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Henry Ford Health System Publication List – January 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 the beginning of February, and then imported into EndNote for formatting.There are 105 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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Allergy and Immunology

Cassidy-Bushrow AE, **Wegienka G**, **Havstad S**, **Levin AM**, Lynch SV, Ownby DR, Rundle AG, **Woodcroft KJ**, **Zoratti EM**, and **Johnson CC**. Race-specific association of caesarean-section delivery with body size at age 2 years *Ethn Dis* 2016; 26(1):61-68. PMID: 26843797. Article Request Form

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OBJECTIVE: African American children are at higher risk of obesity than White children and African American women are more likely to undergo caesarean-section (CS) delivery than White women. CS is associated with childhood obesity; however, little is known whether this relationship varies by race. We examined if the association of CS with obesity at age 2 years varied by race. DESIGN: Longitudinal birth cohort. SETTING: Birth cohort conducted in a health care system in metropolitan Detroit, Michigan with follow-up at age 2 years. PARTICIPANTS: 639 birth cohort participants; 367 children (57.4%) were born to African American mothers and 230 (36.0%) children were born via CS. MAIN OUTCOME MEASURES: Obesity defined as body mass index >/=95th percentile at age 2 years. RESULTS: Slightly more children of African American (n=37; 10.1%) than non-African American mothers (n=18; 6.6%) were obese (P=.12). There was evidence of effect modification between race and delivery mode with obesity at age 2 years (interaction P=.020). In children of African American mothers, CS compared to vaginal birth was associated with a significantly higher odds of obesity (aOR=2.35 (95% CI: 1.16, 4.77), P=.017). In contrast, delivery mode was not associated with obesity at age 2 years in children of non-African American mothers (aOR=.47 (95% CI: .13, 1.71), P=.25). CONCLUSIONS: There is evidence for a race-specific effect of CS on obesity at age 2 years; potential underlying mechanisms may be racial differences in the developing gut microbiome or in epigenetic programming. Future research is needed to determine if this racial difference persists into later childhood.

Allergy and Immunology

Joseph CL, **Zoratti EM**, **Ownby DR**, **Havstad S**, **Nicholas C**, **Nageotte C**, **Misiak R**, **Enberg R**, Ezell J, and **Johnson CC**. Exploring racial differences in IgE-mediated food allergy in the WHEALS birth cohort *Ann Allergy Asthma Immunol* 2016;PMID: 26837607. Full Text

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BACKGROUND: Suspected food allergies are the cause of more than 200,000 visits to the emergency department annually. Racial differences in the prevalence of food allergy have also been reported, but the evidence is less conclusive. Researchers continue to struggle with the identification of food allergy for epidemiologic studies. OBJECTIVE: To explore racial differences in IgE-mediated food allergy (IgE-FA) in a birth cohort. METHODS: We used a panel of board-certified allergists to systematically identify IgE-FA to egg, milk, or peanut in a multiethnic birth cohort in which patient medical history, patient symptoms, and clinical data were available through 36 months of age. RESULTS: Of the 590 infants analyzed, 52.9% were male and 65.8% African American. Sensitization (serum specific IgE >0.35 IU/mL) to the food allergens was significantly higher for African American children compared with non-African American children as has been previously reported. No statistically significant racial/ethnic differences in IgE-FA were observed; however, a higher proportion of African American children were designated as having peanut allergy, and the percentage of African American children with an IgE level greater than 95% predictive decision points for peanut was 1.7% vs 0.5% for non-African American children. With the use of logistic regression, race/ethnicity was not significantly associated with IgE-FA (adjusted odds ratio, 1.12; 95% confidence interval, 0.58-2.17; P = .75) but was associated with sensitization to more than 1 of the food allergens (adjusted odds ratio, 1.80; 95% confidence interval, 1.22-2.65; P = .003). CONCLUSION: We did not observe an elevated risk of IgE-FA for African American children, although established differences in sensitization were observed. Racial/ethnic differences in sensitization must be taken into consideration when investigating disparities in asthma and allergy.

Cardiology / Cardiovascular Research

Blaha MJ, Hung RK, Dardari Z, Feldman DI, Whelton SP, **Nasir K**, Blumenthal RS, **Brawner CA**, **Ehrman JK**, **Keteyian SJ**, and **Al-Mallah MH**. Age-dependent prognostic value of exercise capacity and derivation of fitness-associated biologic age *Heart* 2016;PMID: 26732181. Full Text

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OBJECTIVE: Given the aging population and prevalence of sedentary behaviour in the USA, we investigated the impact of differences in exercise capacity associated with age on long-term outcomes. We derived fitness-associated 'biologic age' as a tool to encourage positive lifestyle changes. METHODS: This retrospective cohort study included 57 085 patients without established coronary artery disease or heart failure (median age 53 years, 49% women, 29% black) who underwent clinically-referred treadmill stress testing at the Henry Ford Health System from 1991 to 2009. Patients were followed for 10.4+/-5 and 5.4+/-4 years for all-cause mortality and myocardial infarction (MI), respectively. We calculated hazard ratios associated with exercise capacity by age deciles using Cox regression models, adjusting for demographic and haemodynamic data, medical history, and medication use. Fitness-associated 'biologic age' was derived as the chronologic age with equivalent mortality or MI risk. RESULTS: There were 6356 deaths and 1646 MIs during follow-up. Exercise capacity declined with increasing age. Higher exercise capacity was strongly associated with greater survival, with per-MET HR ranging from 0.82 (95% CI 0.78 to 0.86) in patients under 40 years of age, to 0.88 (95% CI 0.87 to 0.90) in those over 70 years of age. Biologic age varied markedly-up to three decades-within each age decile, and was a stronger predictor of mortality (C-statistic 0.81 vs 0.77) and MI (C-statistic 0.72 vs 0.68) than chronologic age. CONCLUSIONS: Higher exercise capacity remained a powerful predictor of survival despite lower average exercise capacity at older ages, reinforcing its importance in patients of all ages. Fitness-associated biologic age was a stronger predictor of survival than chronologic age, and may be a useful clinical tool for facilitating patient discussions regarding the impact of exercise capacity on long-term risk.

Cardiology / Cardiovascular Research

Brawner CA, Churilla JR, and **Keteyian SJ**. Prevalence of physical activity is lower among individuals with chronic disease *Med Sci Sports Exerc* 2016;PMID: 26741117. Full Text

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INTRODUCTION: Physical inactivity is associated with increased risk for morbidity and mortality and contributes to healthcare costs. While data supporting the secondary preventive benefits of being physically active continues to grow, there is limited data on the prevalence of sufficient volume of leisure-time physical activity (LTPA) among individuals diagnosed with chronic disease. PURPOSE: To describe the association between select chronic diseases and the prevalence of sufficient volume of aerobic LTPA to achieve substantial health benefits (i.e., >/=150 min/wk) among adults in the United States (US). METHODS: Self-reported LTPA and history of select chronic diseases were obtained from a nationally representative sample of non-institutionalized civilian adults 18 years and older in the US who participated in the 2014 National Health Interview Survey (n = 36,697). RESULTS: Among all adults the prevalence of sufficient volume of aerobic LTPA was 50.1% +/- 0.5% (mean +/- standard error). This prevalence was inversely related to age and was lower in women (47.1% +/- 0.6%) compared to men (53.4% +/- 0.6%; P < 0.001). Prevalence of sufficient volume of aerobic LTPA was lower for each chronic disease (prevalence range = 26.1% to 48.6%) compared to apparently healthy adults (53.6 +/- 0.7%). Relative to no chronic disease, each additional chronic disease was associated with an odds ratio = 0.83 (95% confidence interval 0.81, 0.85; P <0.001) for sufficient volume of aerobic LTPA. CONCLUSIONS: The prevalence of sufficient volume of aerobic LTPA to achieve substantial health benefits is inversely related to age and is lower among women and individuals with a chronic disease. Systems to regularly assess physical activity are needed as well as programs to help individuals be more active.

Cardiology / Cardiovascular Research
Cabrera R, and **Ananthasubramaniam K**. Diagnosis, therapeutic response assessment, and detection of disease recurrence in cardiac sarcoidosis: Integral role of cardiac PET *J Nucl Cardiol* 2016;PMID: 26809438.
Article Request Form

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Cardiology / Cardiovascular Research
Keteyian SJ, and **Kerrigan DJ**. Tugging on a simpler test to evaluate physical mobility and function in patients with heart failure *J Card Fail* 2016;PMID: 26777756. Full Text

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Cardiology / Cardiovascular Research
Kutyifa V, Daubert JP, **Schuger C**, Goldenberg I, Klein H, Aktas MK, McNitt S, Stockburger M, Merkely B, Zareba W, and Moss AJ. Novel ICD Programming and Inappropriate ICD Therapy in CRT-D Versus ICD Patients: A MADIT-RIT Sub-Study *Circ Arrhythm Electrophysiol* 2016; 9(1)PMID: 26743237. Full Text

From the University of Rochester Medical Center, Heart Research Follow-Up Program, Rochester, NY (V.K., I.G., H.K., M.K.A., S.M., W.Z., A.J.M.); Duke University Medical Center, Division of Cardiology, Durham, NC (J.P.D.); Henry Ford Hospital, Detroit, MI (C.S.); Experimental and Clinical Research Center, a Joint Cooperation between the Charite Medical Faculty and the Max-Delbrueck Center for Molecular Medicine, Berlin, Germany (M.S.); and Semmelweis University, Heart and Vascular Center, Budapest, Hungary (B.M.). Valentina.Kutyifa@heart.rochester.edu.
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BACKGROUND: The Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate therapy (MADIT-RIT) trial showed a significant reduction in inappropriate implantable cardioverter defibrillator (ICD) therapy in patients programmed to high-rate cut-off (Arm B) or delayed ventricular tachycardia therapy (Arm C), compared with conventional programming (Arm A). There is limited data on the effect of cardiac resynchronization therapy with a cardioverter defibrillator (CRT-D) on the effect of ICD programming. We aimed to elucidate the effect of CRT-D on ICD programming to reduce inappropriate ICD therapy in patients implanted with CRT-D or an ICD, enrolled in MADIT-RIT. METHODS AND RESULTS: The primary end point of this study was the first inappropriate ICD therapy. Secondary end points were inappropriate anti-tachycardia pacing and inappropriate ICD shock. The study enrolled 742 (49%) patients with an ICD and 757 (51%) patients with a CRT-D. Patients implanted with a CRT-D had 62%

lower risk of inappropriate ICD therapy than those with an ICD only (hazard ratio [HR] =0.38, 95% confidence interval: 0.25-0.57; P<0.001). High-rate cut-off or delayed ventricular tachycardia therapy programming significantly reduced the risk of inappropriate ICD therapy compared with conventional ICD programming in ICD (HR=0.14 [B versus A]; HR=0.21 [C versus A]) and CRT-D patients (HR=0.15 [B versus A]; HR=0.23 [C versus A]; P<0.001 for all). There was a significant reduction in inappropriate anti-tachycardia pacings in both group and a significant reduction in inappropriate ICD shock in CRT-D patients. CONCLUSIONS: Patients implanted with a CRT-D have lower risk of inappropriate ICD therapy than those with an ICD. Innovative ICD programming significantly reduces the risk of inappropriate ICD therapy in both ICD and CRT-D patients. CLINICAL TRIAL REGISTRATION: http://clinicaltrials.gov; Unique identifier: NCT00947310.

Cardiology / Cardiovascular Research

Morgan JA, and **O'Neill WW**. Percutaneous right ventricular assist device support in a patient supported by an LVAD *Asaio j* 2016;PMID: 26771398. Full Text

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Right ventricular failure requiring short-term mechanical support is a relatively common complication after left ventricular assist device (LVAD) implantation. Removal of the temporary right ventricular assist device (RVAD) generally requires a reoperative sternotomy. In this report, we describe an innovative percutaneous approach for placing an RVAD at the time of LVAD implantation using the Impella RP (Abiomed Inc., Danvers, MA.) that does not require reoperation for removal, as the Impella RP can be removed at the patient's bedside.

Cardiology / Cardiovascular Research

Mueller C, Giannitsis E, Christ M, Ordonez-Llanos J, deFilippi C, **McCord J**, Body R, Panteghini M, Jernberg T, Plebani M, Verschuren F, French J, Christenson R, Weiser S, Bendig G, Dilba P, and Lindahl B. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin t *Ann Emerg Med* 2016;PMID: 26794254. Full Text

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Department of Biomedical and Clinical Sciences "Luigi Sacco," University of Milan Medical School, Milan, Italy.
Department of Medicine, Karolinska Institutet, Huddinge, Sweden.
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Department of Acute Medicine, Cliniques Universitaires St-Luc and Universite Catholique de Louvain, Brussels, Belgium.
Liverpool Hospital and University of New South Wales, Liverpool, NSW, Australia.
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STUDY OBJECTIVE: We aim to prospectively validate the diagnostic accuracy of the recently developed 0-h/1-h algorithm, using high-sensitivity cardiac troponin T (hs-cTnT) for the early rule-out and rule-in of acute myocardial infarction. METHODS: We enrolled patients presenting with suspected acute myocardial infarction and recent (<6 hours) onset of symptoms to the emergency department in a global multicenter diagnostic study. Hs-cTnT (Roche Diagnostics) and sensitive cardiac troponin I (Siemens Healthcare) were measured at presentation and after 1 hour, 2 hours, and 4 to 14 hours in a central laboratory. Patient triage according to the predefined hs-cTnT 0-hour/1-hour algorithm (hs-cTnT below 12 ng/L and Delta1 hour below 3 ng/L to rule out; hs-cTnT at least 52 ng/L or Delta1 hour at least 5 ng/L to rule in; remaining patients to the "observational zone") was compared against a centrally adjudicated final diagnosis by 2 independent cardiologists (reference standard). The final diagnosis was based on all available information, including coronary angiography and echocardiography results, follow-up data, and serial measurements of sensitive cardiac troponin I, whereas adjudicators remained blinded to hs-cTnT. RESULTS: Among 1,282 patients enrolled, acute myocardial infarction was the final diagnosis for 213 (16.6%) patients. Applying the hs-

cTnT 0-hour/1-hour algorithm, 813 (63.4%) patients were classified as rule out, 184 (14.4%) were classified as rule in, and 285 (22.2%) were triaged to the observational zone. This resulted in a negative predictive value and sensitivity for acute myocardial infarction of 99.1% (95% confidence interval [CI] 98.2% to 99.7%) and 96.7% (95% CI 93.4% to 98.7%) in the rule-out zone (7 patients with false-negative results), a positive predictive value and specificity for acute myocardial infarction of 77.2% (95% CI 70.4% to 83.0%) and 96.1% (95% CI 94.7% to 97.2%) in the rule-in zone, and a prevalence of acute myocardial infarction of 22.5% in the observational zone. CONCLUSION: The hs-cTnT 0-hour/1-hour algorithm performs well for early rule-out and rule-in of acute myocardial infarction.

Cardiology / Cardiovascular Research

Sabbah HN, **Gupta RC**, **Kohli S**, **Wang M**, **Hachem S**, and **Zhang K**. Chronic Therapy With Elamipretide (MTP-131), a Novel Mitochondria-Targeting Peptide, Improves Left Ventricular and Mitochondrial Function in Dogs With Advanced Heart Failure *Circ Heart Fail* 2016; 9(2):e002206. PMID: 26839394. Full Text

From the Department of Medicine, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI. hsabbah1@hfhs.org.

BACKGROUND: Elamipretide (MTP-131), a novel mitochondria-targeting peptide, was shown to reduce infarct size in animals with myocardial infarction and improve renal function in pigs with acute and chronic kidney injury. This study examined the effects of chronic therapy with elamipretide on left ventricular (LV) and mitochondrial function in dogs with heart failure (HF). METHODS AND RESULTS: Fourteen dogs with microembolization-induced HF were randomized to 3 months monotherapy with subcutaneous injections of elamipretide (0.5 mg/kg once daily, HF+ELA, n=7) or saline (control, HF-CON, n=7). LV ejection fraction, plasma n-terminal pro-brain natriuretic peptide, tumor necrosis factor-alpha, and C-reactive protein were measured before (pretreatment) and 3 months after initiating therapy (post-treatment). Mitochondrial respiration, membrane potential (Deltapsim), maximum rate of ATP synthesis, and ATP/ADP ratio were measured in isolated LV cardiomyocytes obtained at post-treatment. In HF-CON dogs, ejection fraction decreased at post-treatment compared with pretreatment (29+/-1% versus 31+/-2%), whereas in HF+ELA dogs, ejection fraction significantly increased at post-treatment compared with pretreatment (36+/-2% versus 30+/-2%; P<0.05). In HF-CON, n-terminal pro-brain natriuretic peptide increased by 88+/-120 pg/mL during follow-up but decreased significantly by 774+/-85 pg/mL in HF+ELA dogs (P<0.001). Treatment with elamipretide also normalized plasma tumor necrosis factor-alpha and C-reactive protein and restored mitochondrial state-3 respiration, Deltapsim, rate of ATP synthesis, and ATP/ADP ratio (ATP/ADP: 0.38+/-0.04 HF-CON versus 1.16+/-0.15 HF+ELA; P<0.001). CONCLUSIONS: Long-term therapy with elamipretide improves LV systolic function, normalizes plasma biomarkers, and reverses mitochondrial abnormalities in LV myocardium of dogs with advanced HF. The results support the development of elamipretide for the treatment of HF.

Cardiology / Cardiovascular Research

Shaya GE, **Al-Mallah MH**, Hung RK, Nasir K, Blumenthal RS, **Ehrman JK**, **Keteyian SJ**, **Brawner CA**, Qureshi WT, and Blaha MJ. High Exercise Capacity Attenuates the Risk of Early Mortality After a First Myocardial Infarction: The Henry Ford Exercise Testing (FIT) Project *Mayo Clin Proc* 2016; 91(2):129-139. PMID: 26848000. Full Text

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OBJECTIVE: To examine the effect of objectively measured exercise capacity (EC) on early mortality (EM) after a first myocardial infarction (MI). PATIENTS AND METHODS: This retrospective cohort study included 2061 patients without a history of MI (mean age, 62+/-12 years; 38% [n=790] women; 56% [n=1153] white) who underwent clinical treadmill stress testing in the Henry Ford Health System from January 1, 1991, through May 31, 2009, and suffered MI during follow-up (MI event proportion, 3.4%; mean time from the exercise test to MI, 6.1+/-4.3 years). Exercise capacity was categorized on the basis of peak metabolic equivalents (METs) achieved: less than 6, 6 to 9, 10 to 11, and 12 or more METs. Early mortality was defined as all-cause mortality within 28, 90, or 365 days of MI.

Multivariable logistic regression models were used to assess the effect of EC on the risk of mortality at each time point post-MI adjusting for baseline demographic characteristics, cardiovascular risk factors, medication use, indication for stress testing, and year of MI. RESULTS: The 28-day EM rate was 10.6% overall, and 13.9%, 10.7%, 6.9%, and 6.0% in the less than 6, 6 to 9, 10 to 11, and 12 or more METs categories, respectively (P<.001). Patients who died were more likely to be older, be less fit, be nonobese, have treated hypertension, and have a longer duration from baseline to incident MI (P<.05). Adjusted regression analyses revealed a decreased risk of EM with increasing EC categories. A 1-MET higher EC was associated with an 8% to 10% lower risk of mortality across all time points (28 days: odds ratio [OR], 0.92; 95% CI, 0.87-0.98; P=.006; 90 days: OR, 0.90; 95% CI, 0.86-0.95; P<.001; 365 days: OR, 0.91; 95% CI, 0.87-0.94; P<.001). CONCLUSION: Higher baseline EC was independently associated with a lower risk of early death after a first MI.

Cardiology / Cardiovascular Research

Sivanandam A, and **Ananthasubramaniam K**. Midventricular hypertrophic cardiomyopathy with apical aneurysm: Potential for underdiagnosis and value of multimodality imaging *Case Rep Cardiol* 2016; 2016:5. PMID: Not assigned. Full Text

Center for Health Policy and Health Services Research

Neophytou AM, White MJ, Oh SS, Thakur N, Galanter JM, Nishimura KK, Pino-Yanes M, Torgerson DG, Gignoux CR, Eng C, Nguyen EA, Hu D, Mak AC, Kumar R, Seibold MA, Davis A, Farber HJ, Meade K, Avila PC, Serebrisky D, Lenoir MA, Brigino-Buenaventura E, Rodriguez-Cintron W, Bibbins-Domingo K, Thyne SM, **Williams LK**, Sen S, Gilliland FD, Gauderman WJ, Rodriguez-Santana JR, Lurmann F, Balmes JR, Eisen EA, and Burchard EG. Air pollution and lung function in minority youth with asthma in the GALA II & SAGE II Studies *Am J Respir Crit Care Med* 2016;PMID: 26734713. Full Text

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RATIONALE: Adverse effects of exposures to ambient air pollution on lung function are well documented but evidence in racial/ethnic minority children is lacking. OBJECTIVES: Assess the relationship between air pollution and lung function in minority children with asthma, and possible modification by global genetic ancestry. METHODS: The study population consisted of 1,449 Latino and 519 African American children with asthma from five different geographical regions in the mainland U.S. and Puerto Rico. We examined five pollutants [particulate matter </= 10 mum (PM10) and 2.5 mum in diameter (PM2.5), ozone (O3), nitrogen dioxide (NO2), and sulfur dioxide (SO2)], derived from participant residential history and ambient air monitoring data, and assessed over several time windows. We fit generalized additive models for associations between pollutant exposures and lung function parameters, and tested for interaction terms between exposures and genetic ancestry. MEASUREMENTS AND MAIN RESULTS: A 5 mug/m3 increase in average lifetime PM2.5 exposure was associated with a 7.7 % decrease in FEV1 (95% confidence interval: -11.8%, -3.5%) in the overall study population. Global genetic ancestry did not appear to significantly modify these associations, but percent African ancestry was a significant predictor of lung function. CONCLUSIONS: Early-life particulate exposures were associated with reduced lung function in Latino and African American children with asthma. This is the first study to report an association between exposure to fine particulate matter and reduced lung function in minority children in which racial/ethnic status was measured by genome-wide genetic ancestry.

Center for Health Policy and Health Services Research

Pladevall M, Riera-Guardia N, Margulis AV, Varas-Lorenzo C, Calingaert B, and Perez-Gutthann S. Cardiovascular risk associated with the use of glitazones, metformin and sufonylureas: meta-analysis of published observational studies *BMC Cardiovasc Disord* 2016; 16(1):14. PMID: 26769243. Full Text

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BACKGROUND: The results of observational studies evaluating and comparing the cardiovascular safety of glitazones, metformin and sufonylureas are inconsistent.To conduct and evaluate heterogeneity in a meta-analysis of observational studies on the risk of acute myocardial infarction (AMI) or stroke in patients with type 2 diabetes using non-insulin blood glucose-lowering drugs (NIBGLD). METHODS: We systematically identified and reviewed studies evaluating NIBGLD in patients with type 2 diabetes indexed in Medline, Embase, or the Cochrane Library that met prespecified criteria. The quality of included studies was assessed with the RTI item bank. Results were combined using fixed- and random-effects models, and the Higgins I (2) statistic was used to evaluate heterogeneity. Sensitivity analyses by study quality were conducted. RESULTS: The summary relative risk (sRR) (95 % CI) of AMI for rosiglitazone versus pioglitazone was 1.13 (1.04-1.24) [I (2) = 55 %]. In the sensitivity analysis, heterogeneity was reduced [I (2) = 16 %]. The sRR (95 % CI) of stroke for rosiglitazone versus pioglitazone was 1.18 (1.02-1.36) [I (2) = 42 %]. There was strong evidence of heterogeneity related to study quality in the comparisons of rosiglitazone versus metformin and rosiglitazone versus sulfonylureas (I (2) >/= 70 %). The sRR (95 % CI) of AMI for sulfonylurea versus metformin was 1.24 (1.14-1.34) [I (2) = 41 %] and for pioglitazone versus metformin was 1.02 (0.75-1.38) [I (2) = 17 %]. Sensitivity analyses decreased heterogeneity in most comparisons. CONCLUSION/INTERPRETATION: Sulfonylureas increased the risk of AMI by 24 % compared with metformin; an imprecise point estimate indicated no difference in risk of AMI when comparing pioglitazone with metformin. The presence of heterogeneity precluded any conclusions on the other comparisons. The quality assessment was valuable in identifying methodological problems in the individual studies and for analysing potential sources of heterogeneity.

Center for Health Policy and Health Services Research

Scherrer JF, Salas J, Copeland LA, Stock EM, **Ahmedani BK**, Sullivan MD, Burroughs T, Schneider FD, Bucholz KK, and Lustman PJ. Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations *Ann Fam Med* 2016; 14(1):54-62. PMID: 26755784. Full Text

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PURPOSE: Recent results suggests the risk of a new onset of depression increases with longer duration of opioid analgesic use. It is unclear whether new-onset depression related to opioid analgesic use is a function of the dose prescribed or the duration of use or both. METHODS: Using a retrospective cohort design, we collected patient data from 2000 to 2012 from the Veterans Health Administration (VHA), and from 2003 to 2012 from both Baylor Scott & White Health (BSWH) and the Henry Ford Health System (HFHS). Patients (70,997 VHA patients, 13,777 BSWH patients, and 22,981 HFHS patients) were new opioid users, aged 18 to 80 years, without a diagnosis of depression at baseline. Opioid analgesic use duration was defined as 1 to 30, 31 to 90, and more than 90 days, and morphine equivalent dose (MED) was defined as 1 to 50 mg/d, 51 to 100 mg/d, and greater than 100 mg/d of analgesic. Pain and other potential confounders were controlled for by inverse probability of treatment-weighted propensity scores. RESULTS: New-onset depression after opioid analgesic use occurred in 12% of the VHA sample, 9% of the BSWH sample, and 11% of the HFHS sample. Compared with 1- to 30-day users, new-onset depression increased in those with longer opioid analgesic use. Risk of new-onset depression with 31 to 90 days of opioid analgesic use ranged from hazard ratio [HR] = 1.18 (95% CI, 1.10-1.25) in VHA to HR = 1.33 (95% CI, 1.16-1.52) in HFHS; in opioid analgesic use of more than 90 days, it ranged from HR = 1.35 (95% CI, 1.26-1.44) in VHA to HR = 2.05 (95% CI, 1.75-2.40) in HFHS. Dose was not significantly associated with a new onset of depression. CONCLUSIONS: Opioid-related new onset of depression is associated with longer duration of use but not dose. Patients and practitioners

should be aware that opioid analgesic use of longer than 30 days imposes risk of new-onset depression. Opioid analgesic use, not just pain, should be considered a potential source when patients report depressed mood.

