the CSF compartment, especially since this disorder has systemic manifestations beyond the progressive loss of dopaminergic nigrostriatal neurons. METHODS: Our goal was to discover biomarkers of PD progression. Using ultra-high-performance liquid chromatography linked to gas chromatography and tandem mass spectrometry, we measured concentrations of small-molecule (</=1.5 kDa) constituents of plasma and CSF from 49 unmedicated, mildly affected patients with PD (mean age 61.4 years; mean duration of PD 11.4 months). Specimens were collected twice (baseline and final) at intervals up to 24 months. During this time, mean Unified

Parkinson's Disease Rating Scale (UPDRS) parts 2 + 3 scores increased 47% (from 28.8 to 42.2). Measured compounds underwent unbiased univariate and multivariate analyses, including fitting data into multiple linear regression with variable selection using least absolute shrinkage and selection operator (LASSO). RESULTS: Of 575 identified plasma and 383 CSF biochemicals, LASSO led to selection of 15 baseline plasma constituents with high positive correlation (0.87, p = 2.2e-16) to baseline-to-final change in UPDRS parts 2 + 3 scores. Three of the compounds had xanthine structures, and 4 were either medium- or long-chain fatty acids. For the 15 LASSO-selected biomarkers, pathway enrichment software found no overrepresentation among metabolic pathways. CSF concentrations of the dopamine metabolite homovanillate showed little change between baseline and final collections and minimal correlation with worsening UPDRS parts 2 + 3 scores (0.29, p = 0.041). CONCLUSIONS: Metabolomic profiling of plasma yielded strong prediction of PD progression and offered biomarkers that may provide new insights into PD pathogenesis.

Public Health Sciences

McCord J, **Cabrera R**, Lindahl B, Giannitsis E, **Evans K**, **Nowak R**, **Frisoli T**, Body R, Christ M, deFilippi CR, Christenson RH, **Jacobsen G**, Alquezar A, Panteghini M, Melki D, Plebani M, Verschuren F, French J, Bendig G, Weiser S, and Mueller C. Prognostic utility of a modified HEART score in chest pain patients in the emergency department *Circ Cardiovasc Qual Outcomes* 2017; 10(2)PMID: 28167641. Full text

From the Henry Ford Heart & Vascular Institute (J.M., R.C., T.F.), Department of Emergency Medicine (R.N.), and Department of Public Health Sciences (G.J.), Henry Ford Health System, Detroit, MI; Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Sweden (B.L.); Department of Internal Medicine III, Cardiology, Angiology & Pulmonology, University Hospital Heidelberg, Germany (E.G.); Department of Internal Medicine, Henry Ford Hospital Health System, Detroit, MI (K.E.); Central Manchester University Hospitals NHS Foundation Trust, United Kingdom (R.B.); Department of Emergency and Critical Care Medicine, General Hospital, Paracelsus Medical University, Nuremberg, Germany (M.C.); Department of Medicine, Inova Heart and Vascular Institute, Falls Church, VA (C.R.d.); Department of Pathology, University of Maryland School of Medicine, Baltimore (R.H.C.); Department of Emergency Medicine, Hospital de Sant Pau, Barcelona, Spain (A.A.); Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan Medical School, Milano, Italy (M. Panteghini); Department of Medicine, Huddinge, Karolinska Institutet, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden (D.M.); Department of Laboratory Medicine, University Hospital of Padova, Padua, Italy (M. Plebani); Cliniques Universitaires St-Luc and Universite Catholique de Louvain, Brussels, Belgium (F.V.); Liverpool Hospital and University of New South Wales, Sydney, Australia (J.F.); Roche Diagnostics Germany, Penzberg, Germany (G.B., S.W.); and Cardiology & Cardiovascular Research Institute Basel, University Hospital Basel, Switzerland (C.M.). jmccord1@hfhs.org.
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BACKGROUND: The TRAPID-AMI trial study (High-Sensitivity Troponin-T Assay for Rapid Rule-Out of Acute Myocardial Infarction) evaluated high-sensitivity cardiac troponin-T (hs-cTnT) in a 1-hour acute myocardial infarction (AMI) exclusion algorithm. Our study objective was to evaluate the prognostic utility of a modified HEART score (m-HS) within this trial. METHODS AND RESULTS: Twelve centers evaluated 1282 patients in the emergency department for possible AMI from 2011 to 2013. Measurements of hs-cTnT (99th percentile, 14 ng/L) were performed at 0, 1, 2, and 4 to 14 hours. Evaluation for major adverse cardiac events (MACEs) occurred at 30 days (death or AMI). Low-risk patients had an m-HS</=3 and had either hs-cTnT<14 ng/L over serial testing or had AMI excluded by the 1-hour protocol. By the 1-hour protocol, 777 (60%) patients had an AMI excluded. Of those 777 patients, 515 (66.3%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 262 (33.7%) patients had an m-HS>/=4, with 6 (2.3%) patients having MACEs (P=0.007). Over 4 to 14 hours, 661 patients had a hs-cTnT<14 ng/L.

Of those 661 patients, 413 (62.5%) patients had an m-HS</=3, with 1 (0.2%) patient having a MACE, and 248 (37.5%) patients had an m-HS>/=4, with 5 (2.0%) patients having MACEs (P=0.03). CONCLUSIONS: Serial testing of hs-cTnT over 1 hour along with application of an m-HS identified a low-risk population that might be able to be directly discharged from the emergency department.

Public Health Sciences

Yechieli RL, Robbins JR, **Mahan M**, **Siddiqui F**, and **Ajlouni M**. Stereotactic body radiotherapy for elderly patients with medically inoperable pancreatic cancer *Am J Clin Oncol* 2017; 40(1):22-26. PMID: 24879474. Full text

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OBJECTIVES: People over the age of 75 years account for approximately 40% of patients diagnosed with pancreatic cancer, many with comorbidities that may limit their treatment options. This study reports on the use of stereotactic body radiation therapy (SBRT) in this population. MATERIALS AND METHODS: Twenty consecutively treated patients over the age of 75 with pathologically proven localized pancreatic cancer were included in this retrospective review. All had been evaluated by a multidisciplinary team as unable to tolerate surgery or combined chemoradiation therapy. Patient outcomes were analyzed to determine the safety and efficacy of SBRT in this elderly cohort. RESULTS: The median age was 83.2 years (minimum 77 y, maximum 90 y). Eighteen patients were treated at time of initial diagnosis, and 2 for recurrence after surgery. Eleven (55%) of the patients had an Adult Comorbidity Evaluation-27 comorbidity index score of 3 (severe) and 6 (30%) had a score of 2 (moderate). Fourteen patients were treated with 35 Gy in 5 fractions, 5 with 30 Gy in 5 fractions, and 1 patient with 36 Gy in 3 fractions. Seven (35%) patients had common terminology criteria for adverse events (CTCAE) V4.0 toxicity grade of 1-2, and 3 patients had a CTCAE V4.0 toxicity grade of 3-4, 2 with dehydration, and 1 had episodes of gastrointestinal bleeding. Three patients recurred locally, 10 had distant metastases, 4 of whom were found on the first posttreatment scan. Median overall survival was 6.4 months (95% confidence interval, 3.5-10.8 mo). Median recurrence-free survival was 6.8 months (95% confidence interval, 1.3-23.5 mo). Two patients survived >23 months. CONCLUSION: SBRT for pancreatic cancer appears to be a safe and effective method for treatment of elderly patients, even in the setting of severe comorbidities.

