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Henry Ford Health System Publication List – July 2016

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 August, and then imported into EndNote for formatting.There are 110 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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Anesthesiology
El-Bashir J, **Dalela S**, **Owaduge I**, and **Hommel D**. Do not touch the heart ... Please *Transplantation* 2016; 100:S158-S158. PMID: Not assigned. Abstract

[El-Bashir, Jaber; Dalela, Sanjeev; Owaduge, Ibidola; Hommel, Dana] Henry Ford Hosp, Anesthesiol, Detroit, MI 48202 USA.

Anesthesiology
Kim DD, **Asif A**, and **Kataria S**. Presentation of neurolytic effect of 10% lidocaine after perineural ultrasound guided injection of a canine sciatic nerve: A pilot study *Korean J Pain* 2016; 29(3):158-163. PMID: 27413480. Full Text

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BACKGROUND: Phenol and alcohol have been used to ablate nerves to treat pain but are not specific for nerves and can damage surrounding soft tissue. Lidocaine at concentrations > 8% injected intrathecal in the animal model has been shown to be neurotoxic. Tests the hypothesis that 10% lidocaine is neurolytic after a peri-neural blockade in an ex vivo experiment on the canine sciatic nerve. METHODS: Under ultrasound, one canine sciatic nerve was injected peri-neurally with 10 cc saline and another with 10 cc of 10% lidocaine. After 20 minutes, the sciatic nerve was dissected with gross inspection. A 3 cm segment was excised and preserved in 10% buffered formalin fixative solution. Both samples underwent progressive dehydration and infusion of paraffin after which they were placed on paraffin blocks. The sections were cut at 4 microm and stained with hemoxylin and eosin. Microscopic review was performed by a pathologist from Henry Ford Hospital who was blinded to which experimental group each sample was in. RESULTS: The lidocaine injected nerve demonstrated loss of gross architecture on visual inspection while the saline injected nerve did not. No gross changes were seen in the surrounding soft tissue seen in either group. The lidocaine injected sample showed basophilic degeneration with marked cytoplasmic vacuolation in the nerve fibers with separation of individual fibers and endoneurial edema. The saline injected sample showed normal neural tissue. CONCLUSIONS: Ten percent lidocaine causes rapid neurolytic changes with ultrasound guided peri-neural injection. The study was limited by only a single nerve being tested with acute exposure.

Behavioral Health
Jesse MT, **Rubinstein E**, **Eshelman A**, **Wee C**, **Tankasala M**, **Li J**, and **Abouljoud M**. Lifestyle and self-management by those who live it: Patients engaging patients in a chronic disease model *Perm J* 2016; 20(3)PMID: 27455056. Article Request Form

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BACKGROUND: Patients pursuing organ transplantation have complex medical needs, undergo comprehensive evaluation for possible listing, and require extensive education. However, transplant patients and their supports frequently report the need for more lifestyle and self-management strategies for living with organ transplantation. OBJECTIVES: First, to explore feasibility of a successful, patient-run transplant lifestyle educational group (Transplant Living Community), designed to complement medical care and integrated into the clinical setting; and second, to report the major themes of patients' and supports' qualitative and quantitative feedback regarding the group. METHODS: Informal programmatic review and patient satisfaction surveys. RESULTS: A total of 1862 patient satisfaction surveys were disseminated and 823 were returned (response rate, 44.2%). Patients and their supports reported positive feedback regarding the group, including appreciation that the volunteer was a transplant recipient and gratitude for the lifestyle information. Five areas were associated with the success of Transplant Living Community: 1) a "champion" dedicated to the program and its successful integration into a multidisciplinary team; 2) a health care environment receptive to integration of a patient-led group with ongoing community development; 3) a high level of visibility to physicians and staff, patients, and supports; 4) a clearly presented and manageable lifestyle plan ("Play Your ACES"a [Attitude, Compliance, Exercise, and Support]), and 5) a strong volunteer structure with thoughtful training with the ultimate objective of volunteers taking ownership of the program. CONCLUSION: It is feasible to integrate a sustainable patient-led lifestyle and self-management educational group into a busy tertiary care clinic for patients with complex chronic illnesses.

Behavioral Health

Kroll HR, **Macaulay T**, and **Jesse M**. A preliminary survey examining predictors of burnout in pain medicine physicians in the united states *Pain Physician* 2016; 19(5):E689-696. PMID: 27389112. Full Text

Transplant Institute, Henry Ford Health System, Detroit, MI.
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BACKGROUND: Burnout is a prolonged response to chronic emotional and interpersonal stressors on the job, defined by 3 dimensions: exhaustion, depersonalization, and reduced personal accomplishment. While there is a growing body of research on burnout in physicians, there is a dearth of literature on burnout in pain medicine physicians. OBJECTIVE: This study aimed to determine the incidence of burnout amongst pain medicine physicians and whether there are sociodemographic or psychological demand characteristics of the job setting that predict burnout in pain medicine physicians. STUDY DESIGN AND SETTING: Cross-section survey of pain medicine physicians across the United States. METHODS: Pain medicine physicians were asked questions on sociodemographics and professional characteristics and measures of decisional authority, psychological job demands, job insecurity, perceived coworker support, and job dissatisfaction. RESULTS: Two hundred seven pain medicine physicians' responses were analyzed, 60.4% reported high emotional exhaustion, 35.7% reported high depersonalization, and 19.3% reported low personal accomplishment. Greater psychological job demands and greater job dissatisfaction predicted greater emotional exhaustion. Younger age and greater job dissatisfaction predicted higher depersonalization. Lastly, lower coworker support and greater job dissatisfaction predicted lower personal accomplishment. There were no statistical violations of assumptions or collinearity. LIMITATIONS: Low response rate and potential for response bias limit generalizability of the study. CONCLUSION(S): Pain medicine physicians in the United States reported high levels of emotional exhaustion, often considered the most taxing aspect of burnout. Job dissatisfaction appeared to be the leading agent in the development of all 3 components of burnout in pain medicine physicians in the United States.

Cardiology / Cardiovascular Research

Christakopoulos GE, Karmpaliotis D, **Alaswad K**, Yeh RW, Jaffer FA, Wyman RM, Lombardi W, Grantham JA, Kandzari DA, Lembo N, Moses JW, Kirtane A, Parikh M, Green P, Finn M, Garcia S, Doing A, Patel M, Bahadorani J, Christopoulos G, Karatasakis A, Thompson CA, Banerjee S, and Brilakis ES. Contrast utilization during chronic total occlusion percutaneous coronary intervention: Insights from a contemporary multicenter registry *J Invasive Cardiol* 2016; 28(7):288-294. PMID: 27342206. Full Text

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BACKGROUND: Administration of a large amount of contrast volume during chronic total occlusion (CTO) percutaneous coronary intervention (PCI) may lead to contrast-induced nephropathy. METHODS: We examined the association of clinical, angiographic and procedural variables with contrast volume administered during 1330 CTO-PCI procedures performed at 12 experienced United States centers. RESULTS: Technical and procedural success was 90% and 88%, respectively, and mean contrast volume was 289 +/- 138 mL. Approximately 33% of patients received >320 mL of contrast (high contrast utilization group). On univariable analysis, male gender (P=.01), smoking (P=.01), prior coronary artery bypass graft surgery (P=.04), moderate or severe calcification (P=.01), moderate or severe tortuosity (P=.04), proximal cap ambiguity (P=.01), distal cap at a bifurcation (P<.001), side branch at the proximal cap (P<.001), blunt/no stump (P=.01), occlusion length (P<.001), higher J-CTO score (P=.02), use of antegrade dissection and reentry or retrograde approach (P<.001), ad hoc CTO-PCI (P=.04), dual arterial access (P<.001), and 8 Fr guide catheters (P<.001) were associated with higher contrast volume; conversely, diabetes mellitus (P=.01) and in-stent restenosis (P=.01) were associated with lower contrast volume. On multivariable analysis, moderate/severe calcification (P=.04), distal cap at a bifurcation (P<.001), ad hoc CTO-PCI (P<.001), dual arterial access (P=.01), 8 Fr guide catheters (P=.02), and use of antegrade dissection/reentry or the retrograde approach (P<.001) were independently associated with higher contrast use, whereas diabetes (P=.02), larger target vessel diameter (P=.03), and presence of "interventional" collaterals (P<.001) were associated with lower contrast utilization. CONCLUSIONS: Several baseline clinical, angiographic, and procedural characteristics are associated with higher contrast volume administration during CTO-PCI.

Cardiology / Cardiovascular Research

Christopoulos G, Kotsia AP, Rangan BV, Vo M, **Alaswad K**, Karmpaliotis D, Banerjee S, and Brilakis ES. "Subintimal external crush" technique for a "balloon uncrossable" chronic total occlusion *Cardiovasc Revasc Med* 2016;PMID: 27421955. Full Text

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Chronic total occlusion (CTO) revascularization is traditionally limited by the challenges related to lesion crossing. In a smaller number of cases, however, inability to advance the balloon catheter to the crossing site can account for recanalization failure ("balloon uncrossable" CTO). We describe a case of a "balloon uncrossable" CTO in which balloon crossing was achieved after subintimal dilation and "external crushing" of the CTO lesion resulting in significant modification of the CTO atheromatous plaque.

Cardiology / Cardiovascular Research

Gebhard C, Buechel RR, Stahli BE, Gransar H, Achenbach S, Berman DS, Budoff MJ, Callister TQ, Chow B, Dunning A, **Al-Mallah MH**, Cademartiri F, Chinnaiyan K, Rubinshtein R, Marques H, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Shaw LJ, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Chang HJ, Leipsic J, Min JK, and Kaufmann PA. Impact of age and sex on left ventricular function determined by coronary computed tomographic angiography: results from the prospective multicentre CONFIRM study *Eur Heart J Cardiovasc Imaging* 2016;PMID: 27461207. Article Request Form

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BACKGROUND: Left ventricular (LV) volumetric and functional parameters measured with cardiac computed tomography (cardiac CT) augment risk prediction and discrimination for future mortality. Gender- and age-specific standard values for LV dimensions and systolic function obtained by 64-slice cardiac CT are lacking. METHODS AND RESULTS: 1155 patients from the Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry (54.5% males, mean age 53.1 +/- 12.4 years, range: 18-92 years) without known coronary artery disease (CAD), structural heart disease, diabetes, or hypertension who underwent cardiac CT for various indications were categorized according to age and sex. A cardiac CT data acquisition protocol was used that allowed volumetric measuring of LV function. Image interpretation was performed at each site. Patients with significant CAD (>50% stenosis) on cardiac CT were excluded from the analysis. Overall, mean left ventricular ejection fraction (LVEF) was higher in women when compared with men (66.6 +/- 7.7% vs. 64.6 +/- 8.1%, P < 0.001). This gender-difference in overall LVEF was caused by a significantly higher LVEF in women >/=70 years when compared with men >/=70 years (69.95 +/- 8.89% vs. 65.50 +/- 9.42%, P = 0.004). Accordingly, a significant increase in LVEF was observed with age (P = 0.005 for males and P < 0.001 for females), which was more pronounced in females (5.21%) than in males (2.6%). LV end-diastolic volume decreased in females from 122.48 +/- 27.87 (<40 years) to 95.56 +/- 23.17 (>70 years; P < 0.001) and in males from 155.22 +/- 35.07 (<40 years) to 130.26 +/- 27.18 (>70 years; P < 0.001). CONCLUSION: Our findings indicate that the LV undergoes a lifelong remodelling and highlight the need for age and gender adjusted reference values.

Cardiology / Cardiovascular Research

Guerrero M, Dvir D, Himbert D, Urena M, Eleid M, **Wang DD**, **Greenbaum A**, Mahadevan VS, Holzhey D, O'Hair D, Dumonteil N, Rodes-Cabau J, Piazza N, Palma JH, DeLago A, Ferrari E, Witkowski A, Wendler O, Kornowski R, Martinez-Clark P, Ciaburri D, Shemin R, Alnasser S, McAllister D, Bena M, Kerendi F, Pavlides G, Sobrinho JJ, Attizzani GF, George I, Nickenig G, Fassa AA, Cribier A, Bapat V, Feldman T, Rihal C, Vahanian A, Webb J, and **O'Neill W**. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: Results from the first multicenter global registry *JACC Cardiovasc Interv* 2016; 9(13):1361-1371. PMID: 27388824. Full Text

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OBJECTIVES: This study sought to evaluate the outcomes of the early experience of transcatheter mitral valve replacement (TMVR) with balloon-expandable valves in patients with severe mitral annular calcification (MAC) and reports the first large series from a multicenter global registry. BACKGROUND: The risk of surgical mitral valve replacement in patients with severe MAC is high. There are isolated reports of successful TMVR with balloon-expandable valves in this patient population. METHODS: We performed a multicenter retrospective review of clinical outcomes of patients with severe MAC undergoing TMVR. RESULTS: From September 2012 to July of 2015, 64 patients in 32 centers underwent TMVR with compassionate use of balloon-expandable valves. Mean age was 73 +/- 13 years, 66% were female, and mean Society of Thoracic Surgeons score was 14.4 +/- 9.5%. The mean mitral gradient was 11.45 +/- 4.4 mm Hg and the mean mitral area was 1.18 +/- 0.5 cm(2). SAPIEN valves (Edwards Lifesciences, Irvine, California) were used in 7.8%, SAPIEN XT in 59.4%, SAPIEN 3 in 28.1%, and Inovare (Braile Biomedica, Brazil) in 4.7%. Access was transatrial in 15.6%, transapical in 43.8%, and transseptal in 40.6%. Technical success according to Mitral Valve Academic Research Consortium criteria was achieved in 46 (72%) patients, primarily limited by the need for a second valve in 11 (17.2%). Six (9.3%) had left ventricular tract obstruction with hemodynamic compromise. Mean mitral gradient post-procedure was 4 +/- 2.2 mm Hg, paravalvular regurgitation was mild or absent in all. Thirty-day all-cause mortality was 29.7% (cardiovascular = 12.5% and noncardiac = 17.2%); 84% of the survivors with follow-up data available were in New York Heart Association functional class I or II at 30 days (n = 25). CONCLUSIONS: TMVR with balloon-expandable valves in patients with severe MAC is feasible but may be associated with significant adverse events. This strategy might be an alternative for selected high-risk patients with limited treatment options.

Cardiology / Cardiovascular Research

Guerrero M, Urena M, Pursnani A, **Wang DD**, Vahanian A, **O'Neill W**, Feldman T, and Himbert D. Balloon expandable transcatheter heart valves for native mitral valve disease with severe mitral annular calcification *J Cardiovasc Surg (Torino)* 2016; 57(3):401-409. PMID: 27094423. Full Text

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Patients with mitral annular calcification (MAC) have high surgical risk for mitral valve replacement due to associated comorbidities and technical challenges related to calcium burden, precluding surgery in many patients. Transcatheter mitral valve replacement (TMVR) with the compassionate use of balloon expandable aortic transcatheter heart valves has been used in this clinical scenario. The purpose of this review was to summarize the early experience including successes and failures reported. TMVR might evolve into an acceptable alternative for selected patients with severe MAC who are not candidates for conventional mitral valve surgery. However, this field is at a very early stage and the progress will be significantly slower than the development of transcatheter aortic valve replacement due to the complexity of the mitral valve anatomy and its pathology. Optimizing patient selection process by using multimodality imaging tools to accurately measure the mitral valve annulus and evaluate the risk of left ventricular outflow tract obstruction is essential to minimize complications. Strategies for treating and preventing left ventricular outflow tract obstruction are being tested. Similarly, carefully selecting candidates avoiding patients at the end of their disease process, might improve the overall outcomes.

Cardiology / Cardiovascular Research

Kabbani LS, **Wasilenko S**, **Nypaver TJ**, **Weaver MR**, **Taylor AR**, **Abdul-Nour K**, **Borgi J**, and **Shepard AD**. Socioeconomic disparities affect survival after aortic dissection *J Vasc Surg* 2016;PMID: 27374067. Full Text

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OBJECTIVE: The effect of socioeconomic status (SES) on the course of many disease states has been documented in the literature but has not been studied in aortic dissection. This study evaluated the effect of SES on 30-day and long-term survival of patients after aortic dissection. METHODS: Hospital discharge records were used to identify patients with acute aortic dissection. Patient demographics, insurance status, comorbidities, and 30-day mortality were collected. Home addresses were used to estimate each patient's median household income, and the neighborhood deprivation index, a measure of SES, was determined. Long-term survival was assessed by review of the Social Security Death Index. Associations between demographics, insurance status, comorbidities, and poverty level were investigated to determine their effect on survival. RESULTS: There were 212 aortic dissections; of which, 118 were type A and 94 were type B. Median follow-up was 7.6 years. The neighborhood deprivation index (hazard ratio, 1.43; 95% confidence interval, 1.16-1.78; P = .001) was associated with reduced long-term survival and was also significantly associated with 30-day mortality (hazard ratio, 1.43; 95% confidence interval, 1.05-1.93; P = .02). The mean neighborhood deprivation index score was higher in patients with type B aortic dissections (0.45 +/- 0.93) than in those with type A aortic dissections (0.16 +/- 0.96; P = .029). CONCLUSIONS: Patients with a lower SES had reduced short-term and long-term survival after aortic dissection. Patients with type B dissection live in lower socioeconomic neighborhoods than patients with type A dissection.

Cardiology / Cardiovascular Research

Sareen N, **Mariychina A**, **Hector C**, **Mahan M**, and **Ananthasubramaniam K**. Do right ventricular diastolic tissue doppler parameters add diagnostic value in pulmonary hypertension? *J Am Soc Echocardiogr* 2016; 29(6):B101. PMID: Not assigned. Abstract

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Background: The value of right ventricular (RV) tissue doppler (TD) derived diastolic function patterns in pulmonary hypertension (PHTN) is unclear and formed the basis of our study. Methods: Retrospective review of transthoracic echocardiogram (TTE) of 57 patients who had Type I and II PHTN confirmed on right heart catheterization (Type I =33, Type II= 24, mild- moderate PASP = 31, severe PASP= 26). 22 consecutive patients without cardiopulmonary disease served as control. Absolute values of RV e', RV a', RV e'/a' ratio, RV doppler tei index and RV tissue tei index were compared and correlation coefficients were obtained with pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR) on RHC. Chi-square tests and two-group independent t-tests were used for statistical analysis. Results: Both study groups comprised primarily of females. 54% of test group patients had mild to moderate (40-60 mm Hg) and 46 % had severe (>60 mm Hg) PHTN. RV TAPSE, RV S' , RV e' and RV a' values were all significantly decreased in PHTN group (all p=<0.05 vs controls) with no significant difference in RV e'/a' ratio (1.1 cms/sec). Doppler (0.6 vs 0.4, p<0.05) and tissue (1 vs 0.5, p<0.05) Tei index were significantly higher in PHTN group. Significant negative correlation was observed between RV a' velocity and PVR. (p<0.05). Significant correlation of RHC PASP was observed with RV a' velocity, most significant with mild to moderate PHTN (p<0.05) and in patients with Type II PHTN (p<0.05). Tissue Tei index was significantly higher in patients with PHTN on RHC, most significant with severe PHTN (p<0.05) and in Type I PHTN (p<0.05). Conclusions: RV TD and RV tTD Tei index are all abnormal in PHTN. Lower values of RV a' velocity correlates with mild to moderate PHTN and PHTN Type II. Higher values of RV RF Tei index correlates with severe pulmonary pressures and PHTN Type I on RHC. Our study suggests that incorporating RV tissue Doppler parameters and Tei index in TTE evaluation of PHTN adds value.

Cardiology / Cardiovascular Research

Wallentin L, Held C, Armstrong PW, Cannon CP, Davies RY, Granger CB, Hagstrom E, Harrington RA, Hochman JS, Koenig W, Krug-Gourley S, Mohler ER, 3rd, Siegbahn A, Tarka E, Steg PG, Stewart RA, Weiss R, Ostlund O, **W DW**, and White HD. Lipoprotein-associated phospholipase a2 activity is a marker of risk but not a useful target for treatment in patients with stable coronary heart disease *J Am Heart Assoc* 2016; 5(6)PMID: 27329448. Full Text

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BACKGROUND: We evaluated lipoprotein-associated phospholipase A2 (Lp-PLA2) activity in patients with stable coronary heart disease before and during treatment with darapladib, a selective Lp-PLA2 inhibitor, in relation to outcomes and the effects of darapladib in the STABILITY trial. METHODS AND RESULTS: Plasma Lp-PLA2 activity was determined at baseline (n=14 500); at 1 month (n=13 709); serially (n=100) at 3, 6, and 18 months; and at the end of treatment. Adjusted Cox regression models evaluated associations between Lp-PLA2 activity levels and outcomes. At baseline, the median Lp-PLA2 level was 172.4 mumol/min per liter (interquartile range 143.1-204.2 mumol/min per liter). Comparing the highest and lowest Lp-PLA2 quartile groups, the hazard ratios were 1.50 (95% CI 1.23-1.82) for the primary composite end point (cardiovascular death, myocardial infarction, or stroke), 1.95 (95% CI 1.29-2.93) for hospitalization for heart failure, 1.42 (1.07-1.89) for cardiovascular death, and 1.37 (1.03-1.81) for myocardial infarction after adjustment for baseline characteristics, standard laboratory variables, and other prognostic biomarkers. Treatment with darapladib led to a approximately 65% persistent reduction in median Lp-PLA2 activity. There were no associations between on-treatment Lp-PLA2 activity or changes of Lp-PLA2 activity and outcomes, and there were no significant interactions between baseline and on-treatment Lp-PLA2 activity or changes in Lp-PLA2 activity levels and the effects of darapladib on outcomes. CONCLUSIONS: Although high Lp-PLA2 activity was associated with increased risk of cardiovascular events, pharmacological lowering of Lp-PLA2 activity by approximately 65% did not significantly reduce cardiovascular events in patients with stable coronary heart disease, regardless of the baseline level or the magnitude of change of Lp-PLA2 activity. CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00799903.

Cardiology / Cardiovascular Research

Yadav PK, and **Eng MH**. Size does matter but is there an obesity paradox in TAVR? *Catheter Cardiovasc Interv* 2016; 88(1):125-126. PMID: 27400640. Full Text

Division of Cardiovascular Disease, Henry Ford Hospital, Detroit, Michigan.

Patients with low body mass index (<20 kg/m(2)) undergoing transcatheter aortic valve replacement have higher short- and long-term mortality Low BMI is an important tool to consider in patient screening and prognostication Prospective study is needed to accurately assess the effects of BMI in TAVR patients, to prove or refute the obesity paradox.

Center for Health Policy and Health Services Research

Coffey MJ, and **Ahmedani BK**. Pseudocide: A case report *J Psychiatr Pract* 2016; 22(4):333-335. PMID: 27427845. Full Text

COFFEY: Vice President and CIO, The Menninger Clinic, Houston, TX AHMEDANI: Center for Health Policy & Health Services Research, Henry Ford Health System, Detroit, MI.

The authors describe a case of "pseudocide" in which the patient appears to have feigned his own suicide. This case was identified as a result of a routine reconciliation of internally collected suicide data with government-collected mortality data. The authors discuss the evolution of the concept of pseudocide in the clinical literature and consider issues related to deceitful and factitious behaviors and suicide surveillance and measurement.

Center for Health Policy and Health Services Research
Kabbani LS, **Wasilenko S**, **Nypaver TJ**, **Weaver MR**, **Taylor AR**, **Abdul-Nour K**, **Borgi J**, and **Shepard AD**. Socioeconomic disparities affect survival after aortic dissection *J Vasc Surg* 2016;PMID: 27374067. Full Text

Division of Vascular Surgery, Henry Ford Hospital, Detroit, Mich. Electronic address: lkabbani1@hfhs.org.
Division of Vascular Surgery, Henry Ford Hospital, Detroit, Mich.
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Division of Cardiac Surgery, Henry Ford Hospital, Detroit, Mich.

OBJECTIVE: The effect of socioeconomic status (SES) on the course of many disease states has been documented in the literature but has not been studied in aortic dissection. This study evaluated the effect of SES on 30-day and long-term survival of patients after aortic dissection. METHODS: Hospital discharge records were used to identify patients with acute aortic dissection. Patient demographics, insurance status, comorbidities, and 30-day mortality were collected. Home addresses were used to estimate each patient's median household income, and the neighborhood deprivation index, a measure of SES, was determined. Long-term survival was assessed by review of the Social Security Death Index. Associations between demographics, insurance status, comorbidities, and poverty level were investigated to determine their effect on survival. RESULTS: There were 212 aortic dissections; of which, 118 were type A and 94 were type B. Median follow-up was 7.6 years. The neighborhood deprivation index (hazard ratio, 1.43; 95% confidence interval, 1.16-1.78; P = .001) was associated with reduced long-term survival and was also significantly associated with 30-day mortality (hazard ratio, 1.43; 95% confidence interval, 1.05-1.93; P = .02). The mean neighborhood deprivation index score was higher in patients with type B aortic dissections (0.45 +/- 0.93) than in those with type A aortic dissections (0.16 +/- 0.96; P = .029). CONCLUSIONS: Patients with a lower SES had reduced short-term and long-term survival after aortic dissection. Patients with type B dissection live in lower socioeconomic neighborhoods than patients with type A dissection.

Center for Health Policy and Health Services Research
Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, Boggon R, Bunge EM, **Pladevall-Vila M**, and Baril L. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom *Hum Vaccin Immunother* 2016:0. PMID: 27428517.
Article Request Form

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b GSK Vaccines , Avenue Fleming 20, B-1300 Wavre , Belgium.
c Pallas Health Research and Consultancy , Conradstraat 18, 3013 AP Rotterdam , the Netherlands.
d CPRD Research Group , 151 Buckingham Palace Road, Victoria , London SW1W 9SZ , United Kingdom.
e RTI Health Solutions , Travessera de Gracia 56, 08006 Barcelona, Spain , and the Center for Health Policy and Health Services Research , Henry Ford Health System , Detroit , Michigan , USA.

To assess the risk of autoimmune disease (AD) in 9-25 year-old women within 1 year after the first AS04-HPV-16/18vaccine dose, a retrospective, observational database cohort study was conducted using CPRD GOLD. From CPRD GOLD four cohorts (65,000 subjects each) were retrieved: 1 exposed female cohort (received >/=1 AS04-HPV-16/18vaccine dose between Sep2008-Aug2010) and 3 unexposed cohorts: historical female (Sep2005-Aug2007), concurrent male, and historical male. Co-primary endpoints were confirmed neuroinflammatory/ophthalmic AD and other AD, secondary endpoints were confirmed individual AD. Risk of new onset of AD was compared between cohorts (reference: historical cohort) using Poisson regression. The main analysis using confirmed cases showed no neuroinflammatory/ophthalmic AD cases in the female exposed cohort. Incidence rate ratio (IRR) (95% CI) of other AD was 1.41 (0.86 to 2.31) in female and 1.77 (0.94 to 3.35) in male cohorts when compared to the female and male historical cohort, respectively. Secondary endpoints were evaluated for diseases with >10 cases, which were Crohn's disease (IRR: 1.21 [0.37 to 3.95] for female and 4.22 [0.47 to 38.02] for male cohorts), autoimmune thyroiditis (IRR: 3.75 [1.25 to 11.31] for female and no confirmed cases for male cohorts) and type 1 diabetes (IRR: 0.30 [0.11 to 0.83] for female and 2.46 [1.08 to 5.60] for male cohorts). Analysis using confirmed and

non-confirmed cases showed similar results, except for autoimmune thyroiditis in females, IRR: 1.45 (0.79 to 2.64). There was no evidence of an increased risk of AD in women aged 9 to 25 years after AS04-HPV-16/18 vaccination. NCT01953822, ENCEPP/SDPP/4584.

Dermatology
Eichenfield L, Call R, Forsha D, Fowler J, Hebert A, Spellman M, **Gold LS**, Syoc MV, Zane L, and Tschen E. Long-term safety of crisaborole in children and adults with mild-to-moderate atopic dermatitis *Pediatr Dermatol* 2016; 33:S46-S47. PMID: Not assinged. Abstract

L. Eichenfield, Rady Children's Hospital, University of California, San Diego, United States

Background: Long-term topical treatment is often required for atopic dermatitis (AD), a chronic inflammatory skin disease. Unfortunately in the last 15 years there has been little advancement in topical therapies, which are associated with potential safety concerns. To address the need for a safe and targeted long-term treatment, Crisaborole (Crisaborole Topical Ointment, 2%), a novel nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor, is currently being investigated for the treatment of mild-to-moderate AD. Objectives: To evaluate the long-term safety in patients with mild-to-moderate AD, ≥2 years of age who were included in an open-label extension study. Methods: A multicenter, open-label, 48-week safety study enrolled patients (N = 517) who continued treatment after completing a 28-day Phase 3 pivotal study. Every 4 weeks patients were assessed for AD severity and treated as needed with 4-week cycles of crisa-borole (Investigator's Static Global Assessment ≥2 (Mild)). Safety measures included assessment of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examinations, and clinical laboratory results. Results: During the pivotal studies and the open-label extension study, at least 1 treatment- emergent adverse event (TEAE) was reported by 65%of patients, most of which were considered unrelated to treatment (93.1%) and were mild (51.2%) or moderate (44.6%) in severity. Analysis over time (four 12-week treatment periods) of the severity and frequency of TEAEs was well balanced, demonstrating a favorable safety profile for long-term treatment of crisaborole. Overall, 10.2%of patients reported treatment-related AEs; the most frequently reported events were atopic dermatitis (3.1%), application site pain (2.3%), and application site infection (1.2%). In the extension study, none of the 7 reported treatment-emergent SAEs were considered treatment related. During the extension study only 9 patients (1.7%) discontinued the study because of TEAEs. There were no cutaneous adverse reactions such as hypopigmentation, application site atrophy, or telangiectasia reported. Conclusion: Crisaborole demonstrated a favorable safety profile for the long-term treatment of patients with AD.

Dermatology
Liu Z, Wang S, **Mi QS**, and Dong Z. MicroRNAs in pathogenesis of acute kidney injury *Nephron* 2016;PMID: 27322758. Full Text

aDepartment of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China; bDepartment of Cellular Biology and Anatomy, Medical College of Georgia at Georgia Regents University and Charlie Norwood VA Medical Center, Augusta, Ga., and cDepartment of Dermatology and Internal Medicine, Henry Ford Health System, Detroit, Mich., USA

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression mainly by repressing their target gene translation. A large spectrum of human diseases is associated with significant changes in miRNAs. Many miRNAs are induced in diseases, whereas some others are downregulated. The significance of miRNAs has been demonstrated in renal development and physiology, and in major kidney diseases such as acute kidney injury (AKI). Recent studies have further implicated specific miRNAs in the pathogenesis of AKI. miRNAs also have the potential to become new diagnostic biomarkers of AKI. Further investigation will identify the key pathogenic miRNAs in various types of AKI and test miRNA-based therapeutics and diagnosis.

