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Henry Ford Health System Publication List – February 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 March, and then imported into EndNote for formatting.There are 107 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

Wells KE, **Kim H**, **Havstad S**, and **Woodcroft KJ**. Trends in asthma-related pharmacy fills *Pharmacoepidemiol Drug Saf* 2015; 24:139-140. PMID: Not assigned. Abstract

[Wells, Karen E.; Havstad, Suzanne; Woodcroft, Kimberley J.] Henry Ford Hlth Syst, Publ Hlth Sci, Detroit, MI USA. [Kim, Haejin] Henry Ford Hlth Syst, Div Allergy & Clin Immunol, Detroit, MI USA.

Background: National Asthma Education and Prevention Program guidelines recommend inhaled corticosteroids (ICS) plus a long-acting beta-agonist (LABA) as step-up therapy for the management of persistent asthma when ICS alone offers inadequate control of asthma symptoms. The advent of ICS/LABA in a single inhaler may have influenced prescribing trends over time. Objectives: The aim of the study was to investigate the trends in asthma-related pharmacy fills and asthma exacerbations pre- and post-availability of ICS/LABA in a single inhaler. Methods: Detailed longitudinal data on healthcare and medication use from a large covered patient population were used to assess rates of ICS ± LABA, short-acting beta-agonist (SABA), oral corticosteroid (OC) pharmacy fills, and asthma-related exacerbations. Analyses were limited to patients aged 12–56 years with a diagnosis of asthma between 1 January 1999 and 31 December 2011. Patients with a recorded diagnosis of chronic obstructive pulmonary disease were excluded from rate calculations. Time trend analysis was used to identify changes in these rates over time. Results: The analysis comprised 441 867 individuals and 199 797 filled prescriptions for asthma medications from 1 January 1999 to 31 December 2011. The rate of LABA as add-on therapy to ICS in separate inhalers peaked at 117 fills per 100 000 individuals in December of 1999. Within 2.5 years of FDA approval, the fill rate for ICS/LABA in a single inhaler surpassed the monthly rate of ICS fills. Since then, the average fill rate of ICS/LABA more than doubled that of ICS monotherapy (307 vs. 145 fills per 100 000). Rates of SABA fills dropped significantly ($p < 0.0001$) during the same period. Time trend analysis did not show a statistically significant change in rates of OC fills and asthma-related hospitalizations during the observation period ($p = 0.0545$, 0.3633 respectively), while asthma-related emergency department visits significantly increased over time ($p = 0.0018$). Conclusions: ICS/LABA in a single inhaler is the most commonly prescribed asthma controller therapy since 2003. The symptom relief that the addition of LABA provides may motivate regular use, thereby reducing the need for SABAs. There was no reduction in the rate of asthma exacerbations over time.

Anesthesiology

Loomba V, **Kaveeshvar H**, **Upadhyay A**, and **Sibai N**. Neuropathic pain in cancer patients: A brief review *Indian J Cancer* 2015; 52(3):425-428. PMID: 26905158. Full Text

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Neuropathic pain (NP) is initiated or caused by a primary lesion or dysfunction in the nervous system. The NP in cancer patients is typically due to a combination of inflammatory, neuropathic, ischemic, infiltrative, and compression mechanisms that involve one or more anatomic sites. These patients will often have various types of co-existing pain syndromes and co-morbidities. Thus, any treatment plan needs to be individualized. After a thorough clinical assessment and evaluation, a combination therapy including anticonvulsants, antidepressants, N-methyl-D-aspartate antagonists, opiates, topical agents, and interventional procedures should be considered in these patients.

Bone and Mineral Research

Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, Miller PD, **Rao SD**, Kendler DL, Lindsay R, Krege JH, Alam J, Taylor KA, Janos B, and Ruff VA. Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA osteoporosis study *J Clin Endocrinol Metab* 2016:jc20154181. PMID: 26859106. Full Text

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CONTEXT: Denosumab-induced parathyroid hormone (PTH) elevation may stimulate early bone formation. OBJECTIVE: Evaluate whether denosumab-induced changes of intact (i)PTH result in early anabolic effects according to histomorphometry and bone turnover markers (BTM) compared with teriparatide, an established anabolic agent. DESIGN: This open-label, randomized study used quadruple labeling to label bone before/after treatment, with a transiliac bone biopsy at 3 months. SETTING: United States and Canadian sites. PARTICIPANTS: Sixty-nine postmenopausal women with osteoporosis. INTERVENTIONS: Teriparatide (20 mug/day) for 6 months; denosumab (60 mg once). MAIN OUTCOME MEASURE: Between-treatment comparison of change from baseline to month 3 in cancellous mineralizing surface/bone surface (MS/BS); histomorphometric indices in 4 bone envelopes; BTM and iPTH at baseline, 1, 3, and 6 months. RESULTS: After denosumab, iPTH peaked at month 1 (P<0.001) then declined, remaining above baseline through month 6 (P</=0.01); after teriparatide, iPTH declined at all timepoints (P<0.001). From baseline to month 3, cancellous MS/BS increased with teriparatide and decreased with denosumab and at month 3, was higher with teriparatide. Similar results were observed in other bone envelopes. BTMs increased from baseline in teriparatide-treated subjects (procollagen type 1 N-terminal propeptide [P1NP] at month 1 and carboxyterminal cross-linking telopeptide of type 1 collagen [CTX] at month 3); P1NP and CTX decreased from baseline at all timepoints in denosumab-treated subjects. CONCLUSIONS: Denosumab treatment increased iPTH but inhibited bone formation indices. In contrast, teriparatide treatment decreased iPTH but stimulated bone formation indices. These findings are not consistent with the hypothesis of early indirect anabolic effect with denosumab.

Cardiology / Cardiovascular Research

Cohen MG, Matthews R, Maini B, Dixon S, Vetrovec G, Wohns D, Palacios I, Popma J, Ohman EM, Schreiber T, and **O'Neill WW**. Percutaneous left ventricular assist device for high-risk percutaneous coronary interventions: Real-world versus clinical trial experience *Am Heart J* 2015; 170(5):872-879. PMID: 26542494. Full Text

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BACKGROUND: High-risk percutaneous coronary intervention (PCI) supported by percutaneous left ventricular assist devices offers a treatment option for patients with severe symptoms, complex and extensive coronary artery disease, and multiple comorbidities. The extrapolation from clinical trial to real-world practice has inherent uncertainties. We compared the characteristics, procedures, and outcomes of high-risk PCI supported by a microaxial pump (Impella 2.5) in a multicenter registry versus the randomized PROTECT II trial (NCT00562016). METHODS: The USpella registry is an observational multicenter voluntary registry of Impella technology. A total of 637 patients treated between June 2007 and September 2013 were included. Of them, 339 patients would have met enrollment criteria for the PROTECT II trial. These were compared with 216 patients treated in the Impella arm of PROTECT II. RESULTS: Compared to the clinical trial, registry patients were older (70 +/- 11.5 vs 67.5 +/- 11.0 years); more likely to have chronic kidney disease (30% vs 22.7%), prior myocardial infarction (69.3% vs 56.5%), or prior bypass surgery (39.4% vs. 30.2%); and had similar prevalence of diabetes, peripheral vascular disease, and prior stroke. Registry patients had more extensive coronary artery disease (2.2 vs 1.8 diseased vessels) and had a similar Society of Thoracic Surgeons predicted risk of mortality. At hospital discharge, registry patients experienced a similar reduction in New York Heart Association class III to IV symptoms compared to trial patients. Registry patients had a trend toward lower in-hospital mortality (2.7% vs 4.6, P = .27). CONCLUSIONS: USpella provides a real-world and contemporary estimation of the type of procedures and outcomes of high-risk patients undergoing PCI supported by Impella 2.5. Despite the higher risk of registry patients, clinical outcomes appeared to be favorable and consistent compared with the randomized trial.

Cardiology / Cardiovascular Research

El-Refai M, **Hrobowski T**, **Peterson EL**, **Wells K**, Spertus JA, **Williams LK**, and **Lanfear DE**. Race and association of angiotensin converting enzyme/angiotensin receptor blocker exposure with outcome in heart failure *J Cardiovasc Med (Hagerstown)* 2015; 16(9):591-596. PMID: 24842464. Full Text

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PURPOSE: Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been established as a mainstay of heart failure treatment. Current data are limited and conflicting regarding the consistency of ACE/ARB benefit across race groups in heart failure. This study aims to clarify this point. METHODS: This was a retrospective study of insured patients with a documented ejection fraction of less than 50%, hospitalized for heart failure between January 2000 and June 2008. Pharmacy claims data were used to estimate ACE/ARB exposure over 6-month rolling windows. The

association between ACE/ARB exposure and all-cause hospitalization or death was assessed by proportional hazards regression, with adjustment for baseline covariates and beta-blocker exposure. Further analyses were stratified by race, and included an ACE/ARB x Race interaction term. RESULTS: A total of 1095 patients met inclusion criteria (619 African-American individuals). Median follow-up was 2.1 years. In adjusted models, ACE/ARB exposure was associated with lower risk of death or hospitalization in both groups (African-Americans hazard ratio 0.47, P < 0.001; whites hazard ratio 0.55, P < 0.001). A formal test for interaction was consistent with similar effects in each group (P = 0.861, beta = 0.04). CONCLUSION: ACE/ARB exposure was equally associated with a protective effect in preventing death or rehospitalization among heart failure patients with systolic dysfunction in both African-American patients and whites.

Cardiology / Cardiovascular Research

Brawner CA, **Abdul-Nour K**, **Lewis B**, **Schairer JR**, **Modi SS**, **Kerrigan DJ**, **Ehrman JK**, and **Keteyian SJ**. Relationship between exercise workload during cardiac rehabilitation and outcomes in patients with coronary heart disease *Am J Cardiol* 2016;PMID: 26897640. Full Text

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The purpose of this retrospective, observational study was to describe the relation between exercise workload during cardiac rehabilitation (CR), expressed as metabolic equivalents of task (METs), and prognosis among patients with coronary heart disease. We included patients with coronary heart disease who participated in CR between January 1998 and June 2007. METs were calculated from treadmill workload. Cox regression analysis was used to describe the relationship between METs and time to a composite outcome of all-cause mortality, nonfatal myocardial infarction, or heart failure hospitalization. Among 1,726 patients (36% women; median age 59 years [interquartile range, 52 to 66]), there were 467 events (27%) during a median follow-up of 5.8 years (interquartile range, 2.6 to 8.7). In analyses adjusted for age, sex, Charlson co-morbidity index, hypertension, diabetes, and CR referral diagnosis, METs were independently related to the composite outcome at CR start (Wald chi-square 43, hazard ratio 0.59 [95% confidence interval 0.51 to 0.70]) and CR end (Wald chi-square 47, hazard ratio 0.68 [95% confidence interval 0.61 to 0.76]). Patients exercising below 3.5 METs on exit from CR represent a high-risk group with 1- and 3-year event rates >/=7% and >/=18%, respectively. In conclusion, METs during CR is available at no additional cost and can be used to identify patients at increased risk for an event who may benefit from closer follow-up, extended length of stay in CR, and/or participation in other strategies aimed at maximizing adherence to secondary preventive behaviors and improving exercise capacity.

Cardiology / Cardiovascular Research

Brilakis ES, Karmpaliotis D, Vo MN, Carlino M, Galassi AR, Boukhris M, **Alaswad K**, Bryniarski L, Lombardi WL, and Banerjee S. Update on coronary chronic total occlusion percutaneous coronary intervention *Interventional Cardiology Clinics* 2016;PMID: Not assigned. Full Text

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Chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has significantly evolved during recent years. High success rates are being achieved by experienced centers and operators, but not at less-experienced centers. Use of CTO crossing algorithms can help improve the success and efficiency of these potentially lengthy procedures. There is a paucity of clinical trial data examining clinical outcomes of CTO PCI, which is critical for further adoption and refinement of the procedure. We provide a detailed overview of the clinical evidence and current available crossing strategies, with emphasis on recent developments and techniques.

Cardiology / Cardiovascular Research

Ellis CR, Dickerman DI, Orton JM, **Hassan S**, Good ED, Okabe T, Andriulli JA, Quan KJ, and Greenspon AJ. Ampere hour (ah) as a predictor of cardiac resynchronization defibrillator pulse generator battery longevity; a multi-center study *Pacing Clin Electrophysiol* 2016;PMID: 26875541. Article Request Form

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BACKGROUND: CRT-D devices improve survival for NYHA II-IV systolic heart failure patients with QRS >120ms and LVEF <35%. A limitation of 100% CRT pacing is excess battery depletion and pulse generator (PG) replacement compared to VVI or dual chamber systems. Ampere-hour (Ah) measures PG battery capacity and may predict CRT-D device longevity. METHODS: We performed a multi-center retrospective study of all CRT-D devices implanted at our centers from August 1, 2008 to December 31, 2010. Analysis was performed for survival to elective replacement indicator (ERI) between 1.0 Ah, 1.4 Ah, and 2.0 Ah devices, per manufacturers specifications. RESULTS: 1302 patients were studied through December 31, 2014. Patients were followed an average of 3.0 +/- 1.3 years (794 1.0 Ah, 322 2.0 Ah, and 186 1.4 Ah devices under study). CRT-D generator ERI occurred in 13.5% of 1.0 Ah systems (107/794), versus 3.8% in 1.4 Ah, (7/186), and 0.3% in 2.0 Ah devices (1/322) over mean follow up of 3.0 yrs. Odds ratio (OR) for reaching ERI with 1.0 Ah device versus 1.4 Ah or 2.0 Ah was 9.73, p <0.0001. Univariate predictors for ERI included 1.0 Ah device and LV pacing output > 3V @ 1 ms (OR 3.74, p<0.001). LV impedance >1000 ohms predicted improved device survival (OR 0.38, p 0.0025). CONCLUSIONS: CRT-D battery capacity measured by Ampere hour (Ah) is a strong predictor of survival to ERI for modern systems. Further study on cost and morbidity associated with early pulse generator change in 1.0 Ah systems is warranted.