Public Health Sciences

Zakaria HM, **Basheer A**, **Boyce-Fappiano D**, **Elibe E**, **Schultz L**, **Lee I**, **Siddiqui F**, **Griffith B**, and **Chang V**. Application of morphometric analysis to patients with lung cancer metastasis to the spine: a clinical study *Neurosurg Focus* 2016; 41(2):E12. PMID: 27476836. Full text

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OBJECTIVE Predicting the survival rate for patients with cancer is currently performed using the TNM Classification of Malignant Tumors (TNM). Identifying accurate prognostic markers of survival would allow better treatment stratification between more aggressive treatment strategies or palliation. This is especially relevant for patients with spinal metastases, who all have identical TNM staging and whose surgical decision-making is potentially complex. Analytical morphometrics quantifies patient frailty by measuring lean muscle mass and can predict risk for postoperative morbidity after lumbar spine surgery. This study evaluates whether morphometrics can be predictive of survival in patients with spinal metastases. METHODS Utilizing a retrospective registry of patients with spinal metastases who had undergone stereotactic body radiation therapy, the authors identified patients with primary lung cancer. Morphometric measurements were taken of the psoas muscle using CT of the lumbar spine. Additional morphometrics were taken of the L-4 vertebral body. Patients were stratified into tertiles based on psoas muscle area. The primary outcome measure was overall survival, which was measured from the date of the patient's CT scan to date of death. RESULTS A total of 168 patients were identified, with 54% male and 54% having multiple-level metastases. The median survival for all patients was 185.5 days (95% confidence interval [CI] 146-228 days). Survival was not associated with age, sex, or the number of levels of metastasis. Patients in the smallest tertile for the left psoas area had significantly shorter survival compared with a combination of the other two tertiles: 139 days versus 222 days, respectively, hazard ratio (HR) 1.47, 95% CI 1.06-2.04, p = 0.007. Total psoas tertiles were not predictive of mortality, but patients whose total psoas size was below the median size had significantly shorter survival compared with those greater than the median size: 146 days versus 253.5 days, respectively, HR 1.43, 95% CI 1.05-1.94, p = 0.025. To try to differentiate small body habitus from frailty, the ratio of psoas muscle area to vertebral body area was calculated. Total psoas size became predictive of mortality when normalized to vertebral

body ratio, with patients in the lowest tertile having significantly shorter survival (p = 0.017). Left psoas to vertebral body ratio was also predictive of mortality in patients within the lowest tertile (p = 0.021). Right psoas size was not predictive of mortality in any calculations. CONCLUSIONS In patients with lung cancer metastases to the spine, morphometric analysis of psoas muscle and vertebral body size can be used to identify patients who are at risk for shorter survival. This information should be used to select patients who are appropriate candidates for surgery and for the tailoring of oncological treatment regimens.

Public Health Sciences

Zhang J, **Gang Zhang Z**, **Lu M**, **Wang X**, **Shang X**, **Elias SB**, and **Chopp M**. Mir-146a promotes remyelination in a cuprizone model of demyelinating injury *Neuroscience* 2017;PMID: 28237816. Full text

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The death of mature oligodendrocytes (OLs) which are the sole myelinating cells of the central nervous system (CNS), leads to demyelination and functional deficits. Currently, there is lack of effective remyelination therapies for patients with demyelinating diseases. MicroRNAs (miRNAs) mediate OL function. We hypothesized that miR-146a, by inactivating interleukin-1 receptor-associated kinase 1 (IRAK1), promotes differentiation of oligodendrocyte progenitor cells (OPCs) and thereby enhances remyelination. To test this hypothesis, a demyelination model induced by a cuprizone (CPZ) diet was employed, in which C57BL/6J mice were fed with a CPZ diet for 5 weeks. After termination of CPZ diet, the mice were randomly treated with continuous infusion of miR-146a mimics or mimic controls into the corpus callosum for 7 days. Compared to the mimic control, infusion of miR-146a mimics facilitated remyelination assessed by increased myelin basic proteins in the corpus callosum, which was associated with augmentation of newly generated mature OLs. Infusion of miR-146a mimics also substantially elevated miR-146a levels in the corpus callosum and fluorescently-tagged miR-146a mimics were mainly detected in OPCs. Western blot and double immmunofluorescent staining analysis showed that the miR-146a treatment considerably reduced IRAK1 protein levels and the number of IRAK1 positive cells, respectively. Collectively, these data indicate that exogenous miR-146a enhances remyelination, possibly by promoting OPCs to differentiate into myelinated OLs via targeting IRAK1.

Pulmonary

Ouellette DR, and Lavoie KL. Recognition, diagnosis, and treatment of cognitive and psychiatric disorders in patients with COPD *Int J Chron Obstruct Pulmon Dis* 2017; 12:639-650. PMID: 28243081. Full text

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COPD is highly prevalent and associated with substantial morbidity and mortality. Clinicians have long been aware that patients with COPD have problems with cognition and are susceptible to mood (depression) and anxiety disorders. With the increasing awareness of COPD as a multisystem disorder, many studies have evaluated the prevalence of neuropsychiatric conditions in patients with COPD. This review presents evidence regarding the prevalence of neuropsychiatric conditions (cognitive disorders/impairment, depression/anxiety) in COPD, their risk factors, and their impact on relevant outcomes. It also discusses both assessment and treatment of neuropsychiatric conditions and makes recommendations for improved screening and treatment. The findings suggest that clinicians caring for patients with COPD must become familiar with diagnosing these comorbid conditions and that future treatment has the potential to impact these patients and thereby improve COPD outcomes.

Radiation Oncology

Dehkordi AN, Kamali-Asl A, **Ewing JR**, **Wen N**, **Chetty IJ**, and **Bagher-Ebadian H**. An adaptive model for rapid and direct estimation of extravascular extracellular space in dynamic contrast enhanced MRI studies *NMR Biomed* 2017;PMID: 28195664. Full text

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Extravascular extracellular space (ve) is a key parameter to characterize the tissue of cerebral tumors. This study introduces an artificial neural network (ANN) as a fast, direct, and accurate estimator of ve from a time trace of the longitudinal relaxation rate, DeltaR1 (R1 = 1/T1), in DCE-MRI studies. Using the extended Tofts equation, a set of DeltaR1 profiles was simulated in the presence of eight different signal to noise ratios. A set of gain- and noise-insensitive features was generated from the simulated DeltaR1 profiles and used as the ANN training set. A K-fold cross-validation method was employed for training, testing, and optimization of the ANN. The performance of the optimal ANN (12:6:1, 12 features as input vector, six neurons in hidden layer, and one output) in estimating ve at a resolution of 10% (error of +/-5%) was 82%. The ANN was applied on DCE-MRI data of 26 glioblastoma patients to estimate ve in tumor regions. Its results were compared with the maximum likelihood estimation (MLE) of ve . The two techniques showed a strong agreement ($r = 0.82$, $p < 0.0001$). Results implied that the perfected ANN was less sensitive to noise and outperformed the MLE method in estimation of ve .

Radiation Oncology
Jones WE, 3rd, Suh WW, Abdel-Wahab M, Abrams RA, Azad N, Das P, **Dragovic J**, Goodman KA, Jabbour SK, Konski AA, Koong AC, Kumar R, Lee P, Pawlik TM, Small W, Jr., and Herman JM. ACR appropriateness criteria(r) resectable pancreatic cancer *Am J Clin Oncol* 2017;PMID: 28230650. Full text

*University of Texas Health Science Center at San Antonio, San Antonio paragraph signUniversity of Texas MD Anderson Cancer Center, Houston, TX daggerCancer Center of Santa Barbara, Santa Barbara section sign section signStanford Cancer Institute, Stanford paragraph sign paragraph signUniversity of California Los Angeles, Los Angeles, CA double daggerCleveland Clinic, Cleveland, OH ***Stritch School of Medicine Loyola University Chicago, Maywood section signRush University Medical Center, Chicago, IL parallelSidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, American Society of Clinical Oncology daggerdaggerdaggerSidney Kimmel Comprehensive Cancer Center at Johns Hopkins University ##Johns Hopkins University, Baltimore, MD, American College of Surgeons #Henry Ford Hospital, Detroit, MI **University of Colorado School of Medicine Anschutz Medical Campus, Aurora, CO daggerdaggerRutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ double daggerdouble daggerUniversity of Pennsylvania, The Chester County Hospital, West Chester, PA parallel parallelBanner MD Anderson Cancer Center, Gilbert, AZ.

Management of resectable pancreatic adenocarcinoma continues to present a challenge due to a paucity of high-quality randomized studies. Administration of adjuvant chemotherapy is widely accepted due to the high risk of systemic spread associated with pancreatic adenocarcinoma, but the role of radiation therapy is less clear. This paper reviews literature associated with resectable pancreatic cancer to include prognostic factors to aid in the selection of patients appropriate for adjuvant therapies. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.

Radiation Oncology
Liu Q, **Zhang X**, **Yin C**, **Chen X**, **Zhang Z**, **Brown S**, **Xie H**, **Zhou L**, and **Mi QS**. HDAC4 is expressed on multiple T cell lineages but dispensable for their development and function *Oncotarget* 2017;PMID: 28177888. Full text

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Histone deacetylation, reciprocally mediated by histone deacetylases (HDAC) and acetyltransferases, represents one major form of post-translational modification. Previous research indicates that HDACs play an essential regulatory role in the development of various immune cells. However, the specific function of individual HDACs remains largely unexplored. HDAC4, a member of class II HDACs, profoundly investigated in the nervous system, while the expression profile and function of HDAC4 in T cells are barely known. For the first time, we report here that HDAC4 is expressed in the multiple T cell lineages. Using T-cell-specific HDAC4-deficient mice, we discovered that lack of

HDAC4 did not alter the frequencies of conventional T cells, invariant NKT (iNKT) cells or regulatory T cells within both the thymus and secondary lymphoid organs. Moreover, conventional T cells and iNKT cells from wild-type and HDAC4-deficient mice displayed no significant difference in cytokine production. In conclusion, our results imply that under steady stage, HDAC4 is not required for the development and function of multiple T cell lineages, including conventional T cells and iNKT cells.