Center for Health Policy and Health Services Research

Yang JJ, **Li J**, **Williams LK**, and Buu A. An efficient genome-wide association test for multivariate phenotypes based on the Fisher combination function *BMC Bioinformatics* 2016; 17(1):19. PMID: 26729364. Full Text

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BACKGROUND: In genome-wide association studies (GWAS) for complex diseases, the association between a SNP and each phenotype is usually weak. Combining multiple related phenotypic traits can increase the power of gene search and thus is a practically important area that requires methodology work. This study provides a comprehensive review of existing methods for conducting GWAS on complex diseases with multiple phenotypes including the multivariate analysis of variance (MANOVA), the principal component analysis (PCA), the generalizing estimating equations (GEE), the trait-based association test involving the extended Simes procedure (TATES), and the classical Fisher combination test. We propose a new method that relaxes the unrealistic independence assumption of the classical Fisher combination test and is computationally efficient. To demonstrate applications of the proposed method, we also present the results of statistical analysis on the Study of Addiction: Genetics and Environment (SAGE) data. RESULTS: Our simulation study shows that the proposed method has higher power than existing methods while controlling for the type I error rate. The GEE and the classical Fisher combination test, on the other hand, do not control the type I error rate and thus are not recommended. In general, the power of the competing methods decreases as the correlation between phenotypes increases. All the methods tend to have lower power when the multivariate phenotypes come from long tailed distributions. The real data analysis also demonstrates that the proposed method allows us to compare the marginal results with the multivariate results and specify which SNPs are specific to a particular phenotype or contribute to the common construct. CONCLUSIONS: The proposed method outperforms existing methods in most settings and also has great applications in GWAS on complex diseases with multiple phenotypes such as the substance abuse disorders.

Dermatology

Gordon SL, **Porto DA**, **Ozog DM**, and Council ML. Creating and editing video to accompany manuscripts *Dermatol Surg* 2016; 42(2):249-250. PMID: 26845540. Full Text

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BACKGROUND: The use of video can enhance the learning experience by demonstrating procedural techniques that are difficult to relay in writing. Several peer-reviewed journals allow publication of videos alongside articles to complement the written text. OBJECTIVE: The purpose of this article is to instruct the dermatologic surgeon on how to create and edit a video using a smartphone, to accompany a article. METHODS: The authors describe simple tips to optimize surgical videography. The video that accompanies this article further demonstrates the techniques described. RESULTS: Creating a surgical video requires little experience or equipment and can be completed in a modest amount of time. CONCLUSION: Making and editing a video to accompany a article can be accomplished by following the simple recommendations in this article. In addition, the increased use of video in dermatologic surgery education can enhance the learning opportunity.

Dermatology

Miller IM, **McAndrew RJ**, and **Hamzavi I**. Prevalence, risk factors, and comorbidities of hidradenitis suppurativa *Dermatol Clin* 2016; 34(1):7-16. PMID: 26617352. Full Text

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It is challenging to estimate a true prevalence of hidradenitis suppurativa (HS) because it is underdiagnosed and misdiagnosed. Prevalences have been reported from 0.00033% to 4.1%. The incidence seems to be rising. In addition to dermatologic symptoms, HS is associated with metabolic syndrome, and increased cardiovascular risk. The majority of HS patients are smokers. Additional somatic comorbidities complicating HS include autoimmune conditions, follicular syndromes, rheumatologic conditions, and malignancies. HS patients are troubled by psychological comorbidities. When treating HS patients it is imperative not only to treat the skin symptoms, but also address the screening and treatment of possible comorbidities.

Dermatology
Nicholson CL, **Hamzavi I**, and **Ozog DM**. Rapid healing of chronic ulcerations and improvement in range of motion after fractional carbon dioxide (CO2) treatment after CO2 excision of hidradenitis suppurativa axillary lesions: A case report *JAAD Case Reports* 2016; 2(1):4-6. PMID: Not assigned. Article Request Form

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Dermatology
Olsen EA, Hodak E, Anderson T, Carter JB, **Henderson M**, Cooper K, and **Lim HW**. Guidelines for phototherapy of mycosis fungoides and Sezary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium *J Am Acad Dermatol* 2016; 74(1):27-58. PMID: 26547257. Full Text

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BACKGROUND: Ultraviolet light (UVL) is a long established treatment for mycosis fungoides (MF) and Sezary syndrome (SS), subtypes of cutaneous T-cell lymphoma (CTCL). Treatments have traditionally included broadband, narrowband ultraviolet B light (UVB) and psoralen plus ultraviolet A light photochemotherapy (PUVA), but more recently, treatment options have expanded to include UVA1 and excimer laser. UVL is used either as monotherapy or as an adjuvant to systemic therapy, demonstrating efficacy in many cases that equal or surpass systemic medications. Despite its utility and duration of use, the current practice of using UVL guidelines for psoriasis to treat patients with MF/SS is problematic because the goals of prolonging survival and preventing disease progression are unique to CTCL compared to psoriasis. OBJECTIVES: We sought to develop separate guidelines for phototherapy for MF/SS for both clinical practice and for clinical trials. METHODS: Literature review and cutaneous lymphoma expert consensus group recommendations. RESULTS: This paper reviews the published literature for UVB and UVA/PUVA in MF/SS and suggests practical standardized guidelines for their use. LIMITATIONS: New standardization of phototherapy. CONCLUSIONS: These guidelines should allow the comparison of results with phototherapy in MF/SS across different stages of patients, centers, and in combination with other agents in practice and in clinical trials.

Dermatology
St Louis D, Romero R, Plazyo O, Arenas-Hernandez M, Panaitescu B, Xu Y, Milovic T, Xu Z, Bhatti G, **Mi QS**, Drewlo S, Tarca AL, Hassan SS, and Gomez-Lopez N. Invariant NKT cell activation induces late preterm birth that is attenuated by rosiglitazone *J Immunol* 2016; 196(3):1044-1059. PMID: 26740111. Full Text

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Preterm birth (PTB) is the leading cause of neonatal morbidity and mortality worldwide. Although intra-amniotic infection is a recognized cause of spontaneous preterm labor, the noninfection-related etiologies are poorly understood. In this article, we demonstrated that the expansion of activated CD1d-restricted invariant NKT (iNKT) cells in the third trimester by administration of alpha-galactosylceramide (alpha-GalCer) induced late PTB and neonatal mortality. In vivo imaging revealed that fetuses from mice that underwent alpha-GalCer-induced late PTB had bradycardia and died shortly after delivery. Yet, administration of alpha-GalCer in the second trimester did not cause pregnancy loss. Peroxisome proliferator-activated receptor (PPAR)gamma activation, through rosiglitazone treatment, reduced the rate of alpha-GalCer-induced late PTB and improved neonatal survival. Administration of alpha-GalCer in the third trimester suppressed PPARgamma activation, as shown by the downregulation of Fabp4 and Fatp4 in myometrial and decidual tissues, respectively; this suppression was rescued by rosiglitazone treatment. Administration of alpha-GalCer in the third trimester induced an increase in the activation of conventional CD4(+) T cells in myometrial tissues and the infiltration of activated macrophages, neutrophils, and mature dendritic cells to myometrial and/or decidual tissues. All of these effects were blunted after rosiglitazone treatment. Administration of alpha-GalCer also upregulated the expression of inflammatory genes at the maternal-fetal interface and systemically, and rosiglitazone treatment partially attenuated these responses. Finally, an increased infiltration of activated iNKT-like cells in human decidual tissues is associated with noninfection-related preterm labor/birth. Collectively, these results demonstrate that iNKT cell activation in vivo leads to late PTB by initiating innate and adaptive immune responses and suggest that the PPARgamma pathway has potential as a target for prevention of this syndrome.

Emergency Medicine

Belsky JB, **Morris DC**, **Bouchebl R**, Filbin MR, Bobbitt KR, **Jaehne AK**, and **Rivers EP**. Plasma levels of F-actin and F:G-actin ratio as potential new biomarkers in patients with septic shock *Biomarkers* 2016:1-6. PMID: 26754286.
Article Request Form

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OBJECTIVE: To compare plasma levels of F-actin, G-actin and thymosin beta 4 (TB4) in humans with septic shock, noninfectious systemic inflammatory response syndrome (SIRS) and healthy controls. RESULTS: F-actin was significantly elevated in septic shock as compared with noninfectious SIRS and healthy controls. G-actin levels were greatest in the noninfectious SIRS group but significantly elevated in septic shock as compared with healthy controls. TB4 was not detectable in the septic shock or noninfectious SIRS group above the assay's lowest detection range (78 ng/ml). CONCLUSIONS: F-actin is significantly elevated in patients with septic shock as compared with noninfectious SIRS. F-actin and the F:G-actin ratio are potential biomarkers for the diagnosis of septic shock.

Emergency Medicine

Bou Chebl R, **Madden B**, Belsky J, **Harmouche E**, and **Yessayan L**. Diagnostic value of end tidal capnography in patients with hyperglycemia in the emergency department *BMC Emerg Med* 2016; 16(1):7. PMID: 26821648.
Full Text

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BACKGROUND: Diabetic Ketoacidosis (DKA) is a potentially life-threatening emergency that requires prompt diagnosis and treatment. In paediatric populations an end tidal capnography value greater than 36 mmHg was found to be 100 % sensitive in ruling out DKA. METHODS: A cross sectional observational study of adults >/= 17 years of age presenting to the emergency department between January 2014 and May 2014 with glucose > 550 mg/dL. In all patients, nasal capnography and venous blood gas analysis were performed prior to any insulin or intravenous fluid administration. The diagnosis of DKA was based on the presence of anion gap metabolic acidosis, hyperglycaemia and ketonemia. The overall diagnostic performance (area under the curve [AUC]), sensitivity, specificity and likelihood ratios at different end tidal CO2 (ETCO2) cut-offs were determined. RESULTS: 71 patients were enrolled in the study of which 21 (30 %) met the diagnosis of DKA. The area under the curve for ETCO2 was 0.95 with a 95 % CI of 0.91 to 0.99. Test sensitivity for DKA at ETCO2 level >/=35 mmHg was 100 % (95 % CI, 83.9-100). An ETCO2 level </= 21 mmHg was 100 % specific (95 % CI, 92.9-100.0) for DKA. CONCLUSION: Nasal capnography exhibits favourable diagnostic performance in detecting patients with or without DKA among those who present to the emergency department with a glucometer reading > 550 mg/dL.

Emergency Medicine

Bou Chebl R, **Madden B**, Belsky J, **Harmouche E**, and **Yessayan L**. Diagnostic value of end tidal capnography in patients with hyperglycemia in the emergency department *BMC Emerg Med* 2016; 16(1):7. PMID: 26821648.
Full Text

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Emergency Medicine

Grudzen CR, Emlet LL, Kuntz J, Shreves A, **Zimny E**, Gang M, Schaulis M, Schmidt S, Isaacs E, and Arnold R. EM Talk: communication skills training for emergency medicine patients with serious illness *BMJ Support Palliat Care* 2016;PMID: 26762163. Article Request Form

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The emergency department visit for a patient with serious illness represents a sentinel event, signalling a change in the illness trajectory. By better understanding patient and family wishes, emergency physicians can reinforce advance care plans and ensure the hospital care provided matches the patient's values. Despite their importance in care at the end of life, emergency physicians have received little training on how to talk to seriously ill patients and their families about goals of care. To expand communication skills training to emergency medicine, we developed a programme to give emergency medicine physicians the ability to empathically deliver serious news and to talk about goals of care. We have built on lessons from prior studies to design an intervention employing the most effective pedagogical techniques, including the use of simulated patients/families, role-playing and small group learning with constructive feedback from master clinicians. Here, we describe our evidence-based communication skills training course EM Talk using simulation, reflective feedback and deliberate practice.

Emergency Medicine
Harrison MF, Anderson PJ, Johnson JB, Richert M, Miller AD, and Johnson BD. Acute mountain sickness symptom severity at the south pole: The influence of self-selected prophylaxis with acetazolamide *PLoS One* 2016; 11(2):e0148206. PMID: 26848757. Full Text

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INTRODUCTION: Acetazolamide, a carbonic anhydrase inhibitor, remains the only FDA approved pharmaceutical prophylaxis for acute mountain sickness (AMS) though its effectiveness after rapid transport in real world conditions is less clear. METHODS: Over 2 years, 248 healthy adults traveled by airplane from sea level (SL) to the South Pole (ALT, ~3200m) and 226 participants provided Lake Louise Symptom Scores (LLSS) on a daily basis for 1 week; vital signs, blood samples, and urine samples were collected at SL and at ALT. Acetazolamide was available to any participant desiring prophylaxis. Comparisons were made between the acetazolamide with AMS (ACZ/AMS) (n = 42), acetazolamide without AMS (ACZ/No AMS)(n = 49), no acetazolamide with AMS (No ACZ/AMS) (n = 56), and the no acetazolamide without AMS (No ACZ/No AMS) (n = 79) groups. Statistical analysis included Chi-squared and one-way ANOVA with Bonferroni post-hoc tests. Significance was p</=0.05. RESULTS: No significant differences were found for between-group characteristics or incidence of AMS between ACZ and No ACZ groups. ACZ/AMS reported greater LLSS, BMI, and red cell distribution width. ACZ/No AMS had the highest oxygen saturation (O2Sat) at ALT. No significant differences were found in serum electrolyte concentrations or PFT results. DISCUSSION: Acetazolamide during rapid ascent provided no apparent protection from AMS based on LLSS. However, it is unclear if this lack of effect was directly associated with the drug or if perhaps there was some selection bias with individuals taking ACZ more likely to have symptoms or if there may have been more of perceptual phenomenon related to a constellation of side effects.

Emergency Medicine
Harrison MF, Forde KA, Albert WJ, Croll JC, and Neary JP. Posture and helmet load influences on neck muscle activation *Aerosp Med Hum Perform* 2016; 87(1):48-53. PMID: 26735233. Article Request Form

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INTRODUCTION: Night vision goggles (NVG) are linked to increased neck muscle activation and pain. Counterweights (NVGcw) are hypothesized to mitigate these effects. The purpose of this study was to investigate the muscular response to varying helmet loads and postures. METHODS: Volunteering from a representative squadron were 16 male helicopter aviators (pilots, N = 9; flight engineers, N = 7). Subjects performed head movements to assume nine different postures (three directions: left, center, and right, at three different levels: down, level, and up) with four different head loads (no helmet; helmet only; NVG; and NVGcw) in randomized order. Subjects were provided real time visual guidance and feedback while assuming the appropriate posture in a cockpit seat in a laboratory setting. Neck muscle activation was assessed with electromyography (EMG) of four different muscle groups, bilaterally, including the sternocleidomastoid, splenius capitis, and mid and lower trapezius. RESULTS: Two- to fourfold increases in muscle activation were observed in postures to the left (down, level, and up) while subjects wore either the NVG or NVGcw as compared to the baseline of no helmet. This was most prevalent in smaller muscle groups (i.e., the sternocleidomastoid and splenius capitis) as compared to larger muscle groups (i.e., the mid and

lower trapezius). DISCUSSION: The use of NVGcw did not decrease neck muscle activity as compared to NVG only, particularly when the head posture moved the field of view below the horizon. This suggests interventions to decrease neck muscle activity and fatigue in military helicopter aircrew using NVG should focus on task specific guidelines with respect to countermeasures. Harrison MF, Forde KA, Albert WJ, Croll JC, Neary JP. Posture and helmet load influences on neck muscle activiation. Aerosp Med Hum Perform. 2016; 87(1):48-53.

Emergency Medicine
Harrison MF, and **Johnson BD**. Letter to the editor re: Use of statins for prophylaxis against acute mountain sickness: Response *Aerosp Med Hum Perform* 2016; 87(2):148-149. PMID: 26802382. Article Request Form

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Emergency Medicine
Hasegawa K, Brenner BE, **Nowak RM**, Trent SA, Herrera V, Gabriel S, Bittner JC, and Camargo CA, Jr. Association of guideline-concordant acute asthma care in the emergency department with shorter hospital length-of-stay: A multicenter observational study *Acad Emerg Med* 2016;PMID: 26833429. Full Text

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Novartis Pharmaceuticals, East Hanover, NJ.

OBJECTIVES: To determine whether guideline-concordant emergency department (ED) management of acute asthma is associated with a shorter hospital length-of-stay (LOS) among patients hospitalized for asthma. METHODS: A multicenter chart review study of patients aged 2-54 years who were hospitalized for acute asthma at one of the 25 US hospitals during 2012-2013. Based on level-A recommendations from national asthma guidelines, we derived 4 process measures of ED treatment before hospitalization: inhaled beta-agonists, inhaled anticholinergic agents, systemic corticosteroids, and lack of methylxanthines. The outcome measure was hospital LOS. RESULTS: Among 854 ED patients subsequently hospitalized for acute asthma, 532 patients (62%) received care perfectly concordant with the 4 process measures in the ED. Overall, the median hospital LOS was 2 days (IQR, 1-3 days). In the multivariable negative binomial model, patients who received perfectly-concordant ED asthma care had a significantly shorter hospital LOS (-17%; 95%CI, -27% to -5%; P=0.006), compared to other patients. In the mediation analysis, the direct effect of guideline-concordant ED asthma care on hospital LOS was similar to that of primary analysis (-16%; 95%CI, -27% to -5%; P=0.005). By contrast, the indirect effect mediated by quality of inpatient asthma care was not significant, indicating that the effect of ED asthma care on hospital LOS was mediated through pathways other than quality of inpatient care. CONCLUSION: In this multicenter observational study, patients who received perfectly concordant asthma care in the ED had a shorter hospital LOS. Our findings encourage further adoption of guideline-recommended emergency asthma care to improve patient outcomes.

Emergency Medicine
Miller J, Ho CX, Tang J, Thompson R, **Goldberg J**, **Amer A**, and Nahab B. Assessing fluid responsiveness in spontaneously breathing patients *Acad Emerg Med* 2016;PMID: 26764894. Full Text

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI.
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Lincoln Medical and Mental Health Center, Weill Cornell Medical College, New York, NY.

OBJECTIVES: The primary objective of this study was to test if fasting volunteers exhibit fluid responsiveness using noninvasive hemodynamic measurements. The secondary objective was to test a passive leg raise (PLR) maneuver as a diagnostic predictor of fluid responsiveness. METHODS: This was a quasi-experimental design involving healthy volunteers. Subjects were excluded for pregnancy and congestive heart failure. Following a 12-hour fast, subjects had baseline hemodynamic monitoring recorded using noninvasive, continuous pulse contour analysis. Subjects then had a PLR maneuver performed, followed by an intravenous bolus of crystalloid. A rise in stroke volume >/= 10% from baseline with the bolus was considered consistent with fluid responsiveness, and the same rise with a PLR was consistent with a positive PLR maneuver. The primary outcome was the change in stroke volume with a fluid bolus. Univariate analysis assessed changes in hemodynamic parameters. Logistic regression analysis determined the test characteristics of the PLR in predicting subjects who were ultimately fluid responsive. RESULTS: Forty subjects completed the study. The mean change in stroke volume with a crystalloid bolus was 19% (95% confidence interval

[CI] = 16% to 21%). Thirty-six (90%) subjects were fluid responsive. The mean PLR response for the overall cohort was 16% (95% CI = 12% to 19%), and 26 (65%) subjects had a positive PLR maneuver. The PLR was 72% sensitive (95% CI = 55% to 85%) and 100% specific (95% CI = 40% to 100%) for predicting the presence of fluid responsiveness. CONCLUSIONS: Noninvasive assessment of fluid responsiveness in healthy volunteers and prediction of this response with a PLR maneuver is achievable. Further work is indicated to test these methods in acutely ill patients.

Emergency Medicine

Skupski R, **Miller J**, Binz S, Lapkus M, and Walsh M. Delayed sequence intubation: Danger in delaying definitive airway? *Ann Emerg Med* 2016; 67(1):143-144. PMID: 26707526. Full Text

Department of Anesthesiology, Memorial Hospital of South Bend, South Bend, IN.
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Emergency Medicine

Storrow AB, Christenson RH, **Nowak RM**, Diercks DB, Singer AJ, Wu AH, Kulstad E, LoVecchio F, Fromm C, Headden G, Potis T, Hogan CJ, Schrock JW, Zelinski DP, Greenberg MR, Ritchie JC, Chamberlin JS, Bray KR, Rhodes DW, Trainor D, Holmes D, and Southwick PC. Diagnostic performance of cardiac Troponin I for early rule-in and rule-out of acute myocardial infarction: Results of a prospective multicenter trial *Clin Biochem* 2015; 48(4-5):254-259. PMID: 25195101. Article Request Form

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Dept. of Emergency Medicine, Maimonides Medical Center, Brooklyn, NY, USA.
Chest Pain Center, Medical University of South Carolina, Charleston, SC, USA.
Dept. of Emergency Medicine, Covenant Medical Center, Saginaw, MI, USA.
Dept. of Emergency Medicine, Virginia Commonwealth University Medical Center, Richmond, VA, USA.
Dept. of Emergency Medicine, Case Western Reserve University School of Medicine, MetroHealth Medical Center, Cleveland, OH, USA.
Dept. of Emergency Medicine, The Ohio State University Medical Center, Columbus, OH, USA.
Dept. of Emergency Medicine, Lehigh Valley Health Network, Allentown, PA, USA.
Dept. of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA.
Dept. of Clinical Research, Beckman Coulter, Inc., Carlsbad, CA, USA.

OBJECTIVES: To compare emergency department TnI serial sampling intervals, determine optimal diagnostic thresholds, and report representative diagnostic performance characteristics for early rule-in and rule-out of MI. METHODS: We prospectively measured TnI (AccuTnI+3, Beckman Coulter) at serial time intervals in 1929 subjects with chest pain or equivalent ischemic symptoms suggestive of acute coronary syndromes at 14 medical centers. Diagnosis was adjudicated by an independent central committee. RESULTS: TnI >/=0.03ng/mL provided 96.0% sensitivity and 89.4% specificity at 1-3h after admission, and 94.9% sensitivity and 86.7% specificity at 3-6h. NPV (rule-out, non-MI) was 99.5% at 1-3h, and 99.0% at 3-6h when TnI is <0.03ng/mL. NPV was 99.1% when TnI is <0.03ng/mL and time of symptom onset is >/=8h. Approximately 50-58% (PPV) of patients with TnI >/=0.03ng/mL were diagnosed with MI, depending upon time from onset or admission; PPVs emphasize the importance of serial samples and delta TnI (rising or falling pattern) when low cutoffs are used. Nevertheless, even a single elevated TnI value increased the risk of MI. As TnI values rose, the probability of MI increased. Values >/=0.20ng/mL were associated with nearly 90% probability of MI. CONCLUSIONS: We report a large multicenter prospective adjudicated trial assessing troponin for early rule-in and rule-out using the Universal Definition of MI and conducted in primary care hospital-associated emergency departments. Our study demonstrates high diagnostic accuracy at early observation times, and reinforces consensus recommendations for sampling on admission and 3h later, repeated at 6h when clinical suspicion remains high.

Emergency Medicine

Tsalik EL, Henao R, Nichols M, Burke T, Ko ER, McClain MT, Hudson LL, Mazur A, Freeman DH, Veldman T, Langley RJ, Quackenbush EB, Glickman SW, Cairns CB, **Jaehne AK**, **Rivers EP**, **Otero RM**, Zaas AK, Kingsmore SF, Lucas J, Fowler VG, Jr., Carin L, Ginsburg GS, and Woods CW. Host gene expression classifiers diagnose acute respiratory illness etiology *Sci Transl Med* 2016; 8(322):322ra311. PMID: 26791949. Article Request Form

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Acute respiratory infections caused by bacterial or viral pathogens are among the most common reasons for seeking medical care. Despite improvements in pathogen-based diagnostics, most patients receive inappropriate antibiotics. Host response biomarkers offer an alternative diagnostic approach to direct antimicrobial use. This observational cohort study determined whether host gene expression patterns discriminate noninfectious from infectious illness and bacterial from viral causes of acute respiratory infection in the acute care setting. Peripheral whole blood gene expression from 273 subjects with community-onset acute respiratory infection (ARI) or noninfectious illness, as well as 44 healthy controls, was measured using microarrays. Sparse logistic regression was used to develop classifiers for bacterial ARI (71 probes), viral ARI (33 probes), or a noninfectious cause of illness (26 probes). Overall accuracy was 87% (238 of 273 concordant with clinical adjudication), which was more accurate than procalcitonin (78%, $P < 0.03$) and three published classifiers of bacterial versus viral infection (78 to 83%). The classifiers developed here externally validated in five publicly available data sets (AUC, 0.90 to 0.99). A sixth publicly available data set included 25 patients with co-identification of bacterial and viral pathogens. Applying the ARI classifiers defined four distinct groups: a host response to bacterial ARI, viral ARI, coinfection, and neither a bacterial nor a viral response. These findings create an opportunity to develop and use host gene expression classifiers as diagnostic platforms to combat inappropriate antibiotic use and emerging antibiotic resistance.

Endocrinology and Metabolism

Brunton SA, **Kruger DF**, and Funnell MM. Role of emerging insulin technologies in the initiation and intensification of insulin therapy for diabetes in primary care *Clin Diabetes* 2016; 34(1):34-43. PMID: 26807007. Article Request Form

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In Brief This article explores some of the reasons for the delay in insulin initiation in primary care and evaluates new approaches to insulin therapy that may address these barriers and, therefore, improve insulin use by primary care providers.

Endocrinology and Metabolism
Kulkarni P, **Cushman T**, **Donthireddy V**, and **Rao S**. Spontaneously recovered severe thrombocytopaenia following zoledronic acid infusion for osteoporosis *BMJ Case Rep* 2016; 2016PMID: 26843222. Full Text

Henry Ford Hospital, Detroit, Michigan, USA.