Dermatology
Paller A, Tom W, Lebwohl M, Blumenthal R, Boguniewicz M, Call R, Eichenfield L, Forsha D, Rees W, Simpson E, **Gold LS**, Zaenglein A, Spellman M, Zane L, and Hebert A. Two phase 3 studies in atopic dermatitis with crisaborole, the novel, nonsteroidal topical phosphodiesterase 4 inhibitor *Pediatr Dermatol* 2016; 33:S19. PMID: Not assigned. Abstract

L. Eichenfield, University of California, San Diego, United States

Background: Atopic dermatitis (AD), a chronic inflammatory skin disease affecting children and adults, presents withmild-to-moderate disease in the majority of patients (up to 90%). Crisaborole [Crisaborole Topical Ointment, 2%]

(Anacor Pharmaceuticals, Palo Alto, CA) is an investigational topical, nonsteroidal, anti-inflammatory, phosphodiesterase 4 inhibitor. Objectives: To assess the efficacy and safety of crisaborole in patients ≥2 years old with mild-to-moderate AD in two identically designed, vehicle-controlled, double-blind, multicenter, Phase 3 studies (301, 302). Methods: Patients with AD affecting ≥5% of body surface area (BSA) were evaluated on Days 8 (D8), 15, 22, and 29 after being randomized 2:1 to receive crisaborole or vehicle twice daily. The primary efficacy endpoint defined Success in Investigator's Static Global Assessment (ISGA) as “Clear/0” or “Almost clear/1” with a ≥ 2-grade improvement from baseline at D29. Secondary endpoints measured time to success in ISGA and the percentage of patients achieving “Clear/0” or “Almost clear/1” on ISGA. Results: By D8, a greater proportion of crisaborole-treated patients achieved Success in ISGA than vehicle (301: 13.4 vs. 4.5, 302: 15.9 vs. 6.3), which was sustained throughout treatment (D29, 301: 32.8 vs. 25.4, p = 0.038, 302: 31.4 vs. 18.0, p < 0.001). Crisaborole-treated patients achieved success in ISGA significantly earlier (p < 0.001). A greater proportion of crisaborole-treated patients achieved ISGA scores of “Clear/0” or “Almost clear/ 1” by D29 (301: 51.7 vs. 40.6, p = 0.005; 302: 48.5 vs. 29.7, p < 0.001). Treatment-related adverse events (AEs) were infrequent, transient, and mild. AEs resulted in a low rate of study discontinuation for both groups (1.2%). Conclusion: Crisaborole may represent an efficacious and safe treatment for patients ≥2 years of age withmild-to-moderate AD.

Dermatology

Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, Spellman MC, **Stein Gold LF**, Zaenglein AL, Hughes MH, Zane LT, and Hebert AA. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults *J Am Acad Dermatol* 2016;PMID: 27417017. Full Text

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Icahn School of Medicine at Mount Sinai, New York, New York.
Anacor Pharmaceuticals, Inc, Palo Alto, California.
National Jewish Health, Denver, Colorado; University of Colorado School of Medicine, Denver, Colorado.
Clinical Research Partners, Richmond, Virginia.
Jordan Valley Dermatology and Research Center, West Jordan, Utah.
Pi-Coor Clinical Research, Burke, Virginia.
Oregon Health and Science University, Portland, Oregon.
Henry Ford Health System, Detroit, Michigan.
Pennsylvania State University, Hershey, Pennsylvania.
University of Texas Health Science Center Houston, Houston, Texas.

BACKGROUND: Additional topical treatments for atopic dermatitis (AD) are needed that provide relief while minimizing risks. OBJECTIVE: We sought to assess the efficacy and safety of crisaborole ointment, a phosphodiesterase 4 inhibitor, in two phase III AD studies (AD-301: NCT02118766; AD-302: NCT02118792). METHODS: Two identically designed, vehicle-controlled, double-blind studies enrolled and randomly assigned (2:1, crisaborole:vehicle) patients aged 2 years or older with an Investigator's Static Global Assessment (ISGA) score of mild or moderate for twice-daily application for 28 days. The primary end point was ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline. Additional analyses included time to success in ISGA score, percentage of patients achieving clear/almost clear, reduction in severity of AD signs, and time to improvement in pruritus. RESULTS: More crisaborole- than vehicle-treated patients achieved ISGA score success (clear/almost clear with >/=2-grade improvement; AD-301: 32.8% vs 25.4%, P = .038; AD-302: 31.4% vs 18.0%, P < .001), with a greater percentage with clear/almost clear (51.7% vs 40.6%, P = .005; 48.5% vs 29.7%, P < .001). Crisaborole-treated patients achieved success in ISGA score and improvement in pruritus earlier than those treated with vehicle (both P </= .001). Treatment-related adverse events were infrequent and mild to moderate in severity. LIMITATIONS: Short study duration was a limitation. CONCLUSIONS: Crisaborole demonstrated a favorable safety profile and improvement in all measures of efficacy, including overall disease severity, pruritus, and other signs of AD.

Diagnostic Radiology

Rheinboldt M, and **Scher C**. Musculoskeletal ultrasonography in the diagnosis of acute crystalline synovitis *Emerg Radiol* 2016;PMID: 27439716. Full Text

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Both gout and calcium pyrophosphate deposition disease are common metabolic arthopathies, presenting not only diagnostic but also management challenges. Though histological crystal aspiration is definitive, diagnosis is commonly established through a composite of clinical features and laboratory findings. Musculoskeletal ultrasound has a contributory and growing role not only in routine disease surveillance but also in helping render a timely and specific diagnosis for patients presenting with new-onset oligoarticular arthritis in the emergency setting. In this article, we review the various general and characteristic ultrasound features of crystalline arthropathy as well as the published data in regard to sonographic performance metrics.

Emergency Medicine
Goyal N, **Vallee PA**, **Folt J**, **Jaskulka B**, **Baliga S**, **Nagarwala J**, and **Slezak M**. WIREd for milestones *J Grad Med Educ* 2016; 8(3):445-446. PMID: 27413456. Full Text

Program Director, Combined Emergency Medicine/Internal Medicine Residency, Departments of Emergency Medicine and Internal Medicine, Henry Ford Health System.
Associate Program Director, Emergency Medicine Residency, Department of Emergency Medicine, Henry Ford Health System.
Assistant Program Director, Emergency Medicine Residency, Department of Emergency Medicine, Henry Ford Health System.
Senior Staff Physician, Department of Emergency Medicine, Henry Ford Health System.
Associate Medical Director for Quality, Department of Emergency Medicine, Henry Ford Health System.

Emergency Medicine
Hermann G, **Xi AS**, **Stevens B**, and **Goyal N**. Reducing errors in reporting scholarly activity to the ACGME: The annual update scholarly activity monitoring tool *J Grad Med Educ* 2016; 8(3):447-448. PMID: 27413457. Full Text

Resident Physician, Transitional Year Residency Program, Department of Emergency Medicine and Department of Internal Medicine, Henry Ford Health System.
Medical Education Accreditation Coordinator, Department of Graduate Medical Education, Henry Ford Hospital.
Program Director, Transitional Year Residency and Director of Emergency Medicine Informatics, Department of Emergency Medicine and Department of Internal Medicine, Henry Ford Health System.

Emergency Medicine
Jaehne AK, Jayaprakash N, and **Langberg S**. Defining septic shock *Jama* 2016; 316(4):455. PMID: 27458956. Full Text

Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan.
Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota.

Emergency Medicine
Jaehne AK, **Rivers EP**, **Poissons LK**, **Chen Y**, **Gill J**, **Deledda J**, and Suarez A. Plasma proteome in patients with vasopressor dependent septic shock *Shock* 2016; 45(6):131. PMID: Not assigned. Abstract

A.K. Jaehne, Emergency Medicine, Henry Ford Hospital, Harper Woods, United States

Iintroduction: Vasopressor dependent septic shock (VPSS) remains a disease with high mortality. When the initial resuscitation with fluids fails to restore optimal tissue perfusion pressures, patients are considered in septic shock and need supplemental administration of vasoactive agents and possibly steroids. Changes in the plasma proteome can be rapid at the time of VPSS onset and identifiction of specific proteomic profiles may be helpful in determining further interventions and prognostication. Objective: The primary objective of this study was to describe plasma proteomic profiles in patients with VPSS. Methods: This is an observational case series of patients at the onset of VPSS in the medical and surgical ICUs in an academic tertiary care hospital. Samples were analyzed using Millipore multiplex assays. The primary end-point of this study was the identification of differences in plasma proteomic profiles using heat-map analysis in regard to 30 day survival and age. Results: One-hundred seventy-two patients were included. We were able to identify three distinct groups with differences in proteomic profiles. Group 1 (N = 78, 45.3 % of samples) showed no specific elevations in any of the measured 29 cytokines. Group 2 (N = 71, 41.3 % of samples) showed elevations for 12 pro-inflammatory and chemotactic cytokines which were different from the other

groups. Group 3 (N = 23, 13.4% of samples) showed specific elevations for 17 stimulatory and epithelial cytokines. Additionally, we found that there are statistically significant differences in regard to age (60 vs. 67.2 vs. 68.6, p = 0.012) and 30 day mortality (21/78, 33.9% vs. 31/71, 54.4% vs. 5/23, 26.3%; p = 0.03) between the identified groups. Conclusion: Three distinct proteomic profiles exist in patients with VPSS. These cytokine profiles are associated with differences in age and 30 day mortality. Additional analysis needs to further refine cytokine system interactions and possible modifiable changes over time. This understanding may help develop new diagnostic tools for risk stratification and possible therapeutic interventions. (Figure Presented) .

Emergency Medicine

Townsend SR, **Rivers E**, and Tefera L. Definitions for sepsis and septic shock *Jama* 2016; 316(4):457-458. PMID: 27458959. Full Text

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Quality Measurement and Value-Based Incentives Group, Centers for Medicare & Medicaid Services, Baltimore, Maryland.

Family Medicine

Budzynska K, Filippelli AC, Sadikova E, Low Dog T, and Gardiner P. Use and factors associated with herbal/botanical and nonvitamin/nonmineral dietary supplements among women of reproductive age: An analysis of the infant feeding practices study II *J Midwifery Womens Health* 2016; 61(4):419-426. PMID: 27336953. Full Text

INTRODUCTION: Little is known about the changes in prevalence of dietary supplement use in pregnancy, postpartum, and in a comparison group of nonpregnant women. METHODS: We conducted a secondary analysis of the Infant Feeding Practices II study. The purpose of this study is to report the prevalence of herbal or botanical and nonvitamin, nonmineral dietary supplement use by US women with respect to demographic, behavioral, and health factors. We compared pregnant and postpartum women to a comparison group of nonpregnant women who had not given birth in the past 12 months. Our main outcome was the prevalence of dietary supplements. Multiple logistic regression models were used to examine factors associated with herbal or botanical and nonvitamin, nonmineral dietary supplement use during reproductive age, pregnancy, and postpartum. RESULTS: The total sample included 1444 women assessed during the prenatal period, 1422 from the postpartum period, and 1517 women in a comparison group. In terms of herb or botanical use, 15% of the prenatal group, 16% of the postpartum group, and 22% of the comparison group reported using herbs or botanicals. The most frequently used nonvitamin, nonmineral supplement was omega-3 fatty acid. Among the total prenatal group and comparison group, women eating 5 or more servings of fruits or vegetables were less likely to report using herbs or botanicals. Women in the comparison group self-identifying as black were 4 times as likely to report using herbs or botanicals compared to participants self-identifying as white. In addition, women identifying as a race other than white were almost twice as likely to report herb or botanical use across all study groups. DISCUSSION: This is one of the rare studies that shows the changing prevalence of herbs or botanicals and nonvitamin, nonmineral dietary supplement use in women in the reproductive stage of their lives.

Gastroenterology

Jinjuvadia C, **Jinjuvadia R**, Mandapakala C, Durairajan N, Liangpunsakul S, and Soubani AO. Trends in outcomes, financial burden, and mortality for acute exacerbation of chronic obstructive pulmonary disease (copd) in the united states from 2002 to 2010 *Copd* 2016:1-8. PMID: 27419254. Article Request Form

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Chronic obstructive pulmonary disease (COPD) is the cause of substantial economic and social burden. We evaluated the temporal trends of hospitalizations from acute exacerbation of COPD and determined its outcome and financial impact using the National (Nationwide) Inpatient Sample (NIS) databases (2002-2010). Individuals aged >/= 18 years were included. Subjects who were hospitalized with primary diagnosis of COPD exacerbation and those

who were admitted for other causes but had underlying acute exacerbation of COPD (secondary diagnosis) were captured by International Classification of Diseases-Ninth Revision (ICD-9) codes. The hospital outcomes and length of stay were determined. Multivariate logistic regression was used to identify the independent predictors of inpatient mortality. Overall acute exacerbation of COPD-related hospitalizations accounted for nearly 3.31% of all hospitalizations in the year 2002. This did not change significantly to year 2010 (3.43%, p = 0.608). However, there was an increase in hospitalization with secondary diagnosis of COPD. Elderly white patients accounted for most of the hospitalizations. Medicare was the primary payer source for most of the hospitalizations (73-75%). There was a significant decrease in inpatient mortality from 4.8% in 2002 to 3.9% in 2010 (slope -0.096, p < 0.001). Similarly, there was a significant decrease in average length of stay from 6.4 days in 2002 to 6.0 days in 2010 (slope -0.042, p < 0.001). Despite this, the hospitalization cost was increased substantially from $22,187 in 2002 to $38,455 in 2010. However, financial burden has increased over the years.

Gastroenterology

Younossi ZM, Park H, **Gordon SC**, Ferguson JR, Ahmed A, Dieterich D, and Saab S. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naive patients with hepatitis C *Am J Manag Care* 2016; 22(6 Spec No.):Sp205-211. PMID: 27266950. Full Text

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OBJECTIVES: Studies of hepatitis C virus (HCV) regimens have documented substantially reduced effectiveness in sustained virologic response (SVR) in the context of real-world clinical practice compared with clinical trials. Real-world and clinical trial SVR and cost-per-SVR data have not been reported for the all-oral, peginterferon-free and ribavirin (RBV)-free ledipasvir/sofosbuvir (LDV/SOF) regimen. Our objective was to compare the rates of SVR achievement and cost per SVR between pooled data from clinical studies of LDV/SOF and from real-world clinical practice. METHODS: Data were derived from the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET), a real-world, multicenter, prospective, observational study; and from the TRIO Network, a retrospective database of HCV-treated patients. The 1-year cost per SVR was calculated as the total cost of an SVR ([cost of treatment regimen, adverse events, and monitoring costs] per SVR) during the first year of treatment. RESULTS: After 12 weeks, the SVR rates obtained in real-world studies ranged from 94% to 98%, comparing favorably with the SVRs achieved in the ION-1 and ION-3 trials (94% and 95%-99% with 8 and 12 weeks of RBV-free therapy, respectively). A single SVR, on average, cost $84,989 among patients enrolled in the ION-3 trial, with higher costs ($101,204) among patients with compensated cirrhosis compared with noncirrhotic patients ($81,668). In the pooled TARGET/TRIO population, the average cost of an SVR was $84,770, with costs of $101,380 and $81,368 in patients with compensated cirrhosis and patients without cirrhosis, respectively. CONCLUSIONS: Unlike the results obtained with prior HCV regimens, this study suggests that similar SVR rates are achieved with LDV/SOF in clinical trial-based studies and real-world studies. Further, achieving an SVR in real-world clinical practice was not associated with excess costs.

Graduate Medical Education

Hermann G, **Xi AS**, **Stevens B**, and **Goyal N**. Reducing errors in reporting scholarly activity to the ACGME: The annual update scholarly activity monitoring tool *J Grad Med Educ* 2016; 8(3):447-448. PMID: 27413457. Full Text

Resident Physician, Transitional Year Residency Program, Department of Emergency Medicine and Department of Internal Medicine, Henry Ford Health System.
Medical Education Accreditation Coordinator, Department of Graduate Medical Education, Henry Ford Hospital.
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Hematology, Oncology and the Josephine Ford Cancer Institute

Apolo AB, Infante JR, Hamid O, Patel MR, **Wang D**, Kelly K, Mega AE, Britten CD, Mita AC, Ravaud A, Cuillerot JM, von Heydebreck A, and Gulley JL. Safety, clinical activity, and PD-L1 expression of avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with metastatic urothelial carcinoma from the JAVELIN Solid Tumor phase Ib trial *J Clin Oncol* 2016; 34(2):1. PMID: Not assigned. Abstract

NCI, Genitourinary Malignancies Branch, Ctr Canc Res, NIH, Bethesda, MD 20892 USA. Tennessee Oncol PLLC, Sarah Cannon Res Inst, Nashville, TN USA. Angeles Clin & Res Inst, Los Angeles, CA USA. Florida Canc Specialists, Sarah Cannon Res Inst, Sarasota, FL USA. Henry Ford Hosp, Detroit, MI 48202 USA. Univ Calif Davis, Ctr Comprehens Canc, Sacramento, CA USA. Brown Univ, Warren Alpert Med Sch, Providence, RI 02912 USA. Med

Univ S Carolina, Charleston, SC 29425 USA. Cedars Sinai Med Ctr, Samuel Oschin Comprehens Canc Inst, Los Angeles, CA 90048 USA. CHU Bordeaux, Hop St Andre, Bordeaux, France. EMD Serono, Billerica, MA USA. Merck KGaA, Darmstadt, Germany. NCI, NIH, Bethesda, MD 20892 USA.

Hematology, Oncology and the Josephine Ford Cancer Institute
Chow LQ, Smith DC, Tan AR, Denlinger CS, **Wang D**, Shepard DR, Chaudhary A, Lin Y, and Gao L. Lack of pharmacokinetic drug-drug interaction between ramucirumab and paclitaxel in a phase II study of patients with advanced malignant solid tumors *Cancer Chemother Pharmacol* 2016; 78(2):433-441. PMID: 27379498. Full Text

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PURPOSE: The objective of this phase II study was to evaluate pharmacokinetic interaction potential between ramucirumab and paclitaxel in patients with advanced cancer. METHODS: This study was designed to assess 2-way pharmacokinetic drug-drug interactions between ramucirumab and paclitaxel. Twenty-four patients participated in Part A, which consisted of a 2-week monotherapy period in which paclitaxel 80 mg/m(2) was administered on day 1, followed by a 4-week cycle of combination treatment with ramucirumab (8 mg/kg on days 1 and 15; paclitaxel on days 1, 8, and 15). Patients could continue to receive combination therapy with ramucirumab and paclitaxel. In 16 patients in Part B, ramucirumab monotherapy was administered on day 1 of a 3-week cycle. Patients could continue to receive ramucirumab monotherapy or combination therapy with paclitaxel. RESULTS: Concomitant administration of ramucirumab had no effect on pharmacokinetics of paclitaxel, with ratios of geometric least squares (LS) means (with ramucirumab vs. alone) of 1.09 (90 % confidence interval [CI] 0.93, 1.29) for AUC(0-infinity) and 0.97 (90 % CI 0.83, 1.13) for C max. In addition, similar ramucirumab pharmacokinetic characteristics were observed with or without paclitaxel administration. The ratios of geometric LS means of AUC(0-infinity) and C max of ramucirumab (with paclitaxel vs. alone) were 1.00 (90 % CI 0.84, 1.19) for AUC(0-infinity) and 1.07 (90 % CI 0.93, 1.24) for C max, respectively. CONCLUSIONS: Concomitant paclitaxel administration is unlikely to affect the pharmacokinetics of ramucirumab, and vice versa. The incidence and severity of adverse events were consistent with the known safety profiles of paclitaxel and ramucirumab.

Hematology, Oncology and the Josephine Ford Cancer Institute
Hamel LM, Eggly S, Penner L, **Chapman R**, Frank J, Klamerus A, and Albrecht TL. Patient and oncologist discussions of treatment costs *J Clin Oncol* 2016; 34(7s):1. PMID: Not assigned. Abstract

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Hematology, Oncology and the Josephine Ford Cancer Institute
Hamel LM, Eggly S, Penner L, **Chapman R**, Klamerus JFA, and Albrecht TL. Patient and oncologist discussions of treatment costs *J Clin Oncol* 2016; 34(7)PMID: Not assigned. Abstract

L.M. Hamel

Background: Financial toxicity-the burden of treatment costs and its impact on well-being, treatment decisions, and outcomes-affects many cancer patients, especially racial minorities. Discussing cost during clinic visits may ease financial toxicity, but oncologists are often hesitant to discuss cost. A better understanding of cost discussions is needed to improve care and inform oncologist training interventions. We conducted an observational study of patient-oncologist treatment cost discussions during clinic visits. Methods: Data were video-recorded clinic visits of African American patients (114) and their medical oncologists (19) meeting for the first time to discuss treatment. Cost discussions were any verbal expression of a direct (paying for scans) or indirect (time off work) expense to the patient for treatment. Trained coders observed the videos and coded for presence, duration, initiation, topic, oncologist response, and patient reaction of cost discussions. Results: Cost discussions occurred in 44% (n = 50) of the visits with a range of 1-6 per visit for a total of 93 discussions (M = 35 seconds; SD = 28). Patients initiated (61%) more

than oncologists (38%), and patients were more likely to initiate multiple times. Time off work was discussed most (48%), followed by insurance (26%), transportation (12%), paying for treatment (8%), and job loss (4%). Time off work was the most commonly patient initiated topic and insurance was the most commonly oncologist initiated topic. Oncologists typically addressed the issue (72%), and patients often reacted positively (81%) but passively. A few times (9%) the oncologist acknowledged the patient's initiation but did not address it. Negative patient reactions were rare and only occurred when the oncologist responded to a patient initiation (5%). Younger patients were more likely discuss cost than older patients (p = .02) and retired patients were less likely to discuss cost (p = .05). Conclusions: Findings suggest discussing indirect cost is important to patients, but oncologists infrequently initiate and do not always respond adequately when patients initiate. Further research and interventions are needed to address patient-oncologist cost discussions and the economic impact of cancer treatment.

Hematology, Oncology and the Josephine Ford Cancer Institute
Henry NL, Braun T, Lusk E, Munir K, Griggs JJ, Gorski DH, Silver SM, Breslin TM, and **Ali HY**. Variation in use of advanced imaging at the time of breast cancer diagnosis in a statewide registry *J Clin Oncol* 2016; 34(7)PMID: Not assigned. Abstract

N.L. Henry

Background: Advanced imaging for diagnosis of metastatic disease at the time of diagnosis of stage 0-II breast cancer is not recommended according to national guidelines. The purpose of this study was to examine the variation in ordering of CT chest, abdomen, and pelvis, PET, and bone scans across the state of Michigan, and to investigate clinical and non-clinical factors associated with test ordering. Methods: We prospectively collected data from all patients diagnosed with stage 0-II breast cancer from 2008-2014 in 25 health systems in the Michigan Breast Oncology Quality Initiative (MiBOQI), a Blue Cross Blue Shield of Michigan/Blue Care Network-sponsored quality initiative. Demographic, imaging, and pathologic data were abstracted from the medical record. The primary endpoint was the percentage of patients with at least one advanced imaging test performed within 90 days after diagnosis of breast cancer. Analyses were performed using the chi-squared test of association. Results: Of the 27,011 patients, 4799 (17.8%) had at least one staging exam performed within 90 days of diagnosis. Imaging tests were primarily performed post-operatively. The average percentage of patients who had at least one staging exam performed varied by stage and by site (Table). The rate of testing decreased over time for stage 0-IIA cancers but not for stage IIB. On multivariate analysis, younger age, black race, hormone receptor negativity, HER2 positivity, and higher grade were associated with increased likelihood of undergoing imaging. Conclusions: There is considerable variability in ordering of staging scans at the time of diagnosis of early stage breast cancer across Michigan. Factors underlying use of imaging in stage IIB disease should be examined in order to develop interventions for rate reduction. (Table Presented).

Hematology, Oncology and the Josephine Ford Cancer Institute
Henry NL, Braun T, Lusk E, Munir K, Griggs JJ, Gorski DH, Silver SM, Breslin TM, **Ali HY**, and Michigan Breast Oncology Q. Variation in use of advanced imaging at the time of breast cancer diagnosis in a statewide registry *J Clin Oncol* 2016; 34(7):1. PMID: Not assigned. Abstract

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Hypertension Research
Ren Y, **Janic B**, **Kutskill K**, **Peterson EL**, and **Carretero OA**. Mechanisms of connecting tubule glomerular feedback enhancement by aldosterone *Am J Physiol Renal Physiol* 2016:ajprenal.00076.02016. PMID: 27413197. Full Text

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Connecting tubule glomerular feedback (CTGF) is a mechanism where an increase in sodium (Na) concentration in the connecting tubule (CNT) causes the afferent arteriole (Af-Art) to dilate. We recently reported that aldosterone within the CNT lumen enhances CTGF via a nongenomic effect involving GPR30 receptors and sodium/hydrogen exchanger (NHE), but the signaling pathways of this mechanism are unknown. We hypothesize that aldosterone enhances CTGF via cAMP/protein kinase A (PKA) pathway that activates protein kinase C (PKC) and stimulates superoxide (O-2) production. Rabbit Af-Arts and their adherent CNTs were microdissected and simultaneously perfused. Two consecutive CTGF curves were elicited by increasing the CNT luminal NaCl. We found that the main

effect of aldosterone was to sensitize CTGF and we analyzed data by comparing NaCl concentration in the CNT perfusate needed to achieve half of the maximal response (EC50). During the control period, the NaCl concentration that elicited a half-maximal response (EC50) was 37.0+/-2.0 mmol/L; addition of aldosterone (10-8 mol/L) to the CNT lumen decreased EC50 to 19.3+/-1.3 mmol/L (p</=0.001 vs. Control). The specific adenylyl cyclase inhibitor 2',3'-Dideoxyadenosine (ddA) (2x10-4 mol/L) and the PKA inhibitor H-89 dihydrochloride hydrate (H-89) (2x10-6 mol/L) prevented the aldosterone effect. Selective PKC inhibitor GF109203X (10-8 mol/L) also prevented EC50 reduction caused by aldosterone. CNT intraluminal addition of O-2 scavenger tempol (10-4 mol/L) blocked the aldosterone effect. We conclude that aldosterone inside the CNT lumen enhances CTGF via a cAMP/PKA/PKC pathway and stimulates O2 generation and this process may contribute to renal damage by increasing glomerular capillary pressure.

Infection Prevention

Gregory A, **Chami E**, and **Pietsch J**. Emotional motivators: Using visual triggers as an infection control intervention to increase hand hygiene compliance throughout the hospital *Am J Infect Control* 2016; 44(6):S3. PMID: Not Assigned. Abstract

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BACKGROUND: Healthcare acquired infections cost hospitals approximately $9.8 billion every year and there have been over 20 published articles demonstrating the effectiveness of hand hygiene in reducing infections. Despite implementing a variety of societal recommended methodologies to increase rates, our hospital rates have remained static. Recently, a publication suggested an effective way to increase and sustain hand hygiene compliance was to leverage emotional motivators, such as disgust. Having never taken that approach, we aimed to determine if it would be a method for increased compliance. METHODS: To stir a feeling of disgust, we compiled a book of bacterial culture images with congruent Adenosine Triphosphate (ATP)meter readings of healthcare worker hands of objects on the unit. We then compiled hand hygiene compliance data to determine which four units had a low compliance rate (with sufficient stealth observations). Over 2 months we performed 10 intervention days on the selected units, where we would collect ATP readings of staff hands, then show them what a culture of a similar reading looked like. RESULTS: Before beginning the study, the hand hygiene compliance rates of the units were calculated using the number of compliant observations/total number of observation x 100%. The rates were as follows, I1: 47.4%, F6: 50%, C6W: 33.3% and B1: 50%. To evaluate the possible effectiveness of the method we recalculated compliance midway through, or after 5 intervention days. Those rates were 58.3%, 58.3%, 50% and 88.9% respectively. Once we had completed all 10 interventions we recalculated the compliance, I1 58.3%, F6: 68.4%, C6W: 80.9% and B1: 68.8%. CONCLUSIONS: In conclusion, all units experienced an increase of at least 11 percentage points. Using this uncommon methodology, other institutions could also positively impact their rates by influencing their staff to visually connect the images of microbial contamination with noncompliance of hand hygiene, effectively working towards reduced infection rates. (Table Presented).

Infectious Diseases

Chopra T, Awali RA, Biedron C, Vallin E, Bheemreddy S, Saddler CM, Mullins K, **Echaiz JF**, Bernabela L, Severson R, Marchaim D, Lephart P, **Johnson L**, Thyagarajan R, Kaye KS, and **Alangaden G**. Predictors of Clostridium difficile infection-related mortality among older adults *Am J Infect Control* 2016;PMID: 27424303. Full Text

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BACKGROUND: Over 90% of annual deaths caused by Clostridium difficile infection (CDI) occur in persons aged >/=65 years. However, no large-scale studies have been conducted to investigate predictors of CDI-related mortality among older adults. METHODS: This case-control study included 540 CDI patients aged >/=60 years admitted to a tertiary care hospital in Detroit, Michigan, between January 2005 and December 2012. Cases were CDI patients who died within 30 days of CDI date. Controls were CDI patients who survived >30 days after CDI date. Cases were matched to controls on a 1:3 ratio based on age and hospital acquisition of CDI. RESULTS: One-hundred and thirty cases (25%) were compared with 405 controls (75%). Independent predictors of CDI-related mortality included admission from another acute hospital (odds ratio [OR], 8.25; P = .001) or a long-term care facility (OR, 13.12; P =

.012), McCabe score >/=2 (OR, 12.19; P < .001), and high serum creatinine (>/=1.7 mg/dL) (OR, 3.43; P = .021). The regression model was adjusted for the confounding effect of limited activity of daily living score, total number of antibiotic days prior to CDI, ileus on abdominal radiograph, low albumin (</=2.5 g/dL), elevated white blood cell count (>15 x 1,000/mm3), and admission to intensive care unit because of CDI. CONCLUSIONS: Predictors of CDI-related mortality reported in this study could be applied to the development of a bedside scoring system for older adults with CDI.