Radiation Oncology

Mao WH, Rozario T, Lu WG, Gu XJ, Yan YL, Jia X, Sumer B, and Schwartz DL. Online dosimetric evaluation of larynx SBRT: A pilot study to assess the necessity of adaptive replanning *Journal of Applied Clinical Medical Physics* 2017; 18(1):157-163. PMID: Not assigned. Full text

[Mao, Weihua; Rozario, Timothy; Lu, Weiguo; Gu, Xuejun; Yan, Yulong; Jia, Xun; Schwartz, David L.] Univ Texas Southwestern Sch Med, Dept Radiat Oncol, Dallas, TX 75390 USA. [Mao, Weihua] Henry Ford Hosp, Dept Radiat Oncol, Detroit, MI 48202 USA. [Sumer, Baran] Univ Texas Southwestern Sch Med, Dept Otolaryngol, Dallas, TX USA.
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Purpose: We have initiated a multi-institutional phase I trial of 5-fraction stereotactic body radiotherapy (SBRT) for Stage III-IVa laryngeal cancer. We conducted this pilot dosimetric study to confirm potential utility of online adaptive replanning to preserve treatment quality. Methods: We evaluated ten cases: five patients enrolled onto the current trial and five patients enrolled onto a separate phase I SBRT trial for early-stage glottic larynx cancer. Baseline SBRT treatment plans were generated per protocol. Daily cone-beam CT (CBCT) or diagnostic CT images were acquired prior to each treatment fraction. Simulation CT images and target volumes were deformably registered to daily volumetric images, the original SBRT plan was copied to the deformed images and contours, delivered dose distributions were re-calculated on the deformed CT images. All of these were performed on a commercial treatment planning system. In-house software was developed to propagate the delivered dose distribution back to reference CT images using the deformation information exported from the treatment planning system. Dosimetric differences were evaluated via dose-volume histograms. Results: We could evaluate dose within 10 minutes in all cases. Prescribed coverage to gross tumor volume (GTV) and clinical target volume (CTV) was uniformly preserved; however, intended prescription dose coverage of planning treatment volume (PTV) was lost in 53% of daily treatments (mean: 93.9%, range: 83.9-97.9%). Maximum bystander point dose limits to arytenoids, parotids, and spinal cord remained respected in all cases, although variances in carotid artery doses were observed in a minority of cases. Conclusions: Although GTV and CTV SBRT dose coverage is preserved with in-room three-dimensional image guidance, PTV coverage can vary significantly from intended plans and dose to critical structures may exceed tolerances. Online adaptive treatment re-planning is potentially necessary and clinically applicable to fully preserve treatment quality. Confirmatory trial accrual and analysis remains ongoing.

Radiation Oncology

Moran JM, Feng M, Benedetti LA, Marsh R, Griffith KA, Matuszak MM, Hess M, McMullen M, Fisher JH, Nurushev T, Grubb M, **Gardner S**, Nielsen D, Jagsi R, Hayman JA, and Pierce LJ. Development of a model web-based system to support a statewide quality consortium in radiation oncology *Pract Radiat Oncol* 2016;PMID: 28196607.
Article request form

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PURPOSE: A database in which patient data are compiled allows analytic opportunities for continuous improvements in treatment quality and comparative effectiveness research. We describe the development of a novel, web-based system that supports the collection of complex radiation treatment planning information from centers that use diverse techniques, software, and hardware for radiation oncology care in a statewide quality collaborative, the Michigan Radiation Oncology Quality Consortium (MROQC). METHODS AND MATERIALS: The MROQC database seeks to

enable assessment of physician- and patient-reported outcomes and quality improvement as a function of treatment planning and delivery techniques for breast and lung cancer patients. We created tools to collect anonymized data based on all plans. RESULTS: The MROQC system representing 24 institutions has been successfully deployed in the state of Michigan. Since 2012, dose-volume histogram and Digital Imaging and Communications in Medicine-radiation therapy plan data and information on simulation, planning, and delivery techniques have been collected. Audits indicated >90% accurate data submission and spurred refinements to data collection methodology. CONCLUSIONS: This model web-based system captures detailed, high-quality radiation therapy dosimetry data along with patient- and physician-reported outcomes and clinical data for a radiation therapy collaborative quality initiative. The collaborative nature of the project has been integral to its success. Our methodology can be applied to setting up analogous consortiums and databases.

Radiation Oncology
Nejad-Davarani SP, **Bagher-Ebadian H**, **Ewing JR**, Noll DC, **Mikkelsen T**, **Chopp M**, and **Jiang Q**. A parametric model of the brain vascular system for estimation of the arterial input function (AIF) at the tissue level *NMR Biomed* 2017;PMID: 28211963. Full text

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In this paper, we introduce a novel model of the brain vascular system, which is developed based on laws of fluid dynamics and vascular morphology. This model is used to address dispersion and delay of the arterial input function (AIF) at different levels of the vascular structure and to estimate the local AIF in DCE images. We developed a method based on the simplex algorithm and Akaike information criterion to estimate the likelihood of the contrast agent concentration signal sampled in DCE images belonging to different layers of the vascular tree or being a combination of different signal levels from different nodes of this structure. To evaluate this method, we tested the method on simulated local AIF signals at different levels of this structure. Even down to a signal to noise ratio of 5.5 our method was able to accurately detect the branching level of the simulated signals. When two signals with the same power level were combined, our method was able to separate the base signals of the composite AIF at the 50% threshold. We applied this method to dynamic contrast enhanced computed tomography (DCE-CT) data, and using the parameters estimated by our method we created an arrival time map of the brain. Our model corrected AIF can be used for solving the pharmacokinetic equations for more accurate estimation of vascular permeability parameters in DCE imaging studies.

Radiation Oncology
Nejad-Davarani SP, **Bagher-Ebadian H**, **Ewing JR**, Noll DC, **Mikkelsen T**, **Chopp M**, and **Jiang Q**. An extended vascular model for less biased estimation of permeability parameters in DCE-T1 images *NMR Biomed* 2017;PMID: 28211961. Full text

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One of the key elements in dynamic contrast enhanced (DCE) image analysis is the arterial input function (AIF). Traditionally, in DCE studies a global AIF sampled from a major artery or vein is used to estimate the vascular permeability parameters; however, not addressing dispersion and delay of the AIF at the tissue level can lead to biased estimates of these parameters. To find less biased estimates of vascular permeability parameters, a vascular model of the cerebral vascular system is proposed that considers effects of dispersion of the AIF in the vessel branches, as well as extravasation of the contrast agent (CA) to the extravascular-extracellular space. Profiles of the CA concentration were simulated for different branching levels of the vascular structure, combined with the effects of vascular leakage. To estimate the permeability parameters, the extended model was applied to these simulated signals and also to DCE-T1 (dynamic contrast enhanced T1) images of patients with glioblastoma multiforme tumors. The simulation study showed that, compared with the case of solving the pharmacokinetic equation with a global AIF, using the local AIF that is corrected by the vascular model can give less biased estimates of the permeability parameters (Ktrans , vp and Kb). Applying the extended model to signals sampled from different areas of the DCE-T1 image showed that it is able to explain the CA concentration profile in both the normal areas and the tumor area,

where effects of vascular leakage exist. Differences in the values of the permeability parameters estimated in these images using the local and global AIFs followed the same trend as the simulation study. These results demonstrate that the vascular model can be a useful tool for obtaining more accurate estimation of parameters in DCE studies.