Zoledronic acid is widely used for the treatment of various skeletal disorders. While acute phase reactions are commonly seen, hypocalcaemia, femoral shaft fractures, osteonecrosis of the jaw and renal failure are rare. Two cases of fatal thrombocytopaenic purpura have been reported following zoledronic acid infusion. We report a case of non-fatal thrombocytopaenia with spontaneous recovery. A 70-year woman with osteoporosis participated in a research study. Complete blood and platelet counts prior to zoledronic acid infusion were normal (138 000/microL), but had declined slightly from 185 000/microL 2 years ago. One year after the first zoledronic acid infusion, her platelet count declined to 50 000/microL without any clinical manifestations, and rose slowly returning to normal (156 000/microL) over the next 1 year. Extensive evaluation did not reveal any specific abnormalities, and the pathogenesis of her transient severe thrombocytopaenia after two infusions of zoledronic acid remains unclear.

Endocrinology and Metabolism
Kulkarni P, **Lahiri SW**, and **Rao SD**. Letter to the editor: Effect of parathyroidectomy on renal function: Dichotomous results and confusing conclusions *J Clin Endocrinol Metab* 2016; 101(2):L9. PMID: 26840121. Full Text

Division of Endocrinology Diabetes and Bone and Mineral Disorders, Department of Medicine, Henry Ford Health System, Detroit, Michigan 48202.

Gastroenterology
Buti M, **Gordon SC**, Zuckerman E, Lawitz E, Calleja JL, Hofer H, Gilbert C, Palcza J, Howe AY, DiNubile MJ, Robertson MN, Wahl J, Barr E, and Forns X. Grazoprevir, Elbasvir, and Ribavirin for Chronic Hepatitis C Virus Genotype 1 Infection After Failure of Pegylated Interferon and Ribavirin With an Earlier-Generation Protease Inhibitor: Final 24-Week Results From C-SALVAGE *Clin Infect Dis* 2016; 62(1):32-36. PMID: 26371152. Full Text

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Division of Gastroenterology and Hepatology, Medical University of Vienna, Austria.
Merck and Co, Inc, Kenilworth, New Jersey.
Liver Unit, Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer and Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas, Barcelona, Spain.

BACKGROUND: The phase 2 C-SALVAGE study (Hepatitis C-Salvage Study for Patients who Failed DAA/PR Therapy) demonstrated a 96.2% sustained virologic response at 12 weeks (SVR12) rate using the NS3/4A protease inhibitor grazoprevir and the NS5A inhibitor elbasvir together with ribavirin in treatment-experienced patients with chronic hepatitis C virus (HCV) genotype 1 infection. METHODS: C-SALVAGE was a prospective open-label trial of grazoprevir 100 mg once daily and elbasvir 50 mg once daily coadministered with weight-based ribavirin twice daily for 12 weeks in genotype 1-infected cirrhotic and noncirrhotic patients who had failed treatment with >/=4 weeks of pegylated interferon and ribavirin plus either boceprevir, telaprevir, or simeprevir. Although the primary efficacy outcome was SVR12, patients were also evaluated 24 weeks after cessation of study therapy. Population sequencing was performed at baseline and periodically in virologic failures throughout the 24-week posttherapy follow-up period. RESULTS: SVR24 rates were 76 of 79 (96.2%) overall, with all 3 relapses occurring by posttherapy week 8. Every NS3 and NS5A variant detected at baseline reappeared at the time of relapse and persisted throughout the available follow-up period. NS3_A156T emerged in virus from each patient at relapse, but rapidly disappeared over the ensuing 2 weeks in 2 patients. NS5A_Y93H emerged in virus from 2 patients at relapse and persisted for the entire follow-up period. CONCLUSIONS: Grazoprevir and elbasvir with ribavirin for 12 weeks maintained HCV suppression for at least 24 weeks posttherapy without late relapses. Baseline resistance-associated variants (RAVs) stably

reappeared at relapse in all 3 patients with virologic failure. NS5A_RAVs emerging at relapse persisted for the full 24-week follow-up period. If confirmed, this finding could complicate retreatment of the small number of patients failing regimens containing an NS5A inhibitor. CLINICAL TRIALS REGISTRATION: NCT02105454.

Gastroenterology
Lu M, **Li J**, **Zhang T**, **Rupp LB**, **Trudeau S**, Holmberg SD, Moorman AC, Spradling PR, Teshale EH, Xu F, Boscarino JA, Schmidt MA, Vijayadeva V, and **Gordon SC**. Long-term reduction in liver fibrosis, based on serum biomarkers, in patients with sustained viral responses to HCV treatment *Clin Gastroenterol Hepatol* 2016;PMID: 26804385. Full Text

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Division of Gastroenterology and Hepatology, Henry Ford Health System, Detroit, MI. Electronic address: sgordon3@hfhs.org.

BACKGROUND & AIMS: Sustained viral response (SVR) to antiviral therapy for hepatitis C virus (HCV) correlates with changes in biochemical measures of liver function. However, little is known about the long-term effects of SVR on liver fibrosis. We investigated the effects of HCV therapy on fibrosis, based on fibrosis-4 (FIB4) score, over a 10 year period. METHODS: We collected data from participants in the chronic hepatitis C cohort-part of an observational multicenter study of patients with hepatitis C at 4 large US health systems-from January 1, 2006 through December 31, 2013. We calculated patients' FIB4 and aminotransferase-to-platelet ratio index (APRI) scores over a 10 year period. Of 4731 patients with HCV infection, 1657 (35%) were treated and 755 (46%) of these patients achieved an SVR. RESULTS: In propensity score-adjusted analyses, we observed significant longitudinal changes in FIB4 score that varied with treatment and response to treatment. In patients with an SVR, FIB4 scores were initially higher than in patients without SVRs, but then decreased sharply, remaining significantly lower over the 10 year period than in untreated patients or patients with treatment failure (P<.001). In independent analyses, men and patients with HCV genotype 1 or 3 infections had higher FIB4 scores than women or patients with HCV genotype 2 infections (P<.01 for both). Findings were similar in a sensitivity analysis that substituted the APRI as the marker of fibrosis instead of FIB4 score. CONCLUSIONS: An SVR to HCV treatment appears to induce long-term regression of fibrosis, based on FIB4 or APRI scores collected over 10 years patients in a large study. Patients receiving no treatment or with treatment failure had progressive increases in FIB4 scores.

Gastroenterology
Sulejmani N, **Jafri SM**, and **Gordon SC**. Pharmacodynamics and pharmacokinetics of elbasvir and grazoprevir in the treatment of hepatitis C *Expert Opin Drug Metab Toxicol* 2016;PMID: 26849059. Article Request Form

a Henry Ford Hospital , Division of Gastroenterology .

INTRODUCTION: Approximately 130 - 150 million people have chronic Hepatitis C virus HCV infection and upwards of 500,000 deaths annually are attributed to HCV related liver disease worldwide. Pegylated interferon and ribavirin have been the mainstay of treatment for greater than 25 years until recent advent of protease inhibitors which has led

to all oral HCV treatment regimens that have changed the outlook of hepatitis C treatment. Areas covered: This review provides summary of pharmacokinetics, pharmacodynamics, efficacy and safety of grazoprevir/elbasvir therapy for treatment of HCV infection. Expert Opinion: Grazoprevir/elbasvir provides an all-oral once daily treatment option for HCV infection with high rates of efficacy and tolerability in a pangenotypic fashion. It highly efficacious in treating patients with cirrhosis, patients who have previously failed treatment with peginterferon and ribavirin, and patients with HIV co-infection. Grazoprevir/elbasvir has demonstrated higher barrier to resistance even in the presence of variants associated with resistance. It is one of only few HCV treatment regimens evaluated for use in patients with advanced chronic kidney disease and dialysis. Based on the data currently available, it is a very promising regimen for treatment of HCV infection.

Genetics

Monaghan KG, **Gonzalez HC**, **Levin AM**, **Abouljoud MS**, and **Gordon SC**. Post-transplant course of hepatitis C after living donor liver transplantation in association with polymorphisms near IFNL3 *J Interferon Cytokine Res* 2015; 35(4):313-316. PMID: 25343304. Article Request Form

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Donor genotype for polymorphisms near IFNL3 influences hepatitis C virus (HCV) therapy responsiveness. This relationship has not been studied in a sample of HCV-infected living donor liver transplantation (LDLT) recipients in the United States (US). We investigated the association of donor and recipient genotypes near the IFNL3 gene at a large US liver transplant center. Recipient homozygosity for rs12979860 C was associated with increased sustained virologic response (SVR) in antiviral treatment-experienced patients pretransplant (P = 0.055). Consistently, donor homozygosity for rs12979860 C was also associated with increased SVR in patients who received post-transplant antiviral therapy (P = 0.048). Transplantation of an rs12979860 CC graft confers a favorable post-transplant antiviral response among HCV-positive recipients in an LDLT setting. Recipients with the favorable rs12979860 genotype receiving antiviral therapy before transplant are also more likely to achieve SVR. The effect of genotype status in the era of direct-acting antiviral agents will require future study.

Genetics

Procter M, **Wolf B**, and Mao R. Forty-eight novel mutations causing biotinidase deficiency *Mol Genet Metab* 2016;PMID: 26810761. Article Request Form

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ARUP Institute for Clinical and Experimental Pathology, University of Utah, Salt Lake City, UT, USA; Department of Pathology, University of Utah, Salt Lake City, UT, USA.

Biotinidase deficiency is an autosomal recessively inherited disorder that results in the inability to recycle the vitamin biotin and is characterized by neurological and cutaneous symptoms. The symptoms can be ameliorated or prevented by administering pharmacological doses of biotin. Since 2008, approximately 300 samples have been submitted to ARUP's Molecular Sequencing Laboratory for biotinidase mutation analysis. Of these, 48 novel alterations in the biotinidase gene have been identified. Correlating the individual's serum enzymatic activity with the genotype, we have been able to determine the effect of the novel alteration on enzyme activity and, thereby, determine its likelihood of being pathogenic in 44 of these individuals. The novel mutations and uncertain alterations have been added to the database established by ARUP (http://arup.utah.edu/database/BTD/BTD_welcome.phps) to help clinicians make decisions about management and to better counsel their patients based on their genotypes.

Hematology, Oncology and the Josephine Ford Cancer Institute

Gulati R, **Alkhatib Y**, **Donthireddy V**, **Felicella MM**, **Menon MP**, and **Inamdar KV**. Isolated ocular manifestation of relapsed chronic myelogenous leukemia presenting as myeloid blast crisis in a patient on imatinib therapy: A case report and review of the literature *Case Rep Pathol* 2015; 2015:380451. PMID: 26819793. Full Text

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Blast phase in chronic myelogenous leukemia (CML) has rarely been reported to involve extramedullary sites like skin, lymph nodes, and central nervous system. Clinical history, characteristic hematologic findings (elevated leukocyte counts, myelocytic predominance, and basophilia), and Philadelphia chromosome are of high diagnostic significance especially in isolated extramedullary presentations. We describe a unique case of CML relapse with blast

phase involving the eye. A 66-year-old man with a known diagnosis of CML on imatinib and in molecular remission for 3 years presented with a painful blind eye. Histologic examination revealed diffuse involvement of choroid, iris, vitreous humor, and the optic nerve by blast cells. The blasts expressed CD34, aberrant TdT, and a myeloid phenotype (CD13, CD33, and CD117). Fluorescence in situ hybridization (FISH) of vitreous fluid detected BCR-ABL1 gene rearrangement. Additionally, trisomy 8 and gains of 9 and 22 were seen which were not present in the initial diagnostic marrow study 3 years ago. At relapse, the bone marrow, peripheral blood, and the cerebrospinal fluid were not involved by CML. Patient received induction chemotherapy and single dose prophylactic intrathecal methotrexate and was maintained on antityrosine kinase therapy and eventually underwent allogenic stem cell transplantation.

Hematology, Oncology and the Josephine Ford Cancer Institute
Kulkarni P, **Cushman T**, **Donthireddy V**, and **Rao S**. Spontaneously recovered severe thrombocytopaenia following zoledronic acid infusion for osteoporosis *BMJ Case Rep* 2016; 2016PMID: 26843222. Full Text

Henry Ford Hospital, Detroit, Michigan, USA.

Zoledronic acid is widely used for the treatment of various skeletal disorders. While acute phase reactions are commonly seen, hypocalcaemia, femoral shaft fractures, osteonecrosis of the jaw and renal failure are rare. Two cases of fatal thrombocytopaenic purpura have been reported following zoledronic acid infusion. We report a case of non-fatal thrombocytopaenia with spontaneous recovery. A 70-year woman with osteoporosis participated in a research study. Complete blood and platelet counts prior to zoledronic acid infusion were normal (138 000/microL), but had declined slightly from 185 000/microL 2 years ago. One year after the first zoledronic acid infusion, her platelet count declined to 50 000/microL without any clinical manifestations, and rose slowly returning to normal (156 000/microL) over the next 1 year. Extensive evaluation did not reveal any specific abnormalities, and the pathogenesis of her transient severe thrombocytopaenia after two infusions of zoledronic acid remains unclear.

Hematology, Oncology and the Josephine Ford Cancer Institute
Saste A, **Arias-Stella J**, and **Kuriakose P**. Progression of a hepatosplenic gamma delta T-cell leukemia/lymphoma on hyperCVAD/MTX and ara-C: literature review and our institutional treatment approach *Clin Case Rep* 2016; 4(1):67-71. PMID: 26783439. Full Text

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A 24-year-old male presented with abdominal pain, fever, and palpable splenomegaly. His differential count revealed myelocytes, metamyelocytes, and nucleated red cells. A bone marrow biopsy confirmed a diagnosis of hepatosplenic gamma delta T-cell leukemia/lymphoma. We describe here our center's diagnostic and treatment approach for this rare leukemia.

Infectious Diseases
Arshad S, **Hartman P**, **Perri MB**, **Moreno D**, and **Zervos MJ**. Ceftaroline fosamil for treatment of methicillin-resistant staphylococcus aureus hospital-acquired pneumonia and health care–associated pneumonia: A 5-year matched case-control evaluation of epidemiology and outcomes *Infect Dis Clin Pract* 2016;PMID: Not assigned.
Article Request Form

S. Arshad, From the *Division of Infectious Diseases, Henry Ford Health System; and †Wayne State University School of Medicine, Detroit, MI.

PURPOSE: Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia patients treated with current antibiotic therapies have exhibited poor outcomes, increased hospital length of stay, and higher costs of care. Twenty-eight-day mortality rate of 32% was reported with vancomycin therapy for MRSA hospital-acquired pneumonia (HAP) and MRSA health care–associated pneumonia (HCAP) from the same institution. The purpose of this study was to compare the epidemiology and effectiveness of ceftaroline versus alternative antibiotic therapies: linezolid, vancomycin, and/or cefepime, in hospitalized patients with MRSA HAP or HCAP based on clinical outcomes. METHODS: Through retrospective matched case-control study design, the Infectious Diseases Society of America– and Centers for Disease Control and Prevention–defined MRSA HCAP or HAP consecutive hospitalized subjects treated with either ceftaroline fosamil (CPT-F) or alternative antibiotics were compared. Primary outcomes were 28-day mortality and 14-day clinical evaluation. Secondary outcomes included duration of hospitalization, complications with treatment, and clinical response to therapy switches. RESULTS: Overall, 40 cases of MRSA HAP or HCAP treated with CPT-F were matched to 109 control subjects treated with either vancomycin or linezolid based on age,

intensive care unit status, and type of pneumonia infection. The CPT-F cohort had a 10% (n = 4) 28-day mortality rate, and 91% (n = 32) had 14-day clinical success/cure (±1 day) from diagnosis of pneumonia for the 35 evaluable cases. Of the 4 patients who died, 3 had debilitating comorbid conditions and an overall APACHE (Acute Physiology and Chronic Health Evaluation) II score greater than 20. Of those failing on standard antibiotic therapy, 50% (n = 20) were switched to CPT-F; subsequently, all (n = 20) switched patients cleared pneumonia. The overall success rate with CPT-F was 90% versus 75% for comparators. CONCLUSIONS: Treatment of MRSA pneumonia with CPT-F is associated with overall lower 28-day mortality than earlier studies with other agents. These data suggest a possible benefit in the use of CPT-F for therapy of MRSA hospital-acquired and health care–associated pneumonia.

Internal Medicine

Heidemann DL, **Joseph NA**, **Kuchipudi A**, **Perkins DW**, and **Drake S**. Racial and economic disparities in diabetes in a large primary care patient population *Ethn Dis* 2016; 26(1):85-90. PMID: 26843800. Article Request Form

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OBJECTIVE: We sought to determine if, after adjusting for economic status, race is an independent risk factor for glycemic control among diabetic patients in a large primary care patient population. DESIGN SETTING PARTICIPANTS: We performed a retrospective chart review of 264,000 primary care patients at our large, urban academic medical center to identify patients with a diagnosis of diabetes (n=25,123). Zip code was used to derive median income levels using US Census Bureau demographic information. Self-reported race was extracted from registration data. MAIN OUTCOME MEASURES: The prevalence of diabetes, average glycated hemoglobin (A1c), and prevalence of uncontrolled diabetes of White and Black patients at all income levels were determined. RESULTS: White patients had a lower average A1c level and a lower prevalence of diabetes than Black patients in all income quartiles (P<.001). Among White patients, the prevalence of diabetes (P<.001), uncontrolled diabetes (P<.001), and A1c level (P=.014) were inversely proportional to income level. No significant difference in the prevalence of diabetes (P=.214), A1c level (P=.282), or uncontrolled diabetes related to income was seen in Black patients (P=.094). CONCLUSIONS: Race had an independent association with diabetes prevalence and glycemic control. Our study does not support two prominent theories that economic and insurance status are the main factors in diabetes disparities, as we attempted to control for economic status and nearly every patient had insurance. It will be important for future analysis to explore how health care system factors affect these observed gaps in quality.

Internal Medicine

Joseph CL, **Zoratti EM**, **Ownby DR**, **Havstad S**, **Nicholas C**, **Nageotte C**, **Misiak R**, **Enberg R**, Ezell J, and **Johnson CC**. Exploring racial differences in IgE-mediated food allergy in the WHEALS birth cohort *Ann Allergy Asthma Immunol* 2016;PMID: 26837607. Full Text

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BACKGROUND: Suspected food allergies are the cause of more than 200,000 visits to the emergency department annually. Racial differences in the prevalence of food allergy have also been reported, but the evidence is less conclusive. Researchers continue to struggle with the identification of food allergy for epidemiologic studies. OBJECTIVE: To explore racial differences in IgE-mediated food allergy (IgE-FA) in a birth cohort. METHODS: We used a panel of board-certified allergists to systematically identify IgE-FA to egg, milk, or peanut in a multiethnic birth cohort in which patient medical history, patient symptoms, and clinical data were available through 36 months of age. RESULTS: Of the 590 infants analyzed, 52.9% were male and 65.8% African American. Sensitization (serum specific IgE >0.35 IU/mL) to the food allergens was significantly higher for African American children compared with non-African American children as has been previously reported. No statistically significant racial/ethnic differences in IgE-FA were observed; however, a higher proportion of African American children were designated as having peanut allergy, and the percentage of African American children with an IgE level greater than 95% predictive decision points for peanut was 1.7% vs 0.5% for non-African American children. With the use of logistic regression, race/ethnicity was not significantly associated with IgE-FA (adjusted odds ratio, 1.12; 95% confidence interval, 0.58-2.17; P = .75)

but was associated with sensitization to more than 1 of the food allergens (adjusted odds ratio, 1.80; 95% confidence interval, 1.22-2.65; P = .003). CONCLUSION: We did not observe an elevated risk of IgE-FA for African American children, although established differences in sensitization were observed. Racial/ethnic differences in sensitization must be taken into consideration when investigating disparities in asthma and allergy.

Nephrology

Bou Chebl R, **Madden B**, Belsky J, **Harmouche E**, and **Yessayan L**. Diagnostic value of end tidal capnography in patients with hyperglycemia in the emergency department *BMC Emerg Med* 2016; 16(1):7. PMID: 26821648.
Full Text

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BACKGROUND: Diabetic Ketoacidosis (DKA) is a potentially life-threatening emergency that requires prompt diagnosis and treatment. In paediatric populations an end tidal capnography value greater than 36 mmHg was found to be 100 % sensitive in ruling out DKA. METHODS: A cross sectional observational study of adults >/= 17 years of age presenting to the emergency department between January 2014 and May 2014 with glucose > 550 mg/dL. In all patients, nasal capnography and venous blood gas analysis were performed prior to any insulin or intravenous fluid administration. The diagnosis of DKA was based on the presence of anion gap metabolic acidosis, hyperglycaemia and ketonemia. The overall diagnostic performance (area under the curve [AUC]), sensitivity, specificity and likelihood ratios at different end tidal CO2 (ETCO2) cut-offs were determined. RESULTS: 71 patients were enrolled in the study of which 21 (30 %) met the diagnosis of DKA. The area under the curve for ETCO2 was 0.95 with a 95 % CI of 0.91 to 0.99. Test sensitivity for DKA at ETCO2 level >/=35 mmHg was 100 % (95 % CI, 83.9-100). An ETCO2 level </= 21 mmHg was 100 % specific (95 % CI, 92.9-100.0) for DKA. CONCLUSION: Nasal capnography exhibits favourable diagnostic performance in detecting patients with or without DKA among those who present to the emergency department with a glucometer reading > 550 mg/dL.

Nephrology

Bou Chebl R, **Madden B**, Belsky J, **Harmouche E**, and **Yessayan L**. Diagnostic value of end tidal capnography in patients with hyperglycemia in the emergency department *BMC Emerg Med* 2016; 16(1):7. PMID: 26821648.
Full Text

Department of Emergency Medicine, American University of Beirut, Beirut, Lebanon. rb94@aub.edu.lb.
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BACKGROUND: Diabetic Ketoacidosis (DKA) is a potentially life-threatening emergency that requires prompt diagnosis and treatment. In paediatric populations an end tidal capnography value greater than 36 mmHg was found to be 100 % sensitive in ruling out DKA. METHODS: A cross sectional observational study of adults >/= 17 years of age presenting to the emergency department between January 2014 and May 2014 with glucose > 550 mg/dL. In all patients, nasal capnography and venous blood gas analysis were performed prior to any insulin or intravenous fluid administration. The diagnosis of DKA was based on the presence of anion gap metabolic acidosis, hyperglycaemia and ketonemia. The overall diagnostic performance (area under the curve [AUC]), sensitivity, specificity and likelihood ratios at different end tidal CO2 (ETCO2) cut-offs were determined. RESULTS: 71 patients were enrolled in the study of which 21 (30 %) met the diagnosis of DKA. The area under the curve for ETCO2 was 0.95 with a 95 % CI of 0.91 to 0.99. Test sensitivity for DKA at ETCO2 level >/=35 mmHg was 100 % (95 % CI, 83.9-100). An ETCO2 level </= 21 mmHg was 100 % specific (95 % CI, 92.9-100.0) for DKA. CONCLUSION: Nasal capnography exhibits favourable diagnostic performance in detecting patients with or without DKA among those who present to the emergency department with a glucometer reading > 550 mg/dL.

Nephrology
Yee J. Geriatric CKD: Value-based nephrology *Adv Chronic Kidney Dis* 2016; 23(1):1-5. PMID: 26709055. Full Text

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Neurology
Achyut BR, Shankar A, Iskander AS, Ara R, **Knight RA**, **Scicli AG**, and Arbab AS. Chimeric mouse model to track the migration of bone marrow derived cells in glioblastoma following anti-angiogenic treatments *Cancer Biol Ther* 2016:0. PMID: 26797476. Article Request Form

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ABSTARCT Bone marrow derived cells (BMDCs) have been shown to contribute in the tumor development. In vivo animal models to investigate the role of BMDCs in tumor development are poorly explored. We established a novel chimeric mouse model using as low as 5x106 GFP+ BM cells in athymic nude mice, which resulted in >70% engraftment within 14 days. In addition, chimera was established in NOD-SCID mice, which displayed >70% with in 28 days. Since anti-angiogenic therapies (AAT) were used as an adjuvant against VEGF-VEGFR pathway to normalize blood vessels in glioblastoma (GBM), which resulted into marked hypoxia and recruited BMDCs to the tumor microenvironment (TME). We exploited chimeric mice in athymic nude background to develop orthotopic U251 tumor and tested receptor tyrosine kinase inhibitors and CXCR4 antagonist against GBM. We were able to track GFP+ BMDCs in the tumor brain using highly sensitive multispectral optical imaging instrument. Increased tumor growth associated with the infiltration of GFP+ BMDCs acquiring suppressive myeloid and endothelial phenotypes was seen in TME following treatments. Immunofluorescence study showed GFP+ cells accumulated at the site of VEGF, SDF1 and PDGF expression, and at the periphery of the tumors following treatments. In conclusion, we developed a preclinical chimeric model of GBM and phenotypes of tumor infiltrated BMDCs were investigated in context of AATs. Chimeric mouse model could be used to study detailed cellular and molecular mechanisms of interaction of BMDCs and TME in cancer.

Neurology
Hacein-Bey L, **Varelas PN**, Ulmer JL, Mark LP, Raghavan K, and Provenzale JM. Imaging of cerebrovascular disease in pregnancy and the puerperium *AJR Am J Roentgenol* 2016; 206(1):26-38. PMID: 26491895. Full Text

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OBJECTIVE: The purpose of this article is to review the unique physiologic changes that characterize pregnancy and the puerperium, some that substantially affect the cerebrovascular system. Conditions that can cause neurologic deterioration and share features with preeclampsia-eclampsia include postpartum angiopathy, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, and amniotic fluid embolism. Other conditions not specific to this patient group include cerebral venous thrombosis, cervicocephalic arterial dissection, ischemic stroke, and hemorrhagic stroke, which can pose specific diagnostic and therapeutic challenges. CONCLUSION: Radiologists must be familiar with the imaging findings of cerebrovascular complications and pathologic entities encountered during pregnancy and the puerperium. Ongoing improvements in understanding of molecular changes during pregnancy and the puerperium and advances in diagnostic tests should allow radiologists to continue to make important contributions to the care of this patient population.