Cardiology / Cardiovascular Research

Karacsonyi J, Karatasakis A, Karmpaliotis D, **Alaswad K**, Yeh RW, Jaffer FA, Wyman MR, Lombardi WL, Grantham JA, Kandzari DE, Lembo N, Moses JW, Kirtane AJ, Parikh MA, Green P, Finn M, Garcia S, Doing A, Patel M, Bahadorani J, Martinez Parachini JR, Resendes E, Rangan BV, Ungi I, Thompson CA, Banerjee S, and Brilakis ES. Effect of previous failure on subsequent procedural outcomes of chronic total occlusion percutaneous coronary intervention (from a Contemporary Multicenter Registry) *Am J Cardiol* 2016;PMID: 26899493. Full Text

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We sought to examine the impact of previous failure on the outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). We examined the clinical and angiographic characteristics and procedural outcomes of 1,213 consecutive patients who underwent 1,232 CTO PCIs from 2012 to 2015 at 12 US centers. Mean age was 65 +/- 10 years, and 84.8% of patients were men. A previously failed attempt had been performed in 215 patients (17.5%). As compared with patients without previous CTO PCI failure, patients with previous failure had higher Multicenter CTO Registry in Japan CTO score (2.40 +/- 1.13 vs 3.28 +/- 1.29, p <0.0001) and were more likely to have in-stent restenosis (10.5% vs 28.4%, p <0.0001) and to undergo recanalization attempts using the retrograde approach (41% vs 50%, p = 0.011). Technical (90% vs 88%, p = 0.390) and procedural (89% vs 86%, p = 0.184) success were similar in the 2 study groups; however, median procedure time (125 vs 142 minutes, p = 0.026) and fluoroscopy time (45 vs 55 minutes, p = 0.015) were longer in the previous failure group. In conclusion, a previously failed CTO PCI attempt is associated with higher angiographic complexity, longer procedural duration, and fluoroscopy time, but not with the success and complication rates of subsequent CTO PCI attempts.

Cardiology / Cardiovascular Research

Keteyian SJ, Patel M, Kraus WE, **Brawner CA**, McConnell TR, Pina IL, Leifer ES, Fleg JL, Blackburn G, Fonarow GC, Chase PJ, Piner L, Vest M, O'Connor CM, **Ehrman JK**, Walsh MN, Ewald G, Bensimhon D, and Russell SD. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure *J Am Coll Cardiol* 2016; 67(7):780-789. PMID: 26892413. Full Text

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BACKGROUND: Data from a cardiopulmonary exercise (CPX) test are used to determine prognosis in patients with chronic heart failure (HF). However, few published studies have simultaneously compared the relative prognostic strength of multiple CPX variables. OBJECTIVES: The study sought to describe the strength of the association among variables measured during a CPX test and all-cause mortality in patients with HF with reduced ejection fraction (HFrEF), including the influence of sex and patient effort, as measured by respiratory exchange ratio (RER). METHODS: Among patients (n = 2,100, 29% women) enrolled in the HF-ACTION (HF-A Controlled Trial Investigating Outcomes of exercise traiNing) trial, 10 CPX test variables measured at baseline (e.g., peak oxygen uptake [Vo2], exercise duration, percent predicted peak Vo2 [%ppVo2], ventilatory efficiency) were examined. RESULTS: Over a median follow-up of 32 months, there were 357 deaths. All CPX variables, except RER, were related to all-cause mortality (all p < 0.0001). Both %ppVo2 and exercise duration were equally able to predict (Wald chi-square:

approximately 141) and discriminate (c-index: 0.69) mortality. Peak Vo2 (ml.kg(-1).min(-1)) was the strongest predictor of mortality among men (Wald chi-square: 129) and exercise duration among women (Wald chi-square: 41). Multivariable analyses showed that %ppVo2, exercise duration, and peak Vo2 (ml.kg(-1).min(-1)) were similarly able to predict and discriminate mortality. In men, a 10% 1-year mortality rate corresponded to a peak Vo2 of 10.9 ml.kg(-1).min(-1) versus 5.3 ml.kg(-1).min(-1) in women. CONCLUSIONS: Peak Vo2, exercise duration, and % ppVo2 carried the strongest ability to predict and discriminate the likelihood of death in patients with HFrEF. The prognosis associated with a given peak Vo2 differed by sex. (Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure; NCT00047437).

Cardiology / Cardiovascular Research

Marchlinski FE, Haffajee CI, Beshai JF, Dickfeld TM, Gonzalez MD, Hsia HH, **Schuger CD**, Beckman KJ, Bogun FM, Pollak SJ, and Bhandari AK. Long-term success of irrigated radiofrequency catheter ablation of sustained ventricular tachycardia: post-approval THERMOCOOL VT trial *J Am Coll Cardiol* 2016; 67(6):674-683. PMID: 26868693. Full Text

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Los Angeles Cardiology Associates, Los Angeles, California.

BACKGROUND: Radiofrequency catheter ablation is used to treat recurrent ventricular tachycardia (VT). OBJECTIVES: This study evaluated long-term safety and effectiveness of radiofrequency catheter ablation using an open-irrigated catheter. METHODS: Patients with sustained monomorphic ventricular tachycardia associated with coronary disease were analyzed for cardiovascular-specific adverse events within 7 days of treatment, hospitalization duration, 6-month sustained monomorphic ventricular tachycardia recurrence, quality of life measured by the Hospital Anxiety and Depression Scale, long-term (1-, 2-, and 3-year) survival, symptomatic VT control, and amiodarone use. RESULTS: Overall, 249 patients, mean age 67.4 years, were enrolled. The cardiovascular-specific adverse events rate was 3.9% (9 of 233) with no strokes. Noninducibility of targeted VT was achieved in 75.9% of patients. Post-ablation median hospitalization was 2 days. At 6 months, 62.0% (114 of 184) of patients had no sustained monomorphic ventricular tachycardia recurrence; the proportion of patients with implantable cardioverter-defibrillator shocks decreased from 81.2% to 26.8% ($p < 0.0001$); the frequency of VT in implantable cardioverter-defibrillator patients with recurrences was reduced by >/=50% in 63.8% of patients; and the proportion with normal Hospital Anxiety and Depression Scale scores increased from 48.8% to 69.1% ($p < 0.001$). Patient-reported VT remained steady for 1, 2, and 3 years at 22.7%, 29.8%, and 24.1%, respectively. Amiodarone use and hospitalization decreased from 55% and 77.2% pre-ablation to 23.3% and 30.7%, 18.5% and 36.7%, 17.7% and 31.3% at 1, 2, and 3 years, respectively. CONCLUSIONS: Radiofrequency catheter ablation reduced implantable cardioverter-defibrillator shocks and VT episodes and improved quality of life at 6 months. A steady 3-year nonrecurrence rate with reduced amiodarone use and hospitalizations indicate improved long-term outcomes. (NaviStar ThermoCool Catheter for Endocardial RF Ablation in Patients With Ventricular Tachycardia [THERMOCOOL VT]; NCT00412607).

Cardiology / Cardiovascular Research

Mawri S, **Michaels A**, **Gibbs J**, **Shah S**, Rao S, Kugelmass A, Lingam N, Arida M, **Jacobsen G**, Rowlandson I, Iyer K, **Khandelwal A**, and **McCord J**. The comparison of physician to computer interpreted electrocardiograms on ST-elevation myocardial infarction door-to-balloon times *Crit Pathw Cardiol* 2016; 15(1):22-25. PMID: 26881816. Full Text

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OBJECTIVE: The purpose of the project was to study the impact that immediate physician electrocardiogram (ECG) interpretation would have on door-to-balloon times in ST-elevation myocardial infarction (STEMI) as compared with computer-interpreted ECGs. METHODS: This was a retrospective cohort study of 340 consecutive patients from September 2003 to December 2009 with STEMI who underwent emergent cardiac catheterization and percutaneous coronary intervention. Patients were stratified into 2 groups based on the computer-interpreted ECG interpretation: those with acute myocardial infarction identified by the computer interpretation and those not identified as acute myocardial infarction. Patients (n = 173) from September 2003 to June 2006 had their initial ECG reviewed by the triage nurse, while patients from July 2006 to December 2009 (n = 167) had their ECG reviewed by the emergency department physician within 10 minutes. Times for catheterization laboratory activation and percutaneous coronary intervention were recorded in all patients. RESULTS: Of the 340 patients with confirmed STEMI, 102 (30%) patients were not identified by computer interpretation. Comparing the prior protocol of computer ECG to physician interpretation, the latter resulted in significant improvements in median catheterization laboratory activation time {19 minutes [interquartile range (IQR): 10-37] vs. 16 minutes [IQR: 8-29]; P < 0.029} and in median door-to-balloon time [113 minutes (IQR: 86-143) vs. 85 minutes (IQR: 62-106); P < 0.001]. CONCLUSION: The computer-interpreted ECG failed to identify a significant number of patients with STEMI. The immediate review of ECGs by an emergency physician led to faster activation of the catheterization laboratory, and door-to-balloon times in patients with STEMI.

Cardiology / Cardiovascular Research

Mueller-Hennessen M, Lindahl B, Giannitsis E, Biener M, Vafaie M, deFilippi CR, Christ M, Santalo-Bel M, Panteghini M, Plebani M, Verschuren F, Jernberg T, French JK, Christenson RH, Body R, **McCord J**, Dilba P, Katus HA, and Mueller C. Diagnostic and prognostic implications using age- and gender-specific cut-offs for high-sensitivity cardiac troponin T - Sub-analysis from the TRAPID-AMI study *Int J Cardiol* 2016; 209:26-33. PMID: 26878470. Full Text

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OBJECTIVES: To evaluate the impact of age- and gender-specific cut-offs for high-sensitivity cardiac troponin T (hs-cTnT) compared to the general 99th percentile hs-cTnT cut-off on diagnosis and prognosis of acute myocardial infarction (AMI). METHODS: 1282 unselected patients presenting to the emergency department with suspected AMI were enrolled as part of the TRAPID-AMI study. In the present sub-analysis, reclassification of AMI diagnosis was performed by comparing the general hs-cTnT cut-off of 14ng/L to previously proposed age- and gender-dependent hs-cTnT 99th percentile cut-offs (28ng/L for >/=65years, 9ng/L for female and 15.5ng/L for male patients). Patients were further clinically adjudicated into acute coronary syndrome (ACS) and non-ACS. RESULTS: For patients >/=65years, application of age-specified cut-offs resulted in a decrease of AMI from 29.8% to 18.3% in the entire cohort (n=557) and 54.7% to 40.9% in the ACS subcohort (n=225). Using gender-specific cut-offs, AMI-rate increased from 16.6% to 22.6% (entire cohort, n=477) and 62.6% to 71.7% (ACS subcohort, n=99) in women, whereas in men, rates decreased from 23.1% to 21.1% (entire cohort, n=805) and 48.8% to 45.9% (ACS, n=281), respectively. Age-specified cut-offs significantly reclassified patients for outcomes of 1-month and 3-month mortality in the entire and ACS cohort (14.2% net reclassification improvement, p<0.001, respectively). Contrary, no significant differences in outcomes could be found using gender-specific cut-offs. CONCLUSIONS: While influence of gender-specific hs-cTnT cut-offs on diagnostic and prognostic reclassification was only modest in patients with suspected AMI, age-specific cut-offs showed a significant impact and may be considered for further validation.

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; 2016:9717948. PMID: 26904306. Full Text

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We illustrate a case of midventricle obstructive HCM and apical aneurysm diagnosed with appropriate use of multimodality imaging. A 75-year-old African American woman presented with a 3-day history of chest pain and dyspnea with elevated troponins. Her electrocardiogram showed sinus rhythm, left atrial enlargement, left ventricular hypertrophy, prolonged QT, and occasional ectopy. After medical therapy optimization, she underwent coronary angiography for an initial diagnosis of non-ST segment elevation myocardial infarction. Her coronaries were unremarkable for significant disease but her left ventriculogram showed hyperdynamic contractility of the midportion of the ventricle along with a large dyskinetic aneurysmal apical sac. A subsequent transthoracic echocardiogram provided poor visualization of the apical region of the ventricle but contrast enhancement identified an aneurysmal pouch distal to the midventricular obstruction. To further clarify the diagnosis, cardiac magnetic resonance imaging with contrast was performed confirming the diagnosis of midventricular hypertrophic cardiomyopathy with apical aneurysm and fibrosis consistent with apical scar on delayed enhancement. The patient was medically treated and subsequently underwent elective implantable defibrillator placement in the ensuing months for recurrent nonsustained ventricular tachycardia and was initiated on prophylactic oral anticoagulation with warfarin for thromboembolic risk reduction.

Cardiology / Cardiovascular Research

Vavalle JP, van Diepen S, Clare RM, Hochman JS, **Weaver WD**, Mehta RH, Pieper KS, Patel MR, Patel UD, Armstrong PW, Granger CB, and Lopes RD. Renal failure in patients with ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention: Predictors, clinical and angiographic features, and outcomes *Am Heart J* 2016; 173:57-66. PMID: 26920597. Full Text

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BACKGROUND: Among patients presenting with ST-segment elevation myocardial infarction (STEMI) for primary percutaneous coronary intervention (PCI), the associations between clinical outcomes and both baseline renal function and the development of acute kidney injury (AKI) have not been reported in a trial population with unselected baseline renal function. METHODS: Patients enrolled in the APEX-AMI trial who underwent primary PCI for the treatment of STEMI were categorized according to (a) baseline renal function and (b) the development of AKI. Patient characteristics, clinical outcomes, and treatment patterns were analyzed according to baseline renal function and the development of AKI. A prediction model for AKI after primary PCI for STEMI was also developed. RESULTS: A total of 5,244 patients were included in this analysis and stratified according to baseline estimated glomerular filtration rate (eGFR) (milliliters per minute per 1.73 m(2)) of >90, 60 to 90, 30 to 59, or <30 or as dialysis dependent. Patients with lower eGFR were older, more often female, and less often treated with evidence-based medicines and had worse angiographic outcomes and higher mortality. The rates of AKI for patients with a baseline eGFR of >90, 60 to 90, 30 to 59, and <30 were 2.5%, 4.1%, 8.1%, and 1.6%, respectively (P < .0001). The strongest predictors of AKI were age and presenting in Killip class III or IV. CONCLUSIONS: Among patients undergoing primary PCI for STEMI, impaired renal function at presentation and development of post-PCI AKI were highly associated with worse clinical and angiographic outcomes, including death. The risk of developing AKI was low and only modestly associated with baseline renal function.