Internal Medicine
Goyal N, **Vallee PA**, **Folt J**, **Jaskulka B**, **Baliga S**, **Nagarwala J**, and **Slezak M**. WIREd for milestones *J Grad Med Educ* 2016; 8(3):445-446. PMID: 27413456. Full Text

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Internal Medicine
Haque MZ, McIntosh VJ, Abou Samra AB, Mohammad RM, and Lasley RD. Cholesterol depletion alters cardiomyocyte subcellular signaling and increases contractility *PLoS One* 2016; 11(7):e0154151. PMID: 27441649. Full Text

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Membrane cholesterol levels play an important factor in regulating cell function. Sarcolemmal cholesterol is concentrated in lipid rafts and caveolae, which are flask-shaped invaginations of the plasma membrane. The scaffolding protein caveolin permits the enrichment of cholesterol in caveolae, and caveolin interactions with numerous proteins regulate their function. The purpose of this study was to determine whether acute reductions in cardiomyocyte cholesterol levels alter subcellular protein kinase activation, intracellular Ca2+ and contractility. METHODS: Ventricular myocytes, isolated from adult Sprague Dawley rats, were treated with the cholesterol reducing agent methyl-beta-cyclodextrin (MbetaCD, 5 mM, 1 hr, room temperature). Total cellular cholesterol levels, caveolin-3 localization, subcellular, ERK and p38 mitogen activated protein kinase (MAPK) signaling, contractility, and [Ca2+]i were assessed. RESULTS: Treatment with MbetaCD reduced cholesterol levels by ~45 and shifted caveolin-3 from cytoskeleton and triton-insoluble fractions to the triton-soluble fraction, and increased ERK isoform phosphorylation in cytoskeletal, cytosolic, triton-soluble and triton-insoluble membrane fractions without altering their subcellular distributions. In contrast the primary effect of MbetaCD was on p38 subcellular distribution of p38alpha with little effect on p38 phosphorylation. Cholesterol depletion increased cardiomyocyte twitch amplitude and the rates of shortening and relaxation in conjunction with increased diastolic and systolic [Ca2+]i. CONCLUSIONS: These results indicate that acute reductions in membrane cholesterol levels differentially modulate basal cardiomyocyte subcellular MAPK signaling, as well as increasing [Ca2+]i and contractility.

Internal Medicine
Hermann G, **Xi AS**, **Stevens B**, and **Goyal N**. Reducing errors in reporting scholarly activity to the ACGME: The annual update scholarly activity monitoring tool *J Grad Med Educ* 2016; 8(3):447-448. PMID: 27413457. Full Text

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Program Director, Transitional Year Residency and Director of Emergency Medicine Informatics, Department of Emergency Medicine and Department of Internal Medicine, Henry Ford Health System.

Internal Medicine
Joshi S, **Vanderhoek M**, and **Harkness B**. CdZnTe detectors: What you need to know *J Nucl Med* 2016; 57PMID: Not assigned. Abstract

S. Joshi, Henry Ford Hospital, Detroit, United States

Objectives CdZnTe (CZT) is a semiconductor detector material that is increasingly being used in nuclear medicine applications. As more medical imaging devices incorporate CZT, it is important to become familiar with its material properties and associated physics, and their effects on image quality. The purpose of this educational exhibit is to present some basics of CZT detectors to nuclear medicine professionals in an approachable manner. Methods This educational exhibit will include 1) a review of the unique properties of CZT detector materials, 2) a schematic of common geometry and electronic setup 3) a step-by-step description of signal generation starting with photon interaction, electron-cloud formation and transportation, signal readout, and finally image reconstruction, 4) a description of the small-pixel effect and its contribution to improved spatial and energy resolution, and 5) a discussion of the advantages and disadvantages of CZT compared to other materials (e.g. NaI(Tl)) used in nuclear medicine. Results Diagrams, animations, and analogies will be used to explain complex, yet relevant, physics concepts. Explanations will be based on concepts familiar to nuclear medicine professionals. As an example, Figure 1 describes the configuration of a typical CZT detector geometry. The pixel pitch of the anode determines both the spatial resolution and energy resolution due to the small pixel effect. These parameters, as well as others that affect image quality, will be described through visualizations. Conclusions After reading this educational exhibit, participants should have a better understanding of the basic physics of CZT detectors, how signals are created and processed into images, how CZT compares to other detector materials, as well as challenges that must be overcome in the future. (Figure Presented).

Internal Medicine
Rezik MM, and **Ouellette DR**. Pleuritic chest pain in a 24-year-old male with crohn's disease *Am J Respir Crit Care Med* 2016;PMID: 27413816. Full Text

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Internal Medicine
Wilkinson J, Kong XW, Almany S, Kozlowski J, **Krol G**, McNamara M, Kaatz S, Froehlich JB, and Barnes GD. The predictive ability of various risk scores for bleeding in warfarin-treated vte patients *Vascular Medicine* 2016; 21(3):307-307. PMID: Not assigned. Abstract

[Wilkinson, Jared; Kong, Xiaowen; Froehlich, James B.; Barnes, Geoffrey D.] Univ Michigan, Ann Arbor, MI 48109 USA. [Almany, Steve] William Beaumont Hosp, Troy, MI USA. [Kozlowski, Jay] Huron Valley Sinai Hosp, Commerce Township, MI USA. [Krol, Greg] Henry Ford Hosp, Detroit, MI USA. [McNamara, Michael] Spectrum Hlth, Phoenix, MD USA. [Kaatz, Scott] Hurley Med Ctr, Flint, MI USA.

Nephrology
Kramer H, **Yee J**, Weiner DE, Bansal V, Choi MJ, Brereton L, Berns JS, Samaniego-Picota M, Scheel P, Jr., and Rocco M. Ultrafiltration rate thresholds in maintenance hemodialysis: An nkf-kdoqi controversies report *Am J Kidney Dis* 2016;PMID: 27449697. Full Text

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High hemodialysis ultrafiltration rate (UFR) is increasingly recognized as an important and modifiable risk factor for mortality among patients receiving maintenance hemodialysis. Recently, the Kidney Care Quality Alliance (KCQA) developed a UFR measure to assess dialysis unit care quality. The UFR measure was defined as UFR>/=13mL/kg/h for patients with dialysis session length less than 240 minutes and was endorsed by the National Quality Forum as a quality measure in December 2015. Despite this, implementation of a UFR threshold remains controversial. In this NKF-KDOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) Controversies Report, we discuss the concept of the UFR, which is governed by patients' interdialytic weight gain, body weight, and dialysis treatment time. We also examine the potential benefits and pitfalls of adopting a UFR threshold as a clinical performance measure and outline several aspects of UFR thresholds that require further research.

Nephrology

Singasani R, **Ngansop T**, **Kumbar L**, **Li J**, **Yee J**, and **Yessayan L**. Renal sparing in levamisole/cocaine induced systemic vasculitis *Am J Kid Dis* 2016; 67(5):A101-A101. PMID: Nephrology. Abstract

[Singasani, Reddy; Ngansop, Thierry; Kumbar, Lalathaksha; Li, Jian; Yee, Jerry; Yessayan, Lenart] Henry Ford Hosp, Detroit, MI 48202 USA.

Neurology

Bagher-Ebadian H, **Schwalb J**, **Mahmoudi F**, **Air E**, **Shokri S**, **Nazem-Zadeh M**, **Spanaki-Varelas M**, **Wasade V**, and **Soltanian-Zadeh H**. Localized quantitative analysis of positron emission tomography (PET) for temporal lobe epilepsy lateralization and surgical intervention *J Nucl Med* 2016; 57PMID: Not assigned. Abstract

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Objectives We hypothesized that localized quantitative analysis of hypometabolism level in hippocampi using interictal PET scans, in combination with qualitative and quantitative analyses of MRI, can increase the confidence in lateralization and selection of patients for surgical intervention. Methods In this study, 11 patients with refractory epilepsy (ages 18 to 58 years, mean age of 40 years, 8 females, 3 males) were studied. All patients had symptomatic temporal lobe epilepsy and underwent MRI, EEG, and PET/CT scans. MR Imaging: All studies were performed using a 3T GE Excite HD MR system (GE Healthcare, Waukesha, WI) using a standard eight-channel phased-array RF coil and receiver. All patients underwent coronal T2-Fluid attenuated inversion recovery (T2-FLAIR) and T1-weighted (T1WI) MR studies using a spoiled gradient-echo (SPGR) sequence with adequate spatial resolutions appropriate for hippocampal T1 volumetry and FLAIR intensity analysis. PET Scan: All patients were asked to fast for 5 to 6 hours on the day of their scan. The blood glucose level of the patient was checked before the 18F-FDG administration. For each patient, 18F-FDG (8 ~ 12 mCi) was injected via an IV. All patient were scanned using a CT/PET (GE) scanner with a wait time of 60 min. For each patient, using FSL software, FLAIR and PET modalities were skull stripped (BET) and co-registered (rigid-FLIRT) to the skull-stripped T1WI as the reference. The regions of interest (ROIs) enclosing the hippocampi were delineated manually using coronal T1WI. A single investigator (AH) outlined all coronal hippocampal contours using an in-house software. Then, for each subject, the 3D Standard Uptake Value (SUV) was calculated (Figures 1 and 2, note that increased hypomethabolism is red in figure-2) from the co-registered PET modality for the entire brain and for the hippocampi using the hippocampi's ROIs. From Anterior to Posterior, SUV profiles for the left and right hippocampi were calculated and the two profiles were spatially normalized to each other (Figure 3). Then, the normalized profiles (L and R) along with a test of significance (Welch test - unpaired and unequal variances - see Figure 4) were used to estimate the hypometabolism probability profile (HPP) from each individual slice of the hippocampi at the confidence level of 95%. Results As shown in Figure 5, the slice based Welch test along with the proposed sampling method (Figures 3-4) generated a standard HPP profile consisting of three possible conditions for the hippocampi: left hypometabolism area (green), right hypometabolism area (blue), and the area of uncertainty (red - no judgment can be made). In addition to the HPP method, MRI data of the subjects were processed using quantitative lateralization techniques of hippocampal volumetry and T2-FLAIR intensity analysis. The HPP and the scatter plots generated by the MRI methods were used for lateralization and decision making for ECoG. The patient's medical history, laboratory studies, long-term video-electro-encephalographic (EEG) data, and Neuropsychological tests such as Wada were also used in the decision making process. Table 1 shows that, compared to MRI lateralization techniques (27% and 36% for FLAIR intensity and T1 volume, respectively), the judgments of the HPP technique are closer (64%) to the decisions made by the clinicians for the ECoG monitoring study. Conclusions Despite the facts that the final decision made for ECoG may not be the optimal decision and also the population size in this study was small and skewed towards 'right', the results imply that the HPP method could be beneficial for the TLE patients to make a decision regarding the ECoG study and to do presurgical evaluations. We believe that an integrated decision making system that benefits from HPP as well as MRI measures would work best for the decision making process. (Figure Presented).

Neurology
Brennan JR, Wagley N, Kovelman I, **Bowyer SM**, Richard AE, and Lajiness-O'Neill R. Magnetoencephalography shows atypical sensitivity to linguistic sound sequences in autism spectrum disorder *Neuroreport* 2016; 27(13):982-986. PMID: 27468112. Full Text

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Neuroscientific evidence points toward atypical auditory processing in individuals with autism spectrum disorders (ASD), and yet, the consequences of this for receptive language remain unclear. Using magnetoencephalography and a passive listening task, we test for cascading effects on speech sound processing. Children with ASD and age-matched control participants (8-12 years old) listened to nonce linguistic stimuli that either did or did not conform to the phonological rules that govern consonant sequences in English (e.g. legal 'vimp' vs. illegal 'vimk'). Beamformer source analysis was used to isolate evoked responses (0.1-30 Hz) to these stimuli in the left and the right auditory cortex. Right auditory responses from participants with ASD, but not control participants, showed an attenuated response to illegal sequences relative to legal sequences that emerged around 330 ms after the onset of the critical phoneme. These results suggest that phonological processing is impacted in ASD, perhaps because of cascading effects from disrupted initial acoustic processing.

Neurology
Cheung WL, **Chopp M**, **Zhang T**, **Zhang ZG**, and **Morris D**. Irisin induces neurite outgrowth in primary cortical neurons *Brain Injury* 2016; 30(5-6):497-498. PMID: Not assigned. Abstract

[Cheung, Wing Lee; Chopp, Michael; Zhang, Talan; Zhang, Zheng Gang; Morris, Daniel] Henry Ford Hosp, Detroit, MI 48202 USA.

Neurology
Cui C, Ye X, **Chopp M**, **Venkat P**, **Zacharek A**, **Yan T**, **Ning R**, **Yu P**, Cui G, and **Chen J**. Mir-145 regulates diabetes-bone marrow stromal cell-induced neurorestorative effects in diabetes stroke rats *Stem Cells Transl Med* 2016;PMID: 27460851. Article Request Form

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: In rats with type 1 diabetes (T1DM), the therapeutic effects and underlying mechanisms of action of stroke treatment were compared between bone-marrow stromal cells (BMSCs) derived from T1DM rats (DM-BMSCs) and BMSCs derived from normal rats (Nor-BMSCs). The novel role of microRNA-145 (miR-145) in mediating DM-BMSC treatment-induced benefits was also investigated. T1DM rats (n = 8 per group) underwent 2 hours of middle cerebral artery occlusion (MCAo) and were treated 24 hours later with the one of the following (5 x 106 cells administered i.v.): (a) phosphate-buffered saline (PBS); (b) Nor-BMSCs; (c) DM-BMSCs; (d) DM-BMSCs with miR-145 overexpression (miR-145+/+DM-BMSCs); or (e) Nor-BMSCs with miR-145 knockdown. Evaluation of functional outcome, vascular and white-matter remodeling and microRNA expression was made, and in vitro studies were performed. In vitro, DM-BMSCs exhibited decreased miR-145 expression and increased survival compared with Nor-BMSCs. Capillary tube formation and axonal outgrowth in cultured primary cortical neurons were significantly increased by DM-BMSC-conditioned medium compared with Nor-BMSCs, and significantly decreased by miR-145+/+DM-BMSC-conditioned medium compared with DM-BMSCs. In T1DM rats in which stroke had been induced (T1DM stroke rats), DM-BMSC treatment significantly improved functional outcome, increased vascular and white matter remodeling, decreased serum miR-145 expression, and increased expression of the miR-145 target genes adenosine triphosphate-binding cassette transporter 1 (ABCA1) and insulin-like growth factor 1 receptor (IGFR1), compared with Nor-BMSCs or PBS treatment. However, miR-145+/+DM-BMSCs significantly increased serum miR-145 expression and decreased brain

ABCA1 and IGFR1 expression, as well as attenuated DM-BMSC-induced neurorestorative effects in T1DM-MCAo rats. DM-BMSCs exhibited decreased miR-145 expression. In T1DM-MCAo rats, DM-BMSC treatment improved functional outcome and promoted neurorestorative effects. The miR-145/ABCA1/IGFR1 pathway may contribute to the enhanced DM-BMSCs' functional and neurorestorative effects in T1DM stroke rats. SIGNIFICANCE: In rats with type 1 diabetes (T1DM), the therapeutic effects and underlying mechanisms of action of stroke treatment were compared between bone-marrow stromal cells (BMSCs) derived from T1DM rats (DM-BMSCs) and BMSCs derived from normal rats (Nor-BMSCs). In vitro, DM-BMSCs and derived exosomes decreased miR-145 expression and increased DM-BMSC survival, capillary tube formation, and axonal outgrowth, compared with Nor-BMSCs; these effects were decreased by DM-BMSCs in which miR-145 was overexpressed. In vivo, compared with Nor-BMSC or phosphate-buffered saline treatment, DM-BMSC treatment improved functional outcome and vascular and white matter remodeling, decreased serum miR-145 expression, and increased expression of the miR-145 target genes ABCA1 and IGFR1. microRNA-145 mediated the benefits induced by DM-BMSC treatment.

Neurology

Jia L, **Wang L**, **Chopp M**, **Zhang Y**, **Szalad A**, and **Zhang ZG**. MicroRNA 146a locally mediates distal axonal growth of dorsal root ganglia neurons under high glucose and sildenafil conditions *Neuroscience* 2016; 329:43-53. PMID: 27167084. Full Text

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Axonal loss contributes to induction of diabetic peripheral neuropathy. Sildenafil, a phosphodiesterase type 5 inhibitor, ameliorates neurological dysfunction in diabetic peripheral neuropathy. However, the direct effect of high glucose and sildenafil on axonal growth has not been extensively investigated. Using rat primary dorsal root ganglia (DRG) neurons cultured in a microfluidic chamber, we investigated the effect of axonal application of high glucose and sildenafil on distal axonal growth. We found that axonal, but not cell body, application of high glucose locally inhibited distal axonal growth. However, axonal application of sildenafil overcame high glucose-reduced axonal growth. Quantitative real-time RT-PCR (qRT-PCR) and Western blot analysis of distal axonal samples revealed that high glucose reduced axonal miR-146a levels and substantially increased miR-146a target genes, IRAK1 and TRAF6 in the axon. In contrast, sildenafil significantly reversed high glucose-reduced miR-146a levels and high glucose-increased IRAK1 and TRAF6. Gain- and loss-of function of miR-146a in DRG neurons revealed that miR-146a mediated the local effect of high glucose on the distal axonal growth. These in vitro data provide new insights into molecular mechanisms of diabetic peripheral neuropathy.

Neurology

Kroll HR, **Macaulay T**, and **Jesse M**. A preliminary survey examining predictors of burnout in pain medicine physicians in the united states *Pain Physician* 2016; 19(5):E689-696. PMID: 27389112. Full Text

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BACKGROUND: Burnout is a prolonged response to chronic emotional and interpersonal stressors on the job, defined by 3 dimensions: exhaustion, depersonalization, and reduced personal accomplishment. While there is a growing body of research on burnout in physicians, there is a dearth of literature on burnout in pain medicine physicians. OBJECTIVE: This study aimed to determine the incidence of burnout amongst pain medicine physicians and whether there are sociodemographic or psychological demand characteristics of the job setting that predict burnout in pain medicine physicians. STUDY DESIGN AND SETTING: Cross-section survey of pain medicine physicians across the United States. METHODS: Pain medicine physicians were asked questions on sociodemographics and professional characteristics and measures of decisional authority, psychological job demands, job insecurity, perceived coworker support, and job dissatisfaction. RESULTS: Two hundred seven pain medicine physicians' responses were analyzed, 60.4% reported high emotional exhaustion, 35.7% reported high depersonalization, and 19.3% reported low personal accomplishment. Greater psychological job demands and greater job dissatisfaction predicted greater emotional exhaustion. Younger age and greater job dissatisfaction predicted higher depersonalization. Lastly, lower coworker support and greater job dissatisfaction predicted lower personal accomplishment. There were no statistical violations of assumptions or collinearity. LIMITATIONS: Low response rate and potential for response bias limit generalizability of the study. CONCLUSION(S): Pain medicine

physicians in the United States reported high levels of emotional exhaustion, often considered the most taxing aspect of burnout. Job dissatisfaction appeared to be the leading agent in the development of all 3 components of burnout in pain medicine physicians in the United States.

Neurology

Lewis A, Adams N, **Varelas P**, Greer D, and Caplan A. Organ support after death by neurologic criteria: Results of a survey of us neurologists *Neurology* 2016;PMID: 27449064. Full Text

From the Departments of Neurology and Neurosurgery, Division of Neurocritical Care (A.L.), and Department of Population Health, Division of Medical Ethics (A.C.), NYU Langone Medical Center, New York, NY; American Academy of Neurology (N.A.), Minneapolis, MN; Departments of Neurology and Neurosurgery (P.V.), Henry Ford Hospital, Detroit, MI; and Department of Neurology (D.G.), Yale University School of Medicine, New Haven, CT. ariane.kansas.lewis@gmail.com.
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OBJECTIVE: We sought to evaluate how neurologists approach situations in which families request prolonged organ support after declaration of death by neurologic criteria (DNC). METHODS: We surveyed 938 members of the American Academy of Neurology (AAN) who treat critically ill patients, including 50% who practice in states with accommodation exceptions (states that require religious or moral beliefs to be taken into consideration when declaring death or discontinuing organ support: California, Illinois, New Jersey, New York), and 50% who practice in nonaccommodation states. RESULTS: The survey was completed by 201/938 individuals (21% response rate), 96 of whom were from accommodation states and 105 of whom were from nonaccommodation states. Both groups reported encountering situations in which families requested continuation of organ support after DNC (48% from accommodation states and 46% from nonaccommodation states). In a hypothetical scenario where a request is made to continue organ support after DNC (outside of organ donation), 48% of respondents indicated they would continue support due to fear of litigation. In reply to an open-ended question, respondents requested that the AAN generate guidelines and advocate to codify laws regarding organ support after DNC, and to improve public and physician education on DNC. CONCLUSIONS: Our findings suggest that it is relatively common for neurologists who treat critically ill patients to encounter families who object to discontinuation of organ support after DNC at some point during their career. It would be beneficial for physicians, families, and society to rely on clear medicolegal guidelines on management of this situation.

Neurology

Liu LJ, **Brown SL**, **Ewing JR**, Ala BD, Schneider KM, and Schlesinger M. Estimation of tumor interstitial fluid pressure (tifp) noninvasively *PLoS One* 2016; 11(7):e0140892. PMID: 27467886. Full Text

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Tumor interstitial fluid pressure (TIFP), is a physiological parameter with demonstrated predictive value for a tumor's aggressiveness, drug delivery, as well as response to treatments such as radiotherapy and chemotherapy. Despite its utility, measurement of TIFP has been limited by the need for invasive procedures. In this work, the theoretical basis for approaching the absolute value of TIFP and the experimental method for noninvasively measuring TIFP are presented. Given specific boundary and continuity conditions, we convert theoretical variables into measurable variables by applying MRI technology. The work shows that TIFP in the central region of the tumor can be estimated by an analysis of the variation of tissue fluid motion in the tumor rim and surrounding tissue. It is determined from three noninvasive measurable parameters: i) an estimate of the velocity of the tumor interstitial fluid at the tumor surface, which is maximal, ii) a measurement of the distance from the tumor surface to where the tumor exudates are absorbed (or normalized), and iii) an estimate of the hydraulic conductivity of the interstitium through which the tumor exudate travels. We experimentally show that the fluid flow within the tumor rim is not uniform, even for a round shaped tumor, and demonstrate the procedures for the noninvasive measurement of TIFP.

Neurology
Loeffler DA, **LeWitt PA**, and Camp DM. Nocardia asteroides-induced movement abnormalities in mice: Relevance for parkinson's disease? *Mov Disord* 2016;PMID: 27411508. Full Text

Department of Neurology, Beaumont Hospital-Royal Oak, Beaumont Health, Royal Oak, Michigan, USA.
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Neurology
Mestre TA, **Sidiropoulos C**, Hamani C, Poon YY, Lozano AM, Lang AE, and Moro E. Long-term double-blinded unilateral pedunculopontine area stimulation in Parkinson's disease *Mov Disord* 2016;PMID: 27392513. Full Text

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BACKGROUND: Gait-related symptoms are often refractory to current available treatment options with a significant reduction in quality of life in Parkinson's disease. OBJECTIVES: The objective of this study was to determine the long-term efficacy and safety of unilateral pedunculopontine area stimulation for refractory gait and balance impairment in Parkinson's disease. METHODS: This study used periodic randomized double-blinded assessments until 4 years postoperatively. The primary outcomes were gait-related items of the UPDRS part II and the MDS-UPDRS part III. RESULTS: At baseline, the median age and disease duration was 63 years (interquartile range: 62, 65) and 15 years (interquartile range: 11, 20). At 2 years, patient-reported freezing (UPDRS part II, off-time) was significantly better when compared with baseline (P =.028), with 62.5% of responders. At 4 years, there was no significant change in the used outcomes, but 66.7 % (n = 4 of 6) were responders for off-time patient-reported freezing and falling. CONCLUSIONS: Pedunculopontine area stimulation has an initial but not sustained benefit for gait-related symptoms. (c) 2016 International Parkinson and Movement Disorder Society.

Neurology
RM. D, **E. D-B**, **Q. J**, **L. L**, and **M C**. Analysis of white matter tracts of resting state cognitive networks in multiple sclerosis *Int J MS Care* 2016; 18(9s1):62. PMID: Not assigned. Abstract

Background: Cognitive impairment affects 40-70% of patients with MS and these impairments are seen in multiple domains of cognition including attention, memory, speed of information processing. In a previous study using resting-state fMRI we found abnormal connectivity links for most patients with MS in default mode network (DMN) as well as other cognitive networks (attention, memory, language, visual-spatial memory). Objectives: To analyze the white matter damage and topological organization of white matter tracts in specific brain regions responsible for cognition in Multiple Sclerosis (MS) patients and compared with healthy controls. Methods: MRI measurements of DTI, T1, T2, and T2 FLAIR were acquired by GE clinical 3T system of 32 healthy subjects and 20 MS patients. DTI images were preprocessed in MATLAB to calculate the fractional anisotropy (FA) maps. The FA maps then were analyzed by TBSS toolbox in to co-register and create the skeleton map of the white matter (WM) for each case. For each patient, a 5×5×5 kernel was centered on each skeleton point and a one tail t2-test was used to calculate the p-value of the hypothesis testing that the FA values inside that kernel are smaller than the corresponding points in all normal cases. HAMMER package was used to segment each T1-weighted image into 94 regions and then aligned to the DTI space. In each region of each patient's brain segment, the p-values were calculated and the region was considered as significant if the averaged p-value was smaller than 0.05. The percentile of the MS patients having significant FA reduction in each region was calculated. In the next phase, T1-weighted images of the whole brain were segmented in 164 regions using FreeSurfer and fiber tracking between connectivity nodes was assessed. Results: Out of 94

regions, in 46 regions none of the 20 patients showed significant FA reduction while in 17 regions (anterior limb of internal capsule, frontal lobe WM, globus pallidus, hippocampal formation, lateral occipito-temporal gyrus, parietal lobe WM, temporal lobe WM, uncus, corpus callosum), 10 or more patients showed significant FA reduction. On second year follow up MRI 4/8 (50%) showed significant FA further reduction in frontal lobe WM, globus pallidus, hippocampal formation, right lateral occipito-temporal gyrus, occipital lobe WM and uncus. DTI connectivity in DMN and cognitive networks was decreased, while fMRI connectivity showed mixed results.Conclusions: MS patient have significant white matter damage and reduction in various regions in the brain involved in cognitive networks. We report that both anatomical and functional connectivity inside default mode network and cognitive networks showed significant differences compared with healthy subjects. For MS patients with multiple scans over time, further progression of white matter damage was found.

Neurology

Wang L, **Chopp M**, **Szalad A**, **Lu X**, **Jia L**, **Lu M**, **Zhang RL**, and **Zhang ZG**. Tadalafil promotes the recovery of peripheral neuropathy in type II diabetic mice *PLoS One* 2016; 11(7):e0159665. PMID: 27438594. Full Text

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We previously demonstrated that treatment of diabetic peripheral neuropathy with the short (4 hours) half-life phosphodiesterase 5 (PDE5) inhibitor, sildenafil, improved functional outcome in diabetic db/db mice. To further examine the effect of PDE5 inhibition on diabetic peripheral neuropathy, we investigated the effect of another potent PDE5 inhibitor, tadalafil, on diabetic peripheral neuropathy. Tadalafil is pharmacokinetically distinct from sildenafil and has a longer half-life (17+hours) than sildenafil. Diabetic mice (BKS.Cg-m+/+Leprdb/J, db/db) at age 20 weeks were treated with tadalafil every 48 hours for 8 consecutive weeks. Compared with diabetic mice treated with saline, tadalafil treatment significantly improved motor and sensory conduction velocities in the sciatic nerve and peripheral thermal sensitivity. Tadalafil treatment also markedly increased local blood flow and the density of FITC-dextran perfused vessels in the sciatic nerve concomitantly with increased intraepidermal nerve fiber density. Moreover, tadalafil reversed the diabetes-induced reductions of axon diameter and myelin thickness and reversed the diabetes-induced increased g-ratio in the sciatic nerve. Furthermore, tadalafil enhanced diabetes-reduced nerve growth factor (NGF) and platelet-derived growth factor-C (PDGF-C) protein levels in diabetic sciatic nerve tissue. The present study demonstrates that tadalafil increases regional blood flow in the sciatic nerve tissue, which may contribute to the improvement of peripheral nerve function and the amelioration of diabetic peripheral neuropathy.

Neurology

Zhang L, **Chopp M**, **Zhang Y**, **Xiong Y**, **Li C**, **Sadry N**, **Rhaleb I**, **Lu M**, and **Zhang ZG**. Diabetes mellitus impairs cognitive function in middle-aged rats and neurological recovery in middle-aged rats after stroke *Stroke* 2016; 47(8):2112-2118. PMID: 27387991. Full Text

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BACKGROUND AND PURPOSE: Diabetes mellitus (DM) is a common metabolic disease among the middle-aged and older population, which leads to an increase of stroke incidence and poor stroke recovery. The present study was designed to investigate the impact of DM on brain damage and on ischemic brain repair after stroke in aging animals. METHODS: DM was induced in middle-aged rats (13 months) by administration of nicotinamide and streptozotocin. Rats with confirmed hyperglycemia status 30 days after nicotinamide-streptozotocin injection and age-matched non-DM rats were subjected to embolic middle cerebral artery occlusion. RESULTS: Middle-aged rats subjected to nicotinamide-streptozotocin injection became hyperglycemic and developed cognitive deficits 2 months after induction of DM. Histopathologic analysis revealed that there was sporadic vascular disruption, including cerebral microvascular thrombosis, blood-brain barrier leakage, and loss of paravascular aquaporin-4 in the hippocampi. Importantly, middle-aged DM rats subjected to stroke had exacerbated sensorimotor and cognitive deficits compared with age-matched non-DM ischemic rats during stroke recovery. Compared with age-matched non-DM ischemic rats, DM ischemic rats exhibited aggravated neurovascular disruption in the bilateral hippocampi and white matter, suppressed stroke-induced neurogenesis and oligodendrogenesis, and impaired dendritic/spine plasticity. However,

DM did not enlarge infarct volume. CONCLUSIONS: Our data suggest that DM exacerbates neurovascular damage and hinders brain repair processes, which likely contribute to the impairment of stroke recovery.