Neurology
Liu XS, **Chopp M**, **Pan WL**, **Wang XL**, **Fan BY**, **Zhang Y**, **Kassis H**, **Zhang RL**, Zhang XM, and **Zhang ZG**. MicroRNA-146a promotes oligodendrogenesis in stroke *Mol Neurobiol* 2016;PMID: 26738853. Full Text

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Stroke induces new myelinating oligodendrocytes that are involved in ischemic brain repair. Molecular mechanisms that regulate oligodendrogenesis have not been fully investigated. MicroRNAs (miRNAs) are small non-coding RNA molecules that post-transcriptionally regulate gene expression. MiR-146a has been reported to regulate immune response, but the role of miR-146a in oligodendrocyte progenitor cells (OPCs) remains unknown. Adult Wistar rats were subjected to the right middle cerebral artery occlusion (MCAo). In situ hybridization analysis with LNA probes against miR-146a revealed that stroke considerably increased miR-146a density in the corpus callosum and subventricular zone (SVZ) of the lateral ventricle of the ischemic hemisphere. In vitro, overexpression of miR-146a in neural progenitor cells (NPCs) significantly increased their differentiation into O4+ OPCs. Overexpression of miR-146a in primary OPCs increased their expression of myelin proteins, whereas attenuation of endogenous miR-146a suppressed generation of myelin proteins. MiR-146a also inversely regulated its target gene-IRAK1 expression in OPCs. Attenuation of IRAK1 in OPCs substantially increased myelin proteins and decreased OPC apoptosis. Collectively, our data suggest that miR-146a may mediate stroke-induced oligodendrogenesis.

Neurology

Patel AA, **Mahajan A**, Benjo A, Jani VB, Annapureddy N, Agarwal SK, Simoes PK, Pakanati KC, Sinha V, Konstantinidis I, Pathak A, and Nadkarni GN. A national perspective of do-not-resuscitate order utilization predictors in intracerebral hemorrhage *Neurohospitalist* 2016; 6(1):7-10. PMID: 26753051. Full Text

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Nontraumatic intracerebral hemorrhage (ICH) is associated with substantial morbidity and mortality. Do-not-resuscitate (DNR) orders are linked to poorer outcomes in patients with ICH, possibly due to less active management. Demographic, regional, and social factors, not related to ICH severity, have not been adequately looked at as significant predictors of DNR utilization. We reviewed the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (NIS) database in 2011 for adult ICH admissions and DNR status. We generated hierarchical 2-level multivariate regression models to estimate adjusted odds ratios. We analyzed 25 768 ICH hospitalizations, 18% of which (4620 hospitalizations) had DNR orders, corresponding to national estimates of 126 254 and 22 668, respectively. In multivariable regression, female gender, white or Hispanic/Latino ethnicity, no insurance coverage, and teaching hospitals were significantly associated with increased DNR utilization after adjusting for confounders. There was also significantly more interhospital variability in the lowest quartile of hospital volume. In conclusion, demographic factors and insurance status are significantly associated with increased DNR utilization, with more individual hospital variability in low-volume hospitals. The reasons for this are likely qualitative and linked to patient, provider, and hospital practices.

Neurology

Singh J, **Olle B**, **Suhail H**, **Felicella MM**, and **Giri S**. Metformin-induced mitochondrial function and ABCD2 up regulation in X-linked adrenoleukodystrophy involves AMP activated protein kinase *J Neurochem* 2016;PMID: 26849413. Article Request Form

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X-linked adrenoleukodystrophy (X-ALD) is a progressive neurometabolic disease caused by mutations/deletions in the Abcd1 gene. Similar mutations/deletions in the Abcd1 gene often result in diagonally opposing phenotypes of mild adrenomyeloneuropathy (AMN) and severe neuroinflammatory cerebral adrenoleukodystrophy (ALD), which suggests involvement of downstream modifier genes. We recently documented the first evidence of loss of AMP-activated protein kinase alpha1 (AMPKalpha1) in ALD patient-derived cells. Here we report the novel loss of

AMPKalpha1 in postmortem brain white matter of patients with ALD phenotype. Pharmacological activation of AMPK can rescue the mitochondrial dysfunction and inhibit the pro-inflammatory response. The FDA approved anti-diabetic drug Metformin, a well-known AMPK activator, induces mitochondrial biogenesis and is documented for its anti-inflammatory role. We observed a dose-dependent activation of AMPKalpha1 in metformin-treated X-ALD patient-derived fibroblasts. Metformin also induced mitochondrial oxidative phosphorylation (OXPHOS) and ATP levels in X-ALD patient-derived fibroblasts. Metformin treatment decreased very long chain fatty acid levels and pro-inflammatory cytokine gene expressions in X-ALD patient-derived cells. Abcd2 (ALDP related protein) levels were increased in metformin-treated X-ALD patient-derived fibroblasts and Abcd1-KO mice primary mixed glial cells. Abcd2 induction was AMPKalpha1-dependent since metformin failed to induce Abcd2 levels in AMPKalpha1-KO mice-derived primary mixed glial cells. In vivo metformin (100mg/Kg) in drinking water for 60 days induced Abcd2 levels and mitochondrial OXPHOS protein levels in the brain and spinal cord of Abcd1-KO mice. Taken together, these results provide proof-of-principle for therapeutic potential of metformin as a useful strategy for correcting the metabolic and inflammatory derangements in X-ALD by targeting AMPK.

Neurology
Venkat P, **Chopp M**, and **Chen J**. Models and mechanisms of vascular dementia *Exp Neurol* 2015; 272:97-108. PMID: 25987538. Full Text

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Vascular dementia (VaD) is the second leading form of dementia after Alzheimer's disease (AD) plaguing the elderly population. VaD is a progressive disease caused by reduced blood flow to the brain, and it affects cognitive abilities especially executive functioning. VaD is poorly understood and lacks suitable animal models, which constrain the progress on understanding the basis of the disease and developing treatments. This review article discusses VaD, its risk factors, induced cognitive disability, various animal (rodent) models of VaD, pathology, and mechanisms of VaD and treatment options.

Neurology
Wang L, **Chopp M**, **Jia L**, **Lu X**, **Szalad A**, **Zhang Y**, **Zhang R**, and **Zhang ZG**. Therapeutic benefit of extended thymosin beta4 treatment is independent of blood glucose level in mice with diabetic peripheral neuropathy *J Diabetes Res* 2015; 2015:173656. PMID: 25945352. Full Text

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Peripheral neuropathy is a chronic complication of diabetes mellitus. To investigated the efficacy and safety of the extended treatment of diabetic peripheral neuropathy with thymosin beta4 (Tbeta4), male diabetic mice (db/db) at the age of 24 weeks were treated with Tbeta4 or saline for 16 consecutive weeks. Treatment of diabetic mice with Tbeta4 significantly improved motor (MCV) and sensory (SCV) conduction velocity in the sciatic nerve and the thermal and mechanical latency. However, Tbeta4 treatment did not significantly alter blood glucose levels. Treatment with Tbeta4 significantly increased intraepidermal nerve fiber density. Furthermore, Tbeta4 counteracted the diabetes-induced axon diameter and myelin thickness reductions and the g-ratio increase in sciatic nerve. In vitro, compared with dorsal root ganglia (DRG) neurons derived from nondiabetic mice, DRG neurons derived from diabetic mice exhibited significantly decreased neurite outgrowth, whereas Tbeta4 promoted neurite growth in these diabetic DRG neurons. Blockage of the Ang1/Tie2 signaling pathway with a neutralized antibody against Tie2 abolished Tbeta4-increased neurite outgrowth. Our data demonstrate that extended Tbeta4 treatment ameliorates diabetic-induced axonal degeneration and demyelination, which likely contribute to therapeutic effect of Tbeta4 on diabetic neuropathy. The Ang1/Tie2 pathway may mediate Tbeta4-induced axonal remodeling.

Neurology
Yu P, Zhang Z, Li S, Wen X, Quan W, Tian Q, **Chen J**, Zhang J, and Jiang R. Progesterone modulates endothelial progenitor cell (EPC) viability through the CXCL12/CXCR4/PI3K/Akt signalling pathway *Cell Prolif* 2016;PMID: 26818151. Article Request Form

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OBJECTIVES: Progesterone treatment can effectively increase levels of circulating endothelial progenitor cells (EPCs) and improve neurological functional outcome in a traumatic brain injury (TBI) rat model. However, the mechanisms of progesterone's effects on EPC viability remain elusive. The CXCL12/CXCR4 (CXC chemokine ligand 12/CXC chemokine receptor 4) signalling pathway regulates cell proliferation; we hypothesize that it mediates progesterone-induced EPC viability. MATERIALS AND METHODS: EPCs were isolated from bone marrow-derived mononuclear cells (BM-MNCs) and treated with progesterone (5, 10 and 100 nm). MTS assay was used to investigate EPC viability. Protein expression was examined by Western blotting, ELISA assay and flow cytometry. Cell membrane and cytoplasm proteins were extracted with membrane and cytoplasm protein extraction kits. CXCR4 antagonist (AMD3100) and phosphatidylinositol 3-kinases (PI3K) antagonist (LY294002) were used to characterize underlying mechanisms. RESULTS: Progesterone-induced EPC viability was time- and dose-dependent. Administration of progesterone facilitated EPC viability and increased expression of CXCL12 and phosphorylated Akt (also known as protein kinase B, pAkt) activity ($P < 0.05$). Progesterone did not regulate CXCR4 protein expression in cultured EPC membranes or cytoplasm. However, progesterone-induced EPC viability was significantly attenuated by AMD3100 or LY294002. Inhibition of the signalling pathway with AMD3100 and LY294002 subsequently reduced progesterone-induced CXCL12/CXCR4/PI3K/pAkt signalling activity. CONCLUSIONS: The CXCL12/CXCR4/PI3K/pAkt signalling pathway increased progesterone-induced EPC viability.

Neurology

Zhang J, **Zhang ZG**, **Li Y**, **Lu M**, **Zhang Y**, **Elias SB**, and **Chopp M**. Thymosin beta4 promotes oligodendrogenesis in the demyelinating central nervous system *Neurobiol Dis* 2016; 88:85-95. PMID: 26805386. Full Text

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). No effective remyelination therapies are in use. We hypothesized that thymosin beta4 (Tbeta4) is an effective remyelination treatment by promoting differentiation of oligodendrocyte progenitor cells (OPCs), and that the epidermal growth factor receptor (EGFR) signaling pathway contributes to this process. Two demyelination animal models were employed in this study: 1) experimental autoimmune encephalomyelitis (EAE), an animal model of MS. EAE mice were treated daily for 30days, with Tbeta4 or saline treatment initiated on the day of EAE onset; and 2) cuprizone diet model, a non-inflammatory demyelination model. The mice were treated daily for 4weeks with Tbeta4 or saline after fed a cuprizone diet for 5weeks. Immunofluorescent staining and Western blot were performed to measure the differentiation of OPCs, myelin and axons, respectively. To obtain insight into mechanisms of action, the expression and activation of the EGFR pathway was measured. AG1478, an EGFR inhibitor, was employed in a loss-of-function study. Data revealed that animals in both demyelination models exhibited significant reduction of myelin basic protein (MBP+) levels and CNPase+ oligodendrocytes. Treatment of EAE mice with Tbeta4 significantly improved neurological outcome. Double immunofluorescent staining showed that Tbeta4 significantly increased the number of newly generated oligodendrocytes identified by BrdU+/CNPase+ cells and MBP+ mature oligodendrocytes, and reduced axonal damage in the EAE mice compared with the saline treatment. The newly generated mature oligodendrocytes remyelinated axons, and the increased mature oligodendrocytes significantly correlated with functional improvement ($r=0.73$, $p<0.05$). Western blot analysis revealed that Tbeta4 treatment increased expression and activation of the EGFR pathway. In the cuprizone demyelination model, Tbeta4 treatment was confirmed that significantly increased OPC differentiation and remyelination, and increased the expression of EGFR and activated the EGFR pathway in the demyelinating corpus callosum. In cultured OPCs, blockage of the activation of the EGFR pathway with AG1478 abolished the Tbeta4-increased OPC differentiation. Collectively, these findings indicate that: 1) Tbeta4 increases proliferation of OPCs and the maturation of OPCs to myelinating oligodendrocytes which in concert, likely contribute to the beneficial effect of Tbeta4 on EAE, 2) EGFR upregulated and activated by Tbeta4 may mediate the process of OPC differentiation, and 3) Tbeta4 could potentially be developed as a therapy for MS patients, and for other demyelinating neurological disorders.

Neurology

Zhang L, **Chopp M**, **Lu M**, **Zhang T**, Winter S, **Doppler E**, **Meier D**, **Chao L**, **Eapen A**, Pabla P, and **Gang Zhang Z**. Cerebrolysin dose-dependently improves neurological outcome in rats after acute stroke: A prospective, randomized, blinded, and placebo-controlled study *Int J Stroke* 2016;PMID: 26763925. Article Request Form

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BACKGROUND: Cerebrolysin is a mixture of neuropeptides and free amino acids that is clinically used for the treatment of stroke. To further standardize treatment schemes, we assessed the dose response of Cerebrolysin on sensorimotor outcome in a rat model of ischemic stroke. METHODS: This study was a prospective, blinded, placebo-controlled, preclinical experiment. Male and female Wistar rats, subjected to embolic middle cerebral artery occlusion, were randomly treated with Cerebrolysin doses of 0.8, 2.5, 5.0, 7.5 ml/kg or placebo, 4 h after middle cerebral artery occlusion for a total of 10 consecutive days. RESULTS: The primary outcome was neurologic improvement at day 28, lesion volume, mortality, and animal weight were secondary and safety outcomes, respectively. There was a significant ($p < 0.001$) dose effect of Cerebrolysin on neurological outcome. Cerebrolysin at a dose of >/= 2.5 ml/kg significantly ($p < 0.001$) improved neurological outcome (Mean Estimate (95% CL): 0.8 ml/kg: 6.2 (-6.0/18.4), 2.5 ml/kg: -28.9 (-41.6/-16.2), 5.0 ml/kg: -33.4 (-45.0/-21.7), 7.5 ml/kg: -36.3 (-48.2/-24.4). Higher doses (>/=2.5 ml/kg) resulted in better recovery; however, differences between effective doses were not significant. Treatment with 5 ml/kg reduced lesion volume ($p = 0.016$). No treatment gender interactions were found and there were no differences in death or weight loss. CONCLUSION: Collectively, these data on Cerebrolysin efficacy demonstrate the feasibility of a preclinical study setup following a randomized, placebo-controlled, and blinded design with a clinical relevant treatment scheme. Cerebrolysin at doses of >/= 2.5 ml/kg improved functional outcome and at a dose of 5 ml/kg reduced infarct volume.

Neurosurgery

Ali R, Khan M, **Chang V**, **Narang J**, Jain R, **Marin H**, **Rock J**, and **Kole M**. MRI pre- and post-embolization enhancement patterns predict surgical outcomes in intracranial meningiomas *J Neuroimaging* 2016; 26(1):130-135. PMID: 25996574. Article Request Form

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PURPOSE: To evaluate the effects of preoperative embolization on overall surgical outcomes after meningioma resection and determine whether pre- and postembolization tumor enhancement patterns on magnetic resonance imaging (MRI) scans can be used to assess the efficacy of embolization. METHODS: We developed a prospective database of all patients who underwent surgical resection with or without preoperative embolization for extra-axial intracranial meningiomas from 2004 to 2010. Using specialized computer software, the total volume of enhancement was calculated in pre- and postembolization MRI scans to quantify the percentage of embolization, which was described as the embolization fraction (EF). RESULTS: A total of 89 patients underwent surgical resection. Fifty two patients underwent embolization prior to surgery. Tumor location significantly correlated with the decision to embolize preoperatively. Adequate embolization was achieved in 58% of patients. Forty four patients (84.6%) had a postsurgical Karnofsky performance score (KPS) of 80 or above, while 46 patients (88.4%) had a postsurgical Glascow Outcome Score (GOS) of 4 or 5. The mean EF was 25.03% with a median of 18.72%. A greater extent of embolization as quantified by EF led to decreased intraoperative blood loss ($r = -.319$, $P = .022$) and better postsurgical outcomes as defined by KPS ($r = .279$, $P = .044$). CONCLUSIONS: Pre- and postembolization tumor enhancement patterns on magnetic resonance imaging defined as EF correlate with improved surgical facilitation and postoperative functional outcomes in the management of intracranial meningioma.

Neurosurgery

Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA, Morozova O, Newton Y, Radenbaugh A, Pagnotta SM, Anjum S, Wang J, Manyam G, Zoppoli P, Ling S, Rao AA, Grifford M, Cherniack AD, Zhang H, **Poisson L**, Carlotti CG, Jr., Tirapelli DP, Rao A, **Mikkelsen T**, Lau CC, Yung WK, Rabadan R, Huse J, Brat DJ,

Lehman NL, Barnholtz-Sloan JS, Zheng S, Hess K, Rao G, Meyerson M, Beroukhim R, Cooper L, Akbani R, Wrensch M, Haussler D, Aldape KD, Laird PW, Gutmann DH, Noushmehr H, Iavarone A, and Verhaak RG. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma *Cell* 2016; 164(3):550-563. PMID: 26824661. Article Request Form

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Therapy development for adult diffuse glioma is hindered by incomplete knowledge of somatic glioma driving alterations and suboptimal disease classification. We defined the complete set of genes associated with 1,122 diffuse grade II-III-IV gliomas from The Cancer Genome Atlas and used molecular profiles to improve disease classification, identify molecular correlations, and provide insights into the progression from low- to high-grade disease. Whole-genome sequencing data analysis determined that ATRX but not TERT promoter mutations are associated with increased telomere length. Recent advances in glioma classification based on IDH mutation and 1p/19q co-deletion status were recapitulated through analysis of DNA methylation profiles, which identified clinically relevant molecular subsets. A subtype of IDH mutant glioma was associated with DNA demethylation and poor outcome; a group of IDH-wild-type diffuse glioma showed molecular similarity to pilocytic astrocytoma and relatively favorable survival. Understanding of cohesive disease groups may aid improved clinical outcomes.

Neurosurgery

Hacein-Bey L, **Varelas PN**, Ulmer JL, Mark LP, Raghavan K, and Provenzale JM. Imaging of cerebrovascular disease in pregnancy and the puerperium *AJR Am J Roentgenol* 2016; 206(1):26-38. PMID: 26491895. Full Text

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OBJECTIVE: The purpose of this article is to review the unique physiologic changes that characterize pregnancy and the puerperium, some that substantially affect the cerebrovascular system. Conditions that can cause neurologic deterioration and share features with preeclampsia-eclampsia include postpartum angiopathy, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, and amniotic fluid embolism. Other conditions not specific to this patient group include cerebral venous thrombosis, cervicocephalic arterial dissection, ischemic stroke, and hemorrhagic stroke, which can pose specific diagnostic and therapeutic challenges. CONCLUSION: Radiologists must be familiar with the imaging findings of cerebrovascular complications and pathologic entities encountered during pregnancy and the puerperium. Ongoing improvements in understanding of molecular changes during pregnancy and the puerperium and advances in diagnostic tests should allow radiologists to continue to make important contributions to the care of this patient population.

Neurosurgery

Macki M, Syeda S, Kerezoudis P, Gokaslan ZL, **Bydon A**, and Bydon M. Preoperative motor strength and time to surgery are the most important predictors of improvement in foot drop due to degenerative lumbar disease *J Neurol Sci* 2016; 361:133-136. PMID: 26810531. Full Text

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OBJECTIVE: Palsy of dorsiflexion, or foot drop, may be due to degenerative lumbar disease and amenable to posterior spinal decompression. The objective of this study is to measure prognostic factors of and time to foot drop improvement after posterior lumbar decompression. METHODS: We retrospectively reviewed 71 patients undergoing first-time, posterior lumbar decompression for foot drop due to degenerative spinal disease. Patient sex, age, comorbidities (Charlson Comorbidity Index), preoperative anterior tibialis strength (manual muscle testing, MMT), and duration of foot drop were ascertained from clinical notes. Prognostic factors affecting foot drop improvement were calculated with a discrete time proportional hazards model, in which follow-up times and outcome measures were binned into six time intervals: 1week, 6weeks, 3months, 6months, 1year, and >/=1year. RESULTS: Of the 71 patients, the mean age was 54.6+/-16.0years, and 66.2% (n=47) were males. The mean Charlson Comorbidity Index was 2.42. During a mean follow-up of 30.4months, dorsiflexion function improved postoperatively in 73.2% (n=52) of patients. The median time to surgery from onset of foot drop was within 6weeks, and the median preoperative MMT strength of patients with foot drop improvement was 3. Following a discrete-time proportional hazards model, duration of anterior tibialis palsy (HR=0.67, P=0.004) and preoperative muscle strength (HR=1.10, P=0.010) were significant predictors of foot drop improvement. Following an adjusted Kaplan-Meier analysis, the median time to foot drop improvement was within 6weeks of surgical intervention. CONCLUSIONS: Preoperative muscle strength and palsy duration were statistically significant predictors of foot drop improvement. Furthermore, the median time to improvement was 6weeks.

Neurosurgery

Pabaney AH, **Robin AM**, **Basheer A**, and **Malik GM**. Surgical management of dural arteriovenous fistula after craniotomy: Case report and review of literature *World Neurosurg* 2016;PMID: 26844878. Full Text

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BACKGROUND: Development of dural arteriovenous fistula (dAVF) with cortical venous drainage at the site of prior craniotomy is a rare manifestation of non-traumatic subarachnoid hemorrhage (SAH). The authors present a case of post-craniotomy dAVF formation, discuss plausible underlying mechanisms of fistula formation and treatment options as well as review the literature. CASE DESCRIPTION: A 62-year-old, who had undergone craniotomy two decades ago, presented with SAH. Workup revealed a low-flow dAVF with leptomeningeal venous drainage at posterior margin of craniotomy. Surgical resection of fistula was undertaken that resulted in cure. CONCLUSION: Spontaneous SAH in patients with prior history of intracranial procedure (craniotomy, ventriculostomy, etc.) should prompt detailed imaging evaluation. In the absence of a vascular pathology, meticulous review of the angiogram must be undertaken to rule out dAVF at the procedure site and treated definitively.

Neurosurgery
Parajuli P, Anand R, Mandalaparty C, Suryadevara R, Sriranga PU, Michelhaugh SK, **Cazacu S**, **Finniss S**, Thakur A, Lum LG, Schalk D, **Brodie C**, and Mittal S. Preferential expression of functional IL-17R in glioma stem cells: potential role in self-renewal *Oncotarget* 2016;PMID: 26755664. Full Text

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Gliomas are the most common primary brain tumor and one of the most lethal solid tumors. Mechanistic studies into identification of novel biomarkers are needed to develop new therapeutic strategies for this deadly disease. The objective for this study was to explore the potential direct impact of IL-17-IL-17R interaction in gliomas. Immunohistochemistry and flow cytometry analysis of 12 tumor samples obtained from patients with high grade gliomas revealed that a considerable population (2-19%) of cells in all malignant gliomas expressed IL-17RA, with remarkable co-expression of the glioma stem cell (GSC) markers CD133, Nestin, and Sox2. IL-17 enhanced the self-renewal of GSCs as determined by proliferation and Matrigel(R) colony assays. IL-17 also induced cytokine/chemokine (IL-6, IL-8, interferon-gamma-inducible protein [IP-10], and monocyte chemoattractant protein-1 [MCP-1]) secretion in GSCs, which were differentially blocked by antibodies against IL-17R and IL-6R. Western blot analysis showed that IL-17 modulated the activity of signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB), glycogen synthase kinase-3beta (GSK-3beta) and beta-catenin in GSCs. While IL-17R-mediated secretion of IL-6 and IL-8 were significantly blocked by inhibitors of NF-kappaB and STAT3; NF-kappaB inhibitor was more potent than STAT3 inhibitor in blocking IL-17-induced MCP-1 secretion. Overall, our results suggest that IL-17-IL-17R interaction in GSCs induces an autocrine/paracrine cytokine feedback loop, which may provide an important signaling component for maintenance/self-renewal of GSCs via constitutive activation of both NF-kappaB and STAT3. The results also strongly implicate IL-17R as an important functional biomarker for therapeutic targeting of GSCs.

Neurosurgery
Reinard KA, **Zakaria HM**, Qatanani A, **Lee IY**, **Rock JP**, and **Houin HP**. Preoperative external tissue expansion for complex cranial reconstructions *J Neurosurg* 2016:1-8. PMID: 26722853. Full Text

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OBJECTIVE Reconstruction of large solitary cranial defects after multiple craniotomies is challenging because scalp contraction generally requires more than simple subcutaneous undermining to ensure effective and cosmetically appealing closure. In plastic and reconstructive surgery, soft tissue expansion is considered the gold standard for reconstructing scalp defects; however, these techniques are not well known nor are they routinely practiced among neurosurgeons. The authors here describe a simple external tissue expansion technique that is associated with low morbidity and results in high cosmetic satisfaction among patients. METHODS The authors reviewed the medical records of patients with large cranial defects (> 5 cm) following multiple complicated craniotomies who had undergone reconstructive cranioplasty with preoperative tissue expansion using the DermaClose RC device. In addition to gathering data on patient age, sex, primary pathology, number of craniotomies and/or craniectomies, history of radiation therapy, and duration of external scalp tissue expansion, the authors screened patient charts for cerebrospinal fluid (CSF) leak, meningitis, intracranial abscess formation, dermatitis, and patient satisfaction rates. RESULTS The 6 identified patients (5 female, 1 male) had an age range from 36 to 70 years. All patients had complicating factors such as recalcitrant scalp infections after multiple craniotomies or cranial radiation, which led to

secondary scalp tissue scarring and retraction. All patients were deemed to be potential candidates for rotational flaps with or without skin grafts. All patients underwent the same preoperative tissue expansion followed by standard cranial bone reconstruction. None of the patients developed CSF leak, meningitis, intracranial abscess, dermatitis, or permanent cosmetic defects. None of the patients required a reoperation. Mean follow-up was 117 days. CONCLUSIONS Preoperative scalp tissue expansion with the DermaClose RC device allows for simple and reliable completion of complicated cranial reconstruction with low morbidity rates and high cosmetic satisfaction among patients.