Center for Health Policy and Health Services Reseach

El-Refai M, **Hrobowski T**, **Peterson EL**, **Wells K**, Spertus JA, **Williams LK**, and **Lanfear DE**. Race and association of angiotensin converting enzyme/angiotensin receptor blocker exposure with outcome in heart failure *J Cardiovasc Med (Hagerstown)* 2015; 16(9):591-596. PMID: 24842464. Full Text

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PURPOSE: Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been established as a mainstay of heart failure treatment. Current data are limited and conflicting regarding the consistency of ACE/ARB benefit across race groups in heart failure. This study aims to clarify this point. METHODS: This was a retrospective study of insured patients with a documented ejection fraction of less than 50%, hospitalized for heart failure between January 2000 and June 2008. Pharmacy claims data were used to estimate ACE/ARB exposure over 6-month rolling windows. The association between ACE/ARB exposure and all-cause hospitalization or death was assessed by proportional hazards regression, with adjustment for baseline covariates and beta-blocker exposure. Further analyses were stratified by race, and included an ACE/ARB x Race interaction term. RESULTS: A total of 1095 patients met inclusion criteria (619 African-American individuals). Median follow-up was 2.1 years. In adjusted models, ACE/ARB exposure was associated with lower risk of death or hospitalization in both groups (African-Americans hazard ratio 0.47, P < 0.001; whites hazard ratio 0.55, P < 0.001). A formal test for interaction was consistent with similar effects in each group (P = 0.861, beta = 0.04). CONCLUSION: ACE/ARB exposure was equally associated with a protective effect in preventing death or rehospitalization among heart failure patients with systolic dysfunction in both African-American patients and whites.

Dermatology
Ahn JW, **Johnson K**, **Kohen LL**, **Chaffins ML**, and **Shwayder T**. Melanoma gene expression markers for surveillance of epidermolysis bullosa nevi malignant transformation *JAMA Dermatol* 2016;PMID: 26865206. Full Text

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Dermatology
Arias-Stella J, **Kezlarian B**, **Favazza L**, **Schultz D**, and **Chitale DA**. Programmed cell death ligand 1 (pd-l1) expression in estrogen receptor positive (er plus) invasive breast cancers (bc): A pilot study of 148 cases *Lab Invest* 2016; 96:29A-29A. PMID: Not assigned. Abstract

[Arias-Stella, Javier; Kezlarian, Brie; Favazza, Laura; Schultz, Daniel; Chitale, Dhananjay A.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: T-cell inhibitory molecule PD-L1 expression by tumor cells protects the tumor from destruction by cytotoxic T cells. Recent early-phase trials in different carcinomas targeting the PD-L1 have shown clinical efficacy that correlated PD-L1 tumor expression and responses. However, data on PD-L1 expression in breast cancer is limited and on ER+BC, even more scarce. The aim of this study was to determine the frequency of PD-L1 overexpression in ER+BC and its correlation with tumor infiltrating lymphocytes (TILs) and clinicopathologic characteristics including molecular subtypes. Design: From 148 cases of ER+BC, tissue microarrays (TMAs) were constructed, each case represented in triplicate. Immunohistochemistry was performed using antibody
against PD-L1 protein [SP263 Rabbit monoclonal primary antibody, Ventana, Tuscon, AZ) and leukocyte common antigen (LCA) pan-T lymphocyte marker (DAKO, Carpinteria, CA) to assess TIL density accurately. PD-L1 expression was scored in the cytoplasm or on the membrane of the tumor cells as follows : 0: <1%, 1: 1-5%, 2: 5-10%, 3: >10%. The number of positive lymphocytes per core was counted. Multipleclinical and morphologic parameters including histologic type, Nottingham grade tumor size, TMN stage, angiolymphatic invasion, and receptor status were recorded from electronic pathology report. Statistical analysis was performed using t- test and ANOVA for correlations (p-value <0.05 significant). Results: Out of 148 cases of breast carcinomas, there were 97/148 (66%) Luminal A (ER+/PR+/HER-2-/Low MIB1),and 51/148 (34%) Luminal B (ER+/PR+/HER-2+ or high MIB1 labeling >15%). The average tumor size was 1.7 cm (SD: 1.0, range: 0.4-8.5 cm, median: 1.5 cm). There were 48/148 (32%) grade 1, 83/148 (56%) grade
2, and 17/148 (12%) grade 3 tumors. All case were ER+(100%), 130/148 (88%) PR+, 8/148 (5%) HER2+ tumors. PD-L1 expression in tumor cells was noted in only 9/148 (6%) cases vs 103/148 (70%) in the TIL. There was a statistically significant correlationbetween PDL-1 lymphocytes in high grade tumors (p = 0.0476) and luminal B molecular subtype (p = 0.0062). Conclusions: PD-L1 expression in the tumor cells was upregulated in a minority of ER+BC in this pilot cohort. However, PD-L1 expression in the TIL was frequently found in high grade ER+BC . PD-L1 upregulation did correlate with strong local
immune response in this cohort. Our findings suggest that further characterization of the ER+BC immune microenvironment may yield targets for immune-based therapy and prevention in a subset of BC patients.

Dermatology
Friedman BJ, **Mehta D**, and **Chaffins ML**. Friable nodules on the elbow of a transplant patient *JAMA Dermatol* 2016;PMID: 26886712. Full Text

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Dermatology
Hamzavi I. The role of laser therapy *Exp Dermatol* 2016; 25:8-8. PMID: Not assigned. Abstract

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Traditional pharmacologic and surgical therapies for HS have yielded frustrating results particularly in their ability to prevent disease recurrence and progression. The role of novel therapies utilizing laser and light-based technology has become increasingly important, as they are more effective for stabilizing HS lesions and halting disease progression. Depending on Hurley stage and the disease stability, highly individualized treatment plans are needed to effectively manage HS, with the Nd:YAG laser and other long pulsed laser therapy being more appropriate for stabilizing affected zones in Hurley stage I and II patients and more aggressive CO2 laser excision needed for recalcitrant Hurley stage III disease. The efficacy of these adjunctive therapies is related to two distinct mechanisms: (i) decreasing the number of hair follicles, sebaceous glands and reducing bacterial load and (ii) debulking chronic lesions using ablative techniques.
The most extensive research for laser hair reduction has been performed using the 1064 nm Nd:YAG laser, which targets the hair follicle and induces selective photothermolysis. However, other devices including the 800 nm diode laser, intense pulsed light and non-Q switched ruby laser have all been used with some success. Varying degrees of efficacy were also found in the initial literature for the use of PDT, but recent standardization of protocols, and methods to bypass low penetration of the photosensitizer have yielded improved outcomes. Lastly, removing affected tissue and identifying sinus tracts with subsequent destruction by carbon dioxide laser excision has also proven efficacious with low rates of complication and recurrence.

Dermatology
Kircik L, Sung JC, **Stein-Gold L**, and Goldenberg G. United States food and drug administration product label changes *J Clin Aesthet Dermatol* 2016; 9(1):39-48. PMID: Not assigned. Article Request Form

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Once a drug has been approved by the United States Food and Drug Administration and is on the market, the Food and Drug Administration communicates new safety information through product label changes. Most of these label changes occur after a spontaneous report to either the drug manufacturing companies or the Food and Drug Administration MedWatch program. As a result, 400 to 500 label changes occur every year. Actinic keratosis treatments exemplify the commonality of label changes throughout the postmarket course of a drug. Diclofenac gel, 5-fluorouracil cream, imiquimod, and ingenol mebutate are examples of actinic keratosis treatments that have all undergone at least one label revision. With the current system of spontaneous reports leading to numerous label changes, each occurrence does not necessarily signify a radical change in the safety of a drug.

Dermatology
Mehta D, and **Lim HW**. Ultraviolet B phototherapy for psoriasis: Review of practical guidelines *Am J Clin Dermatol* 2016;PMID: 26872953. Article Request Form

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Psoriasis is an inflammatory skin condition that affects approximately 2 % of people worldwide. Topical treatments, systemic treatments, biologic agents, and phototherapy are all treatment options for psoriasis. Ultraviolet (UV) B phototherapy is most appropriate for patients with >10 % affected body surface area who have not responded to topical treatments. This review outlines the use, dosage, safety, and efficacy of narrowband UVB (NB-UVB) and targeted phototherapy. NB-UVB and excimer laser are effective treatment options for psoriasis; they are administered two to three times weekly until clearance followed by maintenance treatment before discontinuation. Long-term data on NB-UVB indicate that it has a good safety profile. NB-UVB is commonly used with adjunctive topical treatments such as emollients,

calcipotriene, cortico-steroids, retinoids, and tar. NB-UVB can be used in selected patients with traditional systemic agents such as methotrexate, mycophenolate mofetil, and cyclosporine, although the duration of the combined treatment should be kept to a minimum and patients need to be closely monitored. Acitretin can be safely used with phototherapy, but robust data on the combination use of biologic agents or phosphodiesterase inhibitors with phototherapy are lacking.

Dermatology

Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, Bowe WP, Graber EM, Harper JC, Kang S, Keri JE, Leyden JJ, Reynolds RV, Silverberg NB, **Stein Gold LF**, Tollefson MM, Weiss JS, Dolan NC, Sagan AA, Stern M, Boyer KM, and Bhushan R. Guidelines of care for the management of acne vulgaris *J Am Acad Dermatol* 2016;PMID: 26897386. Full Text

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Penn Medicine, Philadelphia, Pennsylvania.
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Acne is one of the most common disorders treated by dermatologists and other health care providers. While it most often affects adolescents, it is not uncommon in adults and can also be seen in children. This evidence-based guideline addresses important clinical questions that arise in its management. Issues from grading of acne to the topical and systemic management of the disease are reviewed. Suggestions on use are provided based on available evidence.

Emergency Medicine

Chess LE, and Gagnier JJ. Applicable or non-applicable: investigations of clinical heterogeneity in systematic reviews *BMC Med Res Methodol* 2016; 16(1):19. PMID: 26883215. Full Text

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BACKGROUND: Clinical heterogeneity can be defined as differences in participant characteristics, types or timing of outcome measurements and intervention characteristics. Clinical heterogeneity in systematic reviews has the possibility to significantly affect statistical heterogeneity leading to inaccurate conclusions and misled decision making. The aim of this study is to identify to what extent investigators are assessing clinical heterogeneity in both Cochrane and non-Cochrane systematic reviews. METHODS: The most

recent 100 systematic reviews from the top five journals in medicine-JAMA, Archives of Internal Medicine, British Medical Journal, The Lancet, and PLOS Medicine-and the 100 most recently published and/or updated systematic reviews from Cochrane were collected. Various defined items of clinical heterogeneity were extracted from the included reviews. Investigators used chi-squared tests, logarithmic modeling and linear regressions to determine if the presence of such items served as a predictor for clinical heterogeneity when comparing Cochrane to non-Cochrane reviews. Extracted variables include number of studies, number of participants, presence of quantitative synthesis, exploration of clinical heterogeneity, heterogeneous characteristics explored, basis and methods used for investigating clinical heterogeneity, plotting/visual aids, author contact, inferences from clinical heterogeneity investigation, reporting assessment, and the presence of a priori or post-hoc analysis. RESULTS: A total of 317 systematic reviews were considered, of which 199 were in the final analysis. A total of 81 % of Cochrane reviews and 90 % of non-Cochrane reviews explored characteristics that are considered aspects of clinical heterogeneity and also described the methods they planned to use to investigate the influence of those characteristics. Only 1 % of non-Cochrane reviews and 8 % of Cochrane reviews explored the clinical characteristics they initially chose as potential for clinical heterogeneity. Very few studies mentioned clinician training, compliance, brand, co-interventions, dose route, ethnicity, prognostic markers and psychosocial variables as covariates to investigate as potentially clinically heterogeneous. Addressing aspects of clinical heterogeneity was not different between Cochrane and non-Cochrane reviews. CONCLUSIONS: The ability to quantify and compare the clinical differences of trials within a meta-analysis is crucial to determining its applicability and use in clinical practice. Despite Cochrane Collaboration emphasis on methodology, the proportion of reviews that assess clinical heterogeneity is less than those of non-Cochrane reviews. Our assessment reveals that there is room for improvement in assessing clinical heterogeneity in both Cochrane and non-Cochrane reviews.

Endocrinology

Petraszko A, **Siegal D**, **Flynn M**, **Rao SD**, **Peterson E**, and **van Holsbeeck M**. The advantages of tomosynthesis for evaluating bisphosphonate-related atypical femur fractures compared to radiography *Skeletal Radiol* 2016;PMID: 26861160. Full Text

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OBJECTIVE: To investigate the advantages of using tomosynthesis (TS) compared to radiographs in the detection, characterization, and follow-up of bisphosphonate-related atypical femur fractures (BP-AFF). SUBJECTS AND METHODS: Eight patients were identified retrospectively who underwent TS for radiographic findings suspicious for BP-AFF. Two radiologists independently interpreted 15 radiographs and 16 TS examinations, indicating the presence or absence of the following: (1) cortical "beaking" on radiographs, (2) radiolucent fracture line on radiographs, and (3) fracture lucency on TS corresponding to the site of radiographic abnormality. Radiation dose data were calculated for radiographs and TS using Monte Carlo analysis. RESULTS: There was agreement on 100 % of radiographs regarding the presence or absence of a cortical beak. Regarding the presence or absence of a fracture lucency, there was agreement on 100 % of TS examinations (Kappa = 1.0) and 73 % of radiographs (Kappa = 0.40 +/- 0.24). For the 46 % of radiographs in which one or both radiologists did not visualize a fracture line, there was 100 % agreement for the presence of a fracture line on the corresponding TS. The interobserver agreement for fracture line detection was significantly higher for TS than for radiographs (p = 0.012). The

effective radiation dose using TS was approximately 96 % lower compared to radiography. CONCLUSION: TS outperformed radiographs in the detection and characterization of BP-AFF. TS may also have advantages over radiography for BP-AFF follow-up through its unique ability to visualize fracture healing with lower effective radiation doses to the patient.