Neurosurgery

Bagher-Ebadian H, **Schwalb J**, **Mahmoudi F**, **Air E**, **Shokri S**, **Nazem-Zadeh M**, **Spanaki-Varelas M**, **Wasade V**, and **Soltanian-Zadeh H**. Localized quantitative analysis of positron emission tomography (PET) for temporal lobe epilepsy lateralization and surgical intervention *J Nucl Med* 2016; 57PMID: Not assigned. Abstract

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Objectives We hypothesized that localized quantitative analysis of hypometabolism level in hippocampi using interictal PET scans, in combination with qualitative and quantitative analyses of MRI, can increase the confidence in lateralization and selection of patients for surgical intervention. Methods In this study, 11 patients with refractory epilepsy (ages 18 to 58 years, mean age of 40 years, 8 females, 3 males) were studied. All patients had symptomatic temporal lobe epilepsy and underwent MRI, EEG, and PET/CT scans. MR Imaging: All studies were performed using a 3T GE Excite HD MR system (GE Healthcare, Waukesha, WI) using a standard eight-channel phased-array RF coil and receiver. All patients underwent coronal T2-Fluid attenuated inversion recovery (T2-FLAIR) and T1-weighted (T1WI) MR studies using a spoiled gradient-echo (SPGR) sequence with adequate spatial resolutions appropriate for hippocampal T1 volumetry and FLAIR intensity analysis. PET Scan: All patients were asked to fast for 5 to 6 hours on the day of their scan. The blood glucose level of the patient was checked before the 18F-FDG administration. For each patient, 18F-FDG (8 ~ 12 mCi) was injected via an IV. All patient were scanned using a CT/PET (GE) scanner with a wait time of 60 min. For each patient, using FSL software, FLAIR and PET modalities were skull stripped (BET) and co-registered (rigid-FLIRT) to the skull-stripped T1WI as the reference. The regions of interest (ROIs) enclosing the hippocampi were delineated manually using coronal T1WI. A single investigator (AH) outlined all coronal hippocampal contours using an in-house software. Then, for each subject, the 3D Standard Uptake Value (SUV) was calculated (Figures 1 and 2, note that increased hypomethabolism is red in figure-2) from the co-registered PET modality for the entire brain and for the hippocampi using the hippocampi's ROIs. From Anterior to Posterior, SUV profiles for the left and right hippocampi were calculated and the two profiles were spatially normalized to each other (Figure 3). Then, the normalized profiles (L and R) along with a test of significance (Welch test - unpaired and unequal variances - see Figure 4) were used to estimate the hypometabolism probability profile (HPP) from each individual slice of the hippocampi at the confidence level of 95%. Results As shown in Figure 5, the slice based Welch test along with the proposed sampling method (Figures 3-4) generated a standard HPP profile consisting of three possible conditions for the hippocampi: left hypometabolism area (green), right hypometabolism area (blue), and the area of uncertainty (red - no judgment can be made). In addition to the HPP method, MRI data of the subjects were processed using quantitative lateralization techniques of hippocampal volumetry and T2-FLAIR intensity analysis. The HPP and the scatter plots generated by the MRI methods were used for lateralization and decision making for ECoG. The patient's medical history, laboratory studies, long-term video-electro-encephalographic (EEG) data, and Neuropsychological tests such as Wada were also used in the decision making process. Table 1 shows that, compared to MRI lateralization techniques (27% and 36% for FLAIR intensity and T1 volume, respectively), the judgments of the HPP technique are closer (64%) to the decisions made by the clinicians for the ECoG monitoring study. Conclusions Despite the facts that the final decision made for ECoG may not be the optimal decision and also the population size in this study was small and skewed towards 'right', the results imply that the HPP method could be beneficial for the TLE patients to make a decision regarding the ECoG study and to do presurgical evaluations. We believe that an integrated decision making system that benefits from HPP as well as MRI measures would work best for the decision making process. (Figure Presented).

Neurosurgery

Hodges TR, Ferguson SD, Caruso HG, Kohanbash G, Zhou S, Cloughesy TF, Berger MS, Poste GH, Khasraw M, Ba S, Jiang T, **Mikkelson T**, Yung WK, de Groot JF, Fine H, Cantley LC, Mellinghoff IK, Mitchell DA, Okada H, and Heimberger AB. Prioritization schema for immunotherapy clinical trials in glioblastoma *Oncoimmunology* 2016; 5(6):e1145332. PMID: 27471611. Article Request Form

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BACKGROUND: Emerging immunotherapeutic strategies for the treatment of glioblastoma (GBM) such as dendritic cell (DC) vaccines, heat shock proteins, peptide vaccines, and adoptive T-cell therapeutics, to name a few, have transitioned from the bench to clinical trials. With upcoming strategies and developing therapeutics, it is challenging to critically evaluate the practical, clinical potential of individual approaches and to advise patients on the most promising clinical trials. METHODS: The authors propose a system to prioritize such therapies in an organized and data-driven fashion. This schema is based on four categories of factors: antigenic target robustness, immune-activation and -effector responses, preclinical vetting, and early evidence of clinical response. Each of these categories is subdivided to focus on the most salient elements for developing a successful immunotherapeutic approach for GBM, and a numerical score is generated. RESULTS: The Score Card reveals therapeutics that have the most robust data to support their use, provides a reference prioritization score, and can be applied in a reiterative fashion with emerging data. CONCLUSIONS: The authors hope that this schema will give physicians an evidence-based and rational framework to make the best referral decisions to better guide and serve this patient population.

Neurosurgery
Hodges TR, Ferguson SD, Caruso HG, Kohanbash G, Zhou S, Cloughesy TF, Berger MS, Poste GH, Khasraw M, Ba S, Jiang T, **Mikkelson T**, Yung WK, de Groot JF, Fine H, Cantley LC, Mellinghoff IK, Mitchell DA, Okada H, and Heimberger AB. Prioritization schema for immunotherapy clinical trials in glioblastoma *Oncoimmunology* 2016; 5(6):e1145332. PMID: 27471611. Article Request Form

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Department of Neurosurgery, University of Florida , Gainesville, FL, USA.

BACKGROUND: Emerging immunotherapeutic strategies for the treatment of glioblastoma (GBM) such as dendritic cell (DC) vaccines, heat shock proteins, peptide vaccines, and adoptive T-cell therapeutics, to name a few, have transitioned from the bench to clinical trials. With upcoming strategies and developing therapeutics, it is challenging to critically evaluate the practical, clinical potential of individual approaches and to advise patients on the most promising clinical trials. METHODS: The authors propose a system to prioritize such therapies in an organized and data-driven fashion. This schema is based on four categories of factors: antigenic target robustness, immune-activation and -effector responses, preclinical vetting, and early evidence of clinical response. Each of these categories is subdivided to focus on the most salient elements for developing a successful immunotherapeutic approach for GBM, and a numerical score is generated. RESULTS: The Score Card reveals therapeutics that have the most robust data to support their use, provides a reference prioritization score, and can be applied in a reiterative fashion with emerging data. CONCLUSIONS: The authors hope that this schema will give physicians an evidence-based and rational framework to make the best referral decisions to better guide and serve this patient population.

Neurosurgery
Lownie SP, Larrazabal R, and **Kole MK**. Circle of willis collateral during temporary internal carotid artery occlusion i: Observations from digital subtraction angiography *Can J Neurol Sci* 2016; 43(4):533-537. PMID: 27030296.
Article Request Form

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INTRODUCTION: Impaired collateral circulation can lead to stroke during carotid endarterectomy. Carotid stump pressure (CSP) is used as a surrogate measure of collateral flow. The objective was to determine whether anatomical features obtained from digital subtraction angiography correlate with CSP during temporary internal carotid artery occlusion. The second objective was to use these features in combination to predict CSP. METHODS: Digital subtraction angiographies from 102 patients obtained before endarterectomy were reviewed for anatomical variables including: degree of ipsilateral and contralateral carotid artery stenosis; patency of the anterior communicating artery; presence of cross-flow into ipsilateral middle cerebral artery branches; and size (< or >/=1 mm calibre) of the ipsilateral proximal anterior cerebral (A1), the contralateral A1, and the ipsilateral posterior communicating arteries. At surgery, systemic mean arterial pressure (MAP) and CSP were recorded. Multiple regression analysis was used to assess for anatomical features significantly associated with CSP. A "predicted CSP" equation was applied to 54 subsequent patients and correlated with measured CSP. RESULTS: Variables correlating with CSP included MAP (p=0.001); the presence of severe contralateral carotid stenosis (p=0.002); patency of the anterior communicating artery (p=0.013); and the size of the contralateral A1 segment (p=0.029). Angiographic cross-flow, ipsilateral A1 size, and ipsilateral posterior communicating artery size were not significant. Predicted CSP correlated significantly with measured CSP (p<0.0001; R 2=0.34). CONCLUSIONS: Anatomical features and systemic MAP are associated with carotid stump pressure during internal carotid artery occlusion and account for a significant amount of its variation.

Neurosurgery
Macki M, Syeda S, Kerezoudis P, Bydon A, Witham TF, Sciubba DM, Wolinsky JP, Bydon M, and Gokaslan Z. rhBMP-2 protects against reoperation for pseudoarthrosis and/or instrumentation failure: A matched case-control study of 448 patients *J Clin Neurosci* 2016;PMID: 27396376. Full Text

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The objective of this independent study is to determine the impact of recombinant human bone morphogenetic protein 2 (rhBMP-2) on reoperation for pseudarthrosis and/or instrumentation failure. A nested case-control study of first-time posterolateral, instrumented fusion of the lumbar spine for degenerative spinal disease was undertaken. Cases of reoperation for pseudoarthrosis and/or instrumentation failure were assigned to controls, who did not experience the primary outcome measure at the time of reoperation. Cases and controls were matched on number of interspaces fused and inclusion of interbody. Predictors of reoperation for pseudoarthrosis and/or instrumentation failure were assessed with a conditional logistical regression controlling for rhBMP-2, age, obesity, and smoking. Of the 448 patients, 155 cases of reoperation for pseudoarthrosis and/or instrumentation were matched with 293 controls. Twenty-six percent of first-time surgeries included rhBMP-2, which was statistically more commonly used in the control cohort (33.11%) versus the case cohort (12.90%) (Unadjusted odds ratio [ORunadj]=0.28) (95% confidence interval [CI]: 0.16-0.49). Following a multivariate analysis controlling for age, obesity, and smoking, the rhBMP-2 recipients incurred a 73% lower odds of reoperation for pseudoarthrosis and/or instrumentation failure (95% CI, 0.15-0.48). Neither sarcomatous nor osseous neoplasm was detected in the study population. Mean follow up did not differ between the cases (81.57+/-standard deviation [SD] 4.98months) versus controls (74.75+/-2.49month) (ORunadj=1.01) (95% CI: 1.00-1.01). rhBMP-2 in lumbar fusion constructs protects against reoperation for pseudoarthrosis and/or instrumentation failure. However, the decision to include fusion supplements should be weighted between surgical determinants and clinical outcomes.

Neurosurgery

Shainer R, Almogi-Hazan O, Berger A, Hinden L, Mueller M, **Brodie C**, Simillion C, Paidas M, Barnea ER, and Or R. PreImplantation factor (PIF) therapy provides comprehensive protection against radiation induced pathologies *Oncotarget* 2016;PMID: 27449294. Full Text

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Acute Radiation Syndrome (ARS) may lead to cancer and death and has few effective countermeasures. Efficacy of synthetic PIF treatment was demonstrated in preclinical autoimmune and transplantation models. PIF protected against inflammation and mortality following lethal irradiation in allogeneic bone marrow transplant (BMT) model. Herein, we demonstrate that PIF imparts comprehensive local and systemic protection against lethal and sub-lethal ARS in murine models. PIF treatment 2 h after lethal irradiation led to 100% survival and global hematopoietic recovery at 2 weeks after therapy. At 24 h after irradiation PIF restored hematopoiesis in a semi-allogeneic BMT model. PIF-preconditioning provided improved long-term engraftment. The direct effect of PIF on bone marrow cells was also demonstrated in vitro: PIF promoted pre-B cell differentiation and increased immunoregulatory properties of BM-derived mesenchymal stromal cells. PIF treatment also improved hematopoietic recovery and reduced systemic inflammatory cytokine production after sub-lethal radiation exposure. Here, PIF also prevented colonic crypt and basal membrane damage coupled with reduced nitric oxide synthetase (iNOS) and increased (B7h1) expression. Global upper GI gene pathway analysis revealed PIF's involvement in protein-RNA interactions, mitochondrial oxidative pathways, and responses to cellular stress. Some effects may be attributed to PIF's influence on macrophage differentiation and function. PIF demonstrated a regulatory effect on irradiated macrophages and on classically activated M1 macrophages, reducing inflammatory gene expression (iNOS, Cox2), promoting protective (Arg1) gene expression and inducing pro-tolerance cytokine secretion. Notably, synthetic PIF is stable for long-term field use. Overall, clinical investigation of PIF for comprehensive ARS protection is warranted.

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 *J Neurointerv Surg* 2016;PMID: 27466463. Full Text

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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

Zhang L, **Chopp M**, **Zhang Y**, **Xiong Y**, **Li C**, **Sadry N**, **Rhaleb I**, **Lu M**, and **Zhang ZG**. Diabetes mellitus impairs cognitive function in middle-aged rats and neurological recovery in middle-aged rats after stroke *Stroke* 2016; 47(8):2112-2118. PMID: 27387991. Full Text

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BACKGROUND AND PURPOSE: Diabetes mellitus (DM) is a common metabolic disease among the middle-aged and older population, which leads to an increase of stroke incidence and poor stroke recovery. The present study was designed to investigate the impact of DM on brain damage and on ischemic brain repair after stroke in aging animals. METHODS: DM was induced in middle-aged rats (13 months) by administration of nicotinamide and streptozotocin. Rats with confirmed hyperglycemia status 30 days after nicotinamide-streptozotocin injection and age-matched non-DM rats were subjected to embolic middle cerebral artery occlusion. RESULTS: Middle-aged rats subjected to nicotinamide-streptozotocin injection became hyperglycemic and developed cognitive deficits 2 months after induction of DM. Histopathologic analysis revealed that there was sporadic vascular disruption, including cerebral microvascular thrombosis, blood-brain barrier leakage, and loss of paravascular aquaporin-4 in the hippocampi. Importantly, middle-aged DM rats subjected to stroke had exacerbated sensorimotor and cognitive deficits compared with age-matched non-DM ischemic rats during stroke recovery. Compared with age-matched non-DM ischemic rats, DM ischemic rats exhibited aggravated neurovascular disruption in the bilateral hippocampi and white matter, suppressed stroke-induced neurogenesis and oligodendrogenesis, and impaired dendritic/spine plasticity. However, DM did not enlarge infarct volume. CONCLUSIONS: Our data suggest that DM exacerbates neurovascular damage and hinders brain repair processes, which likely contribute to the impairment of stroke recovery.

Nursing

Klassa PJ, **Dendrinos S**, **Penn A**, and Radke J. Shared decision making: Through the patient's eyes *J Perinat Neonatal Nurs* 2016; 30(3):228-232. PMID: 27465455. Full Text

Henry Ford West Bloomfield Hospital, West Bloomfield, Michigan (Mss Klassa, Dendrinos, and Penn). Ms Radke has no current affiliation.

Birth is an intimate moment in a woman's life, and healthcare providers play a pivotal role in pregnant women having safe and memorable birth experiences. Utilizing the shared decision-making model during the prenatal period involves listening to the voices of identified high-risk patients and giving them options for care during labor and birth. "Through the Patient's Eyes" is an innovative program that evolved from the care planning process for these identified high-risk obstetric patients who are invited back postpartum to describe to the team birth through "their" eyes. Through this program, the team learned that compassionate care comes from truly listening to pregnant women and their families and that nurses play a pivotal role as educators and advocates. Sharing birth stories with the staff who cared for them not only had a positive effect on the staff but also many women described profound healing afterward.

Obstetrics, Gynecology and Women's Health Services

Al Feghali KA, **Robbins JR**, **Mahan M**, **Burmeister C**, **Khan NT**, **Rasool N**, **Munkarah A**, and **Elshaikh MA**. Predictive capacity of 3 comorbidity indices in estimating survival endpoints in women with early-stage endometrial carcinoma *Int J Gynecol Cancer* 2016;PMID: 27488218. Full Text

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OBJECTIVE: The negative impact of comorbidity on survival in women with endometrial carcinoma (EC) is well-known. Few validated comorbidity indices are available for clinical use, such as the Charlson Comorbidity Index (CCI), the Age-Adjusted CCI (AACCI), and the Adult Comorbidity Evaluation-27 (ACE-27). The aim of the study is to determine which index best correlates with survival endpoints in women with EC. MATERIALS AND METHODS: We identified 1132 women with early-stage EC treated at an academic center. Three scores were calculated for each patient using CCI, AACCI, and ACE-27 at the time of hysterectomy. Univariate and multivariable modeling was used to determine predictors of survival. RESULTS: For each of the studied comorbidity indices, the highest scores were significantly correlated with poorer overall survival. The hazard ratio of death from any cause was 3.92 for AACCI, 2.25 for CCI, and 1.57 for ACE-27. All 3 indices were independent predictors of overall survival with a P value of less than 0.001 on multivariate analysis. In addition, lymphovascular space invasion, lower uterine segment involvement, and tumor grade were predictors of overall survival. Lymphovascular space invasion, grade ($P < 0.001$), and high AACCI score were the only significant predictors of recurrence-free survival (RFS). Lymphovascular space invasion and tumor grade were the only 2 predictors of disease-specific survival. CONCLUSIONS: Although all 3 studied comorbidity indices were significant predictors of overall survival in women with early-stage EC, AACCI showed a stronger association. It should be considered for evaluating comorbidity in women with early-stage EC.

Obstetrics, Gynecology and Women's Health Services
Faucher MA, **Collins-Fulea C**, and Breedlove G. Collaboration in practice: Implementing team-based practice: A midwifery perspective *J Midwifery Womens Health* 2016; 61(4):408-410. PMID: 27352212. Full Text

Obstetrics, Gynecology and Women's Health Services
Haley L, **Buekers TE**, **Burmeister C**, and **Elshaikh MA**. Older age is no longer an adverse prognostic factor in women with early-stage endometrial carcinoma: A matched analysis *Gynecol Oncol* 2016; 141:70-71. PMID: Not assigned. Abstract

L. Haley, Henry Ford Hospital, Detroit, United States

Objectives: Older age is viewed as an adverse prognostic factor in women with endometrial carcinoma (EC). It is unclear whether this is because of its interaction with other well-known adverse prognostic factors or its independent prognostic impact. To study this issue, survival endpoints were compared between 2 groups of patients with early-stage EC solely of endometrioid histology: women 70 years or older (group 1) and similarly matched younger women (group 2).Methods: We identified 1,254 patients with 2009 FIGO stage I-II EC who underwent hysterectomy at our institution between January 1990 and December 2014. We created 2 matched groups based on FIGO stage, tumor grade, lymph node dissection status, and the type of adjuvant management (observation, pelvic external beam, or vaginal brachytherapy). Recurrence-free (RFS), disease-specific (DSS), and overall survival (OS) were calculated for the 2 groups.Results: A total of 594 women were included in this study in 2 groups (each with 297 patients, matched 1:1). Median follow-up was 50 months. The two groups were well balanced except for age (P <.001) and higher body mass in younger patients (P <.001). There was no significant difference in the site of initial recurrence between the 2 groups. There were no significant differences between older and younger patients with regard to 5-year RFS (85% vs 87%, P =.52). Similarly, there was no significant difference with regard to DSS (93% for both groups, P =.77). As expected, 5-year OS was shorter in older patients (76% vs 88%, P <.001). On multivariate analysis for RFS and DSS, high tumor grade and the presence of lymphovascular space invasion (LVSI) were the only 2 predictors of shorter RFS and DSS (P =.01, P =.02) and (P =.01, P =.01), respectively. In addition to older age (P <.001), high tumor grade and the presence of LVSI were the only predictors of shorter OS (P =.03 and P =.02, respectively).Conclusions: Although older age is viewed as an adverse prognostic factor in women with early-stage EC, our study suggests that when older patients are matched with younger patients based on tumor stage, grade, and adjuvant management, the prognostic effect of old age disappear. High tumor grade and the presence of lymphovascular invasion remained as independent predictors of survival endpoints in women with early-stage EC.

Obstetrics, Gynecology and Women's Health Services
Hijaz M, Das S, Mert I, **Chhina J**, **Tebbe C**, **Dar S**, Seal S, **Munkarah AR**, and **Rattan R**. Targeting ovarian cancer by folic acid conjugated nanoceria *Gynecol Oncol* 2016; 141:184-185. PMID: Not assigned. Abstract

M. Hijaz, Henry Ford Health System, Detroit, United States

Objectives: Nanoceria (NCe) have recently emerged in biochemical science because of their excellent antioxidant and free radical scavenger properties. Previously we demonstrated that NCe halted ovarian tumor growth in vivo. Folate receptor-α is shown to be overexpressed in ovarian malignancies. To enable NCe to specifically target ovarian cancer cells, we conjugated nanoceria to folic acid (NCe-FA). Our aim was to investigate the preclinical efficacy of NCe-FA alone and in combination with cisplatin.Methods: Ovarian cancer cell lines A2780 and C200 were treated with NCe or FA-NCe. Cell viability was assessed using MTT and colony-forming units (CFU). In vivo studies were carried out in A2780-generated mouse xenografts treated with 0.1 mg/kg NCe, 0.1 mg/kg NCe-FA, and 4 mg/kg cisplatin in biweekly intraperitoneal injections. Tumor weights and burden scores were determined. H&E, immunohistochemistry, and toxicity assays were used to evaluate treatment effects.Results: NCe-FA inhibited in vitro cell proliferation as shown by MTT (P <.01) and CFU (P <.001). Mice treated with FA-NCe had significantly less excised tumors and lower tumor burden score compared with controls and NCe (P <.05 to.001). NCe-FA also augmented the tumoricidal and apoptotic effect of cisplatin in vivo, and cells treated with cisplatin and NCe-FA exhibited the highest degree of oxidative stress. Immunohistochemistry revealed less tumor proliferation (Ki-67) and angiogenesis (CD31) in the NCe-FA-containing treatment arms. Liver and kidney function tests from treated mice showed no treatment toxicities.Conclusions: FA-NCe treatment resulted in efficient inhibition of ovarian tumor growth both in vitro and in vivo and potentiated cisplatin's cytotoxic effect. Thus, NCe-FA should be further evaluated as potential therapeutic agents in ovarian cancer.

Obstetrics, Gynecology and Women's Health Services

Hinshaw HD, Boggess JF, Kowalski LD, Scalici JM, Cantrell LA, Schuler KM, **Hanna RK**, Ivanova A, Matei D, and Rossi EC. The relationship between endometrial cancer sentinel lymph node micro and macro metastases and uterine pathology features *Gynecol Oncol* 2016; 141:30. PMID: Not assigned. Abstract

H.D. Hinshaw, Indiana University School of Medicine, Indianapolis, United States

Objectives: The practice of selective lymphadenectomy based on uterine pathology risk factors has been popularized after risk factors for lymph node metastases were identified in large observational single institution and cooperative group studies. SLN biopsy is an alternative staging technique proposed to overcome the limitations of selective algorithms. The clinical validity of low-volume metastases identified in SLN specimens that have been ultrastaged has been questioned. The objective of this analysis is to identify whether patients with positive SLNs demonstrate the previously identified risk factors for lymph node metastases.Methods: The FIRES trial is a multi-institution, prospective cohort study measuring the accuracy of SLN mapping in clinical stage I endometrial cancer (all histologies) in identifying metastatic disease. All patients received a standardized SLN mapping technique with cervical indocyanine green injection and robotic fluorescence imaging, followed by hysterectomy with pelvic and para-aortic lymphadenectomy. All H&E-negative SLN specimens were ultrastaged with immunohistochemistry (IHC) to cytokeratin. Pathologic results of the SLNs (including volume of disease: macro metastases versus micro metastases [< 2 mm and isolated tumor cells]) were evaluated along with uterine tumor risk factors. Fisher exact test was used to compare dichotomous variables between groups.Results: Among 308 patients, 37 (12%) had nodal metastases, 30 of whom mapped at least 1 SLN (81%). Twelve patients (32%) with nodal metastases were detected only with IHC (≤ 2 mm). Compared with patients with macro metastases, micro metastases were less likely to be associated with high grade or nonendometrioid histology (P =.02), para-aortic metastases (P =.05), and lymphovascular space invasion (P =.001). All but 1 node-positive patient (97%) (including all patients with SLN micro metastases) demonstrated at least 1 previously described uterine pathology risk factor for lymphatic spread (grade 3 histology, outer half myometrial invasion or tumor size > 2 cm).Conclusions: Micro metastases within SLNs appear to be associated with known uterine risk factors for nodal metastases. This supports the validity of metastatic disease identified in SLNs with ultrastaging techniques. The disease-specific outcomes of patients with low-volume disease have not yet been established.

Obstetrics, Gynecology and Women's Health Services

Isrow D, **Burmeister C**, **Munkarah AR**, and **Elshaikh MA**. Survival endpoints for young women with early-stage uterine endometrioid carcinoma: A matched analysis *Gynecol Oncol* 2016; 141:62. PMID: Not assigned. Abstract

D. Isrow, Henry Ford Hospital, Detroit, United States

Objectives: Younger age is viewed as a favorable prognostic factor in women with early-stage endometrial carcinoma (EC) but the available data are controversial. Survival endpoints were compared between 2 groups of patients with early-stage EC solely of endometrioid histology: women 45 years or younger and similarly matched older women.Methods: We identified 1,254 patients with 2009 FIGO stage I-II EC who underwent hysterectomy at our institution between January 1990 and December 2014. We created 2 matched groups based on FIGO stage, tumor grade, lymph node dissection status and the type of adjuvant management (observation, pelvic external beam, or vaginal brachytherapy). Recurrence-free (RFS), disease-specific (DSS), and overall survival (OS) were calculated for the 2 groups.Results: A total of 516 patients (86 younger patients and 430 older patients, matched 1:5) were included in this study. Median follow-up was 42.8 months for the entire study cohort (35.2 months for younger and 49.0 for older patients). The 2 groups were well balanced except for the obvious greater age in the older group (P <.0001) and a higher percentage of myometrial invasion in older patients (P =.003). There were no significant differences between younger and older groups with regard to 5-year RFS (94% younger vs 91% older, P =.69). Similarly, there was no significant difference with regard to DSS (96% younger vs 97% older, P =.90). There was no significant difference between younger and older patients in terms of 5-year OS (89% for both groups, P =.99), but 10-year OS was 83% for younger women compared with 68% for older patients, (P =.1). On multivariate analysis for DSS for the entire study cohort, high tumor grade and the presence of lower uterine segment involvement were the only 2 predictors of shorter DSS (P =.01). On multivariate analysis for RFS, higher stage and the presence of lymphovascular space invasion were the only 2 predictors of shorter RFS (P <.0001 and P =.01, respectively). Older age and higher stage were the only 2 predictors of shorter OS (P <.0001 and P =.01, respectively).Conclusions: When matched based on tumor stage, grade, and adjuvant management, our study suggests that there is no difference between younger and older patients with early-stage EC. High tumor grade, stage, and the presence of lymphovascular invasion remained as independent predictors of survival endpoints in women with early-stage EC.

Obstetrics, Gynecology and Women's Health Services

Jaber S, **Hensley Alford S**, **Munkarah AR**, and **Rasool N**. Ovarian cancer in elderly women ≥ 70 years of age: Our clinical experience *Gynecol Oncol* 2016; 141:60-61. PMID: Not assigned. Abstract

S. Jaber, Henry Ford Hospital, Detroit, United States

Objectives: We sought to review and present our clinical experience in the management of elderly women 70 years of age or older with ovarian cancer.Methods: Single institution retrospective chart review of all ovarian, fallopian tube and peritoneal cancer diagnosed in women ages 70 years or older between January 1993 and December 2012 was performed. Patient demographics, tumor characteristics, treatment history, and postoperative complications were abstracted. Survival was calculated using the log-rank test.Results: A total of 88 patients of age 70 years or older at diagnosis were identified during the study period. The mean age at the time of diagnosis was 76 years (range 70-90 years). Stage was distributed as follows: 9 stage I, 6 stage II, 54 stage III (47 stage IIIC), and 17 stage IV. Two patients were not staged or incompletely staged. Seventy-four percent were found to have serous histology, 9% had at least 3 comorbidities, and 3.4% had 4 or more comorbidities. Of the patients, 4.5% had a synchronous malignancy (1 patient had a grade 3 comorbid malignancy according to the adult comorbidity evaluation-27). Twenty-two patients (25%) received neoadjuvant chemotherapy whereas 59 patients (67%) underwent primary debulking surgery. Among the patients that underwent primary debulking or interval debulking, optimal cytoreduction was achieved in 52 patients (61.18%), suboptimal cytoreduction in 29 (34.12%), and "peek and shriek" in 2 (2.35%). Among all patients who underwent surgery during their treatment, only 22 patients (26.5%) went on to receive adjuvant chemotherapy. The major reason to not proceed with chemotherapy was poor performance status. Eighty patients (91%) had an estimated blood loss of less than 1 L. Postoperative complications included fever (4.65%), anemia requiring blood transfusion (56.98%), postoperative ileus (11.63%), malnutrition requiring initiation of total parenteral nutrition (1.16%), and urinary tract complications (3.49%). The mean length of hospital stay was 6 days (range, 0-18 days). Four perioperative deaths were recorded. Mean overall survival in this cohort was 49 months (3-216 mo) and progression-free survival was 32 months (7-216 mo).Conclusions: Surgery appears to be well tolerated in the elderly who have less than 3 comorbidities and may be comparative to the younger population; however, they are less likely to undergo adjuvant chemotherapy after surgical resection because of low performance status.

Obstetrics, Gynecology and Women's Health Services

Mert I, **Munkarah AR**, **Hanna RK**, **Chhina J**, Carey MS, Llaurado M, and **Rattan R**. Is it time to repurpose metformin for the treatment of low-grade ovarian cancer? *Gynecol Oncol* 2016; 141:55-56. PMID: Not assigned. Abstract

I. Mert, Wayne State University, Detroit, United States

Objectives: Low-grade ovarian cancer (LGOC) constitutes 10% of ovarian cancers and is refractory to chemotherapy. We and others have shown metformin to cause significant growth inhibition in high-grade ovarian cancer (HGOC) both in vitro and in vivo. In the current study, we aimed to analyze if metformin is equally effective in inhibiting proliferation of LGOC cell lines alone and in combination with MEK inhibitors.Methods: LGOC lines; VOA1056, VOA1213 and VOA5646, and HGOS cell line CaOV3 were used for the experiments. Cells were treated with metformin (0-40 mM), tramatenib (0.1-10 μM) and combination of both. Proliferation was assayed with MTT assay. Western blotting was performed to estimate the activation of AMPK pathway.Results: LGOC lines showed significant inhibition with the metformin in a dose-dependent manner. Metformin at 20 mM inhibited proliferation after 72-hour treatment by 56.5% in VOA1056 (P =.0007), by 36.2% in VOA1213 (P =.0004), and by 44.4% in VOA5646 (P =.0001), similar to high-grade cell line CaOV3 (P =.001). IC50 for VOA1056, VOA5646, and VOA1213 were 12.6, 24.1, and 45.4 mM, respectively. Long-term treatment on days 1,3, and 5 with lower dose of metformin (2.5 mM) was more effective than 72-hour treatment in inhibiting the growth of VOA1056 (P =.005) and VOA5646 (P =.001). (See Fig. 1.) Metformin treatment in LGOC cells activated AMPK and phosphorylated its immediate downstream target ACC. In addition, metformin treatment enhanced the cytotoxic effect of tramatenib synergistically at 0.1 μM (VOA1056, P =.09; VOA5646, P <.000.1) with a combination index of 0.3 for both cell lines. (See Fig. 2.)Conclusions: Metformin alone or in combination with MEK inhibitors may be a potential therapy for LGOC, a cancer that is indolent but chemoresistant. Further work is being conducted to confirm these results in animal models. Metformin dose response curve. (figure present).