Obstetrics, Gynecology and Women's Health Services

Khangura RK, Khangura CK, **Desai A**, **Goyert G**, and **Sangha R**. Metastatic colorectal cancer resembling severe preeclampsia in pregnancy *Case Rep Obstet Gynecol* 2015; 2015:487824. PMID: 26770850. Full Text

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Although colorectal cancer (CRC) is the third most common cancer in women, it is a rare malignancy in pregnancy. Symptoms of CRC such as fatigue, malaise, nausea, vomiting, rectal bleeding, anemia, altered bowel habits, and abdominal mass are often considered typical symptoms of pregnancy. Many cases of CRC are diagnosed in advanced stages due to missed warning signs of CRC, which may be misinterpreted as normal symptoms related to pregnancy. This report reviews 2 cases of CRC diagnosed within a 4-month interval at our institution. Both cases were initially thought to be atypical presentations of preeclampsia. Prenatal history, hospital course, and postpartum course were reviewed for both patients. CRC is often diagnosed at advanced stages in pregnancy. Common physiological symptoms of pregnancy should be scrutinized carefully and worked up appropriately, especially if symptoms remain persistent or increase in intensity or severity.

Obstetrics, Gynecology and Women's Health Services

Ondersma SJ, Beatty JR, Rosano TG, **Strickler RC**, Graham AE, and Sokol RJ. Commercial ethyl glucuronide (etg) and ethyl sulfate (ets) testing is not vulnerable to incidental alcohol exposure in pregnant women *Subst Use Misuse* 2016; 51(1):126-130. PMID: 26771303. Article Request Form

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BACKGROUND: Ethyl Glucoronide (EtG) and Ethyl Sulfate (EtS) have shown promise as biomarkers for alcohol and may be sensitive enough for use with pregnant women in whom even low-level alcohol use is important. However, there have been reports of over-sensitivity of EtG and EtS to incidental exposure to sources such as alcohol-based hand sanitizer. Further, few studies have evaluated these biomarkers among pregnant women, in whom the dynamics of these metabolites may differ. OBJECTIVES: This study evaluated whether commercial EtG-EtS testing was vulnerable to high levels of environmental exposure to alcohol in pregnant women. METHODS: Two separate samples of five nurses-one pregnant and the other postpartum, all of whom reported high levels of alcohol-based hand sanitizer use-provided urine samples before and 4-8 hours after rinsing with alcohol-based mouthwash and using hand sanitizer. The five pregnant nurses provided urine samples before, during, and after an 8-hour nursing shift, during which they repeatedly cleansed with alcohol-based hand sanitizer (mean 33.8 uses). The five postpartum nurses used hand sanitizer repeatedly between baseline and follow-up urine samples. RESULTS: No urine samples were positive for EtG-EtS at baseline or follow-up, despite use of mouthwash and-in the pregnant sample-heavy use of hand sanitizer (mean of 33.8 uses) throughout the 8-hour shift. CONCLUSIONS/IMPORTANCE: Current, commercially available EtG-EtS testing does not appear vulnerable to even heavy exposure to incidental sources of alcohol among pregnant and postpartum women.

Obstetrics, Gynecology and Women's Health Services

Vance S, **Burmeister C**, **Rasool N**, **Buekers T**, and **Elshaikh MA**. Salvage versus adjuvant radiation treatment for women with early-stage endometrial carcinoma: A matched analysis *Int J Gynecol Cancer* 2016; 26(2):307-312. PMID: 26745700. Full Text

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OBJECTIVES: Adjuvant radiation treatment (ART) has been shown to reduce local recurrences in early-stage endometrial carcinoma (EC); however, this has not translated into improved overall survival (OS) benefit. As a result, some physicians forgo ART, citing successful salvage rates in cases of recurrence. Survival end points were compared between women treated with salvage RT (SRT) for locoregional recurrence and similarly matched women treated upfront with ART. MATERIALS AND METHODS: We identified 40 patients with stage I to II type 1 EC who underwent hysterectomy and received no adjuvant RT but later developed locoregional recurrence and subsequently received SRT. An additional 374 patients who underwent hysterectomy followed by ART during the same period were identified. Patients in the SRT group were matched to those in the ART group based on FIGO (International Federation of Gynecology and Obstetrics) stage and tumor grade in a 1:3 ratio. Disease-specific survival (DSS) and OS were calculated. RESULTS: A total of 156 women were matched (39:117). Median follow-up was 56 months. The 2 groups were generally well balanced. With regard to the site of tumor recurrence, it was commonly vaginal in the SRT group (74.3% vs 28.6%, P = 0.01). More SRT patients received a combination of pelvic external-beam RT with vaginal brachytherapy (94.8% vs 35%, P < 0.001). The ART group had significantly better 5-year DSS (95% vs 77%, P < 0.001) and 5-year OS (79% vs 72%, P = 0.005) compared with those of the SRT group. CONCLUSIONS: Our study suggests that women who receive SRT for their locoregional recurrence have worse DSS and OS compared with those matched patients who received ART. Further studies are warranted to develop a high-quality cost-effectiveness analysis as well as accurate predictive models of tumor recurrence. Until then, ART should at least be considered in the management of early-stage EC patients with adverse prognostic factors.

Ophthalmology and Eye Care Services

Peracha ZH, **Ahmed SB**, **Desai A**, **Peracha-Riyaz M**, **Kumar N**, and **Desai UR**. Saturday night retinopathy: Characterization of a rare ophthalmic condition *Ophthalmic Surg Lasers Imaging Retina* 2016; 47(1):85-89. PMID: 26731217. Article Request Form

A 48-year-old, black female with a history of heroin and daily alcohol abuse presented to the emergency room in a lethargic state with severe right eye pain and vision loss. She had been unconscious for 10 hours prior to presentation. On exam she was found to have no light perception vision, severe retinal edema, and complete ophthalmoplegia of the right eye. Imaging and clinical course confirmed the diagnosis of Saturday Night Retinopathy - only the second documented case to be published. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:85-89.].

Orthopaedics

Baumer TG, Giles JW, Drake A, **Zauel R**, and **Bey MJ**. Measuring three-dimensional thorax motion via biplane radiographic imaging: Technique and preliminary results *J Biomech Eng* 2016; 138(1)PMID: 26592901. Article Request Form

Measures of scapulothoracic motion are dependent on accurate imaging of the scapula and thorax. Advanced radiographic techniques can provide accurate measures of scapular motion, but the limited 3D imaging volume of these techniques often precludes measurement of thorax motion. To overcome this, a thorax coordinate system was defined based on the position of rib pairs and then compared to a conventional sternum/spine-based thorax coordinate system. Alignment of the rib-based coordinate system was dependent on the rib pairs used, with the rib3:rib4 pairing aligned to within 4.4 +/- 2.1 deg of the conventional thorax coordinate system.

Otolaryngology – Head and Neck Services

Diaz M, **Chang S**, and **Singer M**. Adherence to dietary indexes by diabetes and hypertension status among PLCO cancer screening trial participants *Adv Nutr* 2016; 7(1):38A. PMID: Not assigned. Abstract

Background: A healthy diet is an effective strategy for glycemia and blood pressure control with adherence key to its success. Optimal nutrient intake can be measured via dietary patterns. We quantified adherence to several dietary indices among individuals with diabetes (DM) and/or hypertension (HTN) and compared it with controls in the PLCO Cancer Screening Trial.Methods: Participants in PLCO who filled out a baseline food-frequency questionnaire, with age, sex, body mass index (BMI), DM, and HTN status recorded were selected for analysis. Indices for Healthy Eating 2005 (HEI), Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean (MEDI) diets were calculated. Adherence to each item was given a point with maximum total possible scores of 7, 9, and 10,

respectively. Quartiles of scores for each index were calculated and used to create 4 ordered categories. Their association with DM and/or HTN controlling for differing covariates across exposures was evaluated using logistic regression.Results: 60,408 adults 55–74 y of age provided baseline data. Age, sex, and BMI differed across exposure groups. Participants with DM independently of HTN were twice more likely than controls to high adherence to the HEI diet, and 1.3–1.5 times to the DASH and MEDI diets (all p-v <0.001) (Figure 1). Highest adherence among diabetics was to vegetable, grains, and meat portions in HEI and DASH, and sugar in HEI. They were slightly less compliant with fat rations. Hypertensive adults did not differ in adherence to controls, not even in salt consumption as per DASH. Regular physical activity and female sex was predictive of high adherence.Conclusions: Management of DM in mature and older adults via diet is feasible in about 34% highly adherent to the HEI 2005 diet. A similar level will only be achieved by 20% of those with HTN. Exercising regularly identifies those likely to adhere. Figure 1

Pathology

Gulati R, **Alkhatib Y**, **Donthireddy V**, **Felicella MM**, **Menon MP**, and **Inamdar KV**. Isolated ocular manifestation of relapsed chronic myelogenous leukemia presenting as myeloid blast crisis in a patient on imatinib therapy: A case report and review of the literature *Case Rep Pathol* 2015; 2015:380451. PMID: 26819793. Full Text

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Blast phase in chronic myelogenous leukemia (CML) has rarely been reported to involve extramedullary sites like skin, lymph nodes, and central nervous system. Clinical history, characteristic hematologic findings (elevated leukocyte counts, myelocytic predominance, and basophilia), and Philadelphia chromosome are of high diagnostic significance especially in isolated extramedullary presentations. We describe a unique case of CML relapse with blast phase involving the eye. A 66-year-old man with a known diagnosis of CML on imatinib and in molecular remission for 3 years presented with a painful blind eye. Histologic examination revealed diffuse involvement of choroid, iris, vitreous humor, and the optic nerve by blast cells. The blasts expressed CD34, aberrant TdT, and a myeloid phenotype (CD13, CD33, and CD117). Fluorescence in situ hybridization (FISH) of vitreous fluid detected BCR-ABL1 gene rearrangement. Additionally, trisomy 8 and gains of 9 and 22 were seen which were not present in the initial diagnostic marrow study 3 years ago. At relapse, the bone marrow, peripheral blood, and the cerebrospinal fluid were not involved by CML. Patient received induction chemotherapy and single dose prophylactic intrathecal methotrexate and was maintained on antityrosine kinase therapy and eventually underwent allogenic stem cell transplantation.

Pathology

Newman L, Jiagge E, Bensenhaver J, Jibril A, Awuah B, and **Stark A**. 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 *Annals of Surgical Oncology* 2016; 23:S8-S8. PMID: Not assigned. Abstract

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Introduction: Population-based incidence rates of triple negative breast cancer (TNBC) are higher for African American (AA) compared to White American (WA) women, but it is unclear whether TNBC risk is genetically associated with African ancestry because AA women represent an ancestrally admixed population. Higher frequencies of TNBC have also been observed in western sub-Saharan African breast cancer (BC) patients, and this study represents a first comparison of AA, WA, West and East African cases. Methods: Formalin-fixed, paraffin-embedded invasive BC tumors diagnosed 1998-2014 in AA, WA, Ghana/East Africa, and Ethiopia/West Africa were compared. All African tumors underwent pathology confirmation and immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu expression in the U.S. Statistical analyses were performed in SAS v. 9.0 (Carey, NC). Results: 234 Ghanaian cases (mean age 49 yrs); 271 AA (mean age 60); and 321 WA (mean age 62)(P=0.001) were compared. ER-negative and TNBC were more common among Ghanaian and AA compared to WA cases (frequency ER-negativity 67.5%, 37.1%, and 19.8%, respectively, p<0.0001;frequency TNBC 53.2%, 29.8%, and 15.5%, respectively, p<0.0001). In the age group <50 years, 82 cases (42.5%) were ER+/PR+/HER2-; 65 (33.7%) were TNBC. In this young age group, prevalence of TNBC remained highest among Ghanaian women (50.8%), followed by AA (34.3%) and WA (15.9%); (P=.0006). Highest prevalence of ER+/PR+/HER2+ and ER+/PR+/ HER2- phenotypes was observed in WA, followed by AA and Ghanaians. The addition of 33 cases from Ethiopia revealed a different distribution: the majority (55%) were HER2/neu-overexpressing; 42% were triple-positive;and only 15% were TNBC. Conclusions: This study confirms an association between TNBC and West African ancestry, and AA patients have a TNBC

frequency that is intermediate between WA and Ghanian/West Africans. East Africans appear to have a low frequency of TNBC but an increased risk of HER2/neu overexpression.

Pathology

Saste A, **Arias-Stella J**, and **Kuriakose P**. Progression of a hepatosplenic gamma delta T-cell leukemia/lymphoma on hyperCVAD/MTX and ara-C: literature review and our institutional treatment approach *Clin Case Rep* 2016; 4(1):67-71. PMID: 26783439. Full Text

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A 24-year-old male presented with abdominal pain, fever, and palpable splenomegaly. His differential count revealed myelocytes, metamyelocytes, and nucleated red cells. A bone marrow biopsy confirmed a diagnosis of hepatosplenic gamma delta T-cell leukemia/lymphoma. We describe here our center's diagnostic and treatment approach for this rare leukemia.

Pathology

Singh J, **Olle B**, **Suhail H**, **Felicella MM**, and **Giri S**. Metformin-induced mitochondrial function and ABCD2 up regulation in X-linked adrenoleukodystrophy involves AMP activated protein kinase *J Neurochem* 2016;PMID: 26849413. Article Request Form

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X-linked adrenoleukodystrophy (X-ALD) is a progressive neurometabolic disease caused by mutations/deletions in the Abcd1 gene. Similar mutations/deletions in the Abcd1 gene often result in diagonally opposing phenotypes of mild adrenomyeloneuropathy (AMN) and severe neuroinflammatory cerebral adrenoleukodystrophy (ALD), which suggests involvement of downstream modifier genes. We recently documented the first evidence of loss of AMP-activated protein kinase alpha1 (AMPKalpha1) in ALD patient-derived cells. Here we report the novel loss of AMPKalpha1 in postmortem brain white matter of patients with ALD phenotype. Pharmacological activation of AMPK can rescue the mitochondrial dysfunction and inhibit the pro-inflammatory response. The FDA approved anti-diabetic drug Metformin, a well-known AMPK activator, induces mitochondrial biogenesis and is documented for its anti-inflammatory role. We observed a dose-dependent activation of AMPKalpha1 in metformin-treated X-ALD patient-derived fibroblasts. Metformin also induced mitochondrial oxidative phosphorylation (OXPHOS) and ATP levels in X-ALD patient-derived fibroblasts. Metformin treatment decreased very long chain fatty acid levels and pro-inflammatory cytokine gene expressions in X-ALD patient-derived cells. Abcd2 (ALDP related protein) levels were increased in metformin-treated X-ALD patient-derived fibroblasts and Abcd1-KO mice primary mixed glial cells. Abcd2 induction was AMPKalpha1-dependent since metformin failed to induce Abcd2 levels in AMPKalpha1-KO mice-derived primary mixed glial cells. In vivo metformin (100mg/Kg) in drinking water for 60 days induced Abcd2 levels and mitochondrial OXPHOS protein levels in the brain and spinal cord of Abcd1-KO mice. Taken together, these results provide proof-of-principle for therapeutic potential of metformin as a useful strategy for correcting the metabolic and inflammatory derangements in X-ALD by targeting AMPK.

Pharmacy

Claeys KC, Lagnf AM, Hallesy JA, Compton MT, Gravelin AL, **Davis SL**, and Rybak MJ. Pneumonia caused by methicillin-resistant staphylococcus aureus - does vancomycin heteroresistance matter? *Antimicrob Agents Chemother* 2016;PMID: 26729497. Full Text

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BACKGROUND: Vancomycin remains the mainstay treatment for methicillin-resistant S. aureus (MRSA) infections, including pneumonia. There is concern regarding the emergence of vancomycin tolerance, caused by heterogeneous

vancomycin-intermediate S. aureus (hVISA), and subsequent vancomycin treatment failure. Pneumonia is associated with high morbidity and mortality, especially with delays in appropriate therapy. This study evaluated the clinical outcomes of patients with hVISA compared to vancomycin-susceptible S. aureus (VSSA) pneumonia. METHODS: Retrospective cohort of patients with MRSA pneumonia from 2005 to 2014 matched 2:1 VSSA to hVISA to compare patient characteristics, treatments, and outcomes. hVISA determined by the 48-hour population analysis profile/area-under-the-curve. Characteristics between VSSA and hVISA were compared by univariate analysis and multivariable logistic regression analysis to determine independent risk factors of inpatient mortality. RESULTS: Eighty-seven patients were included: 29 hVISA and 58 VSSA pneumonias. There were no significant differences in demographics or baseline characteristics. Sequential Organ Failure Assessment (SOFA) scores were a median of 7 (IQR 5 - 8) in hVISA patients and 5 (IQR 3 - 8) in VSSA (p = 0.092) patients. Inpatient mortality was significantly higher in hVISA patients (44.8% versus 24.1%, p = 0.049). Predictors of inpatient mortality on multivariable regression were SOFA score (aOR 1.36; 95% CI 1.08 - 1.70), PVL positivity (aOR 6.63; 95% CI 1.79 - 24.64); and hVISA phenotype (aOR 3.95; 95% CI 1.18 - 13.21). CONCLUSIONS: Patients with hVISA pneumonia experienced significantly higher inpatient mortality than those with VSSA. There is a need to consider the presence of vancomycin heteroresistance in pneumonia caused by MRSA in order to potentially improve clinical outcomes.

Pharmacy

Farhat NM, **Hutchinson LS**, and **Peters M**. Elevated international normalized ratio values in a patient receiving warfarin and ceftaroline *Am J Health Syst Pharm* 2016; 73(2):56-59. PMID: 26721534. Full Text

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PURPOSE: The case of a patient whose International Normalized Ratio (INR) became elevated due to a probable interaction between ceftaroline and warfarin is reported. SUMMARY: A 65-year-old African-American man developed an INR of >18.0 after completing 12 days of ceftaroline therapy for the treatment of cellulitis while taking warfarin therapy. The patient was on warfarin due to his history of deep vein thrombosis of a lower extremity and pulmonary embolism, and his INR was consistently therapeutic for approximately 2 years before ceftaroline therapy. The patient reported no known drug allergies, had no history of adverse drug reactions, and had no recent changes in medications or diet. Phytonadione was administered, and the patient's INR began to decrease, returning to a therapeutic range of 2.30 after approximately 48 hours, at which time warfarin was restarted. After six days of hospitalization, the patient was discharged on his previous regimen of warfarin 7.5 mg orally once daily, with a therapeutic INR of 2.11. His cellulitis had resolved, so no further antibiotic therapy was warranted. To determine the likelihood of the drug interaction between warfarin and ceftaroline in this patient, the Drug Interaction Probability Scale of Horn and colleagues was applied and yielded a score of 6, indicating a probable likelihood of an interaction. Rechallenge was not attempted, as the patient's cellulitis had resolved and there were no evident signs or symptoms of infection. CONCLUSION: A 65-year-old man experienced an increase in INR values after the addition of ceftaroline to his medication regimen.

Plastic Surgery

Reinard KA, **Zakaria HM**, Qatanani A, **Lee IY**, **Rock JP**, and **Houin HP**. Preoperative external tissue expansion for complex cranial reconstructions *J Neurosurg* 2016:1-8. PMID: 26722853. Full Text

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OBJECTIVE Reconstruction of large solitary cranial defects after multiple craniotomies is challenging because scalp contraction generally requires more than simple subcutaneous undermining to ensure effective and cosmetically appealing closure. In plastic and reconstructive surgery, soft tissue expansion is considered the gold standard for reconstructing scalp defects; however, these techniques are not well known nor are they routinely practiced among neurosurgeons. The authors here describe a simple external tissue expansion technique that is associated with low morbidity and results in high cosmetic satisfaction among patients. METHODS The authors reviewed the medical records of patients with large cranial defects (> 5 cm) following multiple complicated craniotomies who had undergone reconstructive cranioplasty with preoperative tissue expansion using the DermaClose RC device. In addition to gathering data on patient age, sex, primary pathology, number of craniotomies and/or craniectomies, history of radiation therapy, and duration of external scalp tissue expansion, the authors screened patient charts for cerebrospinal fluid (CSF) leak, meningitis, intracranial abscess formation, dermatitis, and patient satisfaction rates. RESULTS The 6 identified patients (5 female, 1 male) had an age range from 36 to 70 years. All patients had

complicating factors such as recalcitrant scalp infections after multiple craniotomies or cranial radiation, which led to secondary scalp tissue scarring and retraction. All patients were deemed to be potential candidates for rotational flaps with or without skin grafts. All patients underwent the same preoperative tissue expansion followed by standard cranial bone reconstruction. None of the patients developed CSF leak, meningitis, intracranial abscess, dermatitis, or permanent cosmetic defects. None of the patients required a reoperation. Mean follow-up was 117 days. CONCLUSIONS Preoperative scalp tissue expansion with the DermaClose RC device allows for simple and reliable completion of complicated cranial reconstruction with low morbidity rates and high cosmetic satisfaction among patients.

Psychiatry

Ketterer MW, **Alaali Y**, **Yessayan L**, and **Jennings J**. "Alert and oriented x 3?" Correlates of mini-cog performance in a post/nondelirious intensive care unit sample *Psychosomatics* 2015;PMID: 26805587. Full Text

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BACKGROUND: Cognitive impairment has been found to be a predictor of adverse medical outcomes, including nonadherence, recurrent medical crises resulting in early readmissions, and death. OBJECTIVE: The Mini-Cog has been proposed for bedside/clinic cognitive testing. Its validity as a measure of central nervous system (CNS) impairment has never been tested against measures of CNS-medical history, CNS scans, selected laboratory findings, observed in-hospital nondelirious memory impairment, or collateral history from family. METHODS: We observed Mini-Cog performance in 107 post/nondelirious medical intensive care unit patients and tested its association with age, CNS-medical history, CNS scans, selected laboratory findings, and behavioral history (in-hospital observation of memory problems and collateral history from family or significant others). RESULTS: The overall Mini-Cog covaried with age, various measures of CNS impairment, abnormal laboratory findings, and measures of preadmission "forgetfulness" per family and by in-hospital staff observation. Unique variance in predicting overall Mini-Cog scores included age, positive CNS scan, and behavioral history. Of 91 patients found to be "alert and oriented x 3," 76% were impaired in immediate memory, short-term memory, or clock drawing. CONCLUSIONS: The Mini-Cog appears to be a brief, yet valid, measure of CNS dysfunction that significantly enhances sensitivity of evaluation at the bedside. Failure to evaluate patients with a formal examination like the Mini-Cog appears to miss up to 76% of patients with moderate cognitive impairment.

Psychiatry

Pheister M, Stagno S, Cotes R, **Prabhakar D**, Mahr F, Crowell A, and Schwartz A. Simulated patients and scenarios to assess and teach psychiatry residents *Acad Psychiatry* 2016;PMID: 26763534. Full Text

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Public Health Sciences

Arena SK, Bacyinski A, Simon L, and **Peterson EL**. Aneroid blood pressure manometer calibration rates of devices used in home health *Home Healthc Now* 2016; 34(1):23-28. PMID: 26645840. Article Request Form

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Hypertension is associated with cardiovascular disease, stroke, and a range of other medical sequelae. Accurate blood pressure (BP) readings, which depend on the integrity and calibration of the measuring device, are essential to identifying suboptimal BP. This study describes calibration rates of aneroid BP devices (a) utilized in home healthcare (HHC) and (b) having the needle resting within the zero accuracy indicator. BP devices from one branch of a home

care agency were inspected and checked for calibration according to the protocol set forth by the European Society of Hypertension. Of the 125 devices measured, 78.4% were in calibration. Of the 94 devices with the gauge needle resting in the zero accuracy indicator, 11.7% were not in calibration; whereas, 51.6% of the 31 devices with the gauge needle resting outside the zero accuracy indicator were found not in calibration. Twenty-one devices were not checked for calibration due to inflation bulb malfunction, tubing tears, or excessive wear. Furthermore, visual inspection of the needle placement did not confirm a device as being in or out of calibration. Proper maintenance and routine calibration of BP equipment is foundational to assuring accuracy of BP readings obtained by HHC providers.

Public Health Sciences

Belsky JB, **Morris DC**, **Bouchebl R**, Filbin MR, Bobbitt KR, **Jaehne AK**, and **Rivers EP**. Plasma levels of F-actin and F:G-actin ratio as potential new biomarkers in patients with septic shock *Biomarkers* 2016:1-6. PMID: 26754286. Article Request Form

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OBJECTIVE: To compare plasma levels of F-actin, G-actin and thymosin beta 4 (TB4) in humans with septic shock, noninfectious systemic inflammatory response syndrome (SIRS) and healthy controls. RESULTS: F-actin was significantly elevated in septic shock as compared with noninfectious SIRS and healthy controls. G-actin levels were greatest in the noninfectious SIRS group but significantly elevated in septic shock as compared with healthy controls. TB4 was not detectable in the septic shock or noninfectious SIRS group above the assay's lowest detection range (78 ng/ml). CONCLUSIONS: F-actin is significantly elevated in patients with septic shock as compared with noninfectious SIRS. F-actin and the F:G-actin ratio are potential biomarkers for the diagnosis of septic shock.