Endocrinology

Petraszko A, **Siegal D**, **Flynn M**, **Rao SD**, **Peterson E**, and **van Holsbeeck M**. Erratum to: The advantages of tomosynthesis for evaluating bisphosphonate-related atypical femur fractures compared to radiography *Skeletal Radiol* 2016;PMID: 26899141. Full Text

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Hematology, Oncology and the Josephine Ford Cancer Institute

Berdeja JG, Heinrich M, Dakhil S, Goldberg SL, Wadleigh M, Catchatourian R, **Kuriakose P**, Cortes JE, Radich JP, Rizzieri DA, Bonifacio G, Dautaj I, Warsi G, and Mauro MJ. ENESTnext final results: Deep molecular response (MR) with nilotinib (NIL) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) *Blood* 2015; 126(23):4. PMID: Not assigned. Abstract

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Hematology, Oncology and the Josephine Ford Cancer Institute

Farhan SY, **Divine G**, **Neme K**, **Pelland D**, **Wautelet S**, **Mikulandric N**, **Ruemenapp K**, **Peres E**, and **Janakiraman N**. Cytomegalovirus and effect on early chimerism in patients with myeloid disorders undergoing stem cell transplantation using reduced toxicity ablative conditioning regimen *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

[Farhan, Shatha Y.; Neme, Klodiana; Pelland, Danielle; Wautelet, Susan; Mikulandric, Nancy; Ruemenapp, Kenneth; Peres, Edward; Janakiraman, Nalini] Henry Ford Hosp, Stem Cell Transplantat Josephine Ford Canc Inst, Hematol Oncol, Detroit, MI 48202 USA. [Divine, George] Henry Ford Hosp, Detroit, MI 48202 USA.

Cytomegalovirus (CMV) remains a significant cause of morbidity after allogeneic hematopoietic stem cell transplantation (SCT). The influence of CMV on the chimerism in reduced toxicity ablative conditioning

SCT in myeloid disorders is ill defined. A recent report published in Blood by Sellar et al showed that in patients who received alemtuzumab-based regimen, the group of patients who were recipient positive (R+)/ Donor negative (D-) had CMV-specific T cells that are exclusively of recipient origin and significantly influenced the chimerism status toward recipients. To explore the impact of seropositivity and seronegativity of CMV in recipients and donors on early chimerism, we undertook a retrospective analysis of patients with myeloid disorders who received four days of fludarabine and busulfan with or without anti-thymocyte globulin (ATG) at our center in the last 10 years. Methods: Chimerism assay was performed using a quantitative fluorescence-based short tandem repeat-polymerase chain reaction (STR-PCR) with capillary electrophoresis for PCR product resolution. Results: 42 patients were identified and included in the study. All patients received fludarabine (40 mg/m2/day x 4 doses), busulfan (3.2mg/kg/dose IV x 4 doses). Of these 42 patients, 25 had anti-thymocyte globulin. There were 28 male and 14 female patients with a median age of 62 years (range 48-74yrs). Median time to follow up was 8 months (0.8-54 months). Disease risk was considered advanced in 21 patients, intermediate in 4 and early in 17. Median blast number at time of SCT was 5%. Stem cell source included peripheral blood in all patients. There were no primary graft failures. Total recipient cell chimerism showed increase or persistence of recipient chimerism in 5/11 (45%) of R+D- vs 2/6 (33.3%) of R-D- in the group of patients who received ATG, p=1.0, with a mean of recipient chimerism at day 100 of 20.4% in the R+D- group compared to a mean of 17% in the R-D- group. In the group who did not get ATG, recipient chimerism persistence or increase was not that different between the R+D- patients 3/4 (75%) compared to 4/4 (100%) in patients who were seronegative for CMV (R-), p=1.0. The mean of recipient chimerism at day 100 in the R+D- no ATG group was 23.25% with a median of 12% while the mean and median at day 100 in the R- no ATG group were 35.25% and 19.5% respectively (p=0.573).When looking at the persistence or increase in recipient chimerism in the group of patients who were R+D-, in those who got ATG it was 45% increase vs 75% increase in those who did not get ATG (p=0.569) with a median of 12% vs 0% respectively (p=0.49). Also increase or persistence of recipient chimerism was 33.3 % in patients who were R- and got ATG vs 100% in R- no ATG patients (p=0.076)with median at day 100 of 0 vs 19.5% (p=0.098). Conclusion: In this small cohort from a single center, we found that in patients with myeloid disorders who received reduced toxicity ablative conditioning regimen, the group of patients who received ATG, there was no statistically significant increase in recipient chimersim in the R+D- group compared to R-D- group. This is different from what Sellar et al found in a small group of patients who received alemtuzumab. These results may indicate a difference between ATG and alemtuzumab in the effect of CMV seropositivity and negativity on the recipient chimerism, which need to be studied further in a larger retrospective or prospective study. This is especially important in myeloid disorders since persistent or increase in recipient chimerism may identify high-risk patient cohorts who may benefit from additional therapeutic interventions.

Hematology, Oncology and the Josephine Ford Cancer Institute

Jiang F, **Cabrera Fernandez DF**, Church J, **Gulati R**, **Taylor A**, **Menon M**, and **Kuriakose P**. Correlation between peripheral blood counts and day 14 bone marrow biopsy in acute myeloid leukemia during induction chemotherapy *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

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Background Current NCCN guideline recommends that a bone marrow sample be performed 7-10 days (day 14 bone marrow) after completion of induction therapy in newly diagnosed acute myeloid leukemia (AML). However, the value of day 14 bone marrow has been questioned due to the invasive nature of the procedure and lack of specificity pertaining to complete remission in cases of borderline blasts count and cellularity. We examined peripheral blood count and bone marrow from day 0 to day 14, to see if a reduction of peripheral blood correlated and predicted the day 14 bone marrow morphologic changes and complete remission (mCR). Methods We did 10 years retrospective review between year 2004 and 2013 at the Henry Ford Hospital, on patients who had newly diagnosed AML and day 14 bone marrow biopsy. The majority of patients underwent "7+3" or a "7+3"-like regimen for induction chemotherapy. Firstly, we evaluated the relationship of change of peripheral blood count from day 0 to day 14 with blast percentage

and cellularity of bone marrow. Spearman correlations coefficients were computed for each pair of characteristics. Peripheral blood count includes neutrophil (ANC), monocyte, white blood cells (WBC), blast, hemoglobin and platelet. Secondly, we investigated the possible correlation of mCR to peripheral blood and bone marrow changes, using binary univariate logistic regression. mCR as defined by blast percentage <5, absolute neutrophil (ANC) >1000/mm3, platelets>100,000/mm3. Thirdly, we explored differences in peripheral blood counts on day 14 among three bone marrow groups, those with blast percentage <5, 5-20, >20. Results A total of 200 patients were reviewed and 56 patients met the inclusion criteria. Decrease of ANC/WBC correlated with decrease of bone marrow blast/cellularity from day 0 to day 14 (ANC: Blast P ≤ 0.05; ANC: cellularity P ≤ 0.05; WBC: blast P ≤ 0.001, WBC: cellularity P ≤ 0.01). In other words, a larger reduction in ANC/WBC correlated with larger reduction in both blast and cellularity in bone marrow. However, this correlation with bone marrow change was not found in peripheral blast, monocyte, hemoglobin and platelet. We also found that with increasing age, there was less reduction from day 0 to day 14 in bone marrow blast and cellularity. Bone marrow blast and cellularity on day 14 is strongly associated with mCR (P<0.01), the reduction of blast (43.7 +/- 22.86, Odds ratio 1.03 (1.01, 1.06), P=0.012) and cellularity (66.21 +/- 29.98, Odds ratio 1.03 (1.01, 1.05), P=0.003) from day 0 to 14 is also predictive for mCR. Interestingly, there is a trending effect that the reduction of ANC from day 0 to 14 may predict mCR, but it is not statistically significant (Odds ratio 1.22 (1.02, 1.66), P=0.097). The reduction of WBC is not associated with mCR. Furthermore, peripheral blood counts on day 14 are similar among 3 bone marrow groups, those of blast percentage <5, 5-20, and >20% on day 14. Conclusion ANC/WBC decrease from day 0 to day 14 correlated with the decrease in bone marrow blast count and cellularity, and can be used as a predictor for bone marrow change on day 14, but the level of day 14 peripheral blood findings are similar among 3 bone marrow groups (blast percentage <5, 5-20, and >20% on day 14), so it could not be used to predict the level of bone marrow change. Our data confirmed that the significant decrease of bone marrow blast percentage and cellularity from day 0 to 14 predicts mCR. Decrease of ANC from day 0 to 14 may also predict mCR although it is not statistically significant. A larger sample size can be studied in the future to further explore the possibility of using peripheral blood to predict bone marrow changes and mCR. Summary Our data demonstrates a significant reduction of ANC on day 14 after induction therapy in newly diagnosed AML, which correlates with a decrease in bone marrow cellularity and blast percentage. However, a statistically significant association with blast percentage pertaining to mCR was not obtained. In conclusion, while the current findings do not justify replacement of day 14 bone marrow for predicting mCR, further large scale studies are indicated.

Hematology, Oncology and the Josephine Ford Cancer Institute

Machin N, Ragni MV, Malec LM, Brambilla D, Coyle T, Davis JA, Drygalski A, James AH, Jobe SM, Konkle BA, Kouides P, **Kuriakose P**, Ma AD, Majerus EM, Nance D, Neff AT, Philipp CS, Wang TF, and Yaish HM. Von willebrand factor for menorrhagia: A survey and literature review *Blood* 2015; 126(23):4. PMID: Not assigned. Abstract

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Background: von Willebrand disease (VWD) is the most common congenital bleeding disorder. In affected women, menorrhagia is the most common bleeding symptom. Combined oral contraceptives (COCs), the first choice therapy recommended by NHLBI 2007 guidelines, reduce menstrual loss by increasing coagulation factor levels, but at least 30% are unresponsive or intolerant. Non-hormonal options include the antifibrinolytic tranexamic acid (TA), reduces menstrual bleeding by 30-50%, but requires dosing three times a day. Intranasal desmopressin (Stimate) is simpler to use, but ineffective in ~20%. Effective treatment for menorrhagia, thus, remains the greatest unmet health need in women with VWD. Von Willebrand factor (VWF) is used typically when first-line and second-line treatments fail, but few data exist regarding its effectiveness in reducing menorrhagia. Methods: We therefore conducted a survey of U.S. hemophilia treatment centers (HTCs) of current therapy for menorrhagia in VWD, utilizing Centers for Disease Control (CDC) website https://www2a.cdc.gov/ncbddd/htcweb/Main.asp, and the Hemostasis and Research Society (HTRS) site http://htrs.org. To specifically assess the use of VWF concentrate for menorrhagia, we also performed a literature review using medical subject heading (MeSH) search terms "von Willebrand factor," "menorrhagia," and "von Willebrand disease." Statistical analysis was by descriptive statistics. Results: Of 83 surveys distributed to hemophilia treatment centers (HTCs) caring for adult patients, 35 HTC MDs responded (42.2%) but only 20 HTC MDs (24.1%) provided sufficient data for analysis. These 20 HTC MDs reported a total of 1,321 women with VWD age 18-45 years seen during the 3-year period 2011-2014, of whom 816 (61.8%) had menorrhagia. Among these women, the most common first-line therapy was COCs, reported by 50.0% of the 20 HTC MDs, TA in 30.0% and desmopressin (DDAVP) in 20.0%. Overall, including all therapies (first-, second-, third-line), DDAVP was prescribed by 90.0% of the 20 HTC MDs, TA in 80.0%, COCs in 70.0%, aminocaproic acid (amicar) in 25.0%, and the levonorgestrel-releasing intrauterine system (Mirena IUD) in 15.0%. Only 4 HTC MDs (20.0%) prescribed VWF concentrate (VWF) for menorrhagia: all used VWF as third-line therapy after first-line and second-line treatments had failed. In the 13 women with type 1, 2, or 3 VWD and menorrhagia treated with intravenous VWF by these 4 HTC MDs, there was reduction in menorrhagia in all 13 (100%), with no adverse effects. These patients learned intravenous technique and infused VWF at 40-50 IU/kg at home for up to 5 days of menstrual bleeding each cycle, with good acceptability. In the literature search, we identified six published studies, including two prospective clinical trials, two retrospective observational trials, and two observational network studies. A total of 455 subjects with VWD reported in these six studies were treated with either plasma-derived (pdVWF) or recombinant (rVWF) VWF for bleeds. Of these, nearly one-third or 138 (30.3%) were women with type 1, 2, or 3 VWD and menorrhagia who were treated with pdVWF or rVWF at a dose of 36-50 IU/kg for 1-6 days of menstrual cycle bleeding. In these studies, 95-100% of these women reported reduction in menorrhagia, with no reported adverse events. Discussion: This survey and literature review of 151 women with VWD and menorrhagia represent the largest treatment experience to date. DDAVP, TA, and COCs are the most common first-line therapies. VWF is a third-line therapy but safely and effectively reduces menorrhagia in at least 95% of women with VWD. Prospective clinical trials of VWF are needed to establish the minimal dose required for menorrhagia, to determine patient acceptability of this intravenous therapy, and to compare safety and efficacy with standard therapy.

Hematology, Oncology and the Josephine Ford Cancer Institute

Nabi S, Adeel A, **Sudasena D**, Jabbar A, **Bozorgnia F**, and **Kuriakose P**. Impact of blood groups on clinical outcomes in patients with von willebrand disease *Blood* 2015; 126(23):2. PMID: Not assigned. Abstract

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INTRODUCTION Von Willebrand Disease (vWD) is the most common hereditary hemorrhagic disorder with diverse clinical and genetic characteristics. Transmitted as an autosomal dominant trait (except Type III), it is caused primarily by the quantitative or qualitative deficiency of von Willebrand factor (vWF). ABO blood group types can affect the pathology, severity and hence the presentation of this clinically heterogeneous entity as the genes responsible for ABO blood groups also affects vWF levels in the plasma. We conducted a study to analyze and compare different clinico-demographic aspects among O

and non-O blood group patients with Von Willebrand Disease. Our primary aim was to determine the relationship of different blood groups with venous thromboembolism (VTE) in patient with vWD. Our secondary aim was to determine the association of blood groups with different comorbid conditions such as coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic liver disease, chronic kidney disease etc. in patients with vWD. METHODS A retrospective review was carried out to include all patients diagnosed with Von Willebrand Disease from year 2002 to 2012. Patient population was obtained by using International Classification of Diseases, 9th revision (ICD9) codes. Data was collected with the help of electronic medical records. Multiple clinical variables and demographic characteristics of Von Willebrand Disease patients (n=381) were analyzed and compared between those with type O blood group (205 patients; 54%) and those with type non-O blood groups (176 patients; 46%). Univariate logistic regression was used to obtain crude odds ratios. Predictors with statistically significant p-values were included in a multivariable logistic regression model in order to yield adjusted odds ratio. Statistical significance was set at $p<0.05$ RESULTS Patients with O blood groups were less likely to develop VTE (OR 0.29, 95% CI 0.16-0.52, $p < 0.001$) as compared to Non-O blood groups in which the prevalence of VTE was much higher (25% vs. 9%). Additionally, patients with O blood groups had relatively lower factor 8 activity (125.9±90.8%; OR 0.99, 95% CI 0.99-1.00, $p = 0.018$) when compared with Non-O blood groups (168.5±120.6%). Patients with O-blood group had significant, life threatening bleeds at an early age (40.4±20.8 years; OR 0.99, 95% CI 0.97-1.00, $p = 0.008$) when compared with patients with type non-O blood group (Age 47.1±21.9 years). Additionally, O-Blood groups were related to a lesser prevalence of cerebrovascular disease (OR 0.48, 95% CI 0.29-0.79, $p = 0.004$) and peripheral vascular disease (OR 0.47, 95% CI 0.25-0.87, $p = 0.015$) as compared to Non-O blood groups. DISCUSSION Our study consolidates the fact that vWD patients with O blood group have a lesser risk of developing VTE as compared to non-O blood group patients. Additionally, strokes and peripheral vascular disease is also seen less frequently in O blood groups in patients with Von Willebrand disease. These results suggest that the genes responsible for ABO blood groups also have a significant effect on clinical outcomes in patients with vWD. There are multiple proposed mechanisms to explain this association including presence of ABO antigens on several platelet glycoproteins and glycosphingolipids as well as on the surface of vascular endothelium. More sophisticated, large-scale studies are needed to strengthen the associations we observed in our retrospective study.