Obstetrics, Gynecology and Women's Health Services

Modh A, **Ghanem AI**, **Burmeister C**, **Rasool N**, and **Elshaikh MA**. Trends in the utilization of adjuvant vaginal brachytherapy in women with early-stage endometrial carcinoma: Results of an updated period analysis of SEER data *Brachytherapy* 2016;PMID: 27475480. Full Text

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PURPOSE: Adjuvant vaginal brachytherapy (VB) is a well-established and effective radiation treatment modality in women with early-stage endometrial carcinoma. We sought to evaluate and update published trends in the utilization of VB vs. other radiation therapy modalities (pelvic external beam radiation therapy (EBRT) or the combination of VB and pelvic EBRT using the National Cancer Institute's Surveillance, Epidemiology, and End Results database. METHODS AND MATERIALS: The Surveillance, Epidemiology, and End Results database was queried for adult females with histologically confirmed International Federation of Gynecology and Obstetrics 1988 Stage I-II endometrial carcinoma diagnosed from 1995 to 2012 and treated definitively with hysterectomy and adjuvant radiation therapy. Chi-square tests were used to assess differences by radiation type (VB, EBRT, and VB + EBRT) and various demographic and clinical variables. RESULTS: We identified 15,201 patients that met inclusion criteria. There was a significant overall increase in the use of VB was observed from 17.1% in 1995-2000 compared to 57.1% in 2007-2012 ($p < 0.0001$). Similarly, there was a proportional decrease in the use of EBRT from 54.0% to 25.5% ($p < 0.0001$) as well as in the use of VB + EBRT from 28.9% to 17.4% during the same period ($p < 0.0001$). The observed increase in utilization of VB was not limited to any variables (age, race, histological type, International Federation of Gynecology and Obstetrics stage, and the status of lymph node dissection [yes or no]) or the number of dissected lymph nodes. CONCLUSIONS: In this large national database set, there continues to be an increasing trend for the use of VB in the adjuvant setting in women with early-stage endometrial carcinoma.

Obstetrics, Gynecology and Women's Health Services
Modh A, **Ghanem AI**, **Burmeister C**, **Rasool N**, and **Elshaikh MA**. Trends in the utilization of adjuvant radiation treatment in women with early stage type ii endometrial carcinoma: A surveillance, epidemiology, and end-results study *Brachytherapy* 2016; 15:S89. PMID: Not assigned. Abstract

A. Modh, Radiation Oncology, Henry Ford Health System, Detroit, United States

Purpose: Type II endometrial carcinoma (EC) represents a group of aggressive histologies with a relatively poor prognosis. While an increasing trend for utilizing adjuvant vaginal brachytherapy has been reported in women with early stage type I EC, trends in radiation treatment in patients with type II EC have not been fully investigated. We sought to evaluate the trends in adjuvant radiation modalities (pelvic external beam RT [EBRT] versus vaginal brachytherapy [VB] versus the combination of EBRT+VB) in women with early stage type II endometrial carcinoma using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Materials and Methods: The SEER database was queried for adult females with histologically confirmed FIGO (1988) stage I-II endometrial carcinoma type II (serous, clear cell and mixed carcinoma) diagnosed from 1995-2012 and treated definitively with hysterectomy and adjuvant radiation therapy. Patients with multiple primary malignancies, those who received radiation treatment prior to surgery or those who did not have any adjuvant treatment were excluded. Patients were grouped in 5-year intervals, from 1995-2000, 2001-2006, and 2007-2012. Chi-squared tests were used to assess differences in utilization of radiation modality and various demographic and clinical variables. Results: We identified 1,249 patients that met our inclusion criteria. In the entire cohort, 42.5% received EBRT, 36.3% received VB, and 21.1% received VB+EBRT. A lymph node dissection was performed in 79.7% of patients. When a lymph node dissection was performed, the median number of lymph nodes examined in our study increased from 12.0 in 1995-2000 to 17.0 in 2007-2012 ($p <0.0001$). There was an overall increase in the use of VB observed from 15.0% in 1995-2000 to 55.9% in 2007-2012 ($p <0.0001$). This increase in VB utilization was seen in both older (>60) and younger (<60) patients and irrespective of whether a lymph node dissection was performed or not. In parallel, the use of EBRT fell from 56.5% in 1995-2000 to 28.2% in 2007-2012 ($p <0.0001$). The use of VB+ERBT combined also decreased over the same time period, from 28.5% in 1995-2000 to 15.9% in 2007-2012 ($p<0.0001$). Conclusions: Similar to the trends seen in adjuvant radiation treatment in women with type I early stage endometrial carcinoma, there is an increasing trend for the use of adjuvant VB and a declining use of pelvic EBRT in women with type II endometrial carcinoma.

Obstetrics, Gynecology and Women's Health Services
Munkarah AR, **Kim S**, **Buekers TE**, **Chhina J**, **Poisson L**, **Giri S**, and **Rattan R**. Metabolic effects of metformin treatment in ovarian cancer cell lines *Gynecol Oncol* 2016; 141:168. PMID: Not assigned. Abstract

A.R. Munkarah, Henry Ford Health System, Detroit, United States

Objectives: Metformin is being actively repurposed for the treatment of gynecologic malignancies. It is known to alter the cancer cell metabolism, primarily inhibit oxidative phosphorylation, and induce glycolysis. Our aim was to

investigate the metabolite changes occurring in response to metformin treatment in ovarian cancer (OvCa) cell lines.Methods: A2780, C200, SKOV3ip cell lines were treated with metformin (10 mM) for 48 hours and subjected to untargeted global metabolites by ultra-high performance liquid chromatography and gas chromatography mass spectroscopy. Per-metabolite comparisons were made. Interpretive analysis was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and the Ingenuity molecule library.Results: Metformin treatment caused alterations in metabolites in all treated lines: A2780 showed 132 alterations (72 up; 60 down), C200 showed 135 (77 up; 58 down), and SKOV3ip showed 135 (84 up; 51 down); (FDR ≤ 0.1). The 3 cell lines revealed 57 common altered metabolites, of which 30 had consistent direction change. KEGG analysis of these 30 metabolites showed that the amino acid metabolism (alanine, aspartate, glutamate and glycine, serine, threonine metabolism; adjusted P <.0001) was the most significantly affected. Interestingly, metformin affected the energy pathways of glycolysis and oxidative phosphorylation differentially across the 3 cell lines. Cellular proliferation and signaling was the top common network pathway on Ingenuity analysis.Conclusions: Metformin treatment had a significant and widespread effect on metabolism of OvCa cell lines. Although metformin resulted in certain consistent metabolic changes in amino acid metabolism across cell lines, its modulation of glycolysis and oxidative phosphorylation was varied. These differential metabolic changes could indicate the degree of metformin response and suggest it to be context-dependent. Such information about the cancer metabolism may aid in preclinical and clinical assessment of metformin therapy in ovarian and other cancers.

Obstetrics, Gynecology and Women's Health Services

Rattan R, Mert I, **Chhina J**, **Hamid S**, **Hijaz M**, **Poisson L**, **Hensley Alford S**, **Giri S**, and **Munkarah AR**. Targeting of free fatty acid receptor 1 in EOC: A novel strategy to restrict the adipocyte-EOC dependence *Gynecol Oncol* 2016; 141:47. PMID: Not assigned. Abstract

R. Rattan, Henry Ford Health System, Detroit, United States

Objectives: Adipocyte-derived free fatty acids (FFAs) promote epithelial ovarian cancer (EOC) by acting as a fuel source to support the energy requirement of the cancer cells. FFAs may also exert biological effects through signaling pathways. Recently, a family of FFA-activated G-protein-coupled receptors (FFAR/GPCRs) was identified. Our objective was to investigate the role of FFAR/GPCRs in EOC and assess their potential as therapeutic targets.Methods: The mRNA (RT-PCR) expression of FFAR/GPCR family members (FFAR1/GPR40; FFAR2/GPR42, FFAR3/GPR41, FFAR4/GPR120 and GPR84) was examined in: (1) a syngeneic mouse model of EOC fed high-energy diet (60% fat) or regular diet (30% fat), (2) EOC cell lines exposed to FFAs and (3) specimens from 13 histologically normal ovaries and 28 high-grade ovarian serous carcinomas. The GPR 40 antagonist, GW1100, was used to inhibit FFAR1/GPR40 and cell survival was assayed using MTT in various cell lines.Results: High-grade serous carcinoma specimens expressed significantly increased GPR40 compared with normal ovaries (P =.0020). Higher expression was observed to be stage specific and noted to be significant in advanced-stage disease (X2 P =.04). ID8 ovarian tumors from mice fed with high fat diet showed higher GPR40 expression. Exposing EOC cells to FFAs increased GPR40 expression. Treatment of EOC cell lines with GW100 resulted in growth inhibition and was associated with an alteration in their energy metabolismConclusions: FFA-induced cancer cell growth may be partly mediated through FFAR1/GPR40. Targeting of FFAR1/GPR40 may be an attractive treatment strategy in EOC, and possibly offers a targeted treatment for a subset of EOC patients.

Obstetrics, Gynecology and Women's Health Services

Sakr S, Abdulfatah E, **Munkarah AR**, Morris RT, **Elshaikh MA**, Pardeshi V, and Ali-Fehmi R. Prognostic value of loss of MMR protein expression in endometrial carcinoma in African American and White women *Gynecol Oncol* 2016; 141:112. PMID: Not assigned. Abstract

S. Sakr, Wayne State University School of Medicine, Detroit, United States

Objectives: The effect of MMR loss on the prognosis of endometrial cancer (EC) is controversial. Correlations between MMR-related protein expression and clinicopathologic factors of EC in African American (AA) versus white women were analyzed.Methods: A retrospective review of EC (n = 578) between 1995 and 2013 was conducted to analyze clinicopathologic parameters (Table 1). Immunohistochemical evaluation of MMR protein expression (MLH1, PMS2, MSH2, and MSH6) was performed on tumor tissue microarray. Absence of nuclear staining of any of the 4 proteins in tumor cells with positive lymphocytes (internal control) was considered as MMR loss. Data were analyzed using the Fisher's exact test and Kaplan-Meier survival analysis.Results: MMR loss was identified in 116/578 patients (20%) with the highest frequency of loss in both MLH1 and PMS2 (47%), PMS2 (30%), MSH6 (14%), and both MSH2 and MSH6 (9%). White women with MMR loss had significantly higher-grade cancer and shorter disease-free interval (187 vs 594 months). AA women with MMR loss had endometrioid histology (P =.001), higher grade (P =.042), tumor size of 2 cm or greater (P =.019), and tendency toward myometrial invasion compared with AA women with intact

MMR. Disease-free interval was similar for AA and white women with MMR loss (190 vs 187 months).Conclusions: Although EC is reported to have worse prognosis in AA than white women, our study showed no difference between AA women and white women who had MMR loss. (table present).

Obstetrics, Gynecology and Women's Health Services
Sakr S, **Giri S**, **Rattan R**, Abdulfatah E, Pardeshi V, Morris RT, **Munkarah AR**, and Ali-Fehmi R. Expression of alcohol dehydrogenase 5 in ovarian carcinoma: Effect on prognosis and therapeutic potential *Gynecol Oncol* 2016; 141:67. PMID: Abstract

S. Sakr, Wayne State University School of Medicine, Detroit, United States

Objectives: S-nitrosoglutathione (GSNO), a physiologic nitrosylating agent, significantly inhibits ovarian cancer (OC) growth by promoting nitrosylation of various genes and inhibiting inflammation. GSNO is catabolized by alcohol dehydrogenase 5 (ALDH5) leading to reduction in the process of nitrosylation. Our aim was to evaluate ALDH5 expression in type I and type II OC tumor tissue microarray (TMA) and its relation with the expression of inflammatory markers and survival and to explore the role of ALDH5 inhibition in treating OC.Methods: Immunohistochemical (IHC) staining for ALDH5 protein expression was performed on TMA for 360 cases with OC (292 serous, 12 endometrioid, 43 mucinous, and 13 clear cell carcinoma). IHC for COX-2, iNOS, eNOS, and NFkB was performed on a subset of cases (n = 120). Each marker was scored by combining staining intensity and percentage of stained cells to establish H-score. Data were analyzed with the Fisher exact test and Kaplan-Meier survival analysis. Expression of ALDH5 in various OC cell lines was determined using quantitative polymerase chain reaction. OC cell lines were treated with ALDH5 inhibitor (N6022) in the presence or absence of GSNO and cell survival was assayed by MTT. We also investigated the effect of GSNO in an immunocompetent isogenic mouse model of OC which expressed lower level of ALDH5.Results: High ALDH5 expression was significantly associated with type II OC (high-grade serous and endometrioid carcinoma) versus type I (borderline serous, low-grade serous, low-grade endometrioid, mucinous, and clear cell carcinoma) (P =.003). High ALDH5 expression was significantly associated with increased COX-2 (P =.001) and NFkB expression (P =.001). The overall survival (OS) was shorter in patients with high ALDH5 expression (median OS: 32 vs 49 mo) without a significant statistical difference. Expression of ALDH5 in OC cell lines showed inverse correlation with cytotoxic effect of GSNO. Moreover, inhibition of ALDH5 potentiated cytotoxicity of suboptimal doses of GSNO in OC cell lines (P <.05). In a preclinical mouse model, oral administration of GSNO at 1 mg/kg significantly attenuated tumor growth and ascites accumulation (P <.01).Conclusions: High ALDH5 expression was significantly associated with type II OC and inflammatory mediators. Inhibition of ALDH5 could be a potential therapeutic target in OC.

Obstetrics, Gynecology and Women's Health Services
Taylor M, Mert I, **Hijaz M**, **Chhina J**, Morris RT, **Giri S**, **Rattan R**, and **Munkarah AR**. Effects of an olaparib and metformin combination on the AMPK and DNA-damage pathways in ovarian cancer *Gynecol Oncol* 2016; 141:197-198. PMID: Not assigned. Abstract

M. Taylor, Karmanos Cancer Center, Wayne State University, Detroit, United States

Objectives: We previously reported that the combination of olaparib and metformin significantly inhibits the growth of ovarian cancer cell lines carrying the BRCA1 wild-type allele in vitro and in vivo. Our aim in this study was to identify the mechanism behind the combination's synergistic inhibition of cell growth. We investigated the effect of the 2 drugs on the AMPK and DNA-damage pathways.Methods: The effect of olaparib and metformin on PARP activation was assayed using a fluorometric activity kit. Two ovarian cancer cell lines, A2780 and SKOV3, were used to determine the effect of the drugs on phospho(p)-AMPK, pACC, and pH2AX with Western blot analysis. Immunohistochemical (IHC) staining of tumor tissues from A2780 and SKOV3 xenografts in nude mice was performed for pACC, H2AX, and SIRT1. ATP and NAD +/NADH levels were estimated with their respective activity kits.Results: The combination of olaparib and metformin significantly inhibited the growth of BRCA1 wild-type ovarian cancer cells in vitro (P <.01) and in vivo (P <.01). Treatment with olaparib induced activation of AMPK pathway in a dose-dependent manner as evidenced by increased pACC, a 33% increase in ATP levels, and a 41% increase in the NAD +/NADH ratio. Olaparib enhanced metformin-induced activation of AMPK in both cell lines, as reflected on the Western blot. This activation of AMPK was also confirmed in xenografts from mice treated with the drug combination. An increase in SIRT1 mRNA expression further supported activation of AMPK in response to olaparib treatment. Olaparib showed a dose-dependent ability to inhibit PARP activity, whereas metformin had no effect. Furthermore, increased pH2AX was detected with Western blot in response to olaparib but not metformin in both cell lines. Paradoxically, IHC revealed decreased pH2AX staining in mice treated with the combination compared with olaparib alone.Conclusions: The combination of olaparib and metformin acted synergistically to activate the AMPK pathway. Metformin did not have

any effect on PARP activity. Differences in pH2AX staining between treatments in the animal model raise the question of whether metformin may alter olaparib-induced DNA damage. This is a subject of ongoing investigation.

Obstetrics, Gynecology and Women's Health Services

Tran AM, Yang W, Boggess JF, Kowalski LD, Scalici JM, Cantrell LA, Schuler KM, Ivanova A, **Hanna RK**, and Rossi EC. Bilateral SLN mapping for cervical cancer with ICG and robotic fluorescence imaging is associated with greater accuracy in detecting metastatic disease *Gynecol Oncol* 2016; 141:21. PMID: Not assigned. Abstract

A.M. Tran, University of North Carolina at Chapel Hill, Chapel Hill, United States

Objectives: Sentinel lymph node (SLN) mapping with indocyanine green (ICG) and near-infrared fluorescence imaging (NIRFI) has been described for cervical cancers. However, only small published series have evaluated the accuracy of this technique in this disease. The FIRES trial is a multicenter prospective cohort study including women undergoing hysterectomy and lymphadenectomy for endometrial and cervical cancer. Our objective was to evaluate the accuracy of this SLN mapping technique in detecting occult metastatic disease in cervical cancer among patients undergoing a standardized technique by surgeons at multiple centers.Methods: Patients with stage IA2 to 1B1 cervical cancer (all histologies) were enrolled in the study between February 2012 and July 2015. Patients received 1 mg of ICG intracervical injection and underwent SLN mapping using robotic NIRFI as well as completion pelvic lymphadenectomies. Negative SLN specimens underwent ultrastaging with immunohistochemistry to cytokeratin. Detection rate, sensitivity, and false-negative predictive value were calculated. Fisher exact test was used to compare dichotomous variables between node-positive and -negative groups. The study is registered with clinicaltrials.gov.Results: A total of 67 patients were enrolled at 10 centers by 17 surgeons. Of these, 14 patients (21%) had pelvic nodal metastases. In 60 patients, at least 1 SLN was detected (90%). The rate of bilateral mapping was 61%. Of the 11 patients with metastases who underwent mapping, 7 had positive SLNs (sensitivity 64%), with 4 patients having a false-negative SLN (7.5%), and a negative predictive value (NPV) of 92.5%. Of the 4 patients with false-negative SLNs, 3 mapped unilaterally with the positive non-SLN found on the unmapped side. One patient had an empty unilateral SLN specimen on final pathology (false-positive mapping). Patients who had failed bilateral mapping were significantly more likely to have positive lymph nodes (P =.01). Patients with true bilateral mapping had 100% sensitivity and NPV for detecting metastatic disease.Conclusions: Bilateral SLN mapping achieved with ICG and robotic NIRFI is associated with high accuracy in detecting metastatic cervical cancer. In the case of unilateral mapping or failed mapping, a side-specific complete lymphadenectomy should be performed.

Obstetrics, Gynecology and Women's Health Services

Xu Y, **Hanna RK**, **Burmeister C**, **Munkarah AR**, and **Elshaikh MA**. Predictors of survival after recurrence in women with early-stage endometrial carcinoma *Gynecol Oncol* 2016; 141:70. PMID: Not assigned. Abstract

Y. Xu, Henry Ford Hospital, Detroit, United States

Objectives: Factors predictive of survival after recurrent early-stage endometrial cancer have not been thoroughly investigated. The purpose of this study was to explore the impact of different prognostic factors including type of salvage management on disease-specific survival (DSS) and overall survival (OS) after recurrence.Methods: Following institutional review board approval, we identified 104 women with 2009 FIGO stage I-II uterine endometrioid carcinoma who developed disease recurrence between January 1990 and December 2014. Patients who received adjuvant chemotherapy after primary surgery were excluded from this analysis. The Kaplan-Meier approach and Cox regression analysis were used to assess DSS and OS after recurrence and to determine factors influencing survival endpoints.Results: Median age of the study cohort was 65 years with a median follow-up time of 42.8 months after hysterectomy. Sixty patients (57.7%) had stage IA, 30 (28.9%) had stage IB, and 14 (13.5) had stage II disease. Median time to recurrence was 15.8 months. Fifty-six patients (54%) had pelvic-only recurrence (vaginal and/or pelvic), whereas 48 (46%) had extrapelvic recurrences. Patients with low-grade tumors and pelvic-only recurrences were associated with longer DSS and OS compared with patients with grade 3 tumor and/or extrapelvic recurrences (P =.05). Five-year DSS calculated from the date of recurrence for the entire cohort was 44%. The 5-year DSS was longer for patients with pelvic-only recurrence compared with patients with extrapelvic recurrences (66% vs 18%, P <.0001). The 5-year DSS was longer for radiation-naïve patients than for patients who received prior adjuvant radiation therapy (51% vs 34%, P =.023). Neither time to recurrence nor type of salvage treatment was a significant predictor for DSS or OS. On multivariate analysis of DSS and OS, pelvic-only recurrence (P <.001) was the only significant predictor of longer DSS and OS.Conclusions: In women with recurrent early-stage endometrial carcinoma, our study suggests that the site of recurrence (pelvic vs extrapelvic) is the only predictor of survival. In addition, we found that radiation naiveté correlated with longer DSS, while low-grade tumors and pelvic-only recurrence were associated with a significantly improved DSS and OS. Longer time to recurrence and type of salvage treatment were not significant predictors of DSS and OS.

Orthopaedics
Li W, Molnar SL, **Mott M**, White E, and De Las Casas LE. Superficial CD34-positive fibroblastic tumor: Cytologic features, tissue correlation, ancillary studies, and differential diagnosis of a recently described soft tissue neoplasm *Diagn Cytopathol* 2016;PMID: 27432164. Full Text

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Superficial CD34-positive fibroblastic tumor is a low-grade mesenchymal neoplasm of superficial soft tissues characterized by fascicles of spindle to epithelioid cells displaying nuclear pleomorphism and strong diffuse CD34 immunoreactivity. The intraoperative imprint cytology preparations (ICP) of a superficial CD34-positive fibroblastic tumor from a 50-year-old female are described. To the best of our knowledge, there is no report of the cytologic findings of superficial CD34-positive fibroblastic tumor in the English medical literature. The ICP, differential diagnosis, tissue correlation, and ancillary studies of this fascinating entity are discussed.

Orthopaedics
Okoroha KR, **Lynch JR**, **Keller RA**, **Korona J**, **Amato C**, **Rill B**, **Kolowich PA**, and **Muh SJ**. Liposomal bupivacaine versus interscalene nerve block for pain control after shoulder arthroplasty: a prospective randomized trial *J Shoulder Elbow Surg* 2016;PMID: 27422692. Full Text

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HYPOTHESIS: Our hypothesis was that in patients undergoing shoulder arthroplasty, a prospective randomized trial would find no significant differences in average daily pain scores of those treated with interscalene nerve block (INB) vs. local liposomal bupivacaine (LB). METHODS: Sixty patients undergoing primary shoulder arthroplasty were assessed for eligibility. Study arms included either intraoperative local infiltration of LB (20 mL bupivacaine/20 mL saline) or preoperative INB, with a primary outcome of postoperative average daily visual analog scale scores for 4 days. Secondary outcomes assessed included opioid consumption, length of stay, and complications. Randomization was by a computerized algorithm. Only the observer was blinded to the intervention. RESULTS: Three patients were excluded, all before randomization. A total of 57 patients were analyzed. Outcomes showed a significant increase in pain in the LB group between 0 and 8 hours postoperatively (mean [standard deviation] 5.3 [2.2] vs. 2.5 [3.0]; P = .001). A significant increase in intravenous morphine equivalents was found in the INB group at 13 to 16 hours (mean [standard deviation] 1.2 [0.9] vs. 0.6 [0.7]; P = .01). No significant differences were found in any variable after postoperative day 0 between the 2 groups. CONCLUSION: An increase in early postoperative pain on the day of surgery was found with LB, whereas the INB group required more narcotics at the end of the day. After the day of surgery, there were no significant differences found in any variables. These findings suggest that LB provides similar overall pain relief as INB, with no increase in complications or length of stay and a decrease in narcotic requirements on the day of surgery.

Orthopaedics
Wessell NM, Martus JE, Halanski MA, Snyder B, and Truong W. What's new in pediatric spine growth modulation and implant technology for early-onset scoliosis? *J Pediatr Orthop* 2016;PMID: 27403917. Full Text

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BACKGROUND: Early-onset scoliosis (EOS) affects roughly 1 to 2 out of 10,000 live births per year. Because this subset of patients has a yet to achieve a majority of their skeletal growth, a number of treatment challenges need to be addressed before surgical intervention. If left untreated, EOS can cause a number of problems throughout the patient's lifespan, particularly in regards to the growth of the thorax and pulmonary development. A wide variety of surgical systems and techniques are available to the treating surgeon. METHODS: A review of the orthopaedic literature from 2010 to 2015 relating to pediatric spine growth modulation was performed. Ninety-eight papers were identified and, following exclusion criteria, a total of 31 papers were selected for further review. RESULTS: This paper summarizes the recently published literature regarding growth-friendly spinal implants, the status of their Food and Drug Administration approval labeling as well as the indications, applications, and complications associated with their

implementation. CONCLUSIONS: There are a growing number of options at the surgeon's disposal when treating patients with EOS. As surgeons, we must continue to be vigilant in our demand for sound clinical evidence as we strive to provide optimal care for our patients. The rapidly advancing field of spinal growth modulation is exciting. More work must be done to further enhance our ability to predictably modulate growth in the pediatric spine.

Pathology

Baldwin BJ, **Chitale D**, **Chen KM**, **Worsham MJ**, and **Yaremchuk K**. Investigation into the presence of human papillomavirus in patients with obstructive sleep apnea *Laryngoscope* 2016;PMID: 27412085. Full Text

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OBJECTIVES/HYPOTHESIS: The human papillomavirus (HPV) is known to infect the tissues of the oropharynx as demonstrated in HPV-positive oropharyngeal squamous cell carcinoma (OPSCC). HPV has also been shown to induce benign lymphoid hypertrophy. We sought to investigate an association between obstructive sleep apnea (OSA) and the presence of HPV in palatine and lingual tonsillar oropharyngeal tissue. STUDY DESIGN: Case series with chart review. METHODS: This retrospective laboratory-based study of oropharyngeal tissue from patients with OSA included patients >18 years old who underwent surgical treatment for OSA at a single institution between January 2012 and May 2014. Surgical specimens of adequate size were analyzed for HPV6, 11, and 16 using real-time quantitative polymerase chain reaction from DNA extracted from formalin-fixed paraffin-embedded tissue blocks. Student t test, Pearson chi2 test, and linear logistic regression were used to assess comparisons of body mass index (BMI), apnea-hypopnea index (AHI), age, and gender between HPV-positive and HPV-negative groups. RESULTS: Of 99 cases included in the study, six were positive for HPV: two with HPV16 and four with HPV6. BMI, AHI, age, and gender showed no significant differences between the HPV-positive and HPV-negative groups. Logistic regression to predict HPV positivity accounting for each variable and multivariate analysis were not statistically significant. CONCLUSIONS: Our study did not show HPV to have a statistically significant association with OSA. None of the covariates analyzed (BMI, AHI, gender, age) predicted HPV positivity in surgically resected oropharyngeal tissue from OSA patients. LEVEL OF EVIDENCE: 4 Laryngoscope, 2016.

Pathology

Jiagge E, Jibril AS, **Chitale D**, **Bensenhaver JM**, Awuah B, Hoenerhoff M, Adjei E, Bekele M, Abebe E, **Nathanson SD**, **Gyan K**, Salem B, Oppong J, Aitpillah F, Kyei I, Bonsu EO, **Proctor E**, Merajver SD, Wicha M, **Stark A**, and **Newman LA**. Comparative analysis of breast cancer phenotypes in african american, white american, and west versus east african patients: Correlation between african ancestry and triple-negative breast cancer *Ann Surg Oncol* 2016;PMID: 27469125. Full Text

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INTRODUCTION: Triple-negative breast cancer (TNBC) is more common among African American (AA) and western sub-Saharan African breast cancer (BC) patients compared with White/Caucasian Americans (WA) and Europeans. Little is known about TNBC in east Africa. METHODS: Invasive BC diagnosed 1998-2014 were evaluated: WA and AA patients from the Henry Ford Health System in Detroit, Michigan; Ghanaian/west Africans from the Komfo Anokye Teaching Hospital in Kumasi, Ghana; and Ethiopian/east Africans from the St. Paul's Hospital Millennium Medical College in Addis Ababa, Ethiopia. Histopathology and immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression was performed in Michigan on formalin-fixed, paraffin-embedded samples from all cases. RESULTS: A total of 234 Ghanaian (mean age 49 years), 94 Ethiopian (mean age 43 years), 272 AA (mean age 60 years), and 321 WA (mean age 62 years; p = 0.001) patients were compared. ER-negative and TNBC were more common among Ghanaian and AA compared with WA and Ethiopian cases

(frequency ER-negativity 71.1 and 37.1 % vs. 19.8 and 28.6 % respectively, p < 0.0001; frequency TNBC 53.2 and 29.8 % vs. 15.5 and 15.0 %, respectively, p < 0.0001). Among patients younger than 50 years, prevalence of TNBC remained highest among Ghanaians (50.8 %) and AA (34.3 %) compared with WA and Ethiopians (approximately 16 % in each; p = 0.0002). CONCLUSIONS: This study confirms an association between TNBC and West African ancestry; TNBC frequency among AA patients is intermediate between WA and Ghanaian/West Africans consistent with genetic admixture following the west Africa-based trans-Atlantic slave trade. TNBC frequency was low among Ethiopians/East Africans; this may reflect less shared ancestry between AA and Ethiopians.