Public Health Sciences

Cassidy-Bushrow AE, **Wegienka G**, **Havstad S**, **Levin AM**, Lynch SV, Ownby DR, Rundle AG, **Woodcroft KJ**, **Zoratti EM**, and **Johnson CC**. Race-specific association of caesarean-section delivery with body size at age 2 years *Ethn Dis* 2016; 26(1):61-68. PMID: 26843797. Article Request Form

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OBJECTIVE: African American children are at higher risk of obesity than White children and African American women are more likely to undergo caesarean-section (CS) delivery than White women. CS is associated with childhood obesity; however, little is known whether this relationship varies by race. We examined if the association of CS with obesity at age 2 years varied by race. DESIGN: Longitudinal birth cohort. SETTING: Birth cohort conducted in a health care system in metropolitan Detroit, Michigan with follow-up at age 2 years. PARTICIPANTS: 639 birth cohort participants; 367 children (57.4%) were born to African American mothers and 230 (36.0%) children were born via CS. MAIN OUTCOME MEASURES: Obesity defined as body mass index >/=95th percentile at age 2 years. RESULTS: Slightly more children of African American (n=37; 10.1%) than non-African American mothers (n=18; 6.6%) were obese (P=.12). There was evidence of effect modification between race and delivery mode with obesity at age 2 years (interaction P=.020). In children of African American mothers, CS compared to vaginal birth was associated with a significantly higher odds of obesity (aOR=2.35 (95% CI: 1.16, 4.77), P=.017). In contrast, delivery mode was not associated with obesity at age 2 years in children of non-African American mothers (aOR=.47 (95% CI: .13, 1.71), P=.25). CONCLUSIONS: There is evidence for a race-specific effect of CS on obesity at age 2 years; potential underlying mechanisms may be racial differences in the developing gut microbiome or in epigenetic programming. Future research is needed to determine if this racial difference persists into later childhood.

Public Health Sciences

Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA, Morozova O, Newton Y, Radenbaugh A, Pagnotta SM, Anjum S, Wang J, Manyam G, Zoppoli P, Ling S, Rao AA, Grifford M, Cherniack AD, Zhang H, **Poisson L**, Carlotti CG, Jr., Tirapelli DP, Rao A, **Mikkelsen T**, Lau CC, Yung WK, Rabadan R, Huse J, Brat DJ,

Lehman NL, Barnholtz-Sloan JS, Zheng S, Hess K, Rao G, Meyerson M, Beroukhim R, Cooper L, Akbani R, Wrensch M, Haussler D, Aldape KD, Laird PW, Gutmann DH, Noushmehr H, Iavarone A, and Verhaak RG. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma *Cell* 2016; 164(3):550-563. PMID: 26824661. Article Request Form

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Therapy development for adult diffuse glioma is hindered by incomplete knowledge of somatic glioma driving alterations and suboptimal disease classification. We defined the complete set of genes associated with 1,122 diffuse grade II-III-IV gliomas from The Cancer Genome Atlas and used molecular profiles to improve disease classification, identify molecular correlations, and provide insights into the progression from low- to high-grade disease. Whole-genome sequencing data analysis determined that ATRX but not TERT promoter mutations are associated with increased telomere length. Recent advances in glioma classification based on IDH mutation and 1p/19q co-deletion status were recapitulated through analysis of DNA methylation profiles, which identified clinically relevant molecular subsets. A subtype of IDH mutant glioma was associated with DNA demethylation and poor outcome; a group of IDH-wild-type diffuse glioma showed molecular similarity to pilocytic astrocytoma and relatively favorable survival. Understanding of cohesive disease groups may aid improved clinical outcomes.

Public Health Sciences

Crawford EL, **Levin A**, Safi F, Lu M, Baugh A, Zhang X, Yeo J, Khuder SA, Boulos AM, Nana-Sinkam P, Massion PP, Arenberg DA, Midthun D, Mazzone PJ, Nathan SD, Wainz R, Silvestri G, Tita J, and Willey JC. Lung cancer risk test trial: study design, participant baseline characteristics, bronchoscopy safety, and establishment of a biospecimen repository *BMC Pulm Med* 2016; 16(1):16. PMID: 26801409. Full Text

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BACKGROUND: The Lung Cancer Risk Test (LCRT) trial is a prospective cohort study comparing lung cancer incidence among persons with a positive or negative value for the LCRT, a 15 gene test measured in normal bronchial epithelial cells (NBEC). The purpose of this article is to describe the study design, primary endpoint, and safety; baseline characteristics of enrolled individuals; and establishment of a bio-specimen repository. METHODS/DESIGN: Eligible participants were aged 50-90 years, current or former smokers with 20 pack-years or more cigarette smoking history, free of lung cancer, and willing to undergo bronchoscopic brush biopsy for NBEC sample collection. NBEC, peripheral blood samples, baseline CT, and medical and demographic data were collected from each subject. DISCUSSION: Over a two-year span (2010-2012), 403 subjects were enrolled at 12 sites. At baseline 384 subjects remained in study and mean age and smoking history were 62.9 years and 50.4 pack-years respectively, with 34 % current smokers. Obstructive lung disease (FEV1/FVC <0.7) was present in 157 (54 %). No severe adverse events were associated with bronchoscopic brushing. An NBEC and matched peripheral blood bio-specimen repository was established. The demographic composition of the enrolled group is representative of the population for which the LCRT is intended. Specifically, based on baseline population characteristics we expect lung cancer incidence in this cohort to be representative of the population eligible for low-dose Computed Tomography (LDCT) lung cancer screening. Collection of NBEC by bronchial brush biopsy/bronchoscopy was safe and well-tolerated in this population. These findings support the feasibility of testing LCRT clinical utility in this prospective study. If validated, the LCRT has the potential to significantly narrow the population of individuals requiring annual low-dose helical CT screening for early detection of lung cancer and delay the onset of screening for individuals with results indicating low lung cancer risk. For these individuals, the small risk incurred by undergoing once in a lifetime bronchoscopic sample collection for LCRT may be offset by a reduction in their CT-related risks. The LCRT biospecimen repository will enable additional studies of genetic basis for COPD and/or lung cancer risk. TRIAL REGISTRATION: The LCRT Study, NCT 01130285, was registered with Clinicaltrials.gov on May 24, 2010.

Public Health Sciences

Han Y, Rand KA, Hazelett DJ, Ingles SA, Kittles RA, Strom SS, **Rybicki BA**, Nemesure B, Isaacs WB, Stanford JL, Zheng W, Schumacher FR, Berndt SI, Wang Z, Xu J, Rohland N, Reich D, Tandon A, Pasaniuc B, Allen A, Quinque D, Mallick S, Notani D, Rosenfeld MG, Jayani RS, Kolb S, Gapstur SM, Stevens VL, Pettaway CA, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chokkalingam AP, John EM, Murphy AB, Signorello LB, Carpten J, Leske MC, Wu SY, Hennis AJ, **Neslund-Dudas C**, Hsing AW, Chu L, Goodman PJ, Klein EA, Zheng SL, Witte JS, Casey G, Lubwama A, Pooler LC, Sheng X, Coetzee GA, Cook MB, Chanock SJ, Stram DO, Watya S, Blot WJ, Conti DV, Henderson BE, and Haiman CA. Prostate cancer susceptibility in men of African ancestry at 8q24 *J Natl Cancer Inst* 2016; 108(7)PMID: 26823525. Full Text

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The 8q24 region harbors multiple risk variants for distinct cancers, including >8 for prostate cancer. In this study, we conducted fine mapping of the 8q24 risk region (127.8-128.8Mb) in search of novel associations with common and rare variation in 4853 prostate cancer case patients and 4678 control subjects of African ancestry. All statistical tests were two-sided. We identified three independent associations at P values of less than 5.00x10(-8), all of which were replicated in studies from Ghana and Uganda (combined sample = 5869 case patients, 5615 control subjects; rs114798100: risk allele frequency [RAF] = 0.04, per-allele odds ratio [OR] = 2.31, 95% confidence interval [CI] = 2.04 to 2.61, P = 2.38x10(-40); rs72725879: RAF = 0.33, OR = 1.37, 95% CI = 1.30 to 1.45, P = 3.04x10(-27); and rs111906932: RAF = 0.03, OR = 1.79, 95% CI = 1.53 to 2.08, P = 1.39x10(-13)). Risk variants rs114798100 and rs111906923 are only found in men of African ancestry, with rs111906923 representing a novel association signal. The three variants are located within or near a number of prostate cancer-associated long noncoding RNAs (lncRNAs), including PRNCR1, PCAT1, and PCAT2. These findings highlight ancestry-specific risk variation and implicate prostate-specific lncRNAs at the 8q24 prostate cancer susceptibility region.

Public Health Sciences
Johnson CC, and Ownby DR. Allergies and asthma: Do atopic disorders result from inadequate immune homeostasis arising from infant gut dysbiosis? *Expert Rev Clin Immunol* 2016;PMID: 26776722.
Article Request Form

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Our global hypothesis is that atopic conditions and asthma develop because an individual's immune system is not able to appropriately resolve inflammation resulting from allergen exposures. We propose that the failure to appropriately down-regulate inflammation and produce a toleragenic state results primarily from less robust immune homeostatic processes rather than from a tendency to over-respond to allergenic stimuli. An individual with lower immune homeostatic capacity is unable to rapidly and completely terminate, on average over time, immune responses to innocuous allergens, increasing risk of allergic disease. A lack of robust homeostasis also increases the risk of other inflammatory conditions, such as prolonged respiratory viral infections and obesity, leading to the common co-occurrence of these conditions. Further, we posit that the development of vigorous immune homeostatic mechanisms is an evolutionary adaptation strongly influenced by both 1) exposure to a diverse maternal microbiota through the prenatal period, labor and delivery, and, 2) an orderly assemblage process of the infant's gut microbiota ecosystem shaped by breastfeeding and early exposure to a wide variety of ingested foods and environmental microbes. This early succession of microbial communities together with early allergen exposures orchestrate the development of an immune system with a robust ability to optimally control inflammatory responses and a lowered risk for atopic disorders.

Public Health Sciences
Joseph CL, **Zoratti EM**, **Ownby DR**, **Havstad S**, **Nicholas C**, **Nageotte C**, **Misiak R**, **Enberg R**, Ezell J, and **Johnson CC**. Exploring racial differences in IgE-mediated food allergy in the WHEALS birth cohort *Ann Allergy Asthma Immunol* 2016;PMID: 26837607. Full Text

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BACKGROUND: Suspected food allergies are the cause of more than 200,000 visits to the emergency department annually. Racial differences in the prevalence of food allergy have also been reported, but the evidence is less conclusive. Researchers continue to struggle with the identification of food allergy for epidemiologic studies. OBJECTIVE: To explore racial differences in IgE-mediated food allergy (IgE-FA) in a birth cohort. METHODS: We used a panel of board-certified allergists to systematically identify IgE-FA to egg, milk, or peanut in a multiethnic birth cohort in which patient medical history, patient symptoms, and clinical data were available through 36 months of age. RESULTS: Of the 590 infants analyzed, 52.9% were male and 65.8% African American. Sensitization (serum specific IgE >0.35 IU/mL) to the food allergens was significantly higher for African American children compared with non-African American children as has been previously reported. No statistically significant racial/ethnic differences in IgE-FA were observed; however, a higher proportion of African American children were designated as having peanut allergy, and the percentage of African American children with an IgE level greater than 95% predictive decision points for peanut was 1.7% vs 0.5% for non-African American children. With the use of logistic regression, race/ethnicity was not significantly associated with IgE-FA (adjusted odds ratio, 1.12; 95% confidence interval, 0.58-2.17; P = .75) but was associated with sensitization to more than 1 of the food allergens (adjusted odds ratio, 1.80; 95% confidence interval, 1.22-2.65; P = .003). CONCLUSION: We did not observe an elevated risk of IgE-FA for African American children, although established differences in sensitization were observed. Racial/ethnic differences in sensitization must be taken into consideration when investigating disparities in asthma and allergy.

Public Health Sciences

Lu M, **Li J**, **Zhang T**, **Rupp LB**, **Trudeau S**, Holmberg SD, Moorman AC, Spradling PR, Teshale EH, Xu F, Boscarino JA, Schmidt MA, Vijayadeva V, and **Gordon SC**. Long-term reduction in liver fibrosis, based on serum biomarkers, in patients with sustained viral responses to HCV treatment *Clin Gastroenterol Hepatol* 2016;PMID: 26804385. Full Text

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BACKGROUND & AIMS: Sustained viral response (SVR) to antiviral therapy for hepatitis C virus (HCV) correlates with changes in biochemical measures of liver function. However, little is known about the long-term effects of SVR on liver fibrosis. We investigated the effects of HCV therapy on fibrosis, based on fibrosis-4 (FIB4) score, over a 10 year period. METHODS: We collected data from participants in the chronic hepatitis C cohort-part of an observational multicenter study of patients with hepatitis C at 4 large US health systems-from January 1, 2006 through December 31, 2013. We calculated patients' FIB4 and aminotransferase-to-platelet ratio index (APRI) scores over a 10 year period. Of 4731 patients with HCV infection, 1657 (35%) were treated and 755 (46%) of these patients achieved an SVR. RESULTS: In propensity score-adjusted analyses, we observed significant longitudinal changes in FIB4 score

that varied with treatment and response to treatment. In patients with an SVR, FIB4 scores were initially higher than in patients without SVRs, but then decreased sharply, remaining significantly lower over the 10 year period than in untreated patients or patients with treatment failure (P<.001). In independent analyses, men and patients with HCV genotype 1 or 3 infections had higher FIB4 scores than women or patients with HCV genotype 2 infections (P<.01 for both). Findings were similar in a sensitivity analysis that substituted the APRI as the marker of fibrosis instead of FIB4 score. CONCLUSIONS: An SVR to HCV treatment appears to induce long-term regression of fibrosis, based on FIB4 or APRI scores collected over 10 years patients in a large study. Patients receiving no treatment or with treatment failure had progressive increases in FIB4 scores.

Public Health Sciences

Vance S, **Burmeister C**, **Rasool N**, **Buekers T**, and **Elshaikh MA**. Salvage versus adjuvant radiation treatment for women with early-stage endometrial carcinoma: A matched analysis *Int J Gynecol Cancer* 2016; 26(2):307-312. PMID: 26745700. Full Text

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OBJECTIVES: Adjuvant radiation treatment (ART) has been shown to reduce local recurrences in early-stage endometrial carcinoma (EC); however, this has not translated into improved overall survival (OS) benefit. As a result, some physicians forgo ART, citing successful salvage rates in cases of recurrence. Survival end points were compared between women treated with salvage RT (SRT) for locoregional recurrence and similarly matched women treated upfront with ART. MATERIALS AND METHODS: We identified 40 patients with stage I to II type 1 EC who underwent hysterectomy and received no adjuvant RT but later developed locoregional recurrence and subsequently received SRT. An additional 374 patients who underwent hysterectomy followed by ART during the same period were identified. Patients in the SRT group were matched to those in the ART group based on FIGO (International Federation of Gynecology and Obstetrics) stage and tumor grade in a 1:3 ratio. Disease-specific survival (DSS) and OS were calculated. RESULTS: A total of 156 women were matched (39:117). Median follow-up was 56 months. The 2 groups were generally well balanced. With regard to the site of tumor recurrence, it was commonly vaginal in the SRT group (74.3% vs 28.6%, P = 0.01). More SRT patients received a combination of pelvic external-beam RT with vaginal brachytherapy (94.8% vs 35%, P < 0.001). The ART group had significantly better 5-year DSS (95% vs 77%, P < 0.001) and 5-year OS (79% vs 72%, P = 0.005) compared with those of the SRT group. CONCLUSIONS: Our study suggests that women who receive SRT for their locoregional recurrence have worse DSS and OS compared with those matched patients who received ART. Further studies are warranted to develop a high-quality cost-effectiveness analysis as well as accurate predictive models of tumor recurrence. Until then, ART should at least be considered in the management of early-stage EC patients with adverse prognostic factors.

Public Health Sciences

Yang JJ, **Li J**, **Williams LK**, and Buu A. An efficient genome-wide association test for multivariate phenotypes based on the Fisher combination function *BMC Bioinformatics* 2016; 17(1):19. PMID: 26729364. Full Text

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BACKGROUND: In genome-wide association studies (GWAS) for complex diseases, the association between a SNP and each phenotype is usually weak. Combining multiple related phenotypic traits can increase the power of gene search and thus is a practically important area that requires methodology work. This study provides a comprehensive review of existing methods for conducting GWAS on complex diseases with multiple phenotypes including the multivariate analysis of variance (MANOVA), the principal component analysis (PCA), the generalizing estimating equations (GEE), the trait-based association test involving the extended Simes procedure (TATES), and the classical Fisher combination test. We propose a new method that relaxes the unrealistic independence assumption of the classical Fisher combination test and is computationally efficient. To demonstrate applications of the proposed method, we also present the results of statistical analysis on the Study of Addiction: Genetics and Environment (SAGE) data. RESULTS: Our simulation study shows that the proposed method has higher power than existing methods while controlling for the type I error rate. The GEE and the classical Fisher combination test, on the other hand, do not control the type I error rate and thus are not recommended. In general, the power of the competing methods decreases as the correlation between phenotypes increases. All the methods tend to have lower power

when the multivariate phenotypes come from long tailed distributions. The real data analysis also demonstrates that the proposed method allows us to compare the marginal results with the multivariate results and specify which SNPs are specific to a particular phenotype or contribute to the common construct. CONCLUSIONS: The proposed method outperforms existing methods in most settings and also has great applications in GWAS on complex diseases with multiple phenotypes such as the substance abuse disorders.

Public Health Sciences
Zhang J, **Zhang ZG**, **Li Y**, **Lu M**, **Zhang Y**, **Elias SB**, and **Chopp M**. Thymosin beta4 promotes oligodendrogenesis in the demyelinating central nervous system *Neurobiol Dis* 2016; 88:85-95. PMID: 26805386. Full Text

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). No effective remyelination therapies are in use. We hypothesized that thymosin beta4 (Tbeta4) is an effective remyelination treatment by promoting differentiation of oligodendrocyte progenitor cells (OPCs), and that the epidermal growth factor receptor (EGFR) signaling pathway contributes to this process. Two demyelination animal models were employed in this study: 1) experimental autoimmune encephalomyelitis (EAE), an animal model of MS. EAE mice were treated daily for 30days, with Tbeta4 or saline treatment initiated on the day of EAE onset; and 2) cuprizone diet model, a non-inflammatory demyelination model. The mice were treated daily for 4weeks with Tbeta4 or saline after fed a cuprizone diet for 5weeks. Immunofluorescent staining and Western blot were performed to measure the differentiation of OPCs, myelin and axons, respectively. To obtain insight into mechanisms of action, the expression and activation of the EGFR pathway was measured. AG1478, an EGFR inhibitor, was employed in a loss-of-function study. Data revealed that animals in both demyelination models exhibited significant reduction of myelin basic protein (MBP+) levels and CNPase+ oligodendrocytes. Treatment of EAE mice with Tbeta4 significantly improved neurological outcome. Double immunofluorescent staining showed that Tbeta4 significantly increased the number of newly generated oligodendrocytes identified by BrdU+/CNPase+ cells and MBP+ mature oligodendrocytes, and reduced axonal damage in the EAE mice compared with the saline treatment. The newly generated mature oligodendrocytes remyelinated axons, and the increased mature oligodendrocytes significantly correlated with functional improvement ($r=0.73$, $p<0.05$). Western blot analysis revealed that Tbeta4 treatment increased expression and activation of the EGFR pathway. In the cuprizone demyelination model, Tbeta4 treatment was confirmed that significantly increased OPC differentiation and remyelination, and increased the expression of EGFR and activated the EGFR pathway in the demyelinating corpus callosum. In cultured OPCs, blockage of the activation of the EGFR pathway with AG1478 abolished the Tbeta4-increased OPC differentiation. Collectively, these findings indicate that: 1) Tbeta4 increases proliferation of OPCs and the maturation of OPCs to myelinating oligodendrocytes which in concert, likely contribute to the beneficial effect of Tbeta4 on EAE, 2) EGFR upregulated and activated by Tbeta4 may mediate the process of OPC differentiation, and 3) Tbeta4 could potentially be developed as a therapy for MS patients, and for other demyelinating neurological disorders.

Public Health Sciences
Zhang L, **Chopp M**, **Lu M**, **Zhang T**, Winter S, **Doppler E**, **Meier D**, **Chao L**, **Eapen A**, Pabla P, and **Gang Zhang Z**. Cerebrolysin dose-dependently improves neurological outcome in rats after acute stroke: A prospective, randomized, blinded, and placebo-controlled study *Int J Stroke* 2016;PMID: 26763925. Article Request Form

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BACKGROUND: Cerebrolysin is a mixture of neuropeptides and free amino acids that is clinically used for the treatment of stroke. To further standardize treatment schemes, we assessed the dose response of Cerebrolysin on sensorimotor outcome in a rat model of ischemic stroke. METHODS: This study was a prospective, blinded, placebo-controlled, preclinical experiment. Male and female Wistar rats, subjected to embolic middle cerebral artery occlusion,

were randomly treated with Cerebrolysin doses of 0.8, 2.5, 5.0, 7.5 ml/kg or placebo, 4 h after middle cerebral artery occlusion for a total of 10 consecutive days. RESULTS: The primary outcome was neurologic improvement at day 28, lesion volume, mortality, and animal weight were secondary and safety outcomes, respectively. There was a significant ($p < 0.001$) dose effect of Cerebrolysin on neurological outcome. Cerebrolysin at a dose of >/= 2.5 ml/kg significantly ($p < 0.001$) improved neurological outcome (Mean Estimate (95% CL): 0.8 ml/kg: 6.2 (-6.0/18.4), 2.5 ml/kg: -28.9 (-41.6/-16.2), 5.0 ml/kg: -33.4 (-45.0/-21.7), 7.5 ml/kg: -36.3 (-48.2/-24.4). Higher doses (>/=2.5 ml/kg) resulted in better recovery; however, differences between effective doses were not significant. Treatment with 5 ml/kg reduced lesion volume ($p = 0.016$). No treatment gender interactions were found and there were no differences in death or weight loss. CONCLUSION: Collectively, these data on Cerebrolysin efficacy demonstrate the feasibility of a preclinical study setup following a randomized, placebo-controlled, and blinded design with a clinical relevant treatment scheme. Cerebrolysin at doses of >/= 2.5 ml/kg improved functional outcome and at a dose of 5 ml/kg reduced infarct volume.

Pulmonary and Critical Care Medicine

Bou Chebl R, **Madden B**, Belsky J, **Harmouche E**, and **Yessayan L**. Diagnostic value of end tidal capnography in patients with hyperglycemia in the emergency department *BMC Emerg Med* 2016; 16(1):7. PMID: 26821648. Full Text

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BACKGROUND: Diabetic Ketoacidosis (DKA) is a potentially life-threatening emergency that requires prompt diagnosis and treatment. In paediatric populations an end tidal capnography value greater than 36 mmHg was found to be 100 % sensitive in ruling out DKA. METHODS: A cross sectional observational study of adults >/= 17 years of age presenting to the emergency department between January 2014 and May 2014 with glucose > 550 mg/dL. In all patients, nasal capnography and venous blood gas analysis were performed prior to any insulin or intravenous fluid administration. The diagnosis of DKA was based on the presence of anion gap metabolic acidosis, hyperglycaemia and ketonemia. The overall diagnostic performance (area under the curve [AUC]), sensitivity, specificity and likelihood ratios at different end tidal CO2 (ETCO2) cut-offs were determined. RESULTS: 71 patients were enrolled in the study of which 21 (30 %) met the diagnosis of DKA. The area under the curve for ETCO2 was 0.95 with a 95 % CI of 0.91 to 0.99. Test sensitivity for DKA at ETCO2 level >/=35 mmHg was 100 % (95 % CI, 83.9-100). An ETCO2 level </= 21 mmHg was 100 % specific (95 % CI, 92.9-100.0) for DKA. CONCLUSION: Nasal capnography exhibits favourable diagnostic performance in detecting patients with or without DKA among those who present to the emergency department with a glucometer reading > 550 mg/dL.

Pulmonary and Critical Care Medicine

Ketterer MW, **Alaali Y**, **Yessayan L**, and **Jennings J**. "Alert and oriented x 3?" Correlates of mini-cog performance in a post/nondelirious intensive care unit sample *Psychosomatics* 2015;PMID: 26805587. Full Text

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BACKGROUND: Cognitive impairment has been found to be a predictor of adverse medical outcomes, including nonadherence, recurrent medical crises resulting in early readmissions, and death. OBJECTIVE: The Mini-Cog has been proposed for bedside/clinic cognitive testing. Its validity as a measure of central nervous system (CNS) impairment has never been tested against measures of CNS-medical history, CNS scans, selected laboratory findings, observed in-hospital nondelirious memory impairment, or collateral history from family. METHODS: We observed Mini-Cog performance in 107 post/nondelirious medical intensive care unit patients and tested its association with age, CNS-medical history, CNS scans, selected laboratory findings, and behavioral history (in-hospital observation of memory problems and collateral history from family or significant others). RESULTS: The overall Mini-Cog covaried with age, various measures of CNS impairment, abnormal laboratory findings, and measures of preadmission "forgetfulness" per family and by in-hospital staff observation. Unique variance in predicting overall Mini-Cog scores included age, positive CNS scan, and behavioral history. Of 91 patients found to be "alert and oriented x 3," 76% were impaired in immediate memory, short-term memory, or clock drawing.

CONCLUSIONS: The Mini-Cog appears to be a brief, yet valid, measure of CNS dysfunction that significantly enhances sensitivity of evaluation at the bedside. Failure to evaluate patients with a formal examination like the Mini-Cog appears to miss up to 76% of patients with moderate cognitive impairment.

Radiation Oncology
Al Feghali KA, and **Elshaikh MA**. Why brachytherapy boost is the treatment of choice for most women with locally advanced cervical carcinoma? *Brachytherapy* 2016;PMID: 26810408. Full Text

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The standard treatment approach for women with locally advanced cervical carcinoma is definitive radiation treatment with concurrent cisplatin chemotherapy. Radiation treatment is typically external beam radiation therapy to the pelvis followed by intracavitary brachytherapy (BT) boost to the cervix. Numerous studies confirmed very successful outcomes with this approach. In recent years, however, the use of BT to boost the cervix in women with cervical carcinoma was reported to be on the decline. With the advent of advanced external beam radiation therapy techniques, few attempts have been made to substitute the BT boost with stereotactic body radiation therapy or intensity-modulated radiation therapy techniques, but there is a lack of prospective data to justify the routine use of these alternate boost techniques. The aim of this review is to highlight the differences between the use of stereotactic body radiation therapy or intensity-modulated radiation therapy, in lieu of intracavitary BT boost in women with locally advanced cervical cancer, and to argue that BT seems to be truly irreplaceable at the present time and with the knowledge and expertise accumulated to date.