Hematology, Oncology and the Josephine Ford Cancer Institute

Nabi S, **Kahlon P**, and **Kuriakose P**. Analyzing multiple risk factors in patients with sarcomas. A case-control study *Indian J Cancer* 2015; 52(3):337-342. PMID: 26905132. Full Text

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CONTEXT: Sarcomas are a rare group of malignancies. Very little is known about their risk factors. AIMS: The aim was to evaluate different risk factors in patients with sarcomas and to determine the median age at diagnosis, differences in race, gender, histological grades and staging in sarcoma patients. SETTINGS AND DESIGN: A retrospective case-control study was conducted in a tertiary care hospital in the USA. This included patients diagnosed with sarcomas from year 2000 to 2010. MATERIALS AND METHODS: Data were extracted with the help of electronic medical records using International Classification of Diseases, Ninth revision codes. Healthy, matched controls were randomly selected from the same tertiary care hospital database. STATISTICAL ANALYSIS: Univariate comparisons between cases and controls were done using a two-group independent t-test for age and using Chi-square tests for the categorical variables. In order to identify possible independent predictors of sarcomas, a multiple logistic regression model was constructed using sarcoma status as the dependent variable and using, initially, all variables with a univariate $P < 0.2$ as independent variables. Variables were reduced in a manual stepwise manner to arrive at a final model. Statistical significance was set at $P < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). RESULTS: A total of 425 sarcoma patients and 429 age, sex and race matched healthy controls were analyzed in this study. We found that a history of smoking and alcoholism was significantly associated with sarcomas. We also found that the history of cancer in first-degree relatives had a significant relationship. In addition, patients with sarcomas are more likely to have a history of another malignancy when compared with controls. CONCLUSIONS: Smoking and alcohol are potential risk factors for sarcomas. In addition, a history of cancer in the first-degree relative is

also a potential risk factor. Patients with sarcomas are likely to have a history of another malignancy when compared with controls.

Hematology, Oncology and the Josephine Ford Cancer Institute
Bertin MJ, Demirkiran O, Navarro G, Moss NA, Lee J, Goldgof GM, Vigil E, Winzeler EA, **Valeriote FA**, and Gerwick WH. Kalkipyrone B, a marine cyanobacterial gamma-pyrone possessing cytotoxic and anti-fungal activities *Phytochemistry* 2016; 122:113-118. PMID: 26632528. Article Request Form

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Bioassay-guided fractionation of two marine cyanobacterial extracts using the H-460 human lung cancer cell line and the OVC-5 human ovarian cancer cell line led to the isolation of three related alpha-methoxy-beta, beta'-dimethyl-gamma-pyrones each containing a modified alkyl chain, one of which was identified as the previously reported kalkipyrone and designated kalkipyrone A. The second compound was an analog designated kalkipyrone B. The third was identified as the recently reported yoshinone A, also isolated from a marine cyanobacterium. Kalkipyrone A and B were obtained from a field-collection of the cyanobacterium Leptolyngbya sp. from Fagasa Bay, American Samoa, while yoshinone A was isolated from a field-collection of cyanobacteria (cf. Schizothrix sp.) from Panama. One-dimensional and two-dimensional NMR experiments were used to determine the overall structures and relative configurations of the kalkipyrones, and the absolute configuration of kalkipyrone B was determined by (1)H NMR analysis of diastereomeric Mosher's esters. Kalkipyrone A showed good cytotoxicity to H-460 human lung cancer cells (EC50=0.9muM), while kalkipyrone B and yoshinone A were less active (EC50=9.0muM and >10muM, respectively). Both kalkipyrone A and B showed moderate toxicity to Saccharomyces cerevisiae ABC16-Monster strain (IC50=14.6 and 13.4muM, respectively), whereas yoshinone A was of low toxicity to this yeast strain (IC50=63.8muM).

Hematology, Oncology and the Josephine Ford Cancer Institute
Harvey RD, Gore L, **Wang D**, Mita A, Sharma S, Nemunaitis J, Papadopoulos K, Pinchasik D, Ou Y, Demirhan E, Cutler RE, and Tsimberidou AM. A phase I study to assess food effect on oprozomib in patients with advanced malignancies *Clin Pharmacol Ther* 2016; 99:S98-S99. PMID: Not assigned. Abstract

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BACKGROUND: Oprozomib (OPZ) is a selective oral proteasome inhibitor in development, with activity in multiple myeloma. To optimize tolerability, many patients take OPZ with food. We conducted a study to characterize the effect of different prandial states and meal fat content on the relative bioavailability of OPZ compared to the fasted state. METHODS: OPZ Extended Release Tablet (270 mg) was given to 22 subjects with advanced malignancies, in a three-way crossover design. Each OPZ dose was given fasting, and following a low-fat meal (<20% calories from fat) or high-fat meal (~50% calories from fat). Sequence was randomly assigned with a 1 to 6 day washout between OPZ doses. Pharmacokinetic (PK) sampling occurred pre-dose and 0.5, 1, 2, 3, 4, 6, 8 and 24 hours after OPZ dosing. RESULTS: Fasting, low-fat, and high-fat meals were completed by 20, 20 and 14 subjects, respectively. Compared to the fasted state, the low-fat meal produced mean ratios in OPZ area under the concentration-time curve (AUC0-t) of 111% (90% confidence interval [CI] of 93% to 133%) and maximum concentration (Cmax) of 121% (90% CI of 97% to 150%). The high-fat meal produced mean ratios in OPZ AUC0-t of 130% (90% CI of 106% to 159%) and Cmax of 98% (90% CI of 76% to 125%). Increased bioavailability in either fed state was associated with increased PK variability. The %CV (geometric means) for fasting, low-fat, and high-fat meals were 73%, 77% and 90% for AUC, and 59%, 76% and 82% for Cmax, respectively. Median Tmax increased from 2 hr in the fasting state to 3 hr with high-fat meals. CONCLUSION: For OPZ Extended Release Tablets, a mean increase of 30% in AUC was observed with a high-fat meal, compared with fasting. PK variability appears to decrease in the fasted state, suggesting that dosing in the fasted state may achieve more consistent OPZ exposure.

Hematology, Oncology and the Josephine Ford Cancer Institute
Hwang C, Sethi S, Heilbrun LK, **Gupta NS**, **Chitale DA**, Sakr WA, **Menon M**, **Peabody JO**, Smith DW, Sarkar FH, and Heath EI. Anti-androgenic activity of absorption-enhanced 3, 3'-diindolylmethane in prostatectomy patients *Am J Transl Res* 2016; 8(1):166-176. PMID: Not assigned. Full Text

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Consumption of cruciferous vegetables is associated with a decreased risk of developing prostate cancer. Antineoplastic effects of cruciferous vegetables are attributable to bioactive indoles, most prominently, 3, 3'-diindolylmethane (DIM). In addition to effects on proliferation and apoptosis, DIM acts as an antiandrogen in prostate cancer cell lines. This study characterized the effects of prostatic DIM on the androgen receptor (AR) in patients with prostate cancer. Men with localized prostate cancer were treated with a specially formulated DIM capsule designed for enhanced bioavailability (BR-DIM) at a dose of 225 mg orally twice daily for a minimum of 14 days. DIM levels and AR activity were assessed at the time of prostatectomy. Out of 28 evaluable patients, 26 (93%) had detectable prostatic DIM levels, with a mean concentration of 14.2 ng/gm. The mean DIM plasma level on BR-DIM therapy was 9.0 ng/mL; levels were undetectable at baseline and in follow-up samples. AR localization in the prostate was assessed with immunohistochemistry. After BR-DIM therapy, 96% of patients exhibited exclusion of the AR from the cell nucleus. In contrast, in prostate biopsy samples obtained prior to BR-DIM therapy, no patient exhibited AR nuclear exclusion. Declines in PSA were observed in a majority of patients (71%). Compliance was excellent and toxicity was minimal. In summary, BR-DIM treatment resulted in reliable prostatic DIM levels and anti-androgenic biologic effects at well tolerated doses. These results support further investigation of BR-DIM as a chemopreventive and therapeutic agent in prostate cancer.

Hematology, Oncology and the Josephine Ford Cancer Institute
Rybicki BA, Rundle A, Kryvenko ON, **Mitrache N**, Do KC, **Jankowski M**, **Chitale DA**, **Trudeau S**, Belinsky SA, and Tang D. Methylation in benign prostate and risk of disease progression in men subsequently diagnosed with prostate cancer *Int J Cancer* 2016;PMID: 26860439. Full Text

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In DNA from prostate tumors, methylation patterns in gene promoter regions can be a biomarker for disease progression. It remains unclear whether methylation patterns in benign prostate tissue-prior to malignant transformation-may provide similar prognostic information. To determine whether early methylation events predict prostate cancer outcomes, we evaluated histologically benign prostate specimens from 353 men who eventually developed prostate cancer and received "definitive" treatment (radical prostatectomy [58%] or radiation therapy [42%]). Cases were drawn from a large hospital-based cohort of men with benign prostate biopsy specimens collected between 1990 and 2002. Risk of disease progression associated with methylation was estimated using time-to-event analyses. Average follow-up was over 5 years; biochemical recurrence (BCR) occurred in 91 cases (26%). In White men, methylation of the APC gene was associated with increased risk of BCR, even after adjusting for standard clinical risk factors for prostate cancer progression (adjusted hazard ratio (aHR)=2.26; 95%CI 1.23-4.16). APC methylation was most strongly associated with a significant increased risk of BCR in White men with low prostate specific antigen at cohort entry (HR=3.66; 95%CI 1.51-8.85). In additional stratified analyses, we found that methylation of the RARB gene significantly increased risk of BCR in African American cases who demonstrated methylation of at least one of the other four genes under study (HR=3.80; 95%CI 1.07-13.53). These findings may have implications in the early identification of aggressive prostate cancer as well as reducing unnecessary medical procedures and emotional distress for men who present with markers of indolent disease. This article is protected by copyright. All rights reserved.

Hematology, Oncology and the Josephine Ford Cancer Institute
Tsimberidou AM, Ou Y, Xu Y, Wang Z, Harvey RD, Mita A, Sharma S, Papadopoulos K, **Wang D**, Pinchasik D, Demirhan E, Cutler RE, and Gore L. A phase I study of oprozomib to assess drug-drug interaction with midazolam in patients with advanced malignancies *Clin Pharmacol Ther* 2016; 99:S100-S100. PMID: Not assigned. Abstract

[Tsimberidou, A. M.] Univ Texas MD Anderson Canc Ctr, Houston, TX 77030 USA. [Ou, Y.; Wang, Z.; Pinchasik, D.; Demirhan, E.; Cutler, R. E., Jr.] Onyx Pharmaceut Inc, San Francisco, CA USA. [Xu, Y.] Amgen Inc, Thousand Oaks, CA 91320 USA. [Harvey, R. D.] Winship Canc Inst, Atlanta, GA USA. [Mita, A.] Cedars Sinai Med Ctr, Los Angeles, CA 90048 USA. [Sharma, S.] Univ Utah, Hlth Sci Ctr, Huntsman Canc Inst, Salt Lake City, UT USA. [Papadopoulos, K.] South Texas Accelerated Res Therapeut, San Antonio, TX USA. [Wang, D.] Henry Ford Hlth Syst, Detroit, MI USA. [Gore, L.] Univ Colorado, Ctr Canc, Aurora, CO USA.

Hemophilia and Thrombosis Treatment Center
McLaughlin JM, **Lambing A**, Witkop ML, Anderson TL, Munn J, and Tortella B. Racial differences in chronic pain and quality of life among adolescents and young adults with moderate or severe hemophilia *J Racial Ethn Health Disparities* 2016; 3(1):11-20. PMID: 26896101. Full Text

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BACKGROUND AND OBJECTIVE: We explored racial differences in adherence to recommended clotting factor treatment regimens, chronic pain, and quality of life (QoL) among adolescents and young adults (AYAs) diagnosed with moderate or severe hemophilia. METHODS: A convenience sample of hemophilia patients aged 13-25 years completed an online cross-sectional survey in 2012. Chronic pain was measured using the revised Faces Pain Scale (FPS-R) and dichotomized as high (FPS-R >/= 4) or low (FPS-R < 4). QoL was measured with the SF-36. RESULTS: Of 80 AYA participants (79 male), most had severe disease (91 %) and hemophilia A (91 %). Most were white (76 %) and non-Hispanic (88 %). At the

univariate level, compared to whites, non-whites were more likely to have produced an inhibitor against clotting factor treatment (74 vs 38 %, p < .01), less likely to have commercial health insurance (16 vs 63 %, p < .001), more likely to report high levels of chronic pain (FPS-R >/= 4) (63 vs 26 %, p < .01), and had lower SF-36 physical composite summary (PCS) scores. Adjusted logistic and quantile regression modeling, respectively, revealed that non-whites were 5.31 (95 % CI 1.62, 17.4; p < .01) times more likely to report high chronic pain and had median PCS scores that were 26.0 (95 % CI 11.0, 40.9; p < .01) points lower than whites. CONCLUSIONS: Targeted efforts to prevent and manage chronic pain among non-white AYAs with moderate or severe hemophilia are necessary. After accounting for demographic and clinical differences, there were no racial differences in adherence to recommended clotting factor treatment regimens; however, non-whites were more than five times more likely to report high levels of chronic pain, which predicted worse overall physical QoL, bodily pain, physical and social functioning, and greater role limitations due to physical health.