Pathology

Jones LR, **Greene J**, **Chen KM**, **Divine G**, **Chitale D**, **Shah V**, **Datta I**, and **Worsham MJ**. Biological significance of genome-wide DNA methylation profiles in keloids *Laryngoscope* 2016;PMID: 27312686. Full Text

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OBJECTIVES/HYPOTHESIS: To obtain biological insight into keloid pathogenesis and treatment using pathway analysis of genome-wide differentially methylated gene profiles between keloid and normal skin. STUDY DESIGN: Prospective cohort. METHODS: Genome-wide profiling was previously done, with institutional review board approval, on six fresh keloid and six fresh normal skin tissue samples, using the Infinium HumanMethylation450 BeadChip kit. Statistically significant differentially methylated cytosine-phosphodiester bond-guanines (CpGs, n = 197) between keloid and normal tissue mapped to 152 genes. These genes were uploaded into Ingenuity Pathway Analysis (IPA) software to identify biological functions or regulatory networks interacting. The pathways (or "network") with an enrichment probability value </= .01 were subjected to a heuristic filter of keywords associated with keloid pathogenesis. RESULTS: Of the 197 CpGs, 191 were found in the IPA database and mapped to 152 unique genes. The top 10 hypermethylated genes were ACTR3C, LRRC61, PAQR4, C1orf109, SLCO2B1, CMKLR1, AHDC1, FYCO1, CCDC34, and CACNB2. The top 10 hypomethylated genes were GALNT3, SCML4, PPP1R13L, ANKRD11, WIPF1, MX2, IFFO1, DENND1C, CFH, and GHDC. IPA identified nine pathways with enrichment probability values </= .01, of which five (histidine degradation V1, phospholipase C signaling, colorectal cancer metastasis signaling, P2Y purinergic receptor signaling, and Galphai signaling) were associated with keloid keywords and contained "keloid genes" (P < .05). CONCLUSIONS: Genes differentially methylated between keloid and normal skin reside in known bionetwork pathways involved in critical biological functioning and signaling events in the cell. This information could be used to refine screening processes for biological significance to better understand keloid pathogenesis and to develop molecular-targeted therapy. LEVEL OF EVIDENCE: NA Laryngoscope, 2016.

Pathology

Kouba EJ, Eble JN, Simper N, Grignon DJ, Wang M, Zhang S, Wang L, Martignoni G, **Williamson SR**, Brunelli M, Luchini C, Calio A, and Cheng L. High fidelity of driver chromosomal alterations among primary and metastatic renal cell carcinomas: implications for tumor clonal evolution and treatment *Mod Pathol* 2016;PMID: 27469331. Full Text

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Recent studies have demonstrated considerable genomic heterogeneity in both primary and metastatic renal cell carcinoma (RCC). This mutational diversity has serious implications for the development and implementation of targeted molecular therapies. We evaluated 39 cases of primary RCC tumors with their matched metastatic tumors to determine if the hallmark chromosomal anomalies of these tumors are preserved over the course of disease progression. Thirty-nine matched pairs of primary and metastatic RCCs (20 clear cell RCC, 16 papillary RCC, and 3 chromophobe RCC) were analyzed. All clear cell RCC and papillary RCC tumors were evaluated for chromosome 3p deletion, trisomy 7 and 17 using fluorescence in situ hybridization. Chromophobe RCC tumors were evaluated for genetic alterations in chromosomes 1, 2, 6, 10, and 17. Of the 20 clear cell RCC tumors, 18 primary tumors (90%) showed a deletion of chromosome 3p and were disomic for chromosomes 7 and 17. All molecular aberrations were conserved within the matched metastatic tumor. Of the 16 papillary RCC tumors, 10 primary tumors (62%) showed

trisomy for both chromosomes 7 and 17 without 3p deletion. These molecular aberrations and others were conserved in the paired metastatic tumors. Of the three chromophobe RCC tumors, multiple genetic anomalies were identified in chromosomes 1, 2, 6, 10, and 17. These chromosomal aberrations were conserved in the matched metastatic tumors. Our results demonstrated genomic fidelity among the primary and metastatic lesions in RCCs. These findings may have important clinical and diagnostic implications.Modern Pathology advance online publication, 29 July 2016; doi:10.1038/modpathol.2016.133.

Pharmacy

Claeys KC, Zasowski EJ, Casapao AM, Lagnf AM, Nagel JL, Nguyen CT, Hallesy JA, Compton MT, Kaye KS, Levine DP, **Davis SL**, and **Rybak MJ**. Propensity matched analysis of early daptomycin versus vancomycin for methicillin-resistant s. Aureus bloodstream infections: Daptomycin improves outcomes regardless of vancomycin MIC *Antimicrob Agents Chemother* 2016;PMID: 27431221. Full Text

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INTRODUCTION: Vancomycin remains the mainstay treatment for MRSA bloodstream infections (BSIs) despite increased treatment failures. Daptomycin has been shown to improve clinical outcomes in MRSA BSI with vancomycin MICs > 1 mg/L, but these studies relied on automated susceptibility testing. We evaluated outcomes of MRSA BSI with vancomycin MIC determined by standard broth microdilution (BMD). METHODS: Retrospective, matched cohort of MRSA BSI patients treated with vancomycin or daptomycin from January 2010 to March 2015. Patients were matched using propensity-adjusted logistic regression, which included: age, Pitt Bacteremia Score, primary BSI source, and hospital of care. The primary endpoint was clinical failure, which was a composite endpoint of the following metrics: 30-day mortality, bacteremia >/= 7days, or change in MRSA therapy due to persistent/worsening signs/symptoms. Secondary endpoints included MRSA-attributable mortality and days of bacteremia. Independent predictors of failure were determined through conditional backwards-stepwise logistic regression, with vancomycin BMD MIC forced into the model. RESULTS: 262 patients were matched. Clinical failure was significantly higher in the vancomycin cohort (45.0% vs. 29.0%, p = 0.007). All-cause 30-day mortality was significantly higher in the vancomycin cohort (15.3% vs. 6.1%, p = 0.024). These outcomes remained significant when stratified by vancomycin BMD MIC. There was no significant difference in length of bacteremia. Variables independently associated with treatment failure included vancomycin therapy (aOR = 2.16, 95% CI = 1.24 - 3.76), intensive care (aOR = 2.46, 95% CI = 1.34 - 4.54) or primary source infective endocarditis (aOR = 2.33, 95% CI = 1.16 - 4.68) CONCLUSIONS: Treatment of MRSA BSI with daptomycin was associated with reduced clinical failure and 30-day mortality; this finding was independent of vancomycin BMD MIC.

Pharmacy

Wagner JL, **Kenney RM**, Vazquez JA, **Ghanem TA**, and **Davis SL**. Surgical prophylaxis with gram-negative activity for reduction of surgical site infections after microvascular reconstruction for head and neck cancer *Head Neck* 2016;PMID: 27458902. Full Text

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BACKGROUND: The purpose of this study was to determine the incidence of and risk factors for surgical site infections in microvascular reconstruction for patients with head and neck cancer. METHODS: One hundred seventeen patients with head and neck cancer undergoing microvascular reconstruction received postoperative

surgical infection prophylaxis and were followed for 30 days. Surgical infection prophylaxis was categorized by empiric spectrum of activity. Risk factors for surgical site infection development and cumulative incidence of surgical site infections were characterized. RESULTS: Thirty-seven patients developed surgical site infection (cumulative surgical site infection incidence of 31.6%). Risk factors identified in logistic regression include alcohol use (odds ratio [OR] = 2.704; 95% confidence interval [CI] = 1.029-7.106), increased surgical duration (OR = 1.403; 95% CI = 1.185-1.661), American Society of Anesthesiologists (ASA) class IV (OR = 3.075; 95% CI = 1.000-9.459), and lack of postoperative gram-negative coverage (OR = 15.139; 95% CI = 3.083-74.347). CONCLUSION: Alcohol use, longer surgical duration, and lack of gram-negative postoperative prophylactic coverage are modifiable risk factors for surgical site infection development. (c) 2016 Wiley Periodicals, Inc. Head Neck, 2016.

Psychiatry

Fritzler L, and **Prabhakar D**. Green's child and adolescent clinical psychopharmacology, 5th edition *J Am Acad Child Adolesc Psychiatry* 2016; 55(7):633-634. PMID: Not assigned. Full Text

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Public Health Sciences

Al Feghali KA, **Robbins JR**, **Mahan M**, **Burmeister C**, **Khan NT**, **Rasool N**, **Munkarah A**, and **Elshaikh MA**. Predictive capacity of 3 comorbidity indices in estimating survival endpoints in women with early-stage endometrial carcinoma *Int J Gynecol Cancer* 2016;PMID: 27488218. Full Text

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OBJECTIVE: The negative impact of comorbidity on survival in women with endometrial carcinoma (EC) is well-known. Few validated comorbidity indices are available for clinical use, such as the Charlson Comorbidity Index (CCI), the Age-Adjusted CCI (AACCI), and the Adult Comorbidity Evaluation-27 (ACE-27). The aim of the study is to determine which index best correlates with survival endpoints in women with EC. MATERIALS AND METHODS: We identified 1132 women with early-stage EC treated at an academic center. Three scores were calculated for each patient using CCI, AACCI, and ACE-27 at the time of hysterectomy. Univariate and multivariable modeling was used to determine predictors of survival. RESULTS: For each of the studied comorbidity indices, the highest scores were significantly correlated with poorer overall survival. The hazard ratio of death from any cause was 3.92 for AACCI, 2.25 for CCI, and 1.57 for ACE-27. All 3 indices were independent predictors of overall survival with a P value of less than 0.001 on multivariate analysis. In addition, lymphovascular space invasion, lower uterine segment involvement, and tumor grade were predictors of overall survival. Lymphovascular space invasion, grade ($P < 0.001$), and high AACCI score were the only significant predictors of recurrence-free survival (RFS). Lymphovascular space invasion and tumor grade were the only 2 predictors of disease-specific survival. CONCLUSIONS: Although all 3 studied comorbidity indices were significant predictors of overall survival in women with early-stage EC, AACCI showed a stronger association. It should be considered for evaluating comorbidity in women with early-stage EC.

Public Health Sciences

Cassidy-Bushrow AE, Peters RM, **Burmeister C**, Bielak LF, and **Johnson DA**. Neighborhood-level poverty at menarche and prepregnancy obesity in African-American women *J Pregnancy* 2016; 2016:4769121. PMID: 27418977. Full Text

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Introduction. Menarche is a critical time point in a woman's reproductive system development; exposures at menarche may influence maternal health. Living in a poorer neighborhood is associated with adult obesity; however, little is known if neighborhood factors at menarche are associated with prepregnancy obesity. Methods. We examined

the association of neighborhood-level poverty at menarche with prepregnancy body mass index category in 144 pregnant African-American women. Address at menarche was geocoded to census tract (closest to year of menarche); neighborhood-level poverty was defined as the proportion of residents living under the federal poverty level. Cumulative logistic regression was used to examine the association of neighborhood-level poverty at menarche, in quartiles, with categorical prepregnancy BMI. Results. Before pregnancy, 59 (41%) women were obese. Compared to women in the lowest neighborhood-level poverty quartile, women in the highest quartile had 2.9 [1.2, 6.9] times higher odds of prepregnancy obesity; this was slightly attenuated after adjusting for age, marital status, education, and parity (odds ratio: 2.3 [0.9, 6.3]). Conclusions. Living in a higher poverty neighborhood at menarche is associated with prepregnancy obesity in African-American women. Future studies are needed to better understand the role of exposures in menarche on health in pregnancy.

Public Health Sciences

Castillo JJ, Glezerman IG, Boklage SH, Chiodo J, 3rd, Tidwell BA, **Lamerato LE**, and Schulman KL. The occurrence of hyponatremia and its importance as a prognostic factor in a cross-section of cancer patients *BMC Cancer* 2016; 16(1):564. PMID: 27473121. Full Text

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BACKGROUND: Hyponatremia is prognostic of higher mortality in some cancers but has not been well studied in others. We used a longitudinal design to determine the incidence and prognostic importance of euvolemic and hypervolemic hyponatremia in patients following diagnosis with lymphoma, breast (BC), colorectal (CRC), small cell lung (SCLC), or non-small cell lung cancer (NSCLC). METHODS: Medical record and tumor registry data from two large integrated delivery networks were combined for patients diagnosed with lymphoma, BC, CRC, or lung cancers (2002-2010) who had >/=1 administration of radiation/chemotherapy within 6 months of diagnosis and no evidence of hypovolemic hyponatremia. Hyponatremia incidence was measured per 1000 person-years (PY). Cox proportional hazard models assessed the prognostic value of hyponatremia as a time-varying covariate on overall survival (OS) and progression-free survival (PFS). RESULTS: Hyponatremia incidence (%, rate) was 76 % each, 1193 and 2311 per 1000 PY, among NSCLC and SCLC patients, respectively; 37 %, 169 in BC; 64 %, 637 in CRC, and 60 %, 395 in lymphoma. Hyponatremia was negatively associated with OS in BC (HR 3.7; P = <.01), CRC (HR 2.4; P < .01), lung cancer (HR 2.4; P < .01), and lymphoma (HR 4.5; P < .01). Hyponatremia was marginally associated with shorter PFS (HR 1.3, P = .07) across cancer types. CONCLUSIONS: The incidence of hyponatremia is higher than previously reported in lung cancer, is high in lymphoma, BC, and CRC and is a negative prognostic indicator for survival. Hyponatremia incidence in malignancy may be underestimated. The effects of hyponatremia correction on survival in cancer patients require further study.

Public Health Sciences

Jesse MT, **Rubinstein E**, **Eshelman A**, **Wee C**, **Tankasala M**, **Li J**, and **Abouljoud M**. Lifestyle and self-management by those who live it: Patients engaging patients in a chronic disease model *Perm J* 2016; 20(3)PMID: 27455056.
Article Request Form

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BACKGROUND: Patients pursuing organ transplantation have complex medical needs, undergo comprehensive evaluation for possible listing, and require extensive education. However, transplant patients and their supports

frequently report the need for more lifestyle and self-management strategies for living with organ transplantation. OBJECTIVES: First, to explore feasibility of a successful, patient-run transplant lifestyle educational group (Transplant Living Community), designed to complement medical care and integrated into the clinical setting; and second, to report the major themes of patients' and supports' qualitative and quantitative feedback regarding the group. METHODS: Informal programmatic review and patient satisfaction surveys. RESULTS: A total of 1862 patient satisfaction surveys were disseminated and 823 were returned (response rate, 44.2%). Patients and their supports reported positive feedback regarding the group, including appreciation that the volunteer was a transplant recipient and gratitude for the lifestyle information. Five areas were associated with the success of Transplant Living Community: 1) a "champion" dedicated to the program and its successful integration into a multidisciplinary team; 2) a health care environment receptive to integration of a patient-led group with ongoing community development; 3) a high level of visibility to physicians and staff, patients, and supports; 4) a clearly presented and manageable lifestyle plan ("Play Your ACES"a [Attitude, Compliance, Exercise, and Support]), and 5) a strong volunteer structure with thoughtful training with the ultimate objective of volunteers taking ownership of the program. CONCLUSION: It is feasible to integrate a sustainable patient-led lifestyle and self-management educational group into a busy tertiary care clinic for patients with complex chronic illnesses.

Public Health Sciences

Johnson CC, and Ownby DR. The infant gut bacterial microbiota and risk of pediatric asthma and allergic diseases *Transl Res* 2016;PMID: 27469270. Full Text

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Among the many areas being revolutionized by the recent introduction of culture-independent microbial identification techniques is investigation of the relationship between close contact with large animals, antibiotics, breast feeding, mode of birth, and other exposures during infancy as related to a reduced risk of asthma and allergic disease. These exposures were originally clustered under the "Hygiene Hypothesis" which has morphed into the "Microbiota Hypothesis". This review begins by summarizing epidemiologic studies suggesting that the common feature of these allergy risk-related exposures is their influence on the founding and early development of a child's gut microbiota. Next studies using culture-independent techniques are presented showing that the microbiota of children who have experienced the exposures of interest have altered gut microbiota. Finally, selected mouse and human studies are presented which begin to corroborate the protective exposures identified in epidemiologic studies by identifying mechanisms through which microbes can alter immune development and function. These microbially driven immune alterations demonstrate that microbial exposures in many cases could alter the risk of subsequent allergic disease and asthma. Hopefully, a better understanding of how microbes influence allergic disease will lead to safe and effective methods for reducing the prevalence of all forms of allergic disease.

Public Health Sciences

Jones LR, **Greene J**, **Chen KM**, **Divine G**, **Chitale D**, **Shah V**, **Datta I**, and **Worsham MJ**. Biological significance of genome-wide DNA methylation profiles in keloids *Laryngoscope* 2016;PMID: 27312686. Full Text

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OBJECTIVES/HYPOTHESIS: To obtain biological insight into keloid pathogenesis and treatment using pathway analysis of genome-wide differentially methylated gene profiles between keloid and normal skin. STUDY DESIGN: Prospective cohort. METHODS: Genome-wide profiling was previously done, with institutional review board approval, on six fresh keloid and six fresh normal skin tissue samples, using the Infinium HumanMethylation450 BeadChip kit. Statistically significant differentially methylated cytosine-phosphodiester bond-guanines (CpGs, n = 197) between keloid and normal tissue mapped to 152 genes. These genes were uploaded into Ingenuity Pathway Analysis (IPA) software to identify biological functions or regulatory networks interacting. The pathways (or "network") with an enrichment probability value </= .01 were subjected to a heuristic filter of keywords associated with keloid pathogenesis. RESULTS: Of the 197 CpGs, 191 were found in the IPA database and mapped to 152 unique genes. The top 10 hypermethylated genes were ACTR3C, LRRC61, PAQR4, C1orf109, SLCO2B1, CMKLR1, AHDC1, FYCO1, CCDC34, and CACNB2. The top 10 hypomethylated genes were GALNT3, SCML4, PPP1R13L, ANKRD11, WIPF1, MX2, IFFO1, DENND1C, CFH, and GHDC. IPA identified nine pathways with enrichment probability values </= .01, of which five (histidine degradation V1, phospholipase C signaling, colorectal cancer metastasis signaling,

P2Y purinergic receptor signaling, and Galphai signaling) were associated with keloid keywords and contained "keloid genes" (P < .05). CONCLUSIONS: Genes differentially methylated between keloid and normal skin reside in known bionetwork pathways involved in critical biological functioning and signaling events in the cell. This information could be used to refine screening processes for biological significance to better understand keloid pathogenesis and to develop molecular-targeted therapy. LEVEL OF EVIDENCE: NA Laryngoscope, 2016.

Public Health Sciences

Modh A, **Ghanem AI**, **Burmeister C**, **Rasool N**, and **Elshaikh MA**. Trends in the utilization of adjuvant vaginal brachytherapy in women with early-stage endometrial carcinoma: Results of an updated period analysis of SEER data *Brachytherapy* 2016;PMID: 27475480. Full Text

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PURPOSE: Adjuvant vaginal brachytherapy (VB) is a well-established and effective radiation treatment modality in women with early-stage endometrial carcinoma. We sought to evaluate and update published trends in the utilization of VB vs. other radiation therapy modalities (pelvic external beam radiation therapy (EBRT) or the combination of VB and pelvic EBRT using the National Cancer Institute's Surveillance, Epidemiology, and End Results database. METHODS AND MATERIALS: The Surveillance, Epidemiology, and End Results database was queried for adult females with histologically confirmed International Federation of Gynecology and Obstetrics 1988 Stage I-II endometrial carcinoma diagnosed from 1995 to 2012 and treated definitively with hysterectomy and adjuvant radiation therapy. Chi-square tests were used to assess differences by radiation type (VB, EBRT, and VB + EBRT) and various demographic and clinical variables. RESULTS: We identified 15,201 patients that met inclusion criteria. There was a significant overall increase in the use of VB was observed from 17.1% in 1995-2000 compared to 57.1% in 2007-2012 ($p < 0.0001$). Similarly, there was a proportional decrease in the use of EBRT from 54.0% to 25.5% ($p < 0.0001$) as well as in the use of VB + EBRT from 28.9% to 17.4% during the same period ($p < 0.0001$). The observed increase in utilization of VB was not limited to any variables (age, race, histological type, International Federation of Gynecology and Obstetrics stage, and the status of lymph node dissection [yes or no]) or the number of dissected lymph nodes. CONCLUSIONS: In this large national database set, there continues to be an increasing trend for the use of VB in the adjuvant setting in women with early-stage endometrial carcinoma.

Public Health Sciences

Modh A, **Ghanem AI**, **Burmeister C**, **Rasool N**, and **Elshaikh MA**. Trends in the utilization of adjuvant radiation treatment in women with early stage type ii endometrial carcinoma: A surveillance, epidemiology, and end-results study *Brachytherapy* 2016; 15:S89. PMID: Not assigned. Abstract

A. Modh, Radiation Oncology, Henry Ford Health System, Detroit, United States

Purpose: Type II endometrial carcinoma (EC) represents a group of aggressive histologies with a relatively poor prognosis. While an increasing trend for utilizing adjuvant vaginal brachytherapy has been reported in women with early stage type I EC, trends in radiation treatment in patients with type II EC have not been fully investigated. We sought to evaluate the trends in adjuvant radiation modalities (pelvic external beam RT [EBRT] versus vaginal brachytherapy [VB] versus the combination of EBRT+VB) in women with early stage type II endometrial carcinoma using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Materials and Methods: The SEER database was queried for adult females with histologically confirmed FIGO (1988) stage I-II endometrial carcinoma type II (serous, clear cell and mixed carcinoma) diagnosed from 1995-2012 and treated definitively with hysterectomy and adjuvant radiation therapy. Patients with multiple primary malignancies, those who received radiation treatment prior to surgery or those who did not have any adjuvant treatment were excluded. Patients were grouped in 5-year intervals, from 1995-2000, 2001-2006, and 2007-2012. Chi-squared tests were used to assess differences in utilization of radiation modality and various demographic and clinical variables. Results: We identified 1,249 patients that met our inclusion criteria. In the entire cohort, 42.5% received EBRT, 36.3% received VB, and 21.1% received VB+EBRT. A lymph node dissection was performed in 79.7% of patients. When a lymph node dissection was performed, the median number of lymph nodes examined in our study increased from 12.0 in 1995-2000 to 17.0 in 2007-2012 ($p <0.0001$). There was an overall increase in the use of VB observed from 15.0% in 1995-2000 to 55.9% in 2007-2012 ($p <0.0001$). This increase in VB utilization was seen in both older (>60) and younger (<60) patients and irrespective of whether a lymph node dissection was performed or not. In parallel, the use of EBRT fell from 56.5% in 1995-2000 to 28.2% in 2007-2012 ($p <0.0001$). The use of VB+ERBT combined also decreased over the same time period, from 28.5% in 1995-2000 to 15.9% in 2007-2012 ($p<0.0001$). Conclusions:

Similar to the trends seen in adjuvant radiation treatment in women with type I early stage endometrial carcinoma, there is an increasing trend for the use of adjuvant VB and a declining use of pelvic EBRT in women with type II endometrial carcinoma.

Public Health Sciences

Munkarah AR, **Kim S**, **Buekers TE**, **Chhina J**, **Poisson L**, **Giri S**, and **Rattan R**. Metabolic effects of metformin treatment in ovarian cancer cell lines *Gynecol Oncol* 2016; 141:168. PMID: Not assigned. Abstract

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Objectives: Metformin is being actively repurposed for the treatment of gynecologic malignancies. It is known to alter the cancer cell metabolism, primarily inhibit oxidative phosphorylation, and induce glycolysis. Our aim was to investigate the metabolite changes occurring in response to metformin treatment in ovarian cancer (OvCa) cell lines.Methods: A2780, C200, SKOV3ip cell lines were treated with metformin (10 mM) for 48 hours and subjected to untargeted global metabolites by ultra-high performance liquid chromatography and gas chromatography mass spectroscopy. Per-metabolite comparisons were made. Interpretive analysis was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and the Ingenuity molecule library.Results: Metformin treatment caused alterations in metabolites in all treated lines: A2780 showed 132 alterations (72 up; 60 down), C200 showed 135 (77 up; 58 down), and SKOV3ip showed 135 (84 up; 51 down); (FDR ≤ 0.1). The 3 cell lines revealed 57 common altered metabolites, of which 30 had consistent direction change. KEGG analysis of these 30 metabolites showed that the amino acid metabolism (alanine, aspartate, glutamate and glycine, serine, threonine metabolism; adjusted P <.0001) was the most significantly affected. Interestingly, metformin affected the energy pathways of glycolysis and oxidative phosphorylation differentially across the 3 cell lines. Cellular proliferation and signaling was the top common network pathway on Ingenuity analysis.Conclusions: Metformin treatment had a significant and widespread effect on metabolism of OvCa cell lines. Although metformin resulted in certain consistent metabolic changes in amino acid metabolism across cell lines, its modulation of glycolysis and oxidative phosphorylation was varied. These differential metabolic changes could indicate the degree of metformin response and suggest it to be context-dependent. Such information about the cancer metabolism may aid in preclinical and clinical assessment of metformin therapy in ovarian and other cancers.

Public Health Sciences

Rattan R, Mert I, **Chhina J**, **Hamid S**, **Hijaz M**, **Poisson L**, **Hensley Alford S**, **Giri S**, and **Munkarah AR**. Targeting of free fatty acid receptor 1 in EOC: A novel strategy to restrict the adipocyte-EOC dependence *Gynecol Oncol* 2016; 141:47. PMID: Not assigned. Abstract

R. Rattan, Henry Ford Health System, Detroit, United States

Objectives: Adipocyte-derived free fatty acids (FFAs) promote epithelial ovarian cancer (EOC) by acting as a fuel source to support the energy requirement of the cancer cells. FFAs may also exert biological effects through signaling pathways. Recently, a family of FFA-activated G-protein-coupled receptors (FFAR/GPCRs) was identified. Our objective was to investigate the role of FFAR/GPCRs in EOC and assess their potential as therapeutic targets.Methods: The mRNA (RT-PCR) expression of FFAR/GPCR family members (FFAR1/GPR40; FFAR2/GPR42, FFAR3/GPR41, FFAR4/GPR120 and GPR84) was examined in: (1) a syngeneic mouse model of EOC fed high-energy diet (60% fat) or regular diet (30% fat), (2) EOC cell lines exposed to FFAs and (3) specimens from 13 histologically normal ovaries and 28 high-grade ovarian serous carcinomas. The GPR 40 antagonist, GW1100, was used to inhibit FFAR1/GPR40 and cell survival was assayed using MTT in various cell lines.Results: High-grade serous carcinoma specimens expressed significantly increased GPR40 compared with normal ovaries (P =.0020). Higher expression was observed to be stage specific and noted to be significant in advanced-stage disease (X2 P =.04). ID8 ovarian tumors from mice fed with high fat diet showed higher GPR40 expression. Exposing EOC cells to FFAs increased GPR40 expression. Treatment of EOC cell lines with GW100 resulted in growth inhibition and was associated with an alteration in their energy metabolismConclusions: FFA-induced cancer cell growth may be partly mediated through FFAR1/GPR40. Targeting of FFAR1/GPR40 may be an attractive treatment strategy in EOC, and possibly offers a targeted treatment for a subset of EOC patients.

Public Health Sciences

Ren Y, **Janic B**, **Kutskill K**, **Peterson EL**, and **Carretero OA**. Mechanisms of connecting tubule glomerular feedback enhancement by aldosterone *Am J Physiol Renal Physiol* 2016:ajprenal.00076.02016. PMID: 27413197. Full Text

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Connecting tubule glomerular feedback (CTGF) is a mechanism where an increase in sodium (Na) concentration in the connecting tubule (CNT) causes the afferent arteriole (Af-Art) to dilate. We recently reported that aldosterone within the CNT lumen enhances CTGF via a nongenomic effect involving GPR30 receptors and sodium/hydrogen exchanger (NHE), but the signaling pathways of this mechanism are unknown. We hypothesize that aldosterone enhances CTGF via cAMP/protein kinase A (PKA) pathway that activates protein kinase C (PKC) and stimulates superoxide (O-2) production. Rabbit Af-Arts and their adherent CNTs were microdissected and simultaneously perfused. Two consecutive CTGF curves were elicited by increasing the CNT luminal NaCl. We found that the main effect of aldosterone was to sensitize CTGF and we analyzed data by comparing NaCl concentration in the CNT perfusate needed to achieve half of the maximal response (EC50). During the control period, the NaCl concentration that elicited a half-maximal response (EC50) was 37.0+/-2.0 mmol/L; addition of aldosterone (10-8 mol/L) to the CNT lumen decreased EC50 to 19.3+/-1.3 mmol/L (p</=0.001 vs. Control). The specific adenylyl cyclase inhibitor 2',3'-Dideoxyadenosine (ddA) (2x10-4 mol/L) and the PKA inhibitor H-89 dihydrochloride hydrate (H-89) (2x10-6 mol/L) prevented the aldosterone effect. Selective PKC inhibitor GF109203X (10-8 mol/L) also prevented EC50 reduction caused by aldosterone. CNT intraluminal addition of O-2 scavenger tempol (10-4 mol/L) blocked the aldosterone effect. We conclude that aldosterone inside the CNT lumen enhances CTGF via a cAMP/PKA/PKC pathway and stimulates O2 generation and this process may contribute to renal damage by increasing glomerular capillary pressure.

Public Health Sciences

Salafia CM, Thomas DM, Roberts DJ, and **Straughen JK**. Human placental pathology-diagnosis in the 21st century: New approaches and techniques *Birth Defects Research Part a-Clinical and Molecular Teratology* 2016; 106(5):370-370. PMID: Not assigned. Abstract

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Public Health Sciences

Sareen N, **Mariychina A**, **Hector C**, **Mahan M**, and **Ananthasubramaniam K**. Do right ventricular diastolic tissue doppler parameters add diagnostic value in pulmonary hypertension? *J Am Soc Echocardiogr* 2016; 29(6):B101. PMID: Not assigned. Abstract

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Background: The value of right ventricular (RV) tissue doppler (TD) derived diastolic function patterns in pulmonary hypertension (PHTN) is unclear and formed the basis of our study. Methods: Retrospective review of transthoracic echocardiogram (TTE) of 57 patients who had Type I and II PHTN confirmed on right heart catheterization (Type I =33, Type II= 24, mild- moderate PASP = 31, severe PASP= 26). 22 consecutive patients without cardiopulmonary disease served as control. Absolute values of RV e', RV a', RV e'/a' ratio, RV doppler tei index and RV tissue tei index were compared and correlation coefficients were obtained with pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR) on RHC. Chi-square tests and two-group independent t-tests were used for statistical analysis. Results: Both study groups comprised primarily of females. 54% of test group patients had mild to moderate (40-60 mm Hg) and 46 % had severe (>60 mm Hg) PHTN. RV TAPSE, RV S' , RV e' and RV a' values were all significantly decreased in PHTN group (all p=<0.05 vs controls) with no significant difference in RV e'/a' ratio (1.1 cms/sec). Doppler (0.6 vs 0.4, p<0.05) and tissue (1 vs 0.5, p<0.05) Tei index were significantly higher in PHTN group. Significant negative correlation was observed between RV a' velocity and PVR. (p<0.05). Significant correlation of RHC PASP was observed with RV a' velocity, most significant with mild to moderate PHTN (p<0.05) and in patients with Type II PHTN (p<0.05). Tissue Tei index was significantly higher in patients with PHTN on RHC, most significant with severe PHTN (p<0.05) and in Type I PHTN (p<0.05). Conclusions: RV TD and RV tTD Tei index are all abnormal in PHTN. Lower values of RV a' velocity correlates with mild to moderate PHTN and PHTN Type II. Higher values of RV RF Tei index correlates with severe pulmonary pressures and PHTN Type I on RHC. Our study suggests that incorporating RV tissue Doppler parameters and Tei index in TTE evaluation of PHTN adds value.