Radiation Oncology
Chen RC, Hoffman KE, Sher DJ, Showalter TN, Morrell R, Chen AB, Benda R, Nguyen PL, **Movsas B**, and Hardenbergh P. Development of a standard survivorship care plan template for radiation oncologists *Pract Radiat Oncol* 2016; 6(1):57-65. PMID: 26778795. Article Request Form

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Purpose: In response to a need expressed by members of the American Society for Radiation Oncology (ASTRO), the ASTRO Board of Directors approved an initiative to create a radiation oncology-specific survivorship care plan (SCP) template. Methods and Materials: Members of the ASTRO Health Services Research Committee (which was subsequently renamed the Clinical, Translational, and Basic Science Advisory Committee) were charged with this task. Creation of the ASTRO SCP template was informed by existing SCP templates published by other organizations and modified to add radiation treatment details felt to be important by committee members. An emphasis was placed on describing diagnostic and treatment details in ways that patients and referring physicians can understand. The resulting template subsequently underwent ASTRO committee review, public comment, and was ultimately approved by the ASTRO Board of Directors. Results: The standardized template includes 2 components: the first 2 pages represent an SCP that is to be given to the patient and referring physicians, whereas page 3 includes additional technical radiation therapy details which are usually included in a traditional radiation treatment summary. That is, the template serves two purposes-obviating the need for radiation oncologists to create an SCP for patients and a separate treatment completion note. Conclusions: The standardized ASTRO SCP template serves an immediate need of practicing radiation oncologists to have a template that is radiation-specific and meets current requirements for SCP and radiation treatment summary. Potential future work may include development of disease-specific templates that will include more granular details regarding expected toxicities and follow-up care recommendations and working with electronic medical record system vendors to facilitate autocreation of SCP documents to reduce the burden on physicians and other staff. These future developments can make this intervention more helpful to patients, and further reduce the burden of creating SCPs.

Radiation Oncology
Freytag SO, **Zhang Y**, and **Siddiqui F**. Preclinical toxicology of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for prostate cancer *Mol Ther Oncolytics* 2015; 2PMID: 26767191. Full Text

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The purpose of this study was to examine the toxicity of combining oncolytic adenovirus-mediated cytotoxic and interleukin 12 (IL-12) gene therapy in a preclinical model to support future phase 1 trials. One hundred and twenty C57BL/6 male mice received an intraprostatic injection of saline (n = 24) or an oncolytic adenovirus (Ad5-

yCD/mutTKSR39 rep-mIL12) expressing two suicide genes and mouse IL-12 (n = 96). The adenovirus was administered at three dose levels (1.3 x 106, 1.3 x 107, 1.3 x 108 vp/kg) followed by 2 weeks of 5-flurocytosine (5-FC) and gancliclovir (GCV) prodrug therapy. There were no premature deaths. Daily observations of animals did not reveal any obvious clinical problems throughout the 78-day in-life phase of the study. Animals in the highest adenovirus dose group exhibited lymphopenia and transaminitis on day 3, both of which resolved by day 17. Except for mild inflammation of the prostate and seminal vesicles, histopathology of major organs was largely unremarkable. IL-12 and interferon-gamma levels in prostate and serum peaked on day 3 and were either undetectable or returned to baseline levels by day 17. No adenoviral DNA was detected in serum in any group at any time point. The results demonstrate that local administration of an oncolytic adenovirus expressing two suicide genes and IL-12 is well tolerated and support moving this investigational approach into human trials.

Radiation Oncology

Koyfman SA, Cooper JS, Beitler JJ, Busse PM, Jones CU, McDonald MW, Quon H, Ridge JA, Saba NF, Salama JK, **Siddiqui F**, Smith RV, Worden F, Yao M, and Yom SS. Acr appropriateness criteria((r)) aggressive nonmelanomatous skin cancer of the head and neck *Head Neck* 2016; 38(2):175-182. PMID: 26791005.
Article Request Form

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BACKGROUND: Aggressive nonmelanomatous skin cancer (NMSC) of the head and neck presents an increasingly common therapeutic challenge for which prospective clinical trials are lacking. METHODS: The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 3 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment. RESULTS: The American College of Radiology Expert Panel on Radiation Oncology - Head and Neck Cancer developed consensus recommendations for guiding management of aggressive NMSC. CONCLUSION: Multidisciplinary assessment is vital to guiding the ideal use of surgery, radiation, and systemic therapy in this disease.

Radiation Oncology

Vance S, **Burmeister C**, **Rasool N**, **Buekers T**, and **Elshaikh MA**. Salvage versus adjuvant radiation treatment for women with early-stage endometrial carcinoma: A matched analysis *Int J Gynecol Cancer* 2016; 26(2):307-312. PMID: 26745700. Full Text

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OBJECTIVES: Adjuvant radiation treatment (ART) has been shown to reduce local recurrences in early-stage endometrial carcinoma (EC); however, this has not translated into improved overall survival (OS) benefit. As a result, some physicians forgo ART, citing successful salvage rates in cases of recurrence. Survival end points were compared between women treated with salvage RT (SRT) for locoregional recurrence and similarly matched women treated upfront with ART. MATERIALS AND METHODS: We identified 40 patients with stage I to II type 1 EC who underwent hysterectomy and received no adjuvant RT but later developed locoregional recurrence and subsequently received SRT. An additional 374 patients who underwent hysterectomy followed by ART during the same period were

identified. Patients in the SRT group were matched to those in the ART group based on FIGO (International Federation of Gynecology and Obstetrics) stage and tumor grade in a 1:3 ratio. Disease-specific survival (DSS) and OS were calculated. RESULTS: A total of 156 women were matched (39:117). Median follow-up was 56 months. The 2 groups were generally well balanced. With regard to the site of tumor recurrence, it was commonly vaginal in the SRT group (74.3% vs 28.6%, P = 0.01). More SRT patients received a combination of pelvic external-beam RT with vaginal brachytherapy (94.8% vs 35%, P < 0.001). The ART group had significantly better 5-year DSS (95% vs 77%, P < 0.001) and 5-year OS (79% vs 72%, P = 0.005) compared with those of the SRT group. CONCLUSIONS: Our study suggests that women who receive SRT for their locoregional recurrence have worse DSS and OS compared with those matched patients who received ART. Further studies are warranted to develop a high-quality cost-effectiveness analysis as well as accurate predictive models of tumor recurrence. Until then, ART should at least be considered in the management of early-stage EC patients with adverse prognostic factors.

Radiology

Ali R, Khan M, **Chang V**, **Narang J**, Jain R, **Marin H**, **Rock J**, and **Kole M**. MRI pre- and post-embolization enhancement patterns predict surgical outcomes in intracranial meningiomas *J Neuroimaging* 2016; 26(1):130-135. PMID: 25996574. Article Request Form

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PURPOSE: To evaluate the effects of preoperative embolization on overall surgical outcomes after meningioma resection and determine whether pre- and postembolization tumor enhancement patterns on magnetic resonance imaging (MRI) scans can be used to assess the efficacy of embolization. METHODS: We developed a prospective database of all patients who underwent surgical resection with or without preoperative embolization for extra-axial intracranial meningiomas from 2004 to 2010. Using specialized computer software, the total volume of enhancement was calculated in pre- and postembolization MRI scans to quantify the percentage of embolization, which was described as the embolization fraction (EF). RESULTS: A total of 89 patients underwent surgical resection. Fifty two patients underwent embolization prior to surgery. Tumor location significantly correlated with the decision to embolize preoperatively. Adequate embolization was achieved in 58% of patients. Forty four patients (84.6%) had a postsurgical Karnofsky performance score (KPS) of 80 or above, while 46 patients (88.4%) had a postsurgical Glascow Outcome Score (GOS) of 4 or 5. The mean EF was 25.03% with a median of 18.72%. A greater extent of embolization as quantified by EF led to decreased intraoperative blood loss (r = -.319, P = .022) and better postsurgical outcomes as defined by KPS (r = .279, P = .044). CONCLUSIONS: Pre- and postembolization tumor enhancement patterns on magnetic resonance imaging defined as EF correlate with improved surgical facilitation and postoperative functional outcomes in the management of intracranial meningioma.

Radiology

Hosseini MP, **Nazem-Zadeh MR**, Pompili D, Jafari-Khouzani K, Elisevich K, and **Soltanian-Zadeh H**. Comparative performance evaluation of automated segmentation methods of hippocampus from magnetic resonance images of temporal lobe epilepsy patients *Med Phys* 2016; 43(1):538. PMID: 26745947. Article Request Form

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Medical Image Analysis Laboratory, Departments of Radiology and Research Administration, Henry Ford Health System, Detroit, Michigan 48202; Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer Engineering, University of Tehran, Tehran 1439957131, Iran; and School of Cognitive Sciences, Institute for Studies in Theoretical Physics and Mathematics (IPM), Tehran 1954856316, Iran.

PURPOSE: Segmentation of the hippocampus from magnetic resonance (MR) images is a key task in the evaluation of mesial temporal lobe epilepsy (mTLE) patients. Several automated algorithms have been proposed although

manual segmentation remains the benchmark. Choosing a reliable algorithm is problematic since structural definition pertaining to multiple edges, missing and fuzzy boundaries, and shape changes varies among mTLE subjects. Lack of statistical references and guidance for quantifying the reliability and reproducibility of automated techniques has further detracted from automated approaches. The purpose of this study was to develop a systematic and statistical approach using a large dataset for the evaluation of automated methods and establish a method that would achieve results better approximating those attained by manual tracing in the epileptogenic hippocampus. METHODS: A template database of 195 (81 males, 114 females; age range 32-67 yr, mean 49.16 yr) MR images of mTLE patients was used in this study. Hippocampal segmentation was accomplished manually and by two well-known tools (FreeSurfer and hammer) and two previously published methods developed at their institution [Automatic brain structure segmentation (ABSS) and LocalInfo]. To establish which method was better performing for mTLE cases, several voxel-based, distance-based, and volume-based performance metrics were considered. Statistical validations of the results using automated techniques were compared with the results of benchmark manual segmentation. Extracted metrics were analyzed to find the method that provided a more similar result relative to the benchmark. RESULTS: Among the four automated methods, ABSS generated the most accurate results. For this method, the Dice coefficient was 5.13%, 14.10%, and 16.67% higher, Hausdorff was 22.65%, 86.73%, and 69.58% lower, precision was 4.94%, -4.94%, and 12.35% higher, and the root mean square (RMS) was 19.05%, 61.90%, and 65.08% lower than LocalInfo, FreeSurfer, and hammer, respectively. The Bland-Altman similarity analysis revealed a low bias for the ABSS and LocalInfo techniques compared to the others. CONCLUSIONS: The ABSS method for automated hippocampal segmentation outperformed other methods, best approximating what could be achieved by manual tracing. This study also shows that four categories of input data can cause automated segmentation methods to fail. They include incomplete studies, artifact, low signal-to-noise ratio, and inhomogeneity. Different scanner platforms and pulse sequences were considered as means by which to improve reliability of the automated methods. Other modifications were specially devised to enhance a particular method assessed in this study.

Radiology

Riaz RM, **Myers DT**, and **Williams TR**. Multidetector CT imaging of bariatric surgical complications: a pictorial review *Abdom Radiol* 2016; 41(1):174-188. PMID: 26830623. Article Request Form

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The prevalence of obesity is increasing, along with the number of bariatric surgical procedures performed to treat obesity. Laparoscopic sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and laparoscopic gastric banding (GB) comprise the vast majority of procedures with SG now the dominant procedure in the USA. Although multidetector computed tomography (MDCT) is not always the examination of choice for a particular suspected complication, many of these patients present with non-specific abdominal symptoms and undergo MDCT evaluation as an initial diagnostic test. This pictorial essay will review and discuss the normal post-surgical bariatric appearance on MDCT, and the appearance of common and uncommon complications associated with the common bariatric procedures on MDCT with correlative imaging. SG complications include leak/abscess, hemorrhage, splenic injury, and portomesenteric thrombosis. RYGB complications include leak/abscess, gastrogastric fistula, small bowel obstruction, internal hernia, and intussusception. Although GB is waning in popularity, radiologists continue to see the legacy of these patients and complications include gastric prolapse, band erosion, and port/tubing mechanical failures. Awareness of the characteristic findings of bariatric complications on MDCT is critical, allowing for earlier recognition and prompt intervention.

Radiology

Sever A, and **Rheinboldt M**. Unstable abdominal aortic aneurysms: a review of MDCT imaging features *Emerg Radiol* 2016;PMID: 26797025. Full Text

Department of Radiology, Henry Ford Hospital, Detroit, MI, USA. mrheinbold@yahoo.com.

Abdominal aortic aneurysms are commonly encountered during abdominal CT imaging, and size-based parameters for surgical or endovascular repair are well established. Aneurysms greater than 5 cm in diameter are recognized as representing an increased rupture risk and meriting intervention. Increasingly, additional interest has been generated in recognizing imaging features which may herald instability and portend a higher chance for potentially catastrophic rupture. This article will review and illustrate such signs, including hyperattenuation of mural thrombus, rapid expansion, low thrombus to lumen ratio, intimal calcification disruption, posterior mural draping, and saccular outpouching. Other features of complicated abdominal aneurysms including perianeurysmal inflammation, aortocaval and aortoenteric fistula formation will also be addressed. Heightened awareness of these features and their prognostic implications, as well as timely communication with the clinical service, is critical for the interpreting radiologist.

Research Administration

Hosseini MP, **Nazem-Zadeh MR**, Pompili D, Jafari-Khouzani K, Elisevich K, and **Soltanian-Zadeh H**. Comparative performance evaluation of automated segmentation methods of hippocampus from magnetic resonance images of temporal lobe epilepsy patients *Med Phys* 2016; 43(1):538. PMID: 26745947. Article Request Form

Department of Electrical and Computer Engineering, Rutgers University, New Brunswick, New Jersey 08854 and Medical Image Analysis Laboratory, Departments of Radiology and Research Administration, Henry Ford Health System, Detroit, Michigan 48202.
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Medical Image Analysis Laboratory, Departments of Radiology and Research Administration, Henry Ford Health System, Detroit, Michigan 48202; Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer Engineering, University of Tehran, Tehran 1439957131, Iran; and School of Cognitive Sciences, Institute for Studies in Theoretical Physics and Mathematics (IPM), Tehran 1954856316, Iran.

PURPOSE: Segmentation of the hippocampus from magnetic resonance (MR) images is a key task in the evaluation of mesial temporal lobe epilepsy (mTLE) patients. Several automated algorithms have been proposed although manual segmentation remains the benchmark. Choosing a reliable algorithm is problematic since structural definition pertaining to multiple edges, missing and fuzzy boundaries, and shape changes varies among mTLE subjects. Lack of statistical references and guidance for quantifying the reliability and reproducibility of automated techniques has further detracted from automated approaches. The purpose of this study was to develop a systematic and statistical approach using a large dataset for the evaluation of automated methods and establish a method that would achieve results better approximating those attained by manual tracing in the epileptogenic hippocampus. METHODS: A template database of 195 (81 males, 114 females; age range 32-67 yr, mean 49.16 yr) MR images of mTLE patients was used in this study. Hippocampal segmentation was accomplished manually and by two well-known tools (FreeSurfer and hammer) and two previously published methods developed at their institution [Automatic brain structure segmentation (ABSS) and LocalInfo]. To establish which method was better performing for mTLE cases, several voxel-based, distance-based, and volume-based performance metrics were considered. Statistical validations of the results using automated techniques were compared with the results of benchmark manual segmentation. Extracted metrics were analyzed to find the method that provided a more similar result relative to the benchmark. RESULTS: Among the four automated methods, ABSS generated the most accurate results. For this method, the Dice coefficient was 5.13%, 14.10%, and 16.67% higher, Hausdorff was 22.65%, 86.73%, and 69.58% lower, precision was 4.94%, -4.94%, and 12.35% higher, and the root mean square (RMS) was 19.05%, 61.90%, and 65.08% lower than LocalInfo, FreeSurfer, and hammer, respectively. The Bland-Altman similarity analysis revealed a low bias for the ABSS and LocalInfo techniques compared to the others. CONCLUSIONS: The ABSS method for automated hippocampal segmentation outperformed other methods, best approximating what could be achieved by manual tracing. This study also shows that four categories of input data can cause automated segmentation methods to fail. They include incomplete studies, artifact, low signal-to-noise ratio, and inhomogeneity. Different scanner platforms and pulse sequences were considered as means by which to improve reliability of the automated methods. Other modifications were specially devised to enhance a particular method assessed in this study.

Sleep Medicine

Drake CL. The promise of digital CBT-I *Sleep* 2016; 39(1):13-14. PMID: 26564140. Full Text

Henry Ford Hospital Sleep Disorders and Research Center, Detroit, MI.

Sleep Medicine

Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, Krystal AD, Walsh JK, Benca RM, Rosenberg R, Sangal RB, Budd K, Hutzelmann J, Leibensperger H, Froman S, Lines C, **Roth T**, and Michelson D. Suvorexant in patients with insomnia: Results from two 3-month randomized controlled clinical trials *Biol Psychiatry* 2016; 79(2):136-148. PMID: 25526970. Full Text

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Henry Ford Hospital Sleep Center, Detroit, Michigan.

BACKGROUND: Suvorexant is an orexin receptor antagonist for treatment of insomnia. We report results from two pivotal phase 3 trials. METHODS: Two randomized, double-blind, placebo-controlled, parallel-group, 3-month trials in nonelderly (18-64 years) and elderly (>/=65 years) patients with insomnia. Suvorexant doses of 40/30 mg (nonelderly/elderly) and 20/15 mg (nonelderly/elderly) were evaluated. The primary focus was 40/30 mg, with fewer patients randomized to 20/15 mg. There was an optional 3-month double-blind extension in trial 1. Each trial included a 1-week, randomized, double-blind run-out after double-blind treatment to assess withdrawal/rebound. Efficacy was assessed at week 1, month 1, and month 3 by patient-reported subjective total sleep time and time to sleep onset and in a subset of patients at night 1, month 1, and month 3 by polysomnography end points of wakefulness after persistent sleep onset and latency to onset of persistent sleep (LPS). One thousand twenty-one patients were randomized in trial 1 and 1019 patients in trial 2. RESULTS: Suvorexant 40/30 mg was superior to placebo on all subjective and polysomnography end points at night 1/week 1, month 1, and month 3 in both trials, except for LPS at month 3 in trial 2. Suvorexant 20/15 mg was superior to placebo on subjective total sleep time and wakefulness after persistent sleep onset at night 1/week 1, month 1, and month 3 in both trials and at most individual time points for subjective time to sleep onset and LPS in each trial. Both doses of suvorexant were generally well tolerated, with <5% of patients discontinuing due to adverse events over 3 months. The results did not suggest the emergence of marked rebound or withdrawal signs or symptoms when suvorexant was discontinued. CONCLUSIONS: Suvorexant improved sleep onset and maintenance over 3 months of nightly treatment and was generally safe and well tolerated.

Surgery

Go P, and **Hammoud Z**. Eventration of the diaphragm presenting as spontaneous pneumothorax *Cleve Clin J Med* 2016; 83(1):19-20. PMID: 26760517. Full Text

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Division of Thoracic Surgery, Henry Ford Hospital, Detroit, MI, USA.

Surgery

Louwers L, **Schnickel G**, and **Rubinfeld I**. Use of a simplified frailty index to predict clavien 4 complications and mortality after hepatectomy: Analysis of the national surgical quality improvement project database *Am J Surg* 2015;PMID: 26800866. Full Text

Department of Acute Care Surgery/Surgical Critical Care, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202. Electronic address: lisalouwers27@gmail.com.
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Department of Acute Care Surgery/Surgical Critical Care, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202.

BACKGROUND: An aging surgical population places an increasing burden on surgeons to accurately risk stratify and counsel patients. Preoperative frailty assessments are a promising new modality to better evaluate patients but can often be time consuming. Data regarding frailty and hepatectomy outcomes have not been published to date. METHOD: Using the National Surgical Quality Improvement Project database, we examined hepatectomy patients 2005 to 11 and correlated frailty scores with outcomes of major morbidity, mortality, and extended length of stay, using a previously validated modified frailty index score. Frailty was compared against age, American Society of Anesthesiologists class, and other common risk variables. RESULTS: Multivariate regression identified frailty as the strongest predictor of Clavien 4 complications (OR = 40.0, 95% CI = 15.2 to 105.0), and mortality (OR = 26.4, 95% CI = 7.7 to 88.2). As the frailty score increased, there was a statistically significant increase in Clavien 4 complications, mortality, and extended length of stay (P < .001 for all). CONCLUSIONS: Frailty is a significant factor in morbidity and mortality after hepatectomy. Use of the modified frailty index allows for feasibility of data collection in a busy clinical setting.

Surgery

Monaghan KG, **Gonzalez HC**, **Levin AM**, **Abouljoud MS**, and **Gordon SC**. Post-transplant course of hepatitis C after living donor liver transplantation in association with polymorphisms near IFNL3 *J Interferon Cytokine Res* 2015; 35(4):313-316. PMID: 25343304. Article Request Form

1 Medical Genetics, Henry Ford Health System, Detroit, Michigan.

Donor genotype for polymorphisms near IFNL3 influences hepatitis C virus (HCV) therapy responsiveness. This relationship has not been studied in a sample of HCV-infected living donor liver transplantation (LDLT) recipients in the United States (US). We investigated the association of donor and recipient genotypes near the IFNL3 gene at a large US liver transplant center. Recipient homozygosity for rs12979860 C was associated with increased sustained virologic response (SVR) in antiviral treatment-experienced patients pretransplant (P = 0.055). Consistently, donor homozygosity for rs12979860 C was also associated with increased SVR in patients who received post-transplant antiviral therapy (P = 0.048). Transplantation of an rs12979860 CC graft confers a favorable post-transplant antiviral response among HCV-positive recipients in an LDLT setting. Recipients with the favorable rs12979860 genotype receiving antiviral therapy before transplant are also more likely to achieve SVR. The effect of genotype status in the era of direct-acting antiviral agents will require future study.

Surgery

Morgan JA, and **O'Neill WW**. Percutaneous right ventricular assist device support in a patient supported by an LVAD *Asaio j* 2016;PMID: 26771398. Full Text

Divisions of Cardiothoracic Surgery and Cardiology, Heart and Vascular Institute Henry Ford Hospital Detroit, MI, USA.

Right ventricular failure requiring short-term mechanical support is a relatively common complication after left ventricular assist device (LVAD) implantation. Removal of the temporary right ventricular assist device (RVAD) generally requires a reoperative sternotomy. In this report, we describe an innovative percutaneous approach for placing an RVAD at the time of LVAD implantation using the Impella RP (Abiomed Inc., Danvers, MA.) that does not require reoperation for removal, as the Impella RP can be removed at the patient's bedside.

Surgery

Newman L, Jiagge E, Bensenhaver J, Jibril A, Awuah B, and **Stark A**. 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 *Annals of Surgical Oncology* 2016; 23:S8-S8. PMID: Not assigned. Abstract

[Newman, L.] Henry Ford Hlth Syst, Breast Oncol Program, Ann Arbor, MI USA. [Newman, L.; Jiagge, E.; Bensenhaver, J.] Univ Michigan, Ann Arbor, MI 48109 USA. [Stark, A.] Henry Ford Hlth Syst, Detroit, MI USA. [Awuah, B.] Komfo Anoyke Teaching Hosp, Kumasi, Ghana. [Jibril, A.] St Pauls Millenium Hosp, Addis Ababa, Ethiopia.

Introduction: Population-based incidence rates of triple negative breast cancer (TNBC) are higher for African American (AA) compared to White American (WA) women, but it is unclear whether TNBC risk is genetically associated with African ancestry because AA women represent an ancestrally admixed population. Higher frequencies of TNBC have also been observed in western sub-Saharan African breast cancer (BC) patients, and this study represents a first comparison of AA, WA, West and East African cases. Methods: Formalin-fixed, paraffin-embedded invasive BC tumors diagnosed 1998-2014 in AA, WA, Ghana/East Africa, and Ethiopia/West Africa were compared. All African tumors underwent pathology confirmation and immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu expression in the U.S. Statistical analyses were performed in SAS v. 9.0 (Carey, NC). Results: 234 Ghanaian cases (mean age 49 yrs); 271 AA (mean age 60); and 321 WA (mean age 62)(P=0.001) were compared. ER-negative and TNBC were more common among Ghanaian and AA compared to WA cases (frequency ER-negativity 67.5%, 37.1%, and 19.8%, respectively, p<0.0001;frequency TNBC 53.2%, 29.8%, and 15.5%, respectively, p<0.0001). In the age group <50 years, 82 cases (42.5%) were ER+/PR+/HER2-; 65 (33.7%) were TNBC. In this young age group, prevalence of TNBC remained highest among Ghanaian women (50.8%), followed by AA (34.3%) and WA (15.9%); (P=.0006). Highest prevalence of ER+/PR+/HER2+ and ER+/PR+/ HER2- phenotypes was observed in WA, followed by AA and Ghanaians. The addition of 33 cases from Ethiopia revealed a different distribution: the majority (55%) were HER2/neu-overexpressing; 42% were triple-positive;and only 15% were TNBC. Conclusions: This study confirms an association between TNBC and West African ancestry, and AA patients have a TNBC

frequency that is intermediate between WA and Ghanian/West Africans. East Africans appear to have a low frequency of TNBC but an increased risk of HER2/neu overexpression.

Surgery
Newman LA. Parsing the etiology of breast cancer disparities *J Clin Oncol* 2016;PMID: 26786919. Full Text

Henry Ford Health System Breast Oncology Program and International Center for the Study of Breast Cancer Subtypes, Detroit, MI lnewman1@hfhs.org.

Surgery
Park K, **Rosso K**, and **Nathanson S**. Translating a 2-d mammogram into a 3-d breast in the operating room *Ann Surg Oncol* 2016; 23:S48-S48. PMID: Not assigned. Abstract

[Park, K.; Rosso, K.; Nathanson, S.] Henry Ford Hlth Syst, Detroit, MI USA.