Hypertension and Vascular Research

Gonzalez-Vicente A, **Saikumar JH**, **Massey KJ**, Hong NJ, Dominici FP, **Carretero OA**, and Garvin JL. Angiotensin II stimulates superoxide production by nitric oxide synthase in thick ascending limbs *Physiol Rep* 2016; 4(4)PMID: 26884476. Full Text

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Angiotensin II (Ang II) causes nitric oxide synthase (NOS) to become a source of superoxide (O2 (-)) via a protein kinase C (PKC)-dependent process in endothelial cells. Ang II stimulates both NO and O2 (-) production in thick ascending limbs. We hypothesized that Ang II causes O2 (-) production by NOS in thick ascending limbs via a PKC-dependent mechanism. NO production was measured in isolated rat thick ascending limbs using DAF-FM, whereas O2 (-) was measured in thick ascending limb suspensions using the lucigenin assay. Consistent stimulation of NO was observed with 1 nmol/L Ang II (P < 0.001; n = 9). This concentration of Ang II-stimulated O2 (-) production by 50% (1.77 +/- 0.26 vs. 2.62 +/- 0.36 relative lights units (RLU)/s/mug protein; P < 0.04; n = 5). In the presence of the NOS inhibitor L-NAME, Ang II-stimulated O2 (-) decreased from 2.02 +/- 0.29 to 1.10 +/- 0.11 RLU/s/mug protein (P < 0.01; n = 8). L-arginine alone did not change Ang II-stimulated O2 (-) (2.34 +/- 0.22 vs. 2.29 +/- 0.29 RLU/s/mug protein; n = 5). In the presence of Ang II plus the PKC alpha/beta1 inhibitor Go 6976, L-NAME had no effect on O2 (-) production (0.78 +/- 0.23 vs. 0.62 +/- 0.11 RLU/s/mug protein; n = 7). In the presence of Ang II plus apocynin, a NADPH oxidase inhibitor, L-NAME did not change O2 (-) (0.59 +/- 0.04 vs. 0.61 +/- x0.08 RLU/s/mug protein; n = 5). We conclude that: (1) Ang II causes NOS to produce O2 (-) in thick ascending limbs via a PKC- and NADPH oxidase-dependent process; and (2) the effect of Ang II is not due to limited substrate.

Hypertension and Vascular Research

Gordish KL, and **Beierwaltes WH**. Chronic resveratrol reverses a mild angiotensin II-induced pressor effect in a rat model *Integr Blood Press Control* 2016; 9:23-31. PMID: 26869812. Full Text

Department of Physiology, Wayne State School of Medicine, Henry Ford Hospital, Detroit, MI, USA.

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Resveratrol is reported to reduce blood pressure in animal models of hypertension, but the mechanisms are unknown. We have shown that resveratrol infusion increases sodium excretion. We hypothesized that chronic ingestion of resveratrol would reduce angiotensin II (Ang II)-induced increases in blood pressure by decreasing oxidative stress and by also decreasing sodium reabsorption through a nitric oxide-dependent mechanism. We infused rats with vehicle or 80 mug Ang II/d over 4 weeks. Vehicle or Ang II-infused rats were individually housed, pair fed, and placed on a diet of normal chow or normal chow plus 146 mg resveratrol/d. Groups included 1) control, 2) resveratrol-fed, 3) Ang II-treated, and 4) Ang II plus resveratrol. Systolic blood pressure was measured by tail cuff. During the 4th week, rats were placed in metabolic caging for urine collection. NO2/NO3 and 8-isoprostane excretion were measured. Ang II increased systolic blood pressure in the 1st week by +14+/-5 mmHg (P<0.05) in Group 3 and +10+/-3 mmHg (P<0.05) in Group 4, respectively. Blood pressure was unchanged in Groups 1 and 2. After 4 weeks, blood pressure remained elevated in Group 3 rats with Ang II (+9+/-3 mmHg, P<0.05), but in Group 4, blood pressure was no longer elevated (+2+/-2 mmHg). We found no significant differences between the groups in sodium excretion or cumulative sodium balance (18.49+/-0.12, 17.75+/-0.16, 17.97+/-0.17, 18.46+/-0.18 muEq Na+/7 d in Groups 1-4, respectively). Urinary excretion of NO2/NO3 in the four groups was 1) 1631+/-207 mumol/24 h, 2) 1045+/-236 mumol/24 h, 3) 1490+/-161 mumol/24 h, and 4) 609+/-17 mumol/24 h. 8-Isoprostane excretion was 1) 63.85+/-19.39 nmol/24 h, 2) 73.57+/-22.02 nmol/24 h, 3) 100.69+/-37.62 nmol/24 h, and 4) 103.00+/-38.88 nmol/24 h. We conclude that chronic resveratrol supplementation does not blunt Ang II-increased blood pressure, and while resveratrol has mild depressor effects, these do not seem to be due to natriuresis or enhanced renal nitric oxide synthesis.

Internal Medicine

El-Refai M, **Hrobowski T**, **Peterson EL**, **Wells K**, Spertus JA, **Williams LK**, and **Lanfear DE**. Race and association of angiotensin converting enzyme/angiotensin receptor blocker exposure with outcome in heart failure *J Cardiovasc Med (Hagerstown)* 2015; 16(9):591-596. PMID: 24842464. Full Text

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PURPOSE: Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been established as a mainstay of heart failure treatment. Current data are limited and conflicting regarding the consistency of ACE/ARB benefit across race groups in heart failure. This study aims to clarify this point. METHODS: This was a retrospective study of insured patients with a documented ejection fraction of less than 50%, hospitalized for heart failure between January 2000 and June 2008. Pharmacy claims data were used to estimate ACE/ARB exposure over 6-month rolling windows. The association between ACE/ARB exposure and all-cause hospitalization or death was assessed by proportional hazards regression, with adjustment for baseline covariates and beta-blocker exposure. Further analyses were stratified by race, and included an ACE/ARB x Race interaction term. RESULTS: A total of 1095 patients met inclusion criteria (619 African-American individuals). Median follow-up was 2.1 years. In adjusted models, ACE/ARB exposure was associated with lower risk of death or hospitalization in both groups (African-Americans hazard ratio 0.47, P < 0.001; whites hazard ratio 0.55, P < 0.001). A formal test for interaction was consistent with similar effects in each group (P = 0.861, beta = 0.04). CONCLUSION: ACE/ARB exposure was equally associated with a protective effect in preventing death or rehospitalization among heart failure patients with systolic dysfunction in both African-American patients and whites.

Internal Medicine

Jiang F, **Cabrera Fernandez DF**, Church J, **Gulati R**, **Taylor A**, **Menon M**, and **Kuriakose P**. Correlation between peripheral blood counts and day 14 bone marrow biopsy in acute myeloid leukemia during induction chemotherapy *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

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Background Current NCCN guideline recommends that a bone marrow sample be performed 7-10 days (day 14 bone marrow) after completion of induction therapy in newly diagnosed acute myeloid leukemia (AML). However, the value of day 14 bone marrow has been questioned due to the invasive nature of the procedure and lack of specificity pertaining to complete remission in cases of borderline blasts count and cellularity. We examined peripheral blood count and bone marrow from day 0 to day 14, to see if a reduction of peripheral blood correlated and predicted the day 14 bone marrow morphologic changes and complete remission (mCR). Methods We did 10 years retrospective review between year 2004 and 2013 at the Henry Ford Hospital, on patients who had newly diagnosed AML and day 14 bone marrow biopsy. The majority of patients underwent "7+3" or a "7+3"-like regimen for induction chemotherapy. Firstly, we evaluated the relationship of change of peripheral blood count from day 0 to day 14 with blast percentage and cellularity of bone marrow. Spearman correlations coefficients were computed for each pair of characteristics. Peripheral blood count includes neutrophil (ANC), monocyte, white blood cells (WBC), blast, hemoglobin and platelet. Secondly, we investigated the possible correlation of mCR to peripheral blood and bone marrow changes, using binary univariate logistic regression. mCR as defined by blast percentage <5, absolute neutrophil (ANC) >1000/mm3, platelets>100,000/mm3. Thirdly, we explored differences in peripheral blood counts on day 14 among three bone marrow groups, those with blast percentage <5, 5-20, >20. Results A total of 200 patients were reviewed and 56 patients met the inclusion criteria. Decrease of ANC/WBC correlated with decrease of bone marrow blast/cellularity from day 0 to day 14 (ANC: Blast $P \leq 0.05$; ANC: cellularity $P \leq 0.05$; WBC: blast $P \leq 0.001$, WBC: cellularity $P \leq 0.01$). In other words, a larger reduction in ANC/WBC correlated with larger reduction in both blast and cellularity in bone marrow. However, this correlation with bone marrow change was not found in peripheral blast, monocyte, hemoglobin and platelet. We also found that with increasing age, there was less reduction from day 0 to day 14 in bone marrow blast and cellularity. Bone marrow blast and cellularity on day 14 is strongly associated with mCR ($P<0.01$), the reduction of blast (43.7 +/- 22.86, Odds ratio 1.03 (1.01, 1.06), P=0.012) and cellularity (66.21 +/- 29.98, Odds ratio 1.03 (1.01, 1.05), P=0.003) from day 0 to 14 is also predictive for mCR. Interestingly, there is a trending effect that the reduction of ANC from day 0 to 14 may predict mCR, but it is not statistically significant (Odds ratio 1.22 (1.02, 1.66), P=0.097). The reduction of WBC is not associated with mCR. Furthermore, peripheral blood counts on day 14 are similar among 3 bone marrow groups, those of blast percentage <5, 5-20, and >20% on day 14. Conclusion ANC/WBC decrease from day 0 to day 14 correlated with the decrease in bone marrow blast count and cellularity, and can be used as a predictor for bone marrow change on day 14, but the level of day 14 peripheral blood findings are similar among 3 bone marrow groups (blast percentage <5, 5-20, and >20% on day 14), so it could not be used to predict the level of bone marrow change. Our data confirmed that the significant decrease of bone marrow blast percentage and cellularity from day 0 to 14 predicts mCR. Decrease of ANC from day 0 to 14 may also predict mCR although it is not statistically significant. A larger sample size can be studied in the future to further explore the possibility of using peripheral blood to predict bone marrow changes and mCR. Summary Our data demonstrates a significant reduction of ANC on day 14 after induction therapy in newly diagnosed AML, which correlates with a decrease in bone marrow cellularity and blast percentage. However, a statistically significant association with blast percentage pertaining to mCR was not obtained. In conclusion, while the current findings do not justify replacement of day 14 bone marrow for predicting mCR, further large scale studies are indicated.

Internal Medicine

Nabi S, Adeel A, **Sudasena D**, Jabbar A, **Bozorgnia F**, and **Kuriakose P**. Impact of blood groups on clinical outcomes in patients with von willebrand disease *Blood* 2015; 126(23):2. PMID: Not assigned. Abstract

[Nabi, Shahzaib; Sudasena, Daryl; Bozorgnia, Farshid] Henry Ford Hlth Syst, Internal Med, Detroit, MI USA. [Adeel, Arshad] Weill Cornell Univ, Hamad Med Corp, Internal Med, Doha, Qatar. [Jabbar, Absia] Univ Hlth Sci, Psychiat, Lahore, Pakistan. [Kuriakose, Philip] Henry Ford Hlth Syst, Detroit, MI USA.

INTRODUCTION Von Willebrand Disease (vWD) is the most common hereditary hemorrhagic disorder with diverse clinical and genetic characteristics. Transmitted as an autosomal dominant trait (except Type III), it is caused primarily by the quantitative or qualitative deficiency of von Willebrand factor (vWF). ABO blood group types can affect the pathology, severity and hence the presentation of this clinically heterogeneous entity as the genes responsible for ABO blood groups also affects vWF levels in the plasma. We conducted a study to analyze and compare different clinico-demographic aspects among O and non-O blood group patients with Von Willebrand Disease. Our primary aim was to determine the relationship of different blood groups with venous thromboembolism (VTE) in patient with vWD. Our secondary aim was to determine the association of blood groups with different comorbid conditions such as coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic liver disease, chronic kidney disease etc. in patients with vWD. METHODS A retrospective review was carried out to include all patients diagnosed with Von Willebrand Disease from year 2002 to 2012. Patient population was obtained by using International Classification of Diseases, 9th revision (ICD9) codes. Data was collected with the help of electronic medical records. Multiple clinical variables and demographic characteristics of Von Willebrand Disease patients (n=381) were analyzed and compared between those with type O blood group (205 patients; 54%) and those with type non-O blood groups (176 patients; 46%). Univariate logistic regression was used to obtain crude odds ratios. Predictors with statistically significant p-values were included in a multivariable logistic regression model in order to yield adjusted odds ratio. Statistical significance was set at $p<0.05$ RESULTS Patients with O blood groups were less likely to develop VTE (OR 0.29, 95% CI 0.16-0.52, $p < 0.001$) as compared to Non-O blood groups in which the prevalence of VTE was much higher (25% vs. 9%). Additionally, patients with O blood groups had relatively lower factor 8 activity (125.9±90.8%; OR 0.99, 95% CI 0.99-1.00, $p = 0.018$) when compared with Non-O blood groups (168.5±120.6%). Patients with O-blood group had significant, life threatening bleeds at an early age (40.4±20.8 years; OR 0.99, 95% CI 0.97-1.00, $p = 0.008$) when compared with patients with type non-O blood group (Age 47.1±21.9 years). Additionally, O-Blood groups were related to a lesser prevalence of cerebrovascular disease (OR 0.48, 95% CI 0.29-0.79, $p = 0.004$) and peripheral vascular disease (OR 0.47, 95% CI 0.25-0.87, $p = 0.015$) as compared to Non-O blood groups. DISCUSSION Our study consolidates the fact that vWD patients with O blood group have a lesser risk of developing VTE as compared to non-O blood group patients. Additionally, strokes and peripheral vascular disease is also seen less frequently in O blood groups in patients with Von Willebrand disease. These results suggest that the genes responsible for ABO blood groups also have a significant effect on clinical outcomes in patients with vWD. There are multiple proposed mechanisms to explain this association including presence of ABO antigens on several platelet glycoproteins and glycosphingolipids as well as on the surface of vascular endothelium. More sophisticated, large-scale studies are needed to strengthen the associations we observed in our retrospective study.