Radiation Oncology
Yechieli RL, Robbins JR, **Mahan M**, **Siddiqui F**, and **Ajlouni M**. Stereotactic body radiotherapy for elderly patients with medically inoperable pancreatic cancer *Am J Clin Oncol* 2017; 40(1):22-26. PMID: 24879474. Full text

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OBJECTIVES: People over the age of 75 years account for approximately 40% of patients diagnosed with pancreatic cancer, many with comorbidities that may limit their treatment options. This study reports on the use of stereotactic body radiation therapy (SBRT) in this population. MATERIALS AND METHODS: Twenty consecutively treated patients over the age of 75 with pathologically proven localized pancreatic cancer were included in this retrospective review. All had been evaluated by a multidisciplinary team as unable to tolerate surgery or combined chemoradiation therapy. Patient outcomes were analyzed to determine the safety and efficacy of SBRT in this elderly cohort. RESULTS: The median age was 83.2 years (minimum 77 y, maximum 90 y). Eighteen patients were treated at time of initial diagnosis, and 2 for recurrence after surgery. Eleven (55%) of the patients had an Adult Comorbidity Evaluation-27 comorbidity index score of 3 (severe) and 6 (30%) had a score of 2 (moderate). Fourteen patients were treated with 35 Gy in 5 fractions, 5 with 30 Gy in 5 fractions, and 1 patient with 36 Gy in 3 fractions. Seven (35%) patients had common terminology criteria for adverse events (CTCAE) V4.0 toxicity grade of 1-2, and 3 patients had a CTCAE V4.0 toxicity grade of 3-4, 2 with dehydration, and 1 had episodes of gastrointestinal bleeding. Three patients recurred locally, 10 had distant metastases, 4 of whom were found on the first posttreatment scan. Median overall survival was 6.4 months (95% confidence interval, 3.5-10.8 mo). Median recurrence-free survival was 6.8 months (95% confidence interval, 1.3-23.5 mo). Two patients survived >23 months. CONCLUSION: SBRT for pancreatic cancer appears to be a safe and effective method for treatment of elderly patients, even in the setting of severe comorbidities.

Radiation Oncology
Zakaria HM, **Basheer A**, **Boyce-Fappiano D**, **Elibe E**, **Schultz L**, **Lee I**, **Siddiqui F**, **Griffith B**, and **Chang V**. Application of morphometric analysis to patients with lung cancer metastasis to the spine: a clinical study *Neurosurg Focus* 2016; 41(2):E12. PMID: 27476836. Full text

Departments of 1 Neurosurgery.
Radiation Oncology.
Public Health Sciences, and.
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OBJECTIVE Predicting the survival rate for patients with cancer is currently performed using the TNM Classification of Malignant Tumors (TNM). Identifying accurate prognostic markers of survival would allow better treatment stratification between more aggressive treatment strategies or palliation. This is especially relevant for patients with spinal metastases, who all have identical TNM staging and whose surgical decision-making is potentially complex. Analytical morphometrics quantifies patient frailty by measuring lean muscle mass and can predict risk for postoperative morbidity after lumbar spine surgery. This study evaluates whether morphometrics can be predictive of survival in patients with spinal metastases. METHODS Utilizing a retrospective registry of patients with spinal metastases who had undergone stereotactic body radiation therapy, the authors identified patients with primary lung cancer. Morphometric measurements were taken of the psoas muscle using CT of the lumbar spine. Additional morphometrics were taken of the L-4 vertebral body. Patients were stratified into tertiles based on psoas muscle area. The primary outcome measure was overall survival, which was measured from the date of the patient's CT scan to date of death. RESULTS A total of 168 patients were identified, with 54% male and 54% having multiple-level metastases. The median survival for all patients was 185.5 days (95% confidence interval [CI] 146-228 days). Survival was not associated with age, sex, or the number of levels of metastasis. Patients in the smallest tertile for the left psoas area had significantly shorter survival compared with a combination of the other two tertiles: 139 days versus 222 days, respectively, hazard ratio (HR) 1.47, 95% CI 1.06-2.04, p = 0.007. Total psoas tertiles were not predictive of mortality, but patients whose total psoas size was below the median size had significantly shorter survival compared with those greater than the median size: 146 days versus 253.5 days, respectively, HR 1.43, 95% CI 1.05-1.94, p = 0.025. To try to differentiate small body habitus from frailty, the ratio of psoas muscle area to vertebral body area was calculated. Total psoas size became predictive of mortality when normalized to vertebral body ratio, with patients in the lowest tertile having significantly shorter survival (p = 0.017). Left psoas to vertebral

body ratio was also predictive of mortality in patients within the lowest tertile (p = 0.021). Right psoas size was not predictive of mortality in any calculations. CONCLUSIONS In patients with lung cancer metastases to the spine, morphometric analysis of psoas muscle and vertebral body size can be used to identify patients who are at risk for shorter survival. This information should be used to select patients who are appropriate candidates for surgery and for the tailoring of oncological treatment regimens.

Radiology

Frisch NB, **Wessell NM**, **Taliaferro K**, **Van Holsbeeck M**, and **Silverton CD**. Ultrasound findings in asymptomatic patients with modular metal on metal total hip arthroplasty *Skeletal Radiol* 2017;PMID: 28204856. Full text

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OBJECTIVE: The use of metal-on-metal and modular total hip arthroplasty is associated with potentially serious local and systemic complications. The primary aim of this study was to identify the prevalence of a pseudotumor in asymptomatic patients with a particular metal-on-metal hip prosthesis after a minimum follow-up of 5 years using ultrasound evaluation. A secondary purpose was to identify associations between the presence of pseudotumor and serum metal ion levels following implantation. METHODS: We prospectively evaluated data collected from 36 asymptomatic patients who underwent implantation of a Profemur Z metal-on-metal total hip arthroplasty from January 2004 to January 2010. Serum metal ion levels were collected in 2012 and 2015. Hip ultrasounds were performed in 2015. RESULTS: Pseudotumors were found in 7/36 patients (19.4%). The average pseudotumor size measured 38.2 cm3 (range 7.35 cm3-130.81 cm3). Elevated metal ion levels were found in all patients at all time points. No statistical correlation was found between the presence of pseudotumor and patient age, age of the implant, component design, and any of the serum metal ion levels or ratios. CONCLUSIONS: One in every five asymptomatic patients with metal-on-metal implants was found to have a periarticular pseudotumor. There was no dose-dependent relationship found between elevated serum metal ion levels and the development of a pseudotumor. Our findings suggest that in patients with known elevated metal ion levels, continued monitoring of ion levels may not be a reliable predictor of pseudotumor formation, and ultrasound surveillance can and should be routinely used to document the presence and progression of pseudotumor.

Radiology

Larson DB, Durand DJ, and **Siegal DS**. Understanding and applying the concept of value creation in radiology *J Am Coll Radiol* 2017;PMID: 28223112. Full text

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The concept of value in radiology has been strongly advocated in recent years as a means of advancing patient care and decreasing waste. This article explores the concept of value creation in radiology and offers a framework for how radiology practices can create value according to the needs of their referring clinicians. Value only exists in the eyes of a customer. We propose that the primary purpose of diagnostic radiology is to answer clinical questions using medical imaging to help guide management of patient care. Because they are the direct recipient of this service, we propose that referring clinicians are the direct customers of a radiology practice and patients are indirect customers. Radiology practices create value as they understand and fulfill their referring clinicians' needs. To narrow those needs to actionable categories, we propose a framework consisting of four major dimensions: (1) how quickly the clinical question needs to be answered, (2) the degree of specialization required to answer the question, (3) how often the referring clinician uses imaging, and (4) the breadth of imaging that the referring clinician uses. We further identify three major settings in which referring clinicians utilize radiological services: (1) emergent or urgent care, (2) primary care, and (3) specialty care. Practices best meet these needs as they engage with their referring clinicians, create a shared vision, work together as a cohesive team, structure the organization to meet referring clinicians' needs, build the tools, and continually improve in ways that help referring clinicians care for patients.

Radiology

Zakaria HM, **Basheer A**, **Boyce-Fappiano D**, **Elibe E**, **Schultz L**, **Lee I**, **Siddiqui F**, **Griffith B**, and **Chang V**. Application of morphometric analysis to patients with lung cancer metastasis to the spine: a clinical study *Neurosurg Focus* 2016; 41(2):E12. PMID: 27476836. Full text

Departments of 1 Neurosurgery.
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Radiology, Neuroscience Institute, Henry Ford Health System, Detroit, Michigan.