Introduction: Image-guided wire placement helps surgeons find breast lesions during surgical excision. We hypothesized that the direction of wire placement and other physical variables could alter the mammographically 2 D measured distances from skin to lesion versus 3 D measurements while lying supine in the OR. Methods: Distances from skin to metal clip (placed during needle biopsy) and to wire hook measured mammographically (n=50) were compared to those in excised specimen radiographs. Analyzed variables were: Clip segment location, breast size, density, breast thickness in compression and direction of wire placement (chi-square test; Spearman correlation). Results: There were significant ($r2 = 8.92$, $p=0.01$) differences between wire placement direction and hook distance. 10 out of 13 (76.9%) of medially placed wires showed the hook had migrated further into the breast. 11 out of 14 (78.5%) of superiorly placed wires had migrated out of the breast. Thickness of breast in compression at the time of localization and breast size had strong associations with wire displacement in superior wires ($p=0.07$ and $p=0.06$, respectively) but not in medial wires ($p=0.66$ and $p=0.52$, respectively). There were no differences in the distance from skin to clip between the mammogram and the specimen radiograph. Conclusion: The direction in which the guiding wire
was placed had the greatest impact on wire migration. Wires exiting superiorly moved out of the breast while wires exiting medially migrated into the breast between mammographic placement and surgical excision. Compressed breast thickness at the time of the wire placement and overall breast size also impacted wire migration.

Surgery
Shan R, Szmydynger-Chodobska J, Warren OU, **Mohammad F**, Zink BJ, and Chodobski A. A new panel of blood biomarkers for the diagnosis of mild traumatic brain injury/concussion in adults *J Neurotrauma* 2016; 33(1):49-57. PMID: 25794137. Full Text

1 Neurotrauma and Brain Barriers Research Laboratory, Department of Emergency Medicine, Alpert Medical School of Brown University , Providence, Rhode Island.
2 Department of Emergency Medicine, Alpert Medical School of Brown University , Providence, Rhode Island.
3 Department of Surgery, Henry Ford Hospital , Detroit, Michigan.

No routine tests currently exist to objectively diagnose mild traumatic brain injury (mTBI)/concussion. Previously reported biomarkers for mTBI represented proteins released from damaged neurons or glia. However, low levels of these proteins, and/or the complexity of assays used for their detection, limits implementation of these biomarkers in routine practice. Here, we sought to identify proteins whose synthesis is altered post-mTBI and whose blood levels could be measured using standard immunoassays. Adult patients sustaining a concussion within the past 24 h were enrolled. Controls were uninjured subjects and patients with orthopedic injury (OI). Four candidate biomarkers were identified: copeptin; galectin 3 (LGALS3); matrix metalloproteinase 9 (MMP9); and occludin (OCLN). A 3.4-fold decrease ($p<0.0001$) in plasma concentration of copeptin was found in mTBI patients within 8 h after accident, compared to uninjured controls. Plasma levels of LGALS3, MMP9, and OCLN increased 3.6- to 4.5-fold ($p<0.0001$) within the same time frame postinjury. Levels of at least two biomarkers were altered beyond their respective cut-off values in 90% of mTBI patients, whereas in none of uninjured controls were levels of two biomarkers simultaneously changed. A positive correlation ($r=0.681$; $p<0.001$) between plasma levels of LGALS3 and OCLN was also found in mTBI patients, whereas in OI patients or uninjured subjects, these variables did not correlate. This panel of biomarkers discerns, with high accuracy, patients with isolated concussion from uninjured individuals within the first 8 h after accident. These biomarkers can also aid in diagnosing concussion in the presence of OI.

Surgery
Takahashi K, **Putchakayala K**, **Malinzak L**, **Denny J**, **Yoshida A**, **Abouljoud M**, and **Kim D**. Is ketorolac really safe for living donor nephrectomy? *Am J Transplant* 2016; 16:50-50. PMID: Not assigned. Abstract

[Takahashi, Kazuhiro; Putchakayala, Krishna; Malinzak, Lauren; Denny, Jason; Yoshida, Atsushi; Abouljoud, Marwan; Kim, Dean] Henry Ford Hlth Syst, Detroit, MI USA.

Urology
Abdollah F, Briganti A, Montorsi F, Stenzl A, Stief C, Tombal B, Van Poppel H, and Touijer K. Contemporary role of salvage lymphadenectomy in patients with recurrence following radical prostatectomy *Eur Urol* 2015; 67(5):839-849. PMID: 24698524. Full Text

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Department of Urology, Eberhard-Karls-University Tuebingen, Tuebingen, Germany.
Department of Urology, Ludwig-Maximilians-University, Klinikum Grosshadern, Munich, Germany.
Service d'Urologie, Cliniques universitaires Saint Luc, Universite catholique de Louvain, Brussels, Belgium.
Department of Urology, Leuven Cancer Institute, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium.
Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

CONTEXT: Prostate cancer (PCa) patients with isolated clinical lymph node (LN) relapse, limited to the regional and/or retroperitoneal LNs, may represent a distinct group of patients who have a more favorable outcome than men with progression to the bone or to other visceral organs. Some data indirectly denote a beneficial impact of pelvic LN dissection on survival in these patients. OBJECTIVE: To provide an overview of the currently available literature regarding salvage LN dissection (SLND) in PCa patients with clinical relapse limited to LNs after radical prostatectomy (RP). EVIDENCE ACQUISITION: A systematic literature search was conducted using the Medline, Embase, and Web of Science databases to identify original articles, review articles, and editorials regarding SLND. Articles published between 2000 and 2012 were reviewed and selected with the consensus of all the authors. EVIDENCE SYNTHESIS: Contemporary imaging techniques, such as 11C-choline positron emission tomography and diffusion-weighted magnetic resonance imaging, appear to enhance the accuracy in identifying LN relapse in patients with biochemical recurrence (BCR) and after RP. In these individuals, SLND can be considered as a treatment option. The currently available data suggest that SLND can delay clinical progression and postpone hormonal therapy in almost one-third of the patients, although the majority will have BCR. An accurate and attentive preoperative patient selection may help improve these outcomes. The most frequent complication after SLND was lymphorrhea (15.3%), followed by fever (14.5%) and ileus (11.2%). It is noteworthy that all examined cohorts originated from retrospective single-institution series, with limited sample size and short follow-up. Consequently, the current findings cannot be generalized and warrant further investigation in future prospective trials. CONCLUSIONS: The current data suggest that SLND represents an option in patients with disease relapse limited to the LNs after RP; however, more robust data derived from well-designed clinical trials are needed to validate the role of SLND in this selected patient population. PATIENT SUMMARY: Salvage lymph node dissection (SLND) represents a treatment option in for patients with prostate cancer relapse limited to the lymph nodes; however, more robust data derived from well-designed clinical trials are needed to validate the role of SLND in this selected patient population.

Urology
Abdollah F, Sun M, **Sammon JD**, Choueiri TK, **Menon M**, Weissman JS, and Trinh QD. Prevalence of nonrecommended screening for prostate cancer and breast cancer in the United States: A nationwide survey analysis *JAMA Oncol* 2016;PMID: 26794060. Full Text

Center for Outcomes Research, Analytics and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan.
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Urology

Abdullah N, **Dalela D**, **Barod R**, Larson J, Johnson M, Mass A, Zargar H, Allaf M, Bhayani S, Stifelman M, Kaouk J, and **Rogers C**. Robotic partial nephrectomy for renal tumours in obese patients: Perioperative outcomes in a multi-institutional analysis *Can Urol Assoc J* 2015; 9(11-12):E859-862. PMID: 26788235. Full Text

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Division of Urology, Washington University in St. Louis, St. Louis, MO;
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Department of Urology, New York University, New York, NY;
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INTRODUCTION: We sought to evaluate the association of obesity with surgical outcomes of robotic partial nephrectomy (RPN) using a large, multicentre database. METHODS: We identified 1836 patients who underwent RPN from five academic centres from 2006-2014. A total of 806 patients were obese (body mass index [BMI] >/=30 kg/m(2)). Patient characteristics and outcomes were compared between obese and non-obese patients. Multivariable analysis was used to assess the association of obesity on RPN outcomes. RESULTS: A total of 806 (44%) patients were obese with median BMI of 33.8kg/m(2). Compared to non-obese patients, obese patients had greater median tumour size (2.9 vs. 2.5cm, p<0.001), mean RENAL nephrometry score (7.3 vs. 7.1, p=0.04), median operating time (176 vs. 165 min, p=0.002), and median estimated blood loss (EBL, 150 vs. 100 ml, p=0.002), but no difference in complications. Obesity was not an independent predictor of operative time or EBL on regression analysis. Among obese patients, males had a greater EBL (150 vs. 100 ml, p<0.001), operative time (180 vs. 166 min, p<0.001) and warm ischemia time (WIT, 20 vs. 18, p=0.001), and male sex was an independent predictor of these outcomes on regression analysis. CONCLUSIONS: In this large, multicentre study on RPN, obesity was not associated with increased complications and was not an independent predictor of operating time or blood loss. However, in obese patients, male gender was an independent predictor of greater EBL, operative time, and WIT. Our results indicate that obesity alone should not preclude consideration for RPN.

Urology

Dalela D, and **Menon M**. Contemporary trends in radical prostatectomy in the United States: Open vs minimally invasive surgery *Mayo Clin Proc* 2016; 91(1):1-2. PMID: 26763508. Full Text

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Urology

Diaz M, **Chang S**, and **Singer M**. Adherence to dietary indexes by diabetes and hypertension status among PLCO cancer screening trial participants *Adv Nutr* 2016; 7(1):38A. PMID: Not assigned. Abstract

Background: A healthy diet is an effective strategy for glycemia and blood pressure control with adherence key to its success. Optimal nutrient intake can be measured via dietary patterns. We quantified adherence to several dietary indices among individuals with diabetes (DM) and/or hypertension (HTN) and compared it with controls in the PLCO Cancer Screening Trial.Methods: Participants in PLCO who filled out a baseline food-frequency questionnaire, with age, sex, body mass index (BMI), DM, and HTN status recorded were selected for analysis. Indices for Healthy Eating 2005 (HEI), Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean (MEDI) diets were calculated. Adherence to each item was given a point with maximum total possible scores of 7, 9, and 10, respectively. Quartiles of scores for each index were calculated and used to create 4 ordered categories. Their association with DM and/or HTN controlling for differing covariates across exposures was evaluated using logistic regression.Results: 60,408 adults 55–74 y of age provided baseline data. Age, sex, and BMI differed across exposure groups. Participants with DM independently of HTN were twice more likely than controls to high adherence to the HEI diet, and 1.3–1.5 times to the DASH and MEDI diets (all p-v <0.001) (Figure 1). Highest adherence among diabetics was to vegetable, grains, and meat portions in HEI and DASH, and sugar in HEI. They were slightly less compliant with fat rations. Hypertensive adults did not differ in adherence to controls, not even in salt consumption as per DASH. Regular physical activity and female sex was predictive of high adherence.Conclusions: Management of DM in mature and older adults via diet is feasible in about 34% highly adherent to the HEI 2005 diet. A similar level will only be achieved by 20% of those with HTN. Exercising regularly identifies those likely to adhere. Figure 1

Urology
Fossati N, Larcher A, Briganti A, and **Abdollah F**. The Authors Respond *J Natl Compr Canc Netw* 2016; 14(2):117-122. PMID: 26850481. Article Request Form

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Urology
Freedland SJ, Choeurng V, Howard L, De Hoedt A, du Plessis M, Yousefi K, Lam LL, Buerki C, Ra S, Robbins B, Trabulsi EJ, Shah NL, **Abdollah F**, Feng FY, Davicioni E, Dicker AP, Karnes RJ, and Den RB. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy *Eur Urol* 2016;PMID: 26806658. Full Text

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BACKGROUND: Despite salvage radiation therapy (SRT) for recurrent prostate cancer (PCa) after radical prostatectomy (RP), some patients still progress to metastases. Identifying these men would allow them to undergo systemic therapy including testing novel therapies to reduce metastases risk. OBJECTIVE: To test whether the genomic classifier (GC) predicts development of metastatic disease. DESIGN, SETTING, AND PARTICIPANTS: Retrospective multi-center and multi-ethnic cohort study from two academic centers and one Veterans Affairs Medical Center in the United States involving 170 men receiving SRT for recurrent PCa post-RP. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Time from SRT to development of metastatic disease tested using Cox regression, survival c-index, and decision curve analysis. Performance of GC was compared to the Cancer of the Prostate Risk Assessment Score and Briganti risk models based on these metrics. RESULTS AND LIMITATIONS: With a median 5.7 yr follow-up after SRT, 20 patients (12%) developed metastases. On multivariable analysis, for each 0.1 unit increase in GC (scaled from 0 to 1), the hazard ratio for metastasis was 1.58 (95% confidence interval 1.16-2.17; p=0.002). Adjusting for androgen deprivation therapy did not materially change the results. The c-index for GC was 0.85 (95% confidence interval 0.73-0.88) versus 0.63-0.65 for published clinico-pathologic risk models. The 5-yr cumulative incidence of metastasis post-SRT in patients with low, intermediate, and high GC scores was 2.7%, 8.4%, and 33.1%, respectively (p<0.001). CONCLUSIONS: While validation in larger, prospectively collected cohorts is required, these data suggest GC is a strong predictor of metastases among men receiving SRT for recurrent PCa post-RP, accurately identifying men who are excellent candidates for systemic therapy due to their very high-risk of metastases. PATIENT SUMMARY: Genomic classifier and two clinico-pathologic risk models were evaluated on their ability to predict metastases among men receiving salvage radiation therapy for recurrent prostate cancer. Genomic classifier was able to identify candidates for further therapies due to their very high-risk of metastases.

Urology
Ghani KR, Miller DC, Linsell S, Brachulis A, Lane B, Sarle R, **Dalela D**, **Menon M**, Comstock B, Lendvay TS, Montie J, and **Peabody JO**. Measuring to improve: Peer and crowd-sourced assessments of technical skill with robot-assisted radical prostatectomy *Eur Urol* 2016;PMID: 26755338. Full Text

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Because surgical skill may be a key determinant of patient outcomes, there is growing interest in skill assessment. In the Michigan Urological Surgery Improvement Collaborative (MUSIC), we assessed whether peer and crowd-sourced (ie, layperson) video review of robot-assisted radical prostatectomy (RARP) could distinguish technical skill among practicing surgeons. A total of 76 video clips from 12 MUSIC surgeons consisted of one of four parts of RARP and underwent blinded review by MUSIC peer surgeons and prequalified crowd-sourced reviewers. Videos were rated for global skill (Global Evaluation Assessment of Robotic Skills) and procedure-specific skill (Robotic Anastomosis and Competency Evaluation). We fit linear mixed-effects models to estimate mean peer and crowd ratings for each video. Individual video ratings were aggregated to calculate surgeon skill scores. Peers (n=25) completed 351 video ratings over 15 d, whereas crowd-sourced reviewers (n=680) completed 2990 video ratings in 38h. Surgeon global skill scores ranged from 15.8 to 21.7 (peer) and from 19.2 to 20.9 (crowd). Peer and crowd ratings demonstrated strong correlation for both global (r=0.78) and anastomosis (r=0.74) skills. The two groups consistently agreed on the rank order of lower scoring surgeons, suggesting a potential role for crowd-sourced methodology in the assessment of surgical performance. Lack of patient outcomes is a limitation and forms the basis of future study. PATIENT SUMMARY: We demonstrated the large-scale feasibility of assessing the technical skill of robotic surgeons and found that online crowd-sourced reviewers agreed with experts on the rank order of surgeons with the lowest technical skill scores.

Urology

Huang KC, Begin LR, **Palanisamy N**, Donnelly B, and Bismar TA. SPINK1 expression in relation to PTEN and ERG in matched primary and lymph node metastatic prostate cancer: Implications for biomarker development *Urol Oncol* 2015;PMID: 26725250. Full Text

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BACKGROUND: SPINK1, ERG, and PTEN are proposed prognostic biomarkers in prostate cancer (PCA). However, their relations and patterns of expression in primary and metastatic lymph node (LN) PCAs are not fully explored. METHODS: A tissue microarray of matched primary PCA and LN metastasis was constructed from 36 patients. SPINK1, ERG, and PTEN expression statuses were assessed by immunohistochemistry and correlated with each other. RESULTS: SPINK1 and ERG were expressed in 25% and 42.7% of primary PCA cases, respectively. PTEN loss of any degree was observed in 91.7% of primary PCA cases, with 54.2% showing complete loss. In primary PCA, 12.5% of the cases showed SPINK1+/ERG-phenotype, 16.7% showed SPINK1+/ERG+phenotype, 25.0% showed SPINK1-/ERG+phenotype, and 45.8% showed SPINK1-/ERG-phenotype. All PCAs with expression of either SPINK1 or ERG also exhibited PTEN loss, whereas PCA without PTEN loss (2 cases) expressed neither SPINK1 nor ERG. In primary PCA, evaluation of combined ERG and SPINK1 status, but not SPINK1 individually, was associated with a significant difference in proportion of Gleason patterns (P = 0.013), with the SPINK1+/ERG+and SPINK1-/ERG-phenotypes represented more in Gleason pattern>7 PCAs. In LN metastases, the overall SPINK1 protein expression frequency was significantly lower (6.5% of cases) compared with primary PCA (P = 0.03). Only 16.7% of cases with positive SPINK1 expression in primary PCA maintained expression in LN metastases. The down-regulated SPINK1 expression in LN was primarily because of a reduction in the SPINK1+/ERG+PCA subpopulation to 3.5% of cases (P = 0.16 compared with primary PCA). The frequencies of ERG expression and PTEN loss were relatively stable in primary PCA and LN metastases. CONCLUSION: SPINK1 expression is dynamically regulated with up-regulation in primary sites of nodal metastatic PCA and down-regulation in LN metastases. The increased SPINK1 expression in primary site of nodal metastatic PCA is secondary to an increased frequency of SPINK1+/ERG+tumors. In primary PCAs, the SPINK1+/ERG+phenotype is associated with higher Gleason grade, suggesting that this phenotype may mark a more aggressive PCA subpopulation with higher risk of LN metastases.

Urology

Kryvenko ON, **Diaz M**, Matoso A, Kates M, Cohen J, Swanson GP, and Epstein JI. Psa mass density - a measure predicting prostate cancer volume and accounting for overweight and obesity: Related psa hemodilution *Urology* 2016;PMID: 26773349. Full Text

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OBJECTIVE: To test PSA mass density (PSAMD) as a predictor of total tumor volume (TTV) at radical prostatectomy (RP). METHODS: We conducted a detailed pathologic analysis of 469 RP from men with NCCN low risk prostate cancer who had Gleason score 3+3=6 (Grading group 1) at RP. We then compared the ability of PSA, PSA density (PSAD), PSA mass (PSAM - absolute amount of PSA in patient's circulation), and PSAM density (PSAM/prostate weight without seminal vesicles) to predict TTV at RP. PSAM was calculated by multiplying plasma volume (estimated body surface [weight,kg0.425 * height,m0.72 * 0.007184] x 1.67) by PSA. Performance of the above measures in different BMI categories was assessed. Kruskal-Wallis test was used to compare the means and Spearman's rank correlation coefficient to assess the correlations. RESULTS: The 469 men were normal weight (n=129), overweight (n=253), and obese (n=87). Mean age of the patients' was 57.4 years and PSA 4.53 ng/ml. Increase of prostate weight with BMI was reflected in PSAM (both p<0.001) but not in other measures. BMI did not correlate with TTV and PSA. Among PSA, PSAD, PSAM, and PSAMD, PSAMD had the highest correlation with TTV (r=0.336; p<0.001). Prostate weight had stronger (negative) association with PSAMD (r=-0.394; <0.001) than TTV. CONCLUSIONS: PSAMD is the biochemical measure with the best correlation with TTV at RP. Unlike other measures, it is not affected by BMI related hemodilution. Thresholds should be established to use this more objective measure clinically in surveillance algorithms and in planning radical prostatectomy.

Urology

Sarveswaran S, **Ghosh R**, **Morisetty S**, and **Ghosh J**. MK591, a second generation leukotriene biosynthesis inhibitor, prevents invasion and induces apoptosis in the bone-invading C4-2B human prostate cancer cells: implications for the treatment of castration-resistant, bone-metastatic prostate cancer *PLoS One* 2015; 10(4):e0122805. PMID: 25875826. Full Text

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Castration-resistant prostate cancer (CRPC) is a major clinical challenge for which no cure is currently available primarily because of the lack of proper understanding about appropriate molecular target(s). Previously we observed that inhibition of 5-lipoxygenase (5-Lox) activity induces apoptosis in some types of prostate cancer cells, suggesting an important role of 5-Lox in the viability of prostate cancer cells. However, nothing is known about the role of 5-Lox in the survival of castration-resistant, metastatic prostate cancer cells. Thus, we tested the effects of MK591, a second-generation, specific inhibitor of 5-Lox activity, on the viability and metastatic characteristics of CRPC cells. We observed that MK591 effectively kills the bone-invading C4-2B human prostate cancer cells (which bear characteristics of CRPC), but does not affect normal, non-cancer fibroblasts (which do not express 5-Lox) in the same experimental conditions. We also observed that MK591 dramatically inhibits the in vitro invasion and soft-agar colony formation of C4-2B cells. Interestingly, we found that treatment with MK591 dramatically down-regulates the expression of c-Myc and its targets at sub-lethal doses. In light of frequent over-activation of c-Myc in a spectrum of aggressive cancers (including CRPC), and the challenges associated with inhibition of c-Myc (because of its non-enzymatic nature), our novel findings of selective killing, and blockade of invasive and soft-agar colony-forming abilities of the castration-resistant, bone-metastatic C4-2B prostate cancer cells by MK591, open up a new avenue to attack CRPC cells for better management of advanced prostate cancer while sparing normal, non-cancer body cells.

Urology
Sood A, **Abdullah NM**, **Abdollah F**, **Abouljoud MS**, Trinh QD, **Menon M**, and **Sammon JD**. Rates of kidney transplantation from living and deceased donors for blacks and whites in the united states, 1998 to 2011 *JAMA Intern Med* 2015; 175(10):1716-1718. PMID: 26322565. Full Text

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Urology
Sood A, Majumder K, **Kachroo N**, **Sammon JD**, **Abdollah F**, Schmid M, **Hsu L**, **Jeong W**, Meyer CP, Hanske J, **Kalu R**, **Menon M**, and Trinh QD. Adverse event rates, timing of complications, and the impact of specialty on outcomes following adrenal surgery: An analysis of 30-day outcome data from the american college of surgeons national surgical quality improvement program (acs-nsqip) *Urology* 2015;PMID: 26743396. Full Text

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OBJECTIVES: To report on 30-day adverse event rates and timing of complications following adrenal surgery; further, to investigate the impact of specialty (general surgery versus urology) on these outcomes using a large prospective multi-institutional data registry. METHODS: Within the ACS-NSQIP (2005-2012), patients undergoing adrenalectomy were identified (CPT-codes: 60540, 60545, 60650). Outcomes evaluated included complications, blood transfusion, length-of-stay, re-intervention, readmission and mortality. Complications were further evaluated in relation to discharge status (pre-/post-discharge). Multivariable regression models assessed association between specialty and 30-day morbidity/mortality. RESULTS: During the study-period, 4,844 patients underwent adrenalectomy (95.7% general surgery). The overall complication rate was 7.5% (n=363); 43.2% of the complications occurred post-discharge with a substantial proportion of major complications, including cardiac, pulmonary, renal, neurologic, septic and DVT/PE also occurring post-discharge (29.9%). The overall blood transfusion, re-intervention, readmission and mortality rates were 3.9%, 2.0%, 6.4% and 0.6%, respectively. In adjusted-analyses, specialty did not have an effect on any of the outcomes (p>0.05 all). CONCLUSIONS: One in 13 patients suffers a complication post-adrenalectomy. Approximately 40% of these complications occur post-discharge, primarily within the first two weeks of surgery. Accurate knowledge regarding 30-day adverse event rates and timing of complications that this study provides, may facilitate improved patient-physician communication and encourage early patient follow up in this critical window. Lastly, specialty does not seem to affect outcomes in ACS-NSQIP participant hospitals.

Urology
Walz J, Epstein JI, Ganzer R, Graefen M, Guazzoni G, Kaouk J, **Menon M**, Mottrie A, Myers RP, Patel V, Tewari A, Villers A, and Artibani W. A critical analysis of the current knowledge of surgical anatomy of the prostate related to optimisation of cancer control and preservation of continence and erection in candidates for radical prostatectomy: An update *Eur Urol* 2016;PMID: 26850969. Full Text

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CONTEXT: In 2010, we published a review summarising the available literature on surgical anatomy of the prostate and adjacent structures involved in cancer control and the functional outcome of prostatectomy. OBJECTIVE: To provide an update based on new literature to help the surgeon improve oncologic and surgical outcomes of radical prostatectomy (RP). EVIDENCE ACQUISITION: We searched the PubMed database using the keywords radical prostatectomy, anatomy, neurovascular bundle, nerve, fascia, pelvis, sphincter, urethra, urinary continence, and erectile function. Relevant articles and textbook chapters published since the last review were critically reviewed, analysed, and summarised. Moreover, we integrated aspects that were not addressed in the last review into this update. EVIDENCE SYNTHESIS: We found new evidence for several topics. Up to 40% of the cross-sectional surface area of the urethral sphincter tissue is laterally overlapped by the dorsal vascular complex and might be injured during en bloc ligation. Denonvilliers fascia is fused with the base of the prostate in a horizontal fashion dorsally/caudally of the seminal vesicles, requiring sharp detachment when preserved. During extended pelvic lymph node dissection, the erectile nerves are at risk in the presacral and internal iliac area. Dissection planes for nerve sparing can be graded according to the amount of tissue left on the prostate as a safety margin against positive surgical margins. Vascular structures can serve as landmarks. The urethral sphincter and its length after RP are influenced by the shape of the apex. Taking this shape into account allows preservation of additional sphincter length with improved postoperative continence. CONCLUSIONS: This update provides additional, detailed information about the surgical anatomy of the prostate and adjacent tissues involved in RP. This anatomy remains complex and widely variable. These details facilitate surgical orientation and dissection during RP and ideally should translate into improved outcomes. PATIENT SUMMARY: Based on recent anatomic findings regarding the prostate and its surrounding tissue, the urologist can individualise the dissection during RP according to cancer and patient characteristics to improve oncologic and functional results at the same time.