Public Health Sciences

Xu Y, **Hanna RK**, **Burmeister C**, **Munkarah AR**, and **Elshaikh MA**. Predictors of survival after recurrence in women with early-stage endometrial carcinoma *Gynecol Oncol* 2016; 141:70. PMID: Not assigned. Abstract

Y. Xu, Henry Ford Hospital, Detroit, United States

Objectives: Factors predictive of survival after recurrent early-stage endometrial cancer have not been thoroughly investigated. The purpose of this study was to explore the impact of different prognostic factors including type of salvage management on disease-specific survival (DSS) and overall survival (OS) after recurrence.Methods: Following institutional review board approval, we identified 104 women with 2009 FIGO stage I-II uterine endometrioid carcinoma who developed disease recurrence between January 1990 and December 2014. Patients who received adjuvant chemotherapy after primary surgery were excluded from this analysis. The Kaplan-Meier approach and Cox regression analysis were used to assess DSS and OS after recurrence and to determine factors influencing survival endpoints.Results: Median age of the study cohort was 65 years with a median follow-up time of 42.8 months after hysterectomy. Sixty patients (57.7%) had stage IA, 30 (28.9%) had stage IB, and 14 (13.5) had stage II disease. Median time to recurrence was 15.8 months. Fifty-six patients (54%) had pelvic-only recurrence (vaginal and/or pelvic), whereas 48 (46%) had extrapelvic recurrences. Patients with low-grade tumors and pelvic-only recurrences were associated with longer DSS and OS compared with patients with grade 3 tumor and/or extrapelvic recurrences (P =.05). Five-year DSS calculated from the date of recurrence for the entire cohort was 44%. The 5-year DSS was longer for patients with pelvic-only recurrence compared with patients with extrapelvic recurrences (66% vs 18%, P <.0001). The 5-year DSS was longer for radiation-naïve patients than for patients who received prior adjuvant radiation therapy (51% vs 34%, P =.023). Neither time to recurrence nor type of salvage treatment was a significant predictor for DSS or OS. On multivariate analysis of DSS and OS, pelvic-only recurrence (P <.001) was the only significant predictor of longer DSS and OS.Conclusions: In women with recurrent early-stage endometrial carcinoma, our study suggests that the site of recurrence (pelvic vs extrapelvic) is the only predictor of survival. In addition, we found that radiation naiveté correlated with longer DSS, while low-grade tumors and pelvic-only recurrence were associated with a significantly improved DSS and OS. Longer time to recurrence and type of salvage treatment were not significant predictors of DSS and OS.

Public Health Sciences

Zhang L, **Chopp M**, **Zhang Y**, **Xiong Y**, **Li C**, **Sadry N**, **Rhaleb I**, **Lu M**, and **Zhang ZG**. Diabetes mellitus impairs cognitive function in middle-aged rats and neurological recovery in middle-aged rats after stroke *Stroke* 2016; 47(8):2112-2118. PMID: 27387991. Full Text

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BACKGROUND AND PURPOSE: Diabetes mellitus (DM) is a common metabolic disease among the middle-aged and older population, which leads to an increase of stroke incidence and poor stroke recovery. The present study was designed to investigate the impact of DM on brain damage and on ischemic brain repair after stroke in aging animals. METHODS: DM was induced in middle-aged rats (13 months) by administration of nicotinamide and streptozotocin. Rats with confirmed hyperglycemia status 30 days after nicotinamide-streptozotocin injection and age-matched non-DM rats were subjected to embolic middle cerebral artery occlusion. RESULTS: Middle-aged rats subjected to nicotinamide-streptozotocin injection became hyperglycemic and developed cognitive deficits 2 months after induction of DM. Histopathologic analysis revealed that there was sporadic vascular disruption, including cerebral microvascular thrombosis, blood-brain barrier leakage, and loss of paravascular aquaporin-4 in the hippocampi. Importantly, middle-aged DM rats subjected to stroke had exacerbated sensorimotor and cognitive deficits compared with age-matched non-DM ischemic rats during stroke recovery. Compared with age-matched non-DM ischemic rats, DM ischemic rats exhibited aggravated neurovascular disruption in the bilateral hippocampi and white matter, suppressed stroke-induced neurogenesis and oligodendrogenesis, and impaired dendritic/spine plasticity. However, DM did not enlarge infarct volume. CONCLUSIONS: Our data suggest that DM exacerbates neurovascular damage and hinders brain repair processes, which likely contribute to the impairment of stroke recovery.

Pulmonary
Rezik MM, and **Ouellette DR**. Pleuritic chest pain in a 24-year-old male with crohn's disease *Am J Respir Crit Care Med* 2016;PMID: 27413816. Full Text

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Pulmonary
Thompson MP, Reeves MJ, Bogan BL, **DiGiovine B**, Posa PJ, and Watson SR. Protocol-based resuscitation bundle to improve outcomes in septic shock patients: Evaluation of the michigan health and hospital association keystone sepsis collaborative *Crit Care Med* 2016;PMID: 27441897. Full Text

1Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI. 2Keystone Center for Patient Safety & Quality, Michigan Health & Hospital Association, Okemos, MI. 3Division of Pulmonary, Critical Care, and Sleep Medicine, Henry Ford Health System, Detroit, MI. 4St. Joseph Mercy Hospital, Ann Arbor, MI.

OBJECTIVES: To evaluate the impact of a multi-ICU quality improvement collaborative implementing a protocol-based resuscitation bundle to treat septic shock patients. DESIGN: A difference-in-differences analysis compared patient outcomes in hospitals participating in the Michigan Health & Hospital Association Keystone Sepsis collaborative (n = 37) with noncollaborative hospitals (n = 50) pre- (2010-2011) and postimplementation (2012-2013). Collaborative hospitals were also stratified as high (n = 19) and low (n = 18) adherence based on their overall bundle adherence. SETTING: Eighty-seven Michigan hospitals with ICUs. PATIENTS: We compared 22,319 septic shock patients in collaborative hospitals compared to 26,055 patients in noncollaborative hospitals using the Michigan Inpatient Database. INTERVENTIONS: Multidisciplinary ICU teams received informational toolkits, standardized screening tools, and continuous quality improvement, aided by cultural improvement. MEASUREMENTS AND MAIN RESULTS: In-hospital mortality and hospital length of stay significantly improved between pre- and postimplementation periods for both collaborative and noncollaborative hospitals. Comparing collaborative and noncollaborative hospitals, we found no additional reductions in mortality (odds ratio, 0.94; 95% CI, 0.87-1.01; p = 0.106) or length of stay (-0.3 d; 95% CI, -0.7 to 0.1 d; p = 0.174). Compared to noncollaborative hospitals, high adherence hospitals had significant reductions in mortality (odds ratio, 0.84; 95% CI, 0.79-0.93; p < 0.001) and length of stay (-0.7 d; 95% CI, -1.1 to -0.2; p < 0.001), whereas low adherence hospitals did not (odds ratio, 1.07; 95% CI, 0.97-1.19; p = 0.197; 0.2 d; 95% CI, -0.3 to 0.8; p = 0.367). CONCLUSIONS: Participation in the Keystone Sepsis collaborative was unable to improve patient outcomes beyond concurrent trends. High bundle adherence hospitals had significantly greater improvements in outcomes, but further work is needed to understand these findings.

Radiation Oncology
Al Feghali KA, **Robbins JR**, **Mahan M**, **Burmeister C**, **Khan NT**, **Rasool N**, **Munkarah A**, and **Elshaikh MA**. Predictive capacity of 3 comorbidity indices in estimating survival endpoints in women with early-stage endometrial carcinoma *Int J Gynecol Cancer* 2016;PMID: 27488218. Full Text

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OBJECTIVE: The negative impact of comorbidity on survival in women with endometrial carcinoma (EC) is well-known. Few validated comorbidity indices are available for clinical use, such as the Charlson Comorbidity Index (CCI), the Age-Adjusted CCI (AACCI), and the Adult Comorbidity Evaluation-27 (ACE-27). The aim of the study is to determine which index best correlates with survival endpoints in women with EC. MATERIALS AND METHODS: We identified 1132 women with early-stage EC treated at an academic center. Three scores were calculated for each patient using CCI, AACCI, and ACE-27 at the time of hysterectomy. Univariate and multivariable modeling was used to determine predictors of survival. RESULTS: For each of the studied comorbidity indices, the highest scores were significantly correlated with poorer overall survival. The hazard ratio of death from any cause was 3.92 for AACCI, 2.25 for CCI, and 1.57 for ACE-27. All 3 indices were independent predictors of overall survival with a P value of less than 0.001 on multivariate analysis. In addition, lymphovascular space invasion, lower uterine segment involvement, and tumor grade were predictors of overall survival. Lymphovascular space invasion, grade (P < 0.001), and high AACCI score were the only significant predictors of recurrence-free survival (RFS). Lymphovascular space invasion and tumor grade were the only 2 predictors of disease-specific survival. CONCLUSIONS: Although all 3 studied comorbidity indices were significant predictors of overall survival in women with early-stage EC, AACCI showed a stronger association. It should be considered for evaluating comorbidity in women with early-stage EC.

Radiation Oncology

Bagher-Ebadian H, **Schwalb J**, **Mahmoudi F**, **Air E**, **Shokri S**, **Nazem-Zadeh M**, **Spanaki-Varelas M**, **Wasade V**, and **Soltanian-Zadeh H**. Localized quantitative analysis of positron emission tomography (PET) for temporal lobe epilepsy lateralization and surgical intervention *J Nucl Med* 2016; 57PMID: Not assigned. Abstract

H. Bagher-Ebadian, Henry Ford Hospital, Detroit, United States

Objectives We hypothesized that localized quantitative analysis of hypometabolism level in hippocampi using interictal PET scans, in combination with qualitative and quantitative analyses of MRI, can increase the confidence in lateralization and selection of patients for surgical intervention. Methods In this study, 11 patients with refractory epilepsy (ages 18 to 58 years, mean age of 40 years, 8 females, 3 males) were studied. All patients had symptomatic temporal lobe epilepsy and underwent MRI, EEG, and PET/CT scans. MR Imaging: All studies were performed using a 3T GE Excite HD MR system (GE Healthcare, Waukesha, WI) using a standard eight-channel phased-array RF coil and receiver. All patients underwent coronal T2-Fluid attenuated inversion recovery (T2-FLAIR) and T1-weighted (T1WI) MR studies using a spoiled gradient-echo (SPGR) sequence with adequate spatial resolutions appropriate for hippocampal T1 volumetry and FLAIR intensity analysis. PET Scan: All patients were asked to fast for 5 to 6 hours on the day of their scan. The blood glucose level of the patient was checked before the 18F-FDG administration. For each patient, 18F-FDG (8 ~ 12 mCi) was injected via an IV. All patient were scanned using a CT/PET (GE) scanner with a wait time of 60 min. For each patient, using FSL software, FLAIR and PET modalities were skull stripped (BET) and co-registered (rigid-FLIRT) to the skull-stripped T1WI as the reference. The regions of interest (ROIs) enclosing the hippocampi were delineated manually using coronal T1WI. A single investigator (AH) outlined all coronal hippocampal contours using an in-house software. Then, for each subject, the 3D Standard Uptake Value (SUV) was calculated (Figures 1 and 2, note that increased hypomethabolism is red in figure-2) from the co-registered PET modality for the entire brain and for the hippocampi using the hippocampi's ROIs. From Anterior to Posterior, SUV profiles for the left and right hippocampi were calculated and the two profiles were spatially normalized to each other (Figure 3). Then, the normalized profiles (L and R) along with a test of significance (Welch test - unpaired and unequal variances - see Figure 4) were used to estimate the hypometabolism probability profile (HPP) from each individual slice of the hippocampi at the confidence level of 95%. Results As shown in Figure 5, the slice based Welch test along with the proposed sampling method (Figures 3-4) generated a standard HPP profile consisting of three possible conditions for the hippocampi: left hypometabolism area (green), right hypometabolism area (blue), and the area of uncertainty (red - no judgment can be made). In addition to the HPP method, MRI data of the subjects were processed using quantitative lateralization techniques of hippocampal volumetry and T2-FLAIR intensity analysis. The HPP and the scatter plots generated by the MRI methods were used for lateralization and decision making for ECoG. The patient's medical history, laboratory studies, long-term video-electro-encephalographic (EEG) data, and Neuropsychological tests such as Wada were also used in the decision making process. Table 1 shows that, compared to MRI lateralization techniques (27% and 36% for FLAIR intensity and T1 volume, respectively), the judgments of the HPP technique are closer (64%) to the decisions made by the clinicians for the ECoG monitoring study. Conclusions Despite the facts that the final decision made for ECoG may not be the optimal decision and also the population size in this study was small and skewed towards 'right', the results imply that the HPP method could be beneficial for the TLE patients to make a decision regarding the ECoG study and to do presurgical evaluations. We believe that an integrated decision making system that benefits from HPP as well as MRI measures would work best for the decision making process. (Figure Presented).

Radiation Oncology

Barton KN, **Bellon M**, **Crosby S**, **McEveney M**, and **Elshaikh M**. Quantification & dosimetric consequences of air gaps surrounding vaginal cylinders in women undergoing vaginal HDR brachytherapy. Final report of a prospective study *Brachytherapy* 2016; 15:S125-S126. PMID: Not assigned. Abstract

K.N. Barton, Radiation Oncology, Henry Ford Hospital, Detroit, United States

Purpose: With the help of CTimaging, the presence of air gaps surrounding vaginal cylinders is used as an indication of whether or not the appropriate cylinder size was selected for high dose rate (HDR) vaginal cuff brachytherapy. The objective of this study is to correlate the size and number of air gaps with cylinder size and to evaluate the appropriateness of using air gaps alone as measured on CT to determine the optimal cylinder size for vaginal cuff brachytherapy. Materials and Methods: This was an IRB-approved prospective study that was conducted between January 2013 and February 2014 and includes 23 women with endometrial cancer. All patients received 2 pelvic CT scans with a slice thickness of 1 mm during their first HDR brachytherapy simulation. The first scan was acquired with a 2 cm diameter vaginal cylinder inserted; this was followed immediately by a second scan with the clinically determined, optimal size cylinder inserted. On each CT image set, the volume of air gaps found in the cranial 4 cm of the cylinder was contoured and the quantity and diameter were calculated for each air gap. The image sets were then imported into our treatment planning system for comparison. Comparable treatment plans for a singlechannel,

segmented cylinder were generated for both cylinder sizes. Additionally, the doses to the vaginal lymphatics (the proximal 3 mm tissue surrounding cylinderd with and without air gaps), rectum and bladder were calculated. Statistical significance was evaluated by 2-tailed paired Student's T test unless otherwise indicated. Results: The median size for the clinically appropriate vaginal cylinder (treatment) used was 3.5 cm (range, 3-3.5). Compared to treatment cylinders, the magnitude of the quantity and diameter of the air gaps with smaller cylinder was overall smaller than the difference in cylinder diameter. With the 2 cm diameter cylinder, median number of air gaps was 5 (range, 3-8) compared to 0 (range, 0-2) ($p < 0.0001$) for the treatment cylinder. The sizes of the air gaps were generally larger with the 2 cm cylinders (median diameter of 0.36 cm (range, 0.20-0.62 cm) compared to only a median diameter of 0.23 cm (range 0.10-0.83 cm) ($p=0.13$) for the treatment cylinder. Surprisingly, reducing the cylinder size from 3.5 to 2 cm (corresponding to a 0.75 cm reduction in radius) translated to only a median (&range) of 0.13 cm (0.10-0.52 cm) increase in air gap size. Due to the air gaps, the vaginal lymphatic tissue was displaced away from the cylinder reducing the dose to this structure by an average of 32% (range 21-46%) and 20% (range 9-47%) ($p=0.004$) for the 2 cm and treatment cylinders, respectively. Improved coverage of the vaginal lymphatics using treatment cylinders compared to the 2 cm cylinder was also demonstrated ($p<0.0001$) by evaluating the D95 (23% higher), D90 (22% higher) and mean dose (20% higher). The average rectum D2cc was recorded as 2.9 and 3.9 Gy for the 2 cm and treatment cylinders ($p<0.0001$), respectively. Similarly, average D2cc for bladder increased from 2.7 to 3.6 Gy going from a 2 cm to treatment cylinder ($p<0.0001$). Conclusions: Due to the distensible nature of the vagina, the quantity and volume of air gaps as seen on CT images with the use of smaller cylinders could be deceivingly low. Assessment of air gaps as seen on CT images should not be used alone to determine the appropriate size cylinder. Instead, appropriate size cylinder must be determined mainly based on pelvic examination. Due to the presence of air gaps, the smaller size vaginal cylinder results in poorer coverage to the vaginal lymphatic structure (i.e., the target volume).

Radiation Oncology

Chapman CH, Zhu T, **Nazem-Zadeh M**, Tao Y, Buchtel HA, Tsien CI, Lawrence TS, and Cao Y. Diffusion tensor imaging predicts cognitive function change following partial brain radiotherapy for low-grade and benign tumors *Radiother Oncol* 2016;PMID: 27418525. Full Text

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PURPOSE/OBJECTIVES: Radiation injury to parahippocampal cingulum white matter is associated with cognitive decline. Diffusion tensor imaging (DTI) detects micropathologic changes in white matter. Increased radial diffusion (RD) and decreased axial diffusion (AD) correspond to demyelination and axonal degeneration/gliosis respectively. We aimed to develop a predictive model for radiation-induced cognitive changes based upon DTI changes. MATERIALS/METHODS: Twenty-seven adults with benign or low-grade tumors received partial brain radiation therapy (RT) to a median dose of 54Gy. Patients underwent DTI before RT, during RT, and at the end of RT. Cognitive testing was performed before RT, and 6 and 18months after RT. Parahippocampal cingulum white matter was contoured to obtain mean values of AD and RD. RESULTS: By univariate analysis, decreasing AD and increasing RD during RT predicted declines in verbal memory and verbal fluency. By multivariate analysis, baseline neurocognitive score was the only clinical variable predicting verbal memory change; no clinical variables predicted verbal fluency change. In a multivariate model, increased RD at the end of RT significantly predicted decline in verbal fluency 18months after RT. CONCLUSIONS: Imaging biomarkers of white matter injury contributed to predictive models of cognitive function change after RT.

Radiation Oncology

Elshaikh MA, Vance S, Gaffney DK, Biagioli M, Jhingran A, Jolly S, Kidd E, Lee LJ, Li L, Moore DH, Rao GG, Wahl AO, Williams NL, Yashar CM, and Small W, Jr. ACR appropriateness criteria management of recurrent endometrial cancer *Am J Clin Oncol* 2016;PMID: 27400117. Full Text

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OBJECTIVES: In women with endometrial carcinoma (EC), tumor recurrences tend to occur in the 2- to 3-year period following surgical staging. Management of disease recurrence in EC poses significant challenges. These patients represent a heterogenous group where histologic subtypes, previous adjuvant management, interval since completion of adjuvant therapy, and size and site(s) of disease recurrence all have important implications on salvage therapies and prognosis. No randomized controlled trials have been published to determine optimal management in this group of patients. An expert panel was convened to reach consensus on the most appropriate management options in this group of patients. METHODS: 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. RESULTS: Five clinical variants were developed to address common scenarios in the management of women with recurrent EC. Group members reached consensus on the appropriateness of specific evaluation and treatment approaches with numerical ratings. CONCLUSIONS: In combining available medical literature and expert opinions, this manuscript may serve as an aid for other practitioners in the appropriate management of women with recurrent EC.

Radiation Oncology

Isrow D, **Burmeister C**, **Munkarah AR**, and **Elshaikh MA**. Survival endpoints for young women with early-stage uterine endometrioid carcinoma: A matched analysis *Gynecol Oncol* 2016; 141:62. PMID: Not assigned. Abstract

D. Isrow, Henry Ford Hospital, Detroit, United States

Objectives: Younger age is viewed as a favorable prognostic factor in women with early-stage endometrial carcinoma (EC) but the available data are controversial. Survival endpoints were compared between 2 groups of patients with early-stage EC solely of endometrioid histology: women 45 years or younger and similarly matched older women.Methods: We identified 1,254 patients with 2009 FIGO stage I-II EC who underwent hysterectomy at our institution between January 1990 and December 2014. We created 2 matched groups based on FIGO stage, tumor grade, lymph node dissection status and the type of adjuvant management (observation, pelvic external beam, or vaginal brachytherapy). Recurrence-free (RFS), disease-specific (DSS), and overall survival (OS) were calculated for the 2 groups.Results: A total of 516 patients (86 younger patients and 430 older patients, matched 1:5) were included in this study. Median follow-up was 42.8 months for the entire study cohort (35.2 months for younger and 49.0 for older patients). The 2 groups were well balanced except for the obvious greater age in the older group (P <.0001) and a higher percentage of myometrial invasion in older patients (P =.003). There were no significant differences between younger and older groups with regard to 5-year RFS (94% younger vs 91% older, P =.69). Similarly, there was no significant difference with regard to DSS (96% younger vs 97% older, P =.90). There was no significant difference between younger and older patients in terms of 5-year OS (89% for both groups, P =.99), but 10-year OS was 83% for younger women compared with 68% for older patients, (P =.1). On multivariate analysis for DSS for the entire study cohort, high tumor grade and the presence of lower uterine segment involvement were the only 2 predictors of shorter DSS (P =.01). On multivariate analysis for RFS, higher stage and the presence of lymphovascular space invasion were the only 2 predictors of shorter RFS (P <.0001 and P =.01, respectively). Older age and higher stage were the only 2 predictors of shorter OS (P <.0001 and P =.01, respectively).Conclusions: When matched based on tumor stage, grade, and adjuvant management, our study suggests that there is no difference between younger and older patients with early-stage EC. High tumor grade, stage, and the presence of lymphovascular invasion remained as independent predictors of survival endpoints in women with early-stage EC.

Radiation Oncology

Liu LJ, **Brown SL**, **Ewing JR**, Ala BD, Schneider KM, and Schlesinger M. Estimation of tumor interstitial fluid pressure (tifp) noninvasively *PLoS One* 2016; 11(7):e0140892. PMID: 27467886. Full Text

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Tumor interstitial fluid pressure (TIFP), is a physiological parameter with demonstrated predictive value for a tumor's aggressiveness, drug delivery, as well as response to treatments such as radiotherapy and chemotherapy. Despite its utility, measurement of TIFP has been limited by the need for invasive procedures. In this work, the theoretical basis for approaching the absolute value of TIFP and the experimental method for noninvasively measuring TIFP are presented. Given specific boundary and continuity conditions, we convert theoretical variables into measurable variables by applying MRI technology. The work shows that TIFP in the central region of the tumor can be estimated by an analysis of the variation of tissue fluid motion in the tumor rim and surrounding tissue. It is determined from three noninvasive measurable parameters: i) an estimate of the velocity of the tumor interstitial fluid at the tumor surface, which is maximal, ii) a measurement of the distance from the tumor surface to where the tumor exudates are absorbed (or normalized), and iii) an estimate of the hydraulic conductivity of the interstitium through which the tumor exudate travels. We experimentally show that the fluid flow within the tumor rim is not uniform, even for a round shaped tumor, and demonstrate the procedures for the noninvasive measurement of TIFP.

Radiation Oncology

Modh A, **Ghanem AI**, **Burmeister C**, **Rasool N**, and **Elshaikh MA**. Trends in the utilization of adjuvant vaginal brachytherapy in women with early-stage endometrial carcinoma: Results of an updated period analysis of SEER data *Brachytherapy* 2016;PMID: 27475480. Full Text

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PURPOSE: Adjuvant vaginal brachytherapy (VB) is a well-established and effective radiation treatment modality in women with early-stage endometrial carcinoma. We sought to evaluate and update published trends in the utilization of VB vs. other radiation therapy modalities (pelvic external beam radiation therapy (EBRT) or the combination of VB and pelvic EBRT using the National Cancer Institute's Surveillance, Epidemiology, and End Results database. METHODS AND MATERIALS: The Surveillance, Epidemiology, and End Results database was queried for adult females with histologically confirmed International Federation of Gynecology and Obstetrics 1988 Stage I-II endometrial carcinoma diagnosed from 1995 to 2012 and treated definitively with hysterectomy and adjuvant radiation therapy. Chi-square tests were used to assess differences by radiation type (VB, EBRT, and VB + EBRT) and various demographic and clinical variables. RESULTS: We identified 15,201 patients that met inclusion criteria. There was a significant overall increase in the use of VB was observed from 17.1% in 1995-2000 compared to 57.1% in 2007-2012 ($p < 0.0001$). Similarly, there was a proportional decrease in the use of EBRT from 54.0% to 25.5% ($p < 0.0001$) as well as in the use of VB + EBRT from 28.9% to 17.4% during the same period ($p < 0.0001$). The observed increase in utilization of VB was not limited to any variables (age, race, histological type, International Federation of Gynecology and Obstetrics stage, and the status of lymph node dissection [yes or no]) or the number of dissected lymph nodes. CONCLUSIONS: In this large national database set, there continues to be an increasing trend for the use of VB in the adjuvant setting in women with early-stage endometrial carcinoma.

Radiation Oncology

Modh A, **Ghanem AI**, **Burmeister C**, **Rasool N**, and **Elshaikh MA**. Trends in the utilization of adjuvant radiation treatment in women with early stage type ii endometrial carcinoma: A surveillance, epidemiology, and end-results study *Brachytherapy* 2016; 15:S89. PMID: Not assigned. Abstract

A. Modh, Radiation Oncology, Henry Ford Health System, Detroit, United States

Purpose: Type II endometrial carcinoma (EC) represents a group of aggressive histologies with a relatively poor prognosis. While an increasing trend for utilizing adjuvant vaginal brachytherapy has been reported in women with early stage type I EC, trends in radiation treatment in patients with type II EC have not been fully investigated. We sought to evaluate the trends in adjuvant radiation modalities (pelvic external beam RT [EBRT] versus vaginal brachytherapy [VB] versus the combination of EBRT+VB) in women with early stage type II endometrial carcinoma using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Materials and

Methods: The SEER database was queried for adult females with histologically confirmed FIGO (1988) stage I-II endometrial carcinoma type II (serous, clear cell and mixed carcinoma) diagnosed from 1995-2012 and treated definitively with hysterectomy and adjuvant radiation therapy. Patients with multiple primary malignancies, those who received radiation treatment prior to surgery or those who did not have any adjuvant treatment were excluded. Patients were grouped in 5-year intervals, from 1995-2000, 2001-2006, and 2007-2012. Chi-squared tests were used to assess differences in utilization of radiation modality and various demographic and clinical variables. Results: We identified 1,249 patients that met our inclusion criteria. In the entire cohort, 42.5% received EBRT, 36.3% received VB, and 21.1% received VB+EBRT. A lymph node dissection was performed in 79.7% of patients. When a lymph node dissection was performed, the median number of lymph nodes examined in our study increased from 12.0 in 1995-2000 to 17.0 in 2007-2012 (p <0.0001). There was an overall increase in the use of VB observed from 15.0% in 1995-2000 to 55.9% in 2007-2012 (p <0.0001). This increase in VB utilization was seen in both older (>60) and younger (<60) patients and irrespective of whether a lymph node dissection was performed or not. In parallel, the use of EBRT fell from 56.5% in 1995-2000 to 28.2% in 2007-2012 (p <0.0001). The use of VB+ERBT combined also decreased over the same time period, from 28.5% in 1995-2000 to 15.9% in 2007-2012 (p<0.0001). Conclusions: Similar to the trends seen in adjuvant radiation treatment in women with type I early stage endometrial carcinoma, there is an increasing trend for the use of adjuvant VB and a declining use of pelvic EBRT in women with type II endometrial carcinoma.

Radiation Oncology
Ren Y, **Janic B**, **Kutskill K**, **Peterson EL**, and **Carretero OA**. Mechanisms of connecting tubule glomerular feedback enhancement by aldosterone *Am J Physiol Renal Physiol* 2016:ajprenal.00076.02016. PMID: 27413197. Full Text

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Connecting tubule glomerular feedback (CTGF) is a mechanism where an increase in sodium (Na) concentration in the connecting tubule (CNT) causes the afferent arteriole (Af-Art) to dilate. We recently reported that aldosterone within the CNT lumen enhances CTGF via a nongenomic effect involving GPR30 receptors and sodium/hydrogen exchanger (NHE), but the signaling pathways of this mechanism are unknown. We hypothesize that aldosterone enhances CTGF via cAMP/protein kinase A (PKA) pathway that activates protein kinase C (PKC) and stimulates superoxide (O-2) production. Rabbit Af-Arts and their adherent CNTs were microdissected and simultaneously perfused. Two consecutive CTGF curves were elicited by increasing the CNT luminal NaCl. We found that the main effect of aldosterone was to sensitize CTGF and we analyzed data by comparing NaCl concentration in the CNT perfusate needed to achieve half of the maximal response (EC50). During the control period, the NaCl concentration that elicited a half-maximal response (EC50) was 37.0+/-2.0 mmol/L; addition of aldosterone (10-8 mol/L) to the CNT lumen decreased EC50 to 19.3+/-1.3 mmol/L (p</=0.001 vs. Control). The specific adenylyl cyclase inhibitor 2',3'-Dideoxyadenosine (ddA) (2x10-4 mol/L) and the PKA inhibitor H-89 dihydrochloride hydrate (H-89) (2x10-6 mol/L) prevented the aldosterone effect. Selective PKC inhibitor GF109203X (10-8 mol/L) also prevented EC50 reduction caused by aldosterone. CNT intraluminal addition of O-2 scavenger tempol (10-4 mol/L) blocked the aldosterone effect. We conclude that aldosterone inside the CNT lumen enhances CTGF via a cAMP/PKA/PKC pathway and stimulates O2 generation and this process may contribute to renal damage by increasing glomerular capillary pressure.