OBJECTIVE Predicting the survival rate for patients with cancer is currently performed using the TNM Classification of Malignant Tumors (TNM). Identifying accurate prognostic markers of survival would allow better treatment stratification between more aggressive treatment strategies or palliation. This is especially relevant for patients with spinal metastases, who all have identical TNM staging and whose surgical decision-making is potentially complex. Analytical morphometrics quantifies patient frailty by measuring lean muscle mass and can predict risk for postoperative morbidity after lumbar spine surgery. This study evaluates whether morphometrics can be predictive of survival in patients with spinal metastases. METHODS Utilizing a retrospective registry of patients with spinal metastases who had undergone stereotactic body radiation therapy, the authors identified patients with primary lung cancer. Morphometric measurements were taken of the psoas muscle using CT of the lumbar spine. Additional morphometrics were taken of the L-4 vertebral body. Patients were stratified into tertiles based on psoas muscle area. The primary outcome measure was overall survival, which was measured from the date of the patient's CT scan to date of death. RESULTS A total of 168 patients were identified, with 54% male and 54% having multiple-level metastases. The median survival for all patients was 185.5 days (95% confidence interval [CI] 146-228 days). Survival was not associated with age, sex, or the number of levels of metastasis. Patients in the smallest tertile for the left psoas area had significantly shorter survival compared with a combination of the other two tertiles: 139 days versus 222 days, respectively, hazard ratio (HR) 1.47, 95% CI 1.06-2.04, p = 0.007. Total psoas tertiles were not predictive of mortality, but patients whose total psoas size was below the median size had significantly shorter survival compared with those greater than the median size: 146 days versus 253.5 days, respectively, HR 1.43, 95% CI 1.05-1.94, p = 0.025. To try to differentiate small body habitus from frailty, the ratio of psoas muscle area to vertebral body area was calculated. Total psoas size became predictive of mortality when normalized to vertebral body ratio, with patients in the lowest tertile having significantly shorter survival (p = 0.017). Left psoas to vertebral body ratio was also predictive of mortality in patients within the lowest tertile (p = 0.021). Right psoas size was not predictive of mortality in any calculations. CONCLUSIONS In patients with lung cancer metastases to the spine, morphometric analysis of psoas muscle and vertebral body size can be used to identify patients who are at risk for shorter survival. This information should be used to select patients who are appropriate candidates for surgery and for the tailoring of oncological treatment regimens.

Research

Ferreira P, Chan A, and **Wolf B**. Irreversibility of symptoms with biotin therapy in an adult with profound biotinidase deficiency *JIMD Rep* 2017;PMID: 28220409. Article request form

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We report a 36-year-old woman who exhibited progressive optic atrophy at 13 years old, then stroke-like episodes and spastic diplegia in her 20s. Biotinidase deficiency was not readily considered in the differential diagnosis, and the definitive diagnosis was not made until pathological variants of the biotinidase gene (BTD) were found by exome sequencing. Profound biotinidase deficiency was confirmed by enzyme analysis. Unfortunately, her symptoms did not resolve or improve with biotin treatment. Biotin therapy is essential for all individuals with profound biotinidase deficiency and for preventing further damage in those who already exhibit irreversible neurological damage. Newborn screening for the disorder would have avoided years of clinical symptoms that now appear to be irreversible with biotin treatment.

Research

Izadi H, Baniassadi M, Hasanabadi A, Mehrgini B, Memarian H, **Soltanian-Zadeh H**, and Abrinia K. Application of full set of two point correlation functions from a pair of 2D cut sections for 3D porous media reconstruction *J Pet Sci Eng* 2017; 149:789-800. PMID: Not assinged. Article request form

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Three dimensional reconstruction of porous media using limited statistical information has attracted a great interest in Earth sciences and petroleum engineering. In this study, a fast and reliable method for 3D reconstruction is proposed based on approximation of correlation functions and phase recovery algorithm using one and two perpendicular cut sections. In the proposed method, initially, full set of two point correlation functions (TPCFs) are extracted from the cut sections. Afterwards, the TPCF vectors are decomposed and then averaged to improve the accuracy of the 3D-TPCFs approximation and improve the capabilities of the reconstruction procedure. To demonstrate the ability of the proposed method to deal with both connectivity and anisotropic issues existed in 3D reconstruction literature, Berea sandstone and a synthetic representative volume element (RVE) are used. Eventually, the reconstruction results of Berea sandstone and the synthetic RVEs are examined based on tortuosity values, autocorrelation function and also porosity distribution in comparison with their corresponding original RVEs. Evaluation of tortuosity values in the original and reconstructed RVEs for both Berea sandstone and the synthetic RVE reveals that for every axis of interest, there is a satisfactory agreement between the original and reconstructed RVEs realized using those two cut sections that contain the direction of interest as their common axis. This point indicates that the proposed approach which used two perpendicular cut sections provides more reliable and robust 3D reconstruction RVEs.

Sleep Medicine

Dolsen MR, **Cheng P**, Arnedt JT, Swanson L, Casement MD, Kim HS, Goldschmied JR, Hoffmann RF, Armitage R, and Deldin PJ. Neurophysiological correlates of suicidal ideation in major depressive disorder: Hyperarousal during sleep *J Affect Disord* 2017; 212:160-166. PMID: 28192765. Full text

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BACKGROUND: Suicide is a major public health concern, and a barrier to reducing the suicide rate is the lack of objective predictors of risk. The present study considers whether quantitative sleep electroencephalography (EEG) may be a neurobiological correlate of suicidal ideation. METHODS: Participants included 84 (45 female, mean age=26.6) adults diagnosed with major depressive disorder (MDD). The item that measures thoughts of death or suicide on the Quick Inventory of Depressive Symptomatology (QIDS) was used to classify 47 participants as low suicidal ideation (24 females, mean age=26.1) and 37 as high suicidal ideation (21 females, mean age=27.3). Data were obtained from archival samples collected at the University of Michigan and University of Texas Southwestern Medical Center between 2004 and 2012. Sleep EEG was quantified using power spectral analysis, and focused on alpha, beta, and delta frequencies. RESULTS: Results indicated that participants with high compared to low suicidal ideation experienced 1) increased fast frequency activity, 2) decreased delta activity, and 3) increased alpha-delta sleep after adjusting for age, sex, depression, and insomnia symptoms. LIMITATIONS: Limitations include the exclusion of imminent suicidal intent, a single suicidal ideation item, and cross-sectional archival data. CONCLUSIONS: This is one of the first studies to provide preliminary support that electrophysiological brain activity during sleep is associated with increased suicidal ideation in MDD, and may point toward central nervous system (CNS) hyperarousal during sleep as a neurobiological correlate of suicidal ideation.

Surgery

Deeb D, **Gao X**, **Bo Liu Y**, **Zhang Y**, **Shaw J**, **Valeriote FA**, and **Gautam SC**. Inhibition of hTERT in pancreatic cancer cells by pristimerin involves suppression of epigenetic regulators of gene transcription *Oncology Reports* 2017; 37(3):1914-1920. PMID: Not yet assigned. Article request form

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Previously we have shown that the inhibition of proliferation and induction of apoptosis in pancreatic ductal adenocarcinoma (PDA) cells by pristimerin (PM), a quinonemethide triterpenoid, was associated with the inhibition of human telomerase reverse transcriptase (hTERT) mRNA and hTERT protein. Herein we show that PM inhibits transcription factors and epigenetic processes that regulate hTERT expression. Treatment with PM inhibited transcription factors c-Myc, Sp1, NF-κB and kinases p-Akt and p-mTOR that regulate hTERT post-translationally. PM also downregulated DNA methyl transferases DNMT1 and DNMT3a and transcriptionally active chromatin markers, such as acetylated histone H3 (Lys9), acetylated histone H4, di-methyl H3 (Lys4) and trimethyl H3 (Lys9). In addition, chromatin immunoprecipitation (ChIP) analysis showed decrease in c-Myc and Sp1 transcription factors, but not repressive factors CTCF, E2F or Mad1 in the regulatory region of the hTERT promoter after treatment with PM. PM also reduced acetylated histone 3 and 4 and methylated H3 at hTERT promoter. Collectively, these results indicated that PM downregulates hTERT/telomerase through the inhibition of the genetic and epigenetic regulators of hTERT gene expression.

Surgery

Elshatanoufy S, Griffin M, Matthews A, Quinn T, **Jesse M**, **Atiemo HO**, and **Richardson D**. Correlation between michigan incontinence severity index and american urolgical society symptom index in female incontinence patients *Neurourol Urodyn* 2017; 36:S86. PMID: Not assigned. Abstract

S. Elshatanoufy, Henry Ford Health Systems, Detroit, United States

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Surgery

Elshatanoufy S, Griffin M, Quinn T, Matthews A, **Jesse M**, **Atiemo HO**, and **Richardson D**. Preliminary exploration: Can suffering and acceptance be found in the discordance between measures? *Neurourol Urodyn* 2017; 36:S87. PMID: Not assigned. Abstract

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Methods: Patients (N = 144) with clinically diagnosed urinary incontinence completed the Michigan Incontinence Symptom Index (M-isi) and the AUA Symptom score (AUAss) measures. M-isi measures severity of incontinence, and AUAss measures severity of irritative/obstructive symptoms. Each has a bother measure. Both quantify severity and bother on continuous scales. The variables were dichotomized to demonstrate discordance. For severity scores, M-isi (Low 0-9, High 10-32) and AUAss (Low 0-7, High 8-35). Dichotomization of M-isi bother (Low 0-3High 4-8) and AUAss bother (Low 0-2, High 4-5) was also performed. Suffering was defined in patients with low severity and high bother. Acceptance was defined as high severity with low bother. Incontinence type (stress, urge or mixed), age, BMI, and morbidity index were assessed. Analyses included Spearman rank correlation and Pearson chi square. Results: High bother was 76.4% on the AUAss and 54.2% on the M-isi. Low bother was seen in 9.7% on the AUAss and 45.8% on the M-isi. Although there was a significant correlation between bother measures, $p < 0.01$, they are of different constructs with 65.2% of patients with low M-isi bother having high AUAss bother. The percentage of patients identified as suffering or accepting disease is presented in Table 1. Suffering was greater using the AUAss bother in both severity measures. Acceptance of disease using M-isi severity and M-isi bother increased utilizing the AUAss severity scale. No difference in age, BMI, comorbidities, or clinical diagnosis in patients in the suffering or acceptance groups was seen. In these questionnaires, bother/quality of life have different constructs. Both can potentially identify patients in practice who may be suffering and allow us to address concerns beyond the disease state.