Internal Medicine

Nabi S, **Kahlon P**, and **Kuriakose P**. Analyzing multiple risk factors in patients with sarcomas. A case-control study *Indian J Cancer* 2015; 52(3):337-342. PMID: 26905132. Full Text

Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan 48202, United States.

CONTEXT: Sarcomas are a rare group of malignancies. Very little is known about their risk factors. AIMS: The aim was to evaluate different risk factors in patients with sarcomas and to determine the median age at diagnosis, differences in race, gender, histological grades and staging in sarcoma patients. SETTINGS AND DESIGN: A retrospective case-control study was conducted in a tertiary care hospital in the USA.

This included patients diagnosed with sarcomas from year 2000 to 2010. MATERIALS AND METHODS: Data were extracted with the help of electronic medical records using International Classification of Diseases, Ninth revision codes. Healthy, matched controls were randomly selected from the same tertiary care hospital database. STATISTICAL ANALYSIS: Univariate comparisons between cases and controls were done using a two-group independent t-test for age and using Chi-square tests for the categorical variables. In order to identify possible independent predictors of sarcomas, a multiple logistic regression model was constructed using sarcoma status as the dependent variable and using, initially, all variables with a univariate $P < 0.2$ as independent variables. Variables were reduced in a manual stepwise manner to arrive at a final model. Statistical significance was set at $P < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). RESULTS: A total of 425 sarcoma patients and 429 age, sex and race matched healthy controls were analyzed in this study. We found that a history of smoking and alcoholism was significantly associated with sarcomas. We also found that the history of cancer in first-degree relatives had a significant relationship. In addition, patients with sarcomas are more likely to have a history of another malignancy when compared with controls. CONCLUSIONS: Smoking and alcohol are potential risk factors for sarcomas. In addition, a history of cancer in the first-degree relative is also a potential risk factor. Patients with sarcomas are likely to have a history of another malignancy when compared with controls.

Internal Medicine

Batra AK, Alomari A, Chilvery AK, Bandyopadhyay A, and **Grover K**. Piezoelectric power harvesting devices: An overview *Adv Sci Eng Med* 2016; 8(1):1-12. PMID: Not assigned. Article Request Form

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This article reviews the fundamental behavior of piezoelectric for applications in sensors and energy harvesting technologies. In fact, many devices and applications are evolving day-to-day depending on smart materials technology such as, scanning probe microscope (SPM) and cigarette lighters. Today, vibration based energy harvesting via piezoelectric materials has become one of the most prominent ways to provide a limited energy for self-powered wireless sensor and low power electronics. This review provides an insight that involves mathematical modeling of constitutive equations, lumped parameter model, mechanisms of piezoelectric energy conversion, and operating principle of a piezoelectric energy harvesting system. This article also focuses on the dielectric, piezoelectric, mechanical, and pyroelectric properties of piezoelectric and pyroelectric materials open to use from single crystal such as PMN-PT through ceramics PZT and polymers such as PVDF. Recent important literature is also reviewed along with energy harvesting devices proposed for use in industrial and biomedical applications.

Internal Medicine

Essenmacher AC, Khurram N, and **Bismack GT**. A case of reactive arthritis due to colitis *J Community Hosp Intern Med Perspect* 2016; 6(1):30151. PMID: 26908381. Full Text

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Reactive arthritis is an acute, aseptic, inflammatory arthropathy following an infectious process but removed from the site of primary infection. It is often attributed to genitourinary and enteric pathogens, such as Chlamydia, Salmonella, Shigella, Campylobacter, and Yersinia, in susceptible individuals. An uncommon and less recognized cause of this disease is preceding colonic infection with Clostridium difficile, an organism associated with pseudomembranous colitis and diarrhea in hospitalized patients and those recently exposed to antibiotics. Recognition of this association may be complicated by non-specific presentation of diarrhea, the interval between gastrointestinal and arthritic symptoms, and the wide

differential in mono- and oligoarthritis. We present the case of a 61-year-old, hospitalized patient recently treated for C. difficile colitis who developed sudden, non-traumatic, right knee pain and swelling. Physical examination and radiographs disclosed joint effusion, and sterile aspiration produced cloudy fluid with predominant neutrophils and no growth on cultures. Diagnostic accuracy is enhanced by contemporaneous laboratory investigations excluding other entities such as gout and rheumatoid arthritis and other infections that typically precede reactive arthritis. Contribution of Clostridium infection to reactive arthritis is an obscure association frequently difficult to prove, but this organism is warranted inclusion in the differential of reactive arthritis.

Internal Medicine

Gonzalez-Vicente A, **Saikumar JH**, **Massey KJ**, Hong NJ, Dominici FP, **Carretero OA**, and Garvin JL. Angiotensin II stimulates superoxide production by nitric oxide synthase in thick ascending limbs *Physiol Rep* 2016; 4(4)PMID: 26884476. Full Text

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Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, Cleveland, Ohio Department of Internal Medicine, Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, MI.

Angiotensin II (Ang II) causes nitric oxide synthase (NOS) to become a source of superoxide (O2 (-)) via a protein kinase C (PKC)-dependent process in endothelial cells. Ang II stimulates both NO and O2 (-) production in thick ascending limbs. We hypothesized that Ang II causes O2 (-) production by NOS in thick ascending limbs via a PKC-dependent mechanism. NO production was measured in isolated rat thick ascending limbs using DAF-FM, whereas O2 (-) was measured in thick ascending limb suspensions using the lucigenin assay. Consistent stimulation of NO was observed with 1 nmol/L Ang II ($P < 0.001$; $n = 9$). This concentration of Ang II-stimulated O2 (-) production by 50% (1.77 +/- 0.26 vs. 2.62 +/- 0.36 relative lights units (RLU)/s/mug protein; $P < 0.04$; $n = 5$). In the presence of the NOS inhibitor L-NAME, Ang II-stimulated O2 (-) decreased from 2.02 +/- 0.29 to 1.10 +/- 0.11 RLU/s/mug protein ($P < 0.01$; $n = 8$). L-arginine alone did not change Ang II-stimulated O2 (-) (2.34 +/- 0.22 vs. 2.29 +/- 0.29 RLU/s/mug protein; $n = 5$). In the presence of Ang II plus the PKC alpha/beta1 inhibitor Go 6976, L-NAME had no effect on O2 (-) production (0.78 +/- 0.23 vs. 0.62 +/- 0.11 RLU/s/mug protein; $n = 7$). In the presence of Ang II plus apocynin, a NADPH oxidase inhibitor, L-NAME did not change O2 (-) (0.59 +/- 0.04 vs. 0.61 +/- x0.08 RLU/s/mug protein; $n = 5$). We conclude that: (1) Ang II causes NOS to produce O2 (-) in thick ascending limbs via a PKC- and NADPH oxidase-dependent process; and (2) the effect of Ang II is not due to limited substrate.

Internal Medicine

Gordish KL, and **Beierwaltes WH**. Chronic resveratrol reverses a mild angiotensin II-induced pressor effect in a rat model *Integr Blood Press Control* 2016; 9:23-31. PMID: 26869812. Full Text

Department of Physiology, Wayne State School of Medicine, Henry Ford Hospital, Detroit, MI, USA.
Department of Physiology, Wayne State School of Medicine, Henry Ford Hospital, Detroit, MI, USA; Department of Internal Medicine, Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, MI, USA.

Resveratrol is reported to reduce blood pressure in animal models of hypertension, but the mechanisms are unknown. We have shown that resveratrol infusion increases sodium excretion. We hypothesized that chronic ingestion of resveratrol would reduce angiotensin II (Ang II)-induced increases in blood pressure by decreasing oxidative stress and by also decreasing sodium reabsorption through a nitric oxide-dependent mechanism. We infused rats with vehicle or 80 mug Ang II/d over 4 weeks. Vehicle or Ang II-infused rats were individually housed, pair fed, and placed on a diet of normal chow or normal chow plus 146 mg resveratrol/d. Groups included 1) control, 2) resveratrol-fed, 3) Ang II-treated, and 4) Ang II plus resveratrol. Systolic blood pressure was measured by tail cuff. During the 4th week, rats were placed in metabolic caging for urine collection. NO2/NO3 and 8-isoprostane excretion were measured. Ang II increased systolic blood pressure in the 1st week by +14+/-5 mmHg (P<0.05) in Group 3 and +10+/-3 mmHg (P<0.05) in Group 4, respectively. Blood pressure was unchanged in Groups 1 and 2. After 4 weeks, blood pressure remained elevated in Group 3 rats with Ang II (+9+/-3 mmHg, P<0.05), but in Group 4, blood pressure was no longer elevated (+2+/-2 mmHg). We found no significant differences between the groups in sodium excretion or cumulative sodium balance (18.49+/-0.12, 17.75+/-0.16, 17.97+/-0.17, 18.46+/-0.18 muEq Na+/7 d in Groups 1-4, respectively). Urinary excretion of NO2/NO3 in the four groups was 1) 1631+/-207 mumol/24 h, 2) 1045+/-236 mumol/24 h, 3) 1490+/-161 mumol/24 h, and 4) 609+/-17 mumol/24 h. 8-Isoprostane excretion was 1) 63.85+/-19.39 nmol/24 h, 2) 73.57+/-22.02 nmol/24 h, 3) 100.69+/-37.62 nmol/24 h, and 4) 103.00+/-38.88 nmol/24 h. We conclude that chronic resveratrol supplementation does not blunt Ang II-increased blood pressure, and while resveratrol has mild depressor effects, these do not seem to be due to natriuresis or enhanced renal nitric oxide synthesis.

Internal Medicine

Mawri S, **Michaels A**, **Gibbs J**, **Shah S**, Rao S, Kugelmass A, Lingam N, Arida M, **Jacobsen G**, Rowlandson I, Iyer K, **Khandelwal A**, and **McCord J**. The comparison of physician to computer interpreted electrocardiograms on ST-elevation myocardial infarction door-to-balloon times *Crit Pathw Cardiol* 2016; 15(1):22-25. PMID: 26881816. Full Text

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OBJECTIVE: The purpose of the project was to study the impact that immediate physician electrocardiogram (ECG) interpretation would have on door-to-balloon times in ST-elevation myocardial infarction (STEMI) as compared with computer-interpreted ECGs. METHODS: This was a retrospective cohort study of 340 consecutive patients from September 2003 to December 2009 with STEMI who underwent emergent cardiac catheterization and percutaneous coronary intervention. Patients were stratified into 2 groups based on the computer-interpreted ECG interpretation: those with acute myocardial infarction identified by the computer interpretation and those not identified as acute myocardial infarction. Patients (n = 173) from September 2003 to June 2006 had their initial ECG reviewed by the triage nurse, while patients from July 2006 to December 2009 (n = 167) had their ECG reviewed by the emergency department physician within 10 minutes. Times for catheterization laboratory activation and percutaneous coronary intervention were recorded in all patients. RESULTS: Of the 340 patients with confirmed STEMI, 102 (30%) patients were not identified by computer interpretation. Comparing the prior protocol of computer ECG to physician interpretation, the latter resulted in significant improvements in median catheterization laboratory activation time {19 minutes [interquartile range (IQR): 10-37] vs. 16 minutes [IQR: 8-29]; P < 0.029} and in median door-to-balloon time [113 minutes (IQR: 86-143) vs. 85 minutes (IQR: 62-106); P < 0.001]. CONCLUSION: The computer-interpreted ECG failed to identify a significant number of patients with STEMI. The immediate review of ECGs by an emergency physician led to faster activation of the catheterization laboratory, and door-to-balloon times in patients with STEMI.

Internal Medicine
Ramseyer VD, **Ortiz PA**, **Carretero OA**, and Garvin JL. Angiotensin II-mediated hypertension impairs nitric oxide-induced NKCC2 inhibition in thick ascending limbs *Am J Physiol Renal Physiol* 2016:ajprenal.00473.02015. PMID: 26887831. Full Text

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In thick ascending limbs (THALs) NO decreases NaCl reabsorption via cGMP-mediated inhibition of Na/K/2Cl cotransporter (NKCC2). In angiotensin (Ang II)-induced hypertension, endothelin-1 (ET-1)-induced NO production by THALs is impaired. However, whether this alters NO's natriuretic effects and the mechanisms involved are unknown. In other cell types, Ang II augments phosphodiesterase 5 (PDE5)-mediated cGMP degradation. We hypothesized that NO-mediated inhibition of NKCC2 activity and stimulation of cGMP synthesis are blunted via PDE5 in Ang II-induced hypertension. Sprague Dawley rats were infused with vehicle or Ang II (200ng/kg/min) for 5 days. ET-1 reduced NKCC2 activity by 38+/-13% ($p<0.05$) in THALs from vehicle-treated rats but not from Ang II-hypertensive rats (Delta:-9+/-13 %). A NO donor yielded similar results as ET-1. In contrast, dibutyryl-cGMP significantly decreased NKCC2 activity in both vehicle-treated and Ang II-hypertensive rats (control: Delta -44+/-15 % vs Ang II: Delta -41+/-10%). NO increased cGMP by 2.08+/-0.36 fmol/microg protein in THALs from vehicle-treated rats but only 1.06+/-0.25 fmol/microg protein in Ang II-hypertensive rats ($p<0.04$). Vardenafil (25 nM), a PDE5 inhibitor, restored NO's ability to inhibit NKCC2 activity in THALs from Ang II-hypertensive rats (Delta: -60+/-9%, $p<0.003$). Similarly, NO's stimulation of cGMP was also restored by vardenafil (vehicle-treated: 1.89+/-0.71 vs. Ang II-hypertensive: 2.02+/-0.32 fmol/microg protein). PDE5 expression did not differ between vehicle-treated and Ang II-hypertensive rats. We conclude that NO-induced inhibition of NKCC2 and increases in cGMP are blunted in Ang II-hypertensive rats due to PDE5 activation. Defects in the response of THALs to NO may enhance NaCl retention in Ang II-induced hypertension.