Radiation Oncology
Santoso AP, **Song KH**, **Qin Y**, **Gardner SJ**, **Liu C**, **Chetty IJ**, **Movsas B**, **Ajlouni M**, and **Wen N**. Evaluation of gantry speed on image quality and imaging dose for 4D cone-beam CT acquisition *Radiat Oncol* 2016; 11(1):98. PMID: 27473367. Full Text

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BACKGROUND: This study investigates the effect of gantry speed on 4DCBCT image quality and dose for the Varian On-Board Imager(R). METHODS: A thoracic 4DCBCT protocol was designed using a 125 kVp spectrum. Image quality parameters were evaluated for 4DCBCT acquisition using Catphan(R) phantom with real-time position management system for gantry speeds varying between 1.0 to 6.0 degrees /s. Superior-inferior motion of the phantom was executed using a sinusoidal waveform with five second period. Scans were retrospectively sorted into 4 phases (CBCT-4 ph) and 10 phases (CBCT-10 ph); average 4DCBCT (CBCT-ave), using all image data from the 4DCBCT acquisitions was also evaluated. The 4DCBCT images were evaluated using the following image quality

metrics: spatial resolution, contrast-to-noise ratio (CNR), and uniformity index (UI). Additionally, Hounsfield unit (HU) sensitivity compared to a baseline CBCT and percent differences and RMS errors (RMSE) of excursion were also determined. Imaging dose was evaluated using an IBA CC13 ion chamber placed within CIRS Thorax phantom using the same sinusoidal motion and image acquisition settings as mentioned above. RESULTS: Spatial resolution decreased linearly from 5.93 to 3.82 lp/cm as gantry speed increased from 1.0 to 6.0 degrees /s. CNR decreased linearly from 4.80 to 1.82 with gantry speed increasing from 1.0 to 6.0 degrees /s, respectively. No noteworthy variations in UI, HU sensitivity, or excursion metrics were observed with changes in gantry speed. Ion chamber dose rates measured ranged from 2.30 (lung) to 5.18 (bone) E-3 cGy/mAs. CONCLUSIONS: A quantitative analysis of the Varian OBI's 4DCBCT capabilities was explored. Changing gantry speed changes the number of projections used for reconstruction, affecting both image quality and imaging dose if x-ray tube current is held constant. From the results of this study, a gantry speed between 2 and 3 degrees /s was optimal when considering image quality, dose, and reconstruction time. The future of 4DCBCT clinical utility relies on further investigation of image acquisition and reconstruction optimization.

Radiology
Joshi S, **Vanderhoek M**, and **Harkness B**. CdZnTe detectors: What you need to know *J Nucl Med* 2016; 57PMID: Not assigned. Abstract

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Objectives CdZnTe (CZT) is a semiconductor detector material that is increasingly being used in nuclear medicine applications. As more medical imaging devices incorporate CZT, it is important to become familiar with its material properties and associated physics, and their effects on image quality. The purpose of this educational exhibit is to present some basics of CZT detectors to nuclear medicine professionals in an approachable manner. Methods This educational exhibit will include 1) a review of the unique properties of CZT detector materials, 2) a schematic of common geometry and electronic setup 3) a step-by-step description of signal generation starting with photon interaction, electron-cloud formation and transportation, signal readout, and finally image reconstruction, 4) a description of the small-pixel effect and its contribution to improved spatial and energy resolution, and 5) a discussion of the advantages and disadvantages of CZT compared to other materials (e.g. NaI(Tl)) used in nuclear medicine. Results Diagrams, animations, and analogies will be used to explain complex, yet relevant, physics concepts. Explanations will be based on concepts familiar to nuclear medicine professionals. As an example, Figure 1 describes the configuration of a typical CZT detector geometry. The pixel pitch of the anode determines both the spatial resolution and energy resolution due to the small pixel effect. These parameters, as well as others that affect image quality, will be described through visualizations. Conclusions After reading this educational exhibit, participants should have a better understanding of the basic physics of CZT detectors, how signals are created and processed into images, how CZT compares to other detector materials, as well as challenges that must be overcome in the future. (Figure Presented).

Radiology
Samadi S, **Soltanian-Zadeh H**, and Jutten C. Integrated Analysis of EEG and fMRI using sparsity of spatial maps *Brain Topogr* 2016;PMID: 27460558. Full Text

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Integration of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) is an open problem, which has motivated many researches. The most important challenge in EEG-fMRI integration is the unknown relationship between these two modalities. In this paper, we extract the same features (spatial map of neural activity) from both modality. Therefore, the proposed integration method does not need any assumption about the relationship of EEG and fMRI. We present a source localization method from scalp EEG signal using jointly fMRI analysis results as prior spatial information and source separation for providing temporal courses of sources of interest. The performance of the proposed method is evaluated quantitatively along with multiple sparse priors method and sparse Bayesian learning with the fMRI results as prior information. Localization bias and source distribution index are used to measure the performance of different localization approaches with or without a variety of fMRI-EEG mismatches on simulated realistic data. The method is also applied to experimental data of face perception of 16 subjects. Simulation

results show that the proposed method is significantly stable against the noise with low localization bias. Although the existence of an extra region in the fMRI data enlarges localization bias, the proposed method outperforms the other methods. Conversely, a missed region in the fMRI data does not affect the localization bias of the common sources in the EEG-fMRI data. Results on experimental data are congruent with previous studies and produce clusters in the fusiform and occipital face areas (FFA and OFA, respectively). Moreover, it shows high stability in source localization against variations in different subjects.

Radiology
Shaaban S, Alsulami M, Arbab SA, Ara R, Shankar A, Iskander A, Angara K, Jain M, **Bagher-Ebadian H**, Achyut BR, and Arbab AS. Targeting bone marrow to potentiate the anti-tumor effect of tyrosine kinase inhibitor in preclinical rat model of human glioblastoma *Int J Cancer Res* 2016; 12(2):69-81. PMID: 27429653. Full Text

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Antiangiogenic agents caused paradoxical increase in pro-growth and pro-angiogenic factors and caused tumor growth in glioblastoma (GBM). It is hypothesized that paradoxical increase in pro-angiogenic factors would mobilize Bone Marrow Derived Cells (BMDCs) to the treated tumor and cause refractory tumor growth. The purposes of the studies were to determine whether whole body irradiation (WBIR) or a CXCR4 antagonist (AMD3100) will potentiate the effect of vatalanib (a VEGFR2 tyrosine kinase inhibitor) and prevent the refractory growth of GBM. Human GBM were grown orthotopically in three groups of rats (control, pretreated with WBIR and AMD3100) and randomly selected for vehicle or vatalanib treatments for 2 weeks. Then all animals underwent Magnetic Resonance Imaging (MRI) followed by euthanasia and histochemical analysis. Tumor volume and different vascular parameters (plasma volume (vp), forward transfer constant (Ktrans), back flow constant (kep), extravascular extracellular space volume (ve) were determined from MRI. In control group, vatalanib treatment increased the tumor growth significantly compared to that of vehicle treatment but by preventing the mobilization of BMDCs and interaction of CXCR4-SDF-1 using WBIR and ADM3100, respectively, paradoxical growth of tumor was controlled. Pretreatment with WBIR or AMD3100 also decreased tumor cell migration, despite the fact that ADM3100 increased the accumulation of M1 and M2 macrophages in the tumors. Vatalanib also increased Ktrans and ve in control animals but both of the vascular parameters were decreased when the animals were pretreated with WBIR and AMD3100. In conclusion, depleting bone marrow cells or CXCR4 interaction can potentiate the effect of vatalanib.

Radiology
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 *J Neurointerv Surg* 2016;PMID: 27466463. Full Text

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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.

Rheumatology
Namas R, and **Meysami A**. Sarcoidosis of hands *J Clin Rheumatol* 2016; 22(5):278-279. PMID: 27464776. Full Text

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Sleep Medicine
Kalmbach DA, **Pillai V**, Arnedt JT, **Anderson JR**, and **Drake CL**. Sleep system sensitization: evidence for changing roles of etiological factors in insomnia *Sleep Med* 2016; 21:63-69. PMID: 27448474. Full Text

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OBJECTIVES: To test for sensitization of the sleep system in response to insomnia development and major life stress. In addition, to evaluate the impact on depression and anxiety associated with sleep system sensitization. METHODS: A longitudinal study with three annual assessments. The community-based sample included 262 adults with no history of insomnia or depression who developed insomnia one year after baseline (67.6% female; 44.0 +/- 13.4 yr). Measures included the Ford Insomnia Response to Stress Test to assess sleep reactivity, Quick Inventory of Depressive Symptomatology, and Beck Anxiety Inventory. Insomnia classification was based on DSM-IV criteria. Sleep system sensitization was operationally defined as significant increases in sleep reactivity. RESULTS: Sensitization of the sleep system was observed from baseline to insomnia onset at 1-yr follow-up among insomniacs with low premorbid vulnerability ($p < 0.001$), resulting in 68.3% of these individuals re-classified as highly sleep reactive. Major life stress was associated with greater sleep system sensitization ($p = 0.02$). Results showed that sleep reactivity at 2-yr follow-up remained elevated among those with low premorbid vulnerability, even after insomnia remission ($p < 0.01$). Finally, analyses revealed that increases in sleep reactivity predicted greater depression ($p < 0.001$) and anxiety ($p < 0.001$) at insomnia onset. The impact of sensitization on depression was stable at 2-yr follow-up ($p = 0.01$). CONCLUSIONS: Evidence supports sensitization of the sleep system as a consequence of insomnia development and major life stress among individuals with low premorbid sleep reactivity. Sleep system sensitization may serve as a mechanism by which insomnia is perpetuated. Harmful effects of the sensitization process may increase risk for insomnia-related depression and anxiety.

Sleep Medicine

Muzet A, Werner S, Fuchs G, **Roth T**, Saoud JB, Viola AU, Schaffhauser JY, and Luthringer R. Assessing sleep architecture and continuity measures through the analysis of heart rate and wrist movement recordings in healthy subjects: comparison with results based on polysomnography *Sleep Med* 2016; 21:47-56. PMID: 27448472. Full Text

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OBJECTIVE: The objective of the study was to evaluate the reliability of a new methodology for assessing sleep architecture descriptors based on heart rate and body movement recordings. METHODS: Twelve healthy male and female subjects between 18 and 40 years of age, without sleep disorders and not taking any drug or medication that could affect sleep, were recorded continuously during five consecutive nights. Together with the standard polysomnography, heart rate was recorded with a Holter and wrist movements by actimetry. Of the 60 recorded nights, 48 artifact-free nights were analyzed by two independent and well-trained visual scorers according to the rules of the American Academy of Sleep Medicine. Sleep stages were assigned to every 30-s epoch. In parallel, the same nights were analyzed by the new methodology using only heart rate and actimetry data, allowing a 1-s epoch sleep stage classification. Sleep architecture was measured for 48 nights, independently for the two manual scorings and the automatic analysis. RESULTS: Over 42 nights, the intra-class correlation coefficient, used to assess the consistency or reproducibility of quantitative measurements made by different observers, was classified as excellent when all 12 descriptors were combined. Analyses of the individual descriptors showed excellent interclass correlation for eight and good for four of the 12. CONCLUSION: The automatic analysis of heart rate and body movement during sleep allows for the evaluation of sleep architecture and continuity that is equivalent to those obtained by manual scoring of polysomnography. The technique used here is simple and robust to allow for home sleep monitoring.

Surgery

Berian JR, **Mohanty S**, Ko CY, Rosenthal RA, and Robinson TN. Association of loss of independence with readmission and death after discharge in older patients after surgical procedures *JAMA Surg* 2016;PMID: 27409710. Full Text

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Importance: Older adults are at increased risk for adverse events after surgical procedures. Loss of independence (LOI), defined as a decline in function or mobility, increased care needs at home, or discharge to a nonhome destination, is an important patient-centered outcome measure. Objective: To evaluate LOI among older adult patients after surgical procedures and examine the association of LOI with readmission and death after discharge in this population. Design, Setting, and Participants: This retrospective cohort study examined 9972 patients 65 years and older with known baseline function, mobility, and living situation undergoing inpatient operations from January 2014 to December 2014 at 26 hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program Geriatric Surgery Pilot Project. A total of 4895 patients were excluded because they were totally dependent, classified as class 5 by the American Society of Anesthesiologists, undergoing orthopedic or spinal procedures, or died prior to discharge. Exposures: Loss of independence at time of discharge. Main Outcomes and Measures: Readmission and death after discharge. Results: Of the 5077 patients included in this study, 2736 (53.9%) were female and 3876 (76.3%) were white, with a mean (SD) age of 75 (7) years. For this cohort, LOI increased with age; LOI occurred in 1386 of 2780 patients (49.9%) aged 65 to 74 years, 1162 of 1726 (67.3%) aged 75 to 84 years, and 479 of 571 (83.9%) 85 years and older (P < .001). Readmission occurred in 517 patients (10.2%). In a risk-adjusted model, LOI was strongly associated with readmission (odds ratio, 1.7; 95% CI, 1.4-2.2) and postoperative complication (odds ratio, 6.7; 95% CI, 4.9-9.0). Death after discharge occurred in 69 patients (1.4%). After risk adjustment, LOI was the strongest factor associated with death after discharge (odds ratio, 6.7; 95% CI, 2.4-19.3). Postoperative complication was not significantly associated with death after discharge. Conclusions and Relevance: Loss of independence, a patient-centered outcome, was associated with postoperative readmissions and death after discharge. Loss of independence can feasibly be collected across multiple hospitals in a national registry. Clinical initiatives to minimize LOI will be important for improving surgical care for older adults.

Surgery

Jesse MT, **Rubinstein E**, **Eshelman A**, **Wee C**, **Tankasala M**, **Li J**, and **Abouljoud M**. Lifestyle and self-management by those who live it: Patients engaging patients in a chronic disease model *Perm J* 2016; 20(3)PMID: 27455056.
Article Request Form

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BACKGROUND: Patients pursuing organ transplantation have complex medical needs, undergo comprehensive evaluation for possible listing, and require extensive education. However, transplant patients and their supports frequently report the need for more lifestyle and self-management strategies for living with organ transplantation. OBJECTIVES: First, to explore feasibility of a successful, patient-run transplant lifestyle educational group (Transplant Living Community), designed to complement medical care and integrated into the clinical setting; and second, to report the major themes of patients' and supports' qualitative and quantitative feedback regarding the group. METHODS: Informal programmatic review and patient satisfaction surveys. RESULTS: A total of 1862 patient satisfaction surveys were disseminated and 823 were returned (response rate, 44.2%). Patients and their supports reported positive feedback regarding the group, including appreciation that the volunteer was a transplant recipient and gratitude for the lifestyle information. Five areas were associated with the success of Transplant Living Community: 1) a "champion" dedicated to the program and its successful integration into a multidisciplinary team; 2) a health care environment receptive to integration of a patient-led group with ongoing community development; 3) a high level of visibility to physicians and staff, patients, and supports; 4) a clearly presented and manageable lifestyle plan ("Play Your ACES"a [Attitude, Compliance, Exercise, and Support]), and 5) a strong volunteer structure with thoughtful training with the ultimate objective of volunteers taking ownership of the program. CONCLUSION: It is

feasible to integrate a sustainable patient-led lifestyle and self-management educational group into a busy tertiary care clinic for patients with complex chronic illnesses.

Surgery

Jiagge E, Jibril AS, **Chitale D**, **Bensenhaver JM**, Awuah B, Hoenerhoff M, Adjei E, Bekele M, Abebe E, **Nathanson SD**, **Gyan K**, Salem B, Oppong J, Aitpillah F, Kyei I, Bonsu EO, **Proctor E**, Merajver SD, Wicha M, **Stark A**, and **Newman LA**. Comparative analysis of breast cancer phenotypes in african american, white american, and west versus east african patients: Correlation between african ancestry and triple-negative breast cancer *Ann Surg Oncol* 2016;PMID: 27469125. Full Text

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INTRODUCTION: Triple-negative breast cancer (TNBC) is more common among African American (AA) and western sub-Saharan African breast cancer (BC) patients compared with White/Caucasian Americans (WA) and Europeans. Little is known about TNBC in east Africa. METHODS: Invasive BC diagnosed 1998-2014 were evaluated: WA and AA patients from the Henry Ford Health System in Detroit, Michigan; Ghanaian/west Africans from the Komfo Anokye Teaching Hospital in Kumasi, Ghana; and Ethiopian/east Africans from the St. Paul's Hospital Millennium Medical College in Addis Ababa, Ethiopia. Histopathology and immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression was performed in Michigan on formalin-fixed, paraffin-embedded samples from all cases. RESULTS: A total of 234 Ghanaian (mean age 49 years), 94 Ethiopian (mean age 43 years), 272 AA (mean age 60 years), and 321 WA (mean age 62 years; $p = 0.001$) patients were compared. ER-negative and TNBC were more common among Ghanaian and AA compared with WA and Ethiopian cases (frequency ER-negativity 71.1 and 37.1 % vs. 19.8 and 28.6 % respectively, $p < 0.0001$; frequency TNBC 53.2 and 29.8 % vs. 15.5 and 15.0 %, respectively, $p < 0.0001$). Among patients younger than 50 years, prevalence of TNBC remained highest among Ghanaians (50.8 %) and AA (34.3 %) compared with WA and Ethiopians (approximately 16 % in each; $p = 0.0002$). CONCLUSIONS: This study confirms an association between TNBC and West African ancestry; TNBC frequency among AA patients is intermediate between WA and Ghanaian/West Africans consistent with genetic admixture following the west Africa-based trans-Atlantic slave trade. TNBC frequency was low among Ethiopians/East Africans; this may reflect less shared ancestry between AA and Ethiopians.

Surgery

Kabbani LS, **Wasilenko S**, **Nypaver TJ**, **Weaver MR**, **Taylor AR**, **Abdul-Nour K**, **Borgi J**, and **Shepard AD**. Socioeconomic disparities affect survival after aortic dissection *J Vasc Surg* 2016;PMID: 27374067. Full Text

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OBJECTIVE: The effect of socioeconomic status (SES) on the course of many disease states has been documented in the literature but has not been studied in aortic dissection. This study evaluated the effect of SES on 30-day and long-term survival of patients after aortic dissection. METHODS: Hospital discharge records were used to identify patients with acute aortic dissection. Patient demographics, insurance status, comorbidities, and 30-day mortality were collected. Home addresses were used to estimate each patient's median household income, and the neighborhood deprivation index, a measure of SES, was determined. Long-term survival was assessed by review of the Social Security Death Index. Associations between demographics, insurance status, comorbidities, and poverty level were investigated to determine their effect on survival. RESULTS: There were 212 aortic dissections; of which, 118 were type A and 94 were type B. Median follow-up was 7.6 years. The neighborhood deprivation index (hazard

ratio, 1.43; 95% confidence interval, 1.16-1.78; P = .001) was associated with reduced long-term survival and was also significantly associated with 30-day mortality (hazard ratio, 1.43; 95% confidence interval, 1.05-1.93; P = .02). The mean neighborhood deprivation index score was higher in patients with type B aortic dissections (0.45 +/- 0.93) than in those with type A aortic dissections (0.16 +/- 0.96; P = .029). CONCLUSIONS: Patients with a lower SES had reduced short-term and long-term survival after aortic dissection. Patients with type B dissection live in lower socioeconomic neighborhoods than patients with type A dissection.

Surgery
Kroll HR, **Macaulay T**, and **Jesse M**. A preliminary survey examining predictors of burnout in pain medicine physicians in the united states *Pain Physician* 2016; 19(5):E689-696. PMID: 27389112. Full Text

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BACKGROUND: Burnout is a prolonged response to chronic emotional and interpersonal stressors on the job, defined by 3 dimensions: exhaustion, depersonalization, and reduced personal accomplishment. While there is a growing body of research on burnout in physicians, there is a dearth of literature on burnout in pain medicine physicians. OBJECTIVE: This study aimed to determine the incidence of burnout amongst pain medicine physicians and whether there are sociodemographic or psychological demand characteristics of the job setting that predict burnout in pain medicine physicians. STUDY DESIGN AND SETTING: Cross-section survey of pain medicine physicians across the United States. METHODS: Pain medicine physicians were asked questions on sociodemographics and professional characteristics and measures of decisional authority, psychological job demands, job insecurity, perceived coworker support, and job dissatisfaction. RESULTS: Two hundred seven pain medicine physicians' responses were analyzed, 60.4% reported high emotional exhaustion, 35.7% reported high depersonalization, and 19.3% reported low personal accomplishment. Greater psychological job demands and greater job dissatisfaction predicted greater emotional exhaustion. Younger age and greater job dissatisfaction predicted higher depersonalization. Lastly, lower coworker support and greater job dissatisfaction predicted lower personal accomplishment. There were no statistical violations of assumptions or collinearity. LIMITATIONS: Low response rate and potential for response bias limit generalizability of the study. CONCLUSION(S): Pain medicine physicians in the United States reported high levels of emotional exhaustion, often considered the most taxing aspect of burnout. Job dissatisfaction appeared to be the leading agent in the development of all 3 components of burnout in pain medicine physicians in the United States.

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 *J Neurointerv Surg* 2016;PMID: 27466463. Full Text

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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.

Surgery
Xuereb L, **Go PH**, **Kaur B**, **Akrawe S**, **Nemeh HW**, **Borgi J**, **Williams CT**, **Paone G**, and **Morgan JA**. Impact of preoperative atrial fibrillation on postoperative thromboembolic events after left ventricular assist device implantation *Ann Thorac Surg* 2016;PMID: 27469338. Full Text

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BACKGROUND: The incidence of atrial fibrillation (AF) among patients undergoing left ventricular assist device (LVAD) implantation is high. However, the impact of AF on clinical outcomes has not been clarified. We reviewed our 9-year experience of continuous flow (CF) LVADs to determine the impact of preoperative AF on stroke, device thrombosis, and survival. METHODS: Between March 2006 and May 2015, 231 patients underwent implantation of 240 CF LVADs, 127 (52.9%) as bridge to transplantation and 113 (47.1%) as destination therapy. Effect of AF on postoperative outcomes was assessed by using Kaplan-Meier survival and Cox proportional hazard regression. RESULTS: There were 78 patients (32.5%) with preoperative AF with a mean age of 55.7 +/- 11.4 years. A similar incidence of stroke was found in patients with and without AF, 12.8% versus 16.0%, respectively (p = 0.803). Survival was similar, with 1-, 6-, 12-, and 24-month survivals of 96.2%, 91.7%, 84.5%, and 69.2%, respectively, for AF patients, versus 93.1%, 85.0%, 79.4%, and 74.1%, respectively, for non-AF patients (p = 0.424). Preoperative AF was not a significant independent predictor of survival with the use of Cox proportional hazard regression (hazard ratio 1.08, 95% confidence interval: 0.66 to 1.76). CONCLUSIONS: Preoperative AF was associated with a similar incidence of postoperative stroke, device thrombosis, and survival. On the basis of these data, it seems unnecessary to perform a left atrial appendage ligation or to alter postoperative anticoagulation in patients with AF undergoing LVAD implantation.

Urology
Abdullah N, **Rahbar H**, **Barod R**, **Dalela D**, Larson J, Johnson M, Mass A, Zargar H, Allaf M, Bhayani S, Stifelman M, Kaouk J, and **Rogers C**. Multicentre outcomes of robot-assisted partial nephrectomy after major open abdominal surgery *BJU Int* 2016; 118(2):298-301. PMID: 27417163. Full Text

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OBJECTIVE: To evaluate the outcomes of robot-assisted partial nephrectomy RAPN after major prior abdominal surgery (PAS) using a large multicentre database. PATIENTS AND METHODS: We identified 1 686 RAPN from five academic centres between 2006 and 2014. In all, 216 patients had previously undergone major PAS, defined as having an open upper midline/ipsilateral incision. Perioperative outcomes were compared with those 1 470 patients who had had no major PAS. The chi-squared test and Mann-Whitney U-test were used for categorical and continuous variables, respectively. RESULTS: There was no statistically significant difference in Charlson comorbidity index, tumour size, R.E.N.A.L. nephrometry score or preoperative estimated glomerular filtration rate (eGFR) between the groups. Age and body mass index were higher in patients with PAS. The PAS group had a higher estimated blood loss (EBL) but this did not lead to a higher transfusion rate. A retroperitoneal approach was used more often in patients with major PAS (11.2 vs 5.4%), although this group did not have a higher percentage of posterior tumours (38.8 vs 43.3%, P = 0.286). Operative time, warm ischaemia time, length of stay, positive surgical margin, percentage change in eGFR, and perioperative complications were not significantly different between the groups. CONCLUSIONS: RAPN in patients with major PAS is safe and feasible, with increased EBL but no increased rate of transfusion. Patients with major PAS had almost twice the likelihood of having a retroperitoneal approach.

Urology
Karnes J, Ashab HA, Trock BJ, Ross A, Tsai H, Tosoian JJ, Erho N, Choeurng V, Yousefi K, Haddad Z, **Abdollah F**, Klein EA, Nguyen PL, Feng FYC, Dicker A, Den RB, Davicioni E, Jenkins RB, Lotan TL, and Schaeffer EM. Development and validation of an ADT resistance signature to predict adjuvant hormone treatment failure *J Clin Oncol* 2016; 34(2):1. PMID: Not assigned. Abstract

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Urology
Lee HJ, Yousefi K, Haddad Z, **Abdollah F**, Lam LL, Shin H, Alshalalfa M, Godebu E, Wang S, Shabaik A, Davicioni E, and Kane CJ. Evaluation of a genomic classifier in radical prostatectomy patients with lymph node metastasis *Res Rep Urol* 2016; 8:77-84. PMID: 27419104. Full Text

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OBJECTIVE: To evaluate the performance of the Decipher test in predicting lymph node invasion (LNI) on radical prostatectomy (RP) specimens. METHODS: We identified 1,987 consecutive patients with RP who received the Decipher test between February and August 2015 (contemporary cohort). In the contemporary cohort, only the Decipher score from RP specimens was available for analysis. In addition, we identified a consecutive cohort of patients treated with RP between 2006 and 2012 at the University of California, San Diego, with LNI upon pathologic examination (retrospective cohort). The retrospective cohort yielded seven, 22, and 18 tissue specimens from prostate biopsy, RP, and lymph nodes (LNs) for individual patients, respectively. Univariable and multivariable logistic regression analyses were used to evaluate the performance of Decipher in the contemporary cohort with LNI as the endpoint. In the retrospective cohort, concordance of risk groups was assessed using validated cut-points for low (<0.45), intermediate (0.45-0.60), and high (>0.60) Decipher scores. RESULTS: In the contemporary cohort, 51 (2.6%) patients had LNI. Decipher had an odds ratio of 1.73 (95% confidence interval, 1.46-2.05) and 1.42 (95% confidence interval, 1.19-1.7) per 10% increase in score on univariable and multivariable (adjusting for pathologic Gleason score, extraprostatic extension, and seminal vesicle invasion), respectively. No significant difference in the clinical and pathologic characteristics between the LN positive patients of contemporary and retrospective cohorts was observed (all P>0.05). Accordingly, among LN-positive patients in the contemporary cohort and retrospective cohort, 80% and 77% had Decipher high risk scores (P=1). In the retrospective cohort, prostate biopsy cores with the highest Gleason grade and percentage of tumor involvement had 86% Decipher risk concordance with both RP and LN specimens. CONCLUSION: Decipher scores were highly concordant between pre- and post-surgical specimens. Further, Decipher scores from RP tissue were predictive of LNI at RP. If validated in a larger cohort of prostate biopsy specimens for prediction of adverse pathology at RP, Decipher may be useful for improved pre-operative staging.

Urology

Sarveswaran S, **Ghosh R**, **Parikh R**, and **Ghosh J**. Wedelolactone, an anti-inflammatory botanical, interrupts c-Myc oncogenic signaling and synergizes with enzalutamide to induce apoptosis in prostate cancer cells *Mol Cancer Ther* 2016;PMID: 27474149. Article Request Form

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The c-Myc gene encodes an oncoprotein transcription factor which is frequently up-regulated in almost all cancer types, and is the subject of intense investigation for management of cancer because of its pleiotropic effects controlling a spectrum of cellular functions. However, due of its non-enzymatic nature, development of suitable strategies to block its protein-protein or protein-DNA interaction is challenging. Thus, c-Myc has been recognized as an elusive molecular target for cancer control and various approaches are in development to inhibit c-Myc-transcriptional activity. We observed that wedelolactone (WDL), an anti-inflammatory botanical compound, severely down-regulates the expression of c-Myc mRNA in prostate cancer cells. Moreover, WDL dramatically decreases the protein level, nuclear localization, DNA-binding, and transcriptional activities of c-Myc. c-Myc is a transforming oncogene widely expressed in prostate cancer cells and is critical for maintaining their transformed phenotype. Interestingly, WDL was found to strongly affect the viability of Myc-activated prostate cancer cells, and completely blocks their invasion as well as soft-agar colony-formation in vitro. WDL was also found to down-regulate c-Myc in vivo in nude mice xenografts. Moreover, WDL synergizes with enzalutamide to decrease the viability of androgen-sensitive prostate cancer cells via induction of apoptosis. These findings reveal a novel anticancer mechanism of the natural compound, WDL, and suggest that the oncogenic function of c-Myc in prostate cancer cells can be effectively down-regulated by WDL for the development of a new therapeutic strategy against Myc-driven prostate cancer.

Urology

Trinh VQ, Ravi P, **Abd-El-Barr AE**, **Jhaveri JK**, Gervais MK, Meyer CP, Hanske J, **Sammon JD**, and Trinh QD. Pneumonia after major cancer surgery: Temporal trends and patterns of care *Can Respir J* 2016; 2016:6019416. PMID: 27445554. Full Text

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Rationale. Pneumonia is a leading cause of postoperative complication. Objective. To examine trends, factors, and mortality of postoperative pneumonia following major cancer surgery (MCS). Methods. From 1999 to 2009, patients undergoing major forms of MCS were identified using the Nationwide Inpatient Sample (NIS), a Healthcare Cost and Utilization Project (HCUP) subset, resulting in weighted 2,508,916 patients. Measurements. Determinants were examined using logistic regression analysis adjusted for clustering using generalized estimating equations. Results. From 1999 to 2009, 87,867 patients experienced pneumonia following MCS and prevalence increased by 29.7%. The estimated annual percent change (EAPC) of mortality after MCS was -2.4% (95% CI: -2.9 to -2.0, $P < 0.001$); the EAPC of mortality associated with pneumonia after MCS was -2.2% (95% CI: -3.6 to 0.9, $P = 0.01$). Characteristics associated with higher odds of pneumonia included older age, male, comorbidities, nonprivate insurance, lower income, hospital volume, urban, Northeast region, and nonteaching status. Pneumonia conferred a 6.3-fold higher odd of mortality. Conclusions. Increasing prevalence of pneumonia after MCS, associated with stable mortality rates, may result from either increased diagnosis or more stringent coding. We identified characteristics associated with pneumonia after MCS which could help identify at-risk patients in order to reduce pneumonia after MCS, as it greatly increases the odds of mortality.