Surgery

Eng MH, **Greenbaum A**, **Dee Wang D**, **Wyman J**, **Dnp**, **Arjomand H**, **Yadav P**, **Nemeh H**, **Paone G**, Guerrero M, and **O'Neill W**. Thrombotic valvular dysfunction with transcatheter mitral interventions for postsurgical failures *Catheter Cardiovasc Interv* 2017;PMID: 28185392. Full text

Department of Medicine, Henry Ford Health System, Center for Structural Heart Disease, Detroit, Michigan.
Division of Cardiothoracic Surgery, Henry Ford Health System, Detroit, Michigan.
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BACKGROUND: Degenerated surgical mitral valve repairs or surgical prostheses are currently being treated with transcatheter mitral valve replacement (TMVR). We report the procedural and mid-term assessment of thirteen cases. METHODS: From 12/2013 to 12/2015, 13 consecutive patients with degenerated mitral valve repair or valve replacement were treated. Patients were assessed for mitral valve academic valve consortium (MVARC) defined outcomes. RESULTS: Immediate procedural MVARC defined technical success was 92%. At 30 days MVARC device and procedure success were 61% and 84%, respectively. Mean follow-up was 150 days [IQR 40-123 days]. There were 2 late major adverse outcomes, a noncardiac related death (628 days) and a stroke (382 days). The mean mitral gradient decreased from 9.5 +/- 3.4 to 5.5 +/- 2.6 mm Hg ($P < 0.01$). Three patients were found to have high gradients, two presented with heart failure while another patient was found to have reduced leaflet motion and abnormal thickening postprocedure. The two patients with heart failure were treated with enoxaparin, which caused subsequent resolution of increased valve gradients in one patient. The other patient could not tolerate prolonged treatment from anticoagulation due to gastrointestinal bleeding. Three of 13 patients were treated with dual-antiplatelet therapy and were suspected to have valve thrombosis. CONCLUSION: Thrombotic related dysfunction post-TMVR occurred in 15% (2/13) of patients and one patient had abnormal leaflet thickening that may have been thrombus related. Dual-antiplatelet therapy was used in all 3 cases suggesting the possible need for oral anticoagulation postmitral valve-in-valve therapy. (c) 2017 Wiley Periodicals, Inc.

Surgery

Jesse MT, **Abouljoud M**, **Eshelman A**, De Reyck C, and Lerut J. Professional interpersonal dynamics and burnout in european transplant surgeons *Clin Transplant* 2017;PMID: 28185307. Full text

Consultation-Liaison Psychiatry, Behavioral Health, Henry Ford Health System, Detroit, MI, USA.
Transplant Institute, Henry Ford Health System, Detroit, MI, USA.
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Burnout within the health professions has become an increasingly important topic. Evidence suggests there are differences in burnout across different countries. Research has yet to examine burnout in transplant surgeons throughout Europe. METHODS: A cross-sectional survey of transplant surgeons across Europe. Survey included sociodemographics, professional characteristics, frequency and discomfort with difficult patient interactions, decisional autonomy, psychological job demands, support (coworker, supervisor, and hospital administration), and

burnout including emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA). RESULTS: 108 transplant surgeons provided data; 33 (30.6%) reported high EE, 19 (17.6%) reported high DP, and 29 (26.9%) reported low PA. Three hierarchical multiple linear regressions examined the burnout subscales as outcomes (EE, DP, and PA) and predictors selected based upon theoretical relationships with the outcomes. Greater psychological job demands, greater discomfort in managing difficult patient interactions, and lower levels of perceived supervisor support predicting greater EE. Only decisional autonomy significantly predicted DP, accounting for a small proportion of the variance. None of the steps for PA were significant. CONCLUSIONS: Given prior research on burnout, there were several surprising findings from this study. For example, the relatively low levels of emotional exhaustion compared to U.S. physicians and surgeons. At this time, we can only hypothesize why this finding occurred but there are multiple possible explanations including cultural effects, response bias, or other factors unknown at this time. Research is needed to attempt to clarify these findings.

Surgery
Ketterer MW, **Chawa M**, and **Paone G**. Prospective correlates of early (30 day) readmissions on a cardiothoracic surgery service *Psychol Health Med* 2017:1-8. PMID: 28161983. Article request form

a Department of Behavioral Health , Henry Ford Hospital/WSU , Detroit , MI , USA.
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Known to vary widely among hospitals for unclear reasons, early readmissions are associated with higher mortality and are suspected to frequently be due to inadequate discharge preparation/planning. It has been previously documented that the strongest and most consistent predictor of early readmissions in CHF patients is chronic cognitive impairment, and compensatory assistance with adherence on discharge improves early readmission rates. Prospective observational study. The present investigation examined multiple putative perioperative predictors of early readmission in a hospitalized Cardiothoracic Surgery Service. A subtest of the Mini-Cog, Short Term Memory, was the strongestunivariate predictor of early readmissions ($p < .001$), but the overall Mini-Cog ($p = .024$), Age ($p = .045$), Number of Admissions over the Preceding Year ($p = .036$), an Anxiety Scale ($p = .035$), Years of Education ($p = .055$) and a Depression Scale ($p = .056$) also demonstrated covariation. In a Logistic Regression, only Short Term Memory survived as a predictor variable ($p = .007$), correctly classifying 76% of patients. Chronic cognitive impairment is a predictor of early readmissions in Cardiothoracic patients. A brief bedside exam interpreted in medical context may permit identification of patients requiring familial assistance for adherence on discharge.

Surgery
Tahir RA, **Asmaro K**, **Pabaney A**, **Kole M**, **Nypaver T**, and **Marin H**. Separate origins of the left internal and external carotid arteries from the aortic arch and cervical internal carotid artery aneurysm in a patient with Noonan syndrome *BMJ Case Rep* 2016; 2016PMID: 27440846. Full text

Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan, USA.
Department of Vascular Surgery, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Interventional Neuroradiology, Henry Ford Hospital, Detroit, Michigan, USA.

Distinct origins of the external carotid artery and the internal carotid artery (ICA) from the aortic arch have been rarely described, and represent an aberrant development of the aortic arches during fetal life. This anatomical variation is usually discovered incidentally; infrequently, an aneurysm of the cervical ICA might accompany this rare configuration. We describe one such case in a patient with Noonan syndrome who presented with pulsatile neck mass. The diagnostic features and management of the aneurysm and a review of the literature are presented.

Urogynecology
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bother measures. No comparison studies exist. This study aims to determine the magnitude of symptoms using AUAss, if a correlation exists between AUAss symptom severity and M-isi bother measures, and relationship between clinical diagnosis and severity/bother scores. Methods: Patients presenting to a tertiary care FPMRS clinic complete M-isi and AUAss as part of routine care. A chart review of patients with a clinical diagnosis of urinary incontinence from 1/2015-7/2015 collected variables that included M-isi total severity (M-tot), M-isi subset scores (M-stress, M-urge), M-isi bother (M-bot), AUAss severity (A-tot), AUAss QOL (A-bot), age, body mass index (BMI), comorbidities via the Charlson Comorbidity index (CCI), and final clinical diagnosis. Analyses included Spearman rank correlation, Pearson Chi square, and ANOVA. Results: Data included 144 patients. Patients reported moderate (46.5%) and severe (37%) irritative symptoms on the AUAss. M-tot and A-tot correlated, as did M-bot and A-bot. Table-1 presents other correlates. The clinical diagnosis of mixed, stress, and urge incontinence were not significantly related to age, BMI or CCI. Age was positively correlated with CCI, $p < 0.01$, and negatively correlated to BMI, $p < 0.01$. A significant difference between M-stress and M-urge across clinical diagnoses was seen. Mixed incontinence patients reported significantly greater M-stress scores than urge patients, $p < 0.01$, and vice versa, $p < 0.01$. There were no significant differences between clinical diagnosis and A-tot, M-tot, A-bot, M-bot, age, BMI, or CCI. Conclusion: A large percentage of women had irritative symptoms in moderate-severe range on the AUAss. Significant correlation between both severity measures and their respective bother elements existed. Only the M-isi subscales of urge and stress significantly correlated to final clinical diagnosis indicating its usefulness in assessing patients with incontinence.