Internal Medicine
Syed H, Bachuwa G, Upadhaya S, and **Abed F**. Nitrofurantoin-induced interstitial pneumonitis: albeit rare, should not be missed *BMJ Case Rep* 2016; 2016PMID: 26912767. Full Text

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Interstitial lung disease (ILD) is a rare adverse effect of nitrofurantoin and can range from benign infiltrates to a fatal condition. Nitrofurantoin acts via inhibiting the protein synthesis in bacteria by helping reactive intermediates and is known to produce primary lung parenchymal injury through an oxidant mechanism. Stopping the drug leads to complete recovery of symptoms. In this report, we present a case of nitrofurantoin-induced ILD with the recovery of symptoms and disease process after stopping the drug.

Nephrology
Neyra JA, Canepa-Escaro F, **Yee J**, and **Yessayan L**. Hyperchloremia versus nonhyperchloremia or hyperchloremia versus normochloremia? Reply *Crit Care Med* 2016; 44(1):E53-E54. PMID: Not assigned. Abstract

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We reviewed Jo et al (1) correspondence in which they have raised an important question regarding the contribution of hypochloremia to our analysis (2). In our original study (n = 1,940) (2), we stratified our primary cohort by the presence (n = 615) or absence (n = 1,325) of hyperchloremia (serum chloride >= 110 mEq/L) on ICU admission. Jo et al (1) suggested that the strength of the association between higher serum chloride levels and hospital mortality in the hyperchloremic group may perhaps be stronger if patients with hypochloremia were excluded from the nonhyperchloremic group for comparison. Consequently, we identified 361 patients with hypochloremia (serum chloride <= 100 mEq/L) on ICU admission in our primary cohort. To eliminate the effect of hypochloremia in our results, we performed a sensitivity analysis in a secondary cohort that excluded patients with hypochloremia on ICU admission. This secondary cohort consisted of 615 patients with hyperchloremia and 964 with normochloremia (101–109 mEq/L) on ICU admission. We obtained similar results and nearly identical univariate and multivariate logistic regression estimates for the association of higher serum chloride levels with hospital mortality in the hyperchloremic group as our published results (Table 1). Graphic Table 1 Small observational studies have demonstrated the association between hypochloremia and mortality in critically ill and postoperative patients (3, 4). Jo et al (1) raised the question of a possible bimodal effect of serum chloride levels on mortality outcomes. However, in our primary cohort, there was no association between serum chloride levels at 72 hours and hospital mortality in the hypochloremic group (n = 361): the univariate odds ratio for each 5 mEq/L decrease in serum chloride was 0.96 (95% CI, 0.77–1.21). The study by Tani et al (4) comprised interesting observations of serum chloride levels and adverse hospital outcomes in critically ill patients. Importantly, in the multivariate model, serum chloride was not independently associated with hospital mortality. However, the authors also reported the frequency of hospital mortality in three subgroups (hypochloremia, normochloremia, and hyperchloremia) and found the highest risk for mortality in the hypochloremic group. The risk for hospital mortality was not different between the normochloremic and hyperchloremic groups: 14 of 364 (3.8%) versus three of 81 (3.7%). The lack of difference between these two subgroups is statistically evident by Fisher exact test (p = 1.00). We consider that this work constitutes a negative study for the association between hyperchloremia and hospital mortality as discussed in our article

Neurology

Loomba V, **Kaveeshvar H**, **Upadhyay A**, and **Sibai N**. Neuropathic pain in cancer patients: A brief review *Indian J Cancer* 2015; 52(3):425-428. PMID: 26905158. Full Text

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Neuropathic pain (NP) is initiated or caused by a primary lesion or dysfunction in the nervous system. The NP in cancer patients is typically due to a combination of inflammatory, neuropathic, ischemic, infiltrative, and compression mechanisms that involve one or more anatomic sites. These patients will often have various types of co-existing pain syndromes and co-morbidities. Thus, any treatment plan needs to be individualized. After a thorough clinical assessment and evaluation, a combination therapy including anticonvulsants, antidepressants, N-methyl-D-aspartate antagonists, opiates, topical agents, and interventional procedures should be considered in these patients.

Neurology

Barone FC, Gustafson D, Crystal HA, Moreno H, Adamski MG, Arai K, Baird AE, Balucani C, Brickman AM, Cechetto D, Gorelick P, Biessels GJ, Kiliaan A, Launer L, Schneider J, Sorond FA, Whitmer R, Wright C, and **Zhang ZG**. First translational 'Think Tank' on cerebrovascular disease, cognitive impairment and dementia *J Transl Med* 2016; 14(1):50. PMID: 26873444. Full Text

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As the human population continues to age, an increasing number of people will exhibit significant deficits in cognitive function and dementia. It is now recognized that cerebrovascular, metabolic and neurodegenerative diseases all play major roles in the evolution of cognitive impairment and dementia. Thus with our more recent recognition of these relationships and our need to understand and more positively impact on this world health problem, "The Leo and Anne Albert Charitable Trust" (Gene Pranzo, Trustee with significant support from Susan Brogan, Meeting Planner) provided generous support for this inaugural international workshop that was held from April 13-16, 2015 at the beautiful Ritz Carlton Golf Resort in North Naples, Florida. Researchers from SUNY Downstate Medical Center, Brooklyn, NY organized the event by selecting the present group of translationally inclined preclinical, clinical and population scientists focused on cerebrovascular disease (CVD) risk and its progression to vascular cognitive impairment (VCI) and dementia. Participants at the workshop addressed important issues related to aging, cognition and dementia by: (1) sharing new data, information and perspectives that intersect vascular, metabolic and neurodegenerative diseases, (2) discussing gaps in translating population risk, clinical and preclinical information to the progression of cognitive loss, and (3) debating new approaches and methods to fill these gaps that can translate into future therapeutic interventions. Participants agreed on topics for group discussion prior to the meeting and focused on specific translational goals that included promoting better understanding of dementia mechanisms, the identification of potential therapeutic targets for intervention, and discussed/debated the potential utility of diagnostic/prognostic markers. Below summarizes the new data-presentations, concepts, novel directions

and specific discussion topics addressed by this international translational team at our "First Leo and Anne Albert Charitable Trust 'Think Tank' VCI workshop".

Neurology

Ding G, **Chen J**, **Chopp M**, **Li L**, **Yan T**, **Li Q**, **Cui C**, **Davarani SP**, and **Jiang Q**. Cell treatment for stroke in type two diabetic rats improves vascular permeability measured by MRI *PLoS One* 2016; 11(2):e0149147. PMID: 26900843.
Full Text

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Treatment of stroke with bone marrow stromal cells (BMSC) significantly enhances brain remodeling and improves neurological function in non-diabetic stroke rats. Diabetes is a major risk factor for stroke and induces neurovascular changes which may impact stroke therapy. Thus, it is necessary to test our hypothesis that the treatment of stroke with BMSC has therapeutic efficacy in the most common form of diabetes, type 2 diabetes mellitus (T2DM). T2DM was induced in adult male Wistar rats by administration of a high fat diet in combination with a single intraperitoneal injection (35mg/kg) of streptozotocin. These rats were then subjected to 2h of middle cerebral artery occlusion (MCAo). T2DM rats received BMSC (5x106, n = 8) or an equal volume of phosphate-buffered saline (PBS) (n = 8) via tail-vein injection at 3 days after MCAo. MRI was performed one day and then weekly for 5 weeks post MCAo for all rats. Compared with vehicle treated control T2DM rats, BMSC treatment of stroke in T2DM rats significantly ($p<0.05$) decreased blood-brain barrier disruption starting at 1 week post stroke measured using contrast enhanced T1-weighted imaging with gadopentetate, and reduced cerebral hemorrhagic spots starting at 3 weeks post stroke measured using susceptibility weighted imaging, although BMSC treatment did not reduce the ischemic lesion volumes as demarcated by T2 maps. These MRI measurements were consistent with histological data. Thus, BMSC treatment of stroke in T2DM rats initiated at 3 days after stroke significantly reduced ischemic vascular damage, although BMSC treatment did not change infarction volume in T2DM rats, measured by MRI.

Neurology

Lewis A, **Varelas P**, and Greer D. Controversies after brain death: When families ask for more *Chest* 2016; 149(2):607-608. PMID: 26867848. Full Text

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Neurology

LeWitt PA, Poewe W, Elmer LW, Asgharnejad M, Boroojerdi B, Grieger F, and Bauer L. The efficacy profile of rotigotine during the waking hours in patients with advanced parkinson's disease: A post hoc analysis *Clin Neuropharmacol* 2016;PMID: 26882318. Full Text

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OBJECTIVES: Transdermal delivery of rotigotine maintains stable plasma concentrations for 24 hours. Three phase 3 studies of rotigotine as add-on to levodopa in advanced Parkinson's disease showed a

significant reduction in "off" time from baseline to end of maintenance (EoM). However, detailed analyses over the range of a day have not yet been performed. The objective was to examine the time course of the efficacy profile of rotigotine throughout the day. METHODS: Post hoc analysis of diary data from 3 double-blind, placebo-controlled studies of rotigotine in patients with advanced Parkinson's disease inadequately controlled with levodopa, with average "off" time of >/=2.5 h/d (CLEOPATRA-PD [NCT00244387], 16-week maintenance; PREFER, 24-week maintenance; SP921 [NCT00522379], 12-week maintenance). Patients marked 30-minute intervals as "off," "on without troublesome dyskinesia," "on with troublesome dyskinesia," or "sleep." Diaries completed on the 3 days before EoM were analyzed. A 2-sample t test was performed for comparison of rotigotine + levodopa versus placebo + levodopa for mean percentage of time per status during four 6-hour periods: 12:00AM (midnight) to 6:00AM, 6:00AM to 12:00PM (noon), noon to 6:00PM, and 6:00PM to midnight. RESULTS: Data were available for 967 patients (placebo + levodopa, 260; rotigotine + levodopa, 707). During the 24-hour period at EoM, an advantage in mean percentage time spent "off" and "on without troublesome dyskinesia" was observed with rotigotine + levodopa versus placebo + levodopa during the three 6-hour periods from 6:00AM to midnight ($P < 0.05$; exploratory analysis). CONCLUSIONS: These exploratory analyses of patients with motor fluctuations suggest that the efficacy of rotigotine transdermal patch, as captured by diary data, in reducing "off" time and increasing "on time without troublesome dyskinesia" may cover the full waking day.

Neurology

Singh J, **Deshpande M**, **Suhail H**, **Rattan R**, and **Giri S**. Targeted stage-specific inflammatory microrna profiling in urine during disease progression in experimental autoimmune encephalomyelitis: Markers of disease progression and drug response *J Neuroimmune Pharmacol* 2016; 11(1):84-97. PMID: 26277791. Full Text

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Recently, microRNAs (miRNAs) have been implicated in regulating neuroinflammatory and demyelinative responses in multiple sclerosis (MS) and its mouse model of experimental autoimmune encephalomyelitis (EAE). miRNAs have also been studied as biomarkers of disease pathology and drug-response in MS. However, no complete miRNA profiling at various stages of EAE disease has been examined, especially in the urine. We carried out a systematic analysis of miRNAs in the urine exosomes as well as in the plasma and spinal cord at pre-onset, onset and peak stages of EAE established in the chronic B6 mice model. For the first time, we provide evidence that urine exosomes can be a specific and sensitive source of miRNA biomarkers for all 3 stages of EAE disease. In a significant observation, we observed that miR-155-5p expression increased in urine exosomes, plasma and spinal cord 6 days before the onset of disease, suggesting its early involvement in the pathology of EAE disease. We also analyzed the effect of Glatiramer acetate (GA; copaxone) treatment, an approved treatment for MS patients, in modulating miRNA expression at the peak of EAE disease. We identified miR-155-5p, miR-27a-3p, miR-9-5p and miR-350-5p as putative GA-treatment responsive miRNA biomarkers. Since, EAE is a mainly CD4 cells mediated disease, we also examined the above set of miRNAs and found to be significantly altered in T cells polarized to Th1 and Th17 phenotype, similar to urine exosomes. Thus, urine exosome miRNAs hold the potential to be defined as novel accessible stage-specific biomarkers of EAE (MS) disease as well as treatment response.

Neurosurgery

Lewis A, **Varelas P**, and Greer D. Controversies after brain death: When families ask for more *Chest* 2016; 149(2):607-608. PMID: 26867848. Full Text

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Neurosurgery

Schiff D, Desjardins A, Cloughesy T, **Mikkelsen T**, Glantz M, Chamberlain MC, Reardon DA, and Wen PY. Phase 1 dose escalation trial of the safety and pharmacokinetics of cabozantinib concurrent with temozolomide and radiotherapy or temozolomide after radiotherapy in newly diagnosed patients with high-grade gliomas *Cancer* 2016; 122(4):582-587. PMID: 26588662. Full Text

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BACKGROUND: Cabozantinib inhibits mesenchymal-epithelial transition factor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2) and has demonstrated activity in patients with recurrent glioblastoma, warranting evaluation of the addition of cabozantinib to radiotherapy (RT) and temozolomide (TMZ) for patients with newly diagnosed high-grade glioma. METHODS: Cabozantinib doses of 40 mg and 60 mg were explored. Patients on the concurrent treatment arm received cabozantinib daily with standard TMZ and after RT continued cabozantinib daily with adjuvant TMZ. In the maintenance arm, patients who completed RT and >/=1 adjuvant cycle of TMZ continued adjuvant TMZ with added cabozantinib (3 schedules: days 1-28, days 1-14, or days 8-21). RESULTS: A total of 26 patients (25 with recurrent glioblastoma and 1 patient with anaplastic astrocytoma) aged 30 to 72 years were enrolled (10 to the concurrent arm and 16 to the maintenance arm). The median number of post-RT TMZ cycles was 4.5 (range, 0-14 cycles) in the concurrent arm and 5.5 (range, 1-12 cycles) in the maintenance arm. Cabozantinib at a dose of 60 mg daily was the maximum administered dose and a dose of 40 mg daily was determined to be the maximum tolerated dose for both treatment arms (schedule of days 1-28). The most frequent grade 3/4 adverse events were thrombocytopenia (31% of patients), leukopenia (27% of patients, including 5 patients with neutropenia), and deep vein thrombosis and/or pulmonary embolism (23% of patients) (adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]). CONCLUSIONS: Cabozantinib at a dose of 40 mg daily with RT plus TMZ and post-RT TMZ for patients with newly diagnosed high-grade glioma was generally well tolerated, and demonstrated no pharmacokinetic interactions with concurrent TMZ. Given the strong theoretical rationale for combining anti-VEGF and anti-MET activity with standard therapy, cabozantinib at a dose of 40 mg daily warrants evaluation in combination with standard therapy for