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Urogynecology

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Introduction: Mid-urethral slings (MUS) are the most widely accepted and studied minimally invasive procedure for the management of stress urinary incontinence (SUI). However, studies have suggested decrease in efficacy of MUS procedures in the morbidly obese patients. In our urban population, we are encountering an increasing number of morbidly obese patients (BMI ≥ 40) with stress urinary incontinence interested in surgical options. The aim of our study was to assess the success rate of MUS in morbidly obese patients. Our secondary outcome was to assess

difference in complication rates between patients with BMI ≥ 40 and <40. Methods: This is a retrospective chart review. Data was collected on all patients that have undergone a sling procedure between 2010 and 2015. Failure was defined as reported SUI symptoms or treatment for SUI. Variables collected were BMI, smoking status, comorbidities, perioperative complications(within 24 hours), short term (within 30 days) and long term complications (>30 days) and follow-up time. Analyses included ANOVA, Chi-square test, logistic, Kaplan Meier method and Cox regression. Results: We identified 382 patients, 80 were eliminated as they had a sling procedure other than MUS or, for follow-up time <6 months. Analysis included 302 patients, 36 were morbidly obese (mean = 44.8 +/- 5.6), 119 with BMI of 30-39 (mean = 33.7 +/- 2.52) and 69 with BMI ≤25 (mean = 23.1 +/- 1.69). Our mean follow-up time was 54 months. There was no difference in failure rate between all three groups (p = 0.6) even after controlling for potential confounders such as diabetes mellitus (DM), smoking status, or chronic obstructive pulmonary disease (COPD) (p = 0.61). COPD independently was associated with an increased risk of failure, odds ratio (OR) = 2.11 (1.07-4.06) p = 0.03. BMI category was not a significant predictor of peri-operative, short-term post-operative or long-term postoperative complications (p = 0.41, p = 0.19 and p = 0.18 respectively) and also after controlling for other comorbidities as potential confounders. However, active smoking status was linked to a significantly higher risk of long-term post-operative complications than nonsmokers OR = 4.14 (1.16-13.56) p = 0.02. Conclusion: BMI has no significant impact on the success of MUS in the morbidly obese patients. Smoking status was linked to an increased risk of long term postoperative complications. COPD independently and after stratification based on BMI category was associated with a higher failure rate and recurrence of stress urinary incontinence.

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Urology

Hawken SR, Auffenberg GB, Miller DC, Lane BR, Cher ML, **Abdollah F**, Cho H, and Ghani KR. Calculating life expectancy to inform prostate cancer screening and treatment decisions *BJU Int* 2017;PMID: 28199761. Full text

Department of Urology, University of Michigan, Ann Arbor, MI, USA.
College of Human Medicine, Michigan State University, Section of Urology, Spectrum Health Medical Group, Grand Rapids, MI, USA.
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Current guidelines for prostate cancer (PCa) consider life expectancy (LE) an important factor when making screening and treatment decisions. For patients with LE<10 years, most guidelines recommend against PCa screening and active surveillance or definitive treatment of low risk disease.1,2 Nevertheless, recent work has demonstrated that men with limited LE often undergo PSA screening and biopsy for PCa.3,4 With an increasing emphasis on guideline-directed management, pragmatic tools for point-of-care 10-year LE estimates are needed to inform these clinical decisions.

Urology
Hussein AA, Ahmed YE, Kozlowski JD, May P, Nyquist J, Sexton S, Curtin L, **Peabody JO**, Abol-Enein H, and Guru KA. Robot-assisted approach to w configuration urinary diversion:A step-by-step technique *BJU Int* 2017;PMID: 28220593. Full text

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Department of Urology, Cairo University, Egypt.
Henry Ford Health System, Detroit, MI.
Department of Urology and Nephrology, Mansoura, Egypt.

INTRODUCTION: To describe a detailed step-by-step approach of our technique to robot-assisted intracorporeal "W" orthotopic ileal neobladder (ICNB). METHODS: Five patients underwent robot-assisted radical cystectomy (RARC), extended pelvic lymph node dissection (ePLND) and ICNB. ICNB was divided into 6 key steps to facilitate and enable a detailed analysis and auditing of the technique. No conversion to open surgery was required. Timing for each step was noted. All patients had at least 3 months of follow up. RESULTS: Mean age was 57 years. Mean overall console and diversion times were 357 and 193 minutes, respectively. None of the patients had any evidence of residual disease following RARC. Four of five patients experienced complications; 3 developed fevers due to urinary tract infection (one required readmission), and 1 patient developed myocardial infarction and required coronary angiography and stenting. Looking at the timing for the individual steps, bowel detubularization and construction of posterior plate were consistently the longest among the key steps (average 46 minutes, 13% of the overall operative time), followed by uretero-ileal anastomosis (37 minutes, 10%), neobladder-urethral anastomosis (23 minutes, 6%) and identification and fixation of the bowel (26 minutes, 7%). CONCLUSION: We described our step-by-step technique and initial perioperative outcomes of our first five intracorporeal neobladders with "W" configuration

Urology
Jindal T, **Kachroo N**, **Sammon J**, **Dalela D**, **Sood A**, **Vetterlein MW**, **Karabon P**, **Jeong W**, **Menon M**, Trinh QD, and **Abdollah F**. Racial differences in prostate-specific antigen-based prostate cancer screening: State-by-state and region-by-region analyses *Urol Oncol* 2017;PMID: 28256311. Full text

Vattikuti Urology Institute, Vattikuti Urology Institute (VUI) Center for Outcomes Research Analytics and Evaluation, Henry Ford Hospital, Detroit, MI.
Vattikuti Urology Institute, Vattikuti Urology Institute (VUI) Center for Outcomes Research Analytics and Evaluation, Henry Ford Hospital, Detroit, MI; Division of Urology, Center for Outcomes Research and Evaluation, Maine Medical Center, Portland, ME.
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OBJECTIVE: Black men are more prone to harbor prostate cancer. They are more likely to succumb to this tumor than their White counterparts and may benefit from early detection and treatment. In this study, we assess the nationwide and regional disparity in prostate-specific antigen (PSA) screening for prostate cancer between Black men and non-Hispanic Whites (NHWs). METHODS: A total of 247,079 (weighted 55,185,102) men, aged 40 to 99 years, who responded to the 2012 and 2014 behavioral risk factor surveillance system surveys were used for our analysis. End points consisted of self-reported PSA screening and self-reported nonrecommended PSA screening within 12

months of the interview. The latter was defined as screening in men with <10-year life expectancy. Available sociodemographic variables were used to predict these end points. The independent predictors from multivariate models were used to calculate the adjusted prevalence of PSA screening and nonrecommended PSA screening on a nationwide and regional level. These numbers were calculated for Blacks and NHWs separately and were compared between the 2 groups. RESULTS: Prevalence of PSA screening was 30.7% in NHWs vs. 28.1% in Blacks (P<0.001). On a region-based analysis, New England, Middle Atlantic, South Atlantic, East North Central, East South Central, West South Central, and Mountain showed a significantly higher rate of PSA screening in NHWs as compared to Blacks (all P<0.001). Middle Atlantic had a significantly higher prevalence of nonrecommended screening in NHWs as compared to Blacks, whereas South Atlantic, West South Central, and Pacific had a significantly higher prevalence of nonrecommended screening in Blacks as compared to NHWs (all P<0.001). Overall, 43 states performed screening more frequently to NHWs, whereas only 8 states performed it more frequently to Black men. The nonrecommended screening was performed more frequently to NHWs in 19 states, whereas 24 states performed it more frequently to Black men. CONCLUSION: Our study demonstrates that on a regional-level (and state-level), there are significant racial differences in overall and nonrecommended PSA screening across the United States. Further research is necessary to identify the reasons for the differences and help overcoming it.

Urology

Kachroo N, **Irish V**, and **Atiemo HO**. Effectiveness of sacral neuromodulation in the treatment of non-obstructive urinary retention in women with subacute lower lumbar injury *Neurourol Urodyn* 2017; 36:S101. PMID: Not assigned. Abstract

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Introduction: Patients with lumbar back injuries or who undergo lumbar back surgery can often develop persistent urinary symptoms, including urinary retention, which can be difficult to treat. This study aims to determine the success rate of Interstim placement in treating non-obstructive urinary retention in women with subacute lower lumbar back injury. Methods: A single institution, retrospective analysis of women with a history of lower lumbar injury or recent lumbar back surgery and subsequent voiding abnormality who underwent sacral nerve stimulation with Interstim for refractory, non-obstructive urinary retention (proven on clinical and urodynamic evaluation) between January 2015 and August 2016. Institutional Review Board approval was obtained. Median post-operative follow up was six months. Differences in voiding frequency, volume per post void catheterization, catheterization frequency, AUA symptom scores, Quality of life (QOL) scores, Incontinence Severity Index (ISI) scores and Bother scores pre and post treatment were compared using paired t-tests (SPSS) to determine treatment efficacy. Results: Ten patients were identified that met our study inclusion criteria. Two patients had prior lumbar back surgery and the other eight had lumbar injuries. The mean duration of urinary retention was 31 months (ranging from 2-223 months). No change was noted in voiding frequency after Interstim placement, however there was a significant reduction in post void residual urine volume (median pretreatment: 275mls vs post treatment: 100mls, p = 0.003) with most no longer requiring regular intermittent selfcatheterization. There was also a statistically significant improvement in AUA symptom scores (median: 14 vs 4, p = 0.01) and QOL scores (median 6 (terrible) vs 1 (pleased), p = 0.007). No post-operative complications were reported. Conclusion: This study demonstrates the effectiveness of Sacral Neuromodulation in the treatment of non-obstructive urinary retention in women with a history of lower lumber injury. A significant improvement was noted immediately in a number of voiding parameters resulting in a substantial improvement in patient QOL.

Urology

Pucheril DT, **Elshatanoufy S**, **Irish V**, **Diaz M**, and **Atiemo HO**. Does ureaplasma urealyticum have an active role in female lower urinary tract symptoms? *Neurourol Urodyn* 2017; 36:S63-S64. PMID: Not assigned. Abstract

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Introduction: Ureaplasma Urealyticum has been implicated as a source of non-gonoccocal urethritis and urethral syndrome in men. The contribution of this infection to lower urinary tract symptoms (LUTS) in women is not clear and guidelines regarding screening are lacking. We sought to evaluate the prevalence of this infection in women with symptomatic LUTS in an outpatient setting. Methods: IRB approval was obtained for a retrospective EMR review of all female patients with LUTS tested for ureaplasma from January 2013 toDecember 2015 in a single provider's (HA) clinic. Patient characteristics considered were age, race, BMI, hemoglobin A1C, marital status, and urinary quality of life/symptoms instruments prior to management (AUASS, QOL, M-ISI). Statistical significance of the association of these characteristics with a positive culture were examined with the ttest for continuous characteristics (age, BMI, hemoglobin A1C, AUASS), and with a chi-square test for categorical variables. Results: Ninety women with LUTS and negative urine cultures were screened for ureaplasma infection. All patients were enrolled in behavioral

modification and pelvic floor physical therapy; patients with positive cultures were treated with doxycycline. Fortywomen had a positive culture demonstrating a prevalence of 44.4%. Women with a positive culture were significantly younger, slightly heavier, and more likely to be African-American. More single women had a positive culture, although this difference was statistically marginal. There was no difference in quality of life measures between women with positive and negative cultures. Considering the variables with significance level<0.10 in univariate analysis, only age and race remained independent predictors of a positive culture, age OR = 0.95 95% CI (0.91, 0.99), and African-American vs. Caucasian OR = 4.23 95% CI (1.61, 11.11). Conclusion: This study demonstrates a 44% prevalence of ureaplasma infection in women presenting with LUTS. This estimate is higher than a contemporary series, which identified 30% positive test result in symptomatic women, but is in the lower end of prevalence among asymptomatic sexually active women. Given the high prevalence of this infection in symptomatic women, screening and treatment for ureaplasma infection may be warranted in the management of LUTS. Further studies evaluating the cost effectiveness of evaluation and treatment are needed.

Urology
Pucheril DT, **Karabon P**, Trinh QD, Chughtai BI, and **Atiemo HO**. Antimuscarinic use in the elderly: A poisoned apple? *Neurourol Urodyn* 2017; 36:S150-S151. PMID: Not assigned. Abstract

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Introduction: Overactive bladder (OAB) is characterized by urinary urgency, frequency, nocturia, and urinary incontinence. The prevalence of OAB increases significantly with age, and 20-40% of the elderly report symptoms of OAB. The first-line therapy for OAB is antimuscarinic medication (AM), some of which have deleterious side-effects, including cognitive decline. Against this backdrop, we examine the incidence and prevalence of AM prescriptions among elderly persons ≥ age 65. Methods: The National Ambulatory Medical Care Survey (NAMCS) is an annual, national, survey of randomly sampled outpatient physician visits. The 2006-12 NAMCS data were queried for patients with newly given or renewed prescriptions for any of 6 AMs. Within these cohorts, frequencies of patient/physician attributes and annual trends in drug prescription were determined. Introduction of 'Neurologic Exam' data in the NAMCS 2012 data allowed for determination of exam frequency amongst patients continuing or receiving new AM prescriptions. Results: A weighted estimate of 47.68 million individuals had AMs renewed, and 12.77 million patients received a new prescription. The majority of patients receiving new AMs were elderly (55.2%), and within this cohort, most were female (69.2%), white (61.7%), and Medicare insured (84.1%). Oxybutynin (OB) was a frequently prescribed (incidence 27.3%) and continued (prevalence 33.2 %) AM among elderly patients. In 2012, only a small percentage of patients received a neurologic exam at the time of medication prescription (9.0%) or continuation (8.8%). Conclusion: The elderly withOAB constitutes a growing and vulnerable population, and AMs represents first-line medical therapy. We found alarmingly high prescription rates of OB, pharmacologically the least suitable AM, for which studies have consistently demonstrated higher rates of cognitive impairment in the elderly. Frequent OB prescription is likely driven by tiered Medicare formularies. Additionally, we found that providers rarely perform routine neurologic examination when AMs are prescribed. Accordingly, we propose the revision of Medicare formularies and the implementation.

Urology
Seisen T, Trinh QD, and **Abdollah F**. Could lead-time bias explain the apparent benefits of early salvage radiotherapy? *Nat Rev Urol* 2017;PMID: 28169994. Article request form

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Urology
Sood A, **Kachroo N**, **Abdollah F**, **Sammon JD**, Loppenberg B, **Jindal T**, Sun M, Trinh QD, **Menon M**, and **Peabody JO**. An evaluation of the timing of surgical complications following radical cystectomy: Data from the american college of surgeons national surgical quality improvement program (ACS-NSQIP) *Urology* 2017;PMID: 28216450.
Full text

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OBJECTIVES: To examine time-to-event data for 19 common postoperative complications within 30 days following radical cystectomy (RC). METHODS: Patients undergoing RC were identified within the ACS-NSQIP database (2005-2011). The primary endpoint was time-to-complication; secondary endpoints included length-of-stay (LOS), re-intervention, readmission and 30-day mortality. Further, the complications were stratified into pre-/post-discharge and the predictors were identified. Lastly, the effect of time-to-complication on secondary outcomes was evaluated. RESULTS: Overall, 1,118 patients underwent RC. The overall complication rate was 52.1%; the median LOS was 8 days. The vast majority of complications (85.2%) were contained within the first 2 weeks of surgery with a median time-to-complications of 8.5 days; 31.4% of the complications occurred post-discharge. In adjusted analyses, increasing age (OR=1.02, p<0.001), black race (OR=1.67, p=0.001) and creatinine >/=1.2 mg/dl (OR=1.26, p=0.002) were significant predictors of pre-discharge complications, while diabetes (OR=1.40, p<0.001), cardiopulmonary disease (OR=1.27, p=0.005), neoadjuvant therapy (OR=1.35, p=0.007) and continent diversions (OR=1.30, p=0.004) were significant predictors of post-discharge complications. BMI >/=30 was associated with increased odds of pre- as well as post-discharge complications (p<0.01). For a given complication, timing did not affect the mortality odds (p=0.310), but the risk of re-intervention, readmission and prolonged LOS varied. CONCLUSIONS: One in two patients suffers a complication within 30-days of undergoing RC. A vast majority of complications occur early-on postoperatively, either pre- or post-discharge, highlighting the need for rigorous inpatient as well as outpatient surveillance during this period - knowledge regarding the time-to-complications, their effect, and risk-factors may facilitate improved patient-physician communication and allow patient-tailored follow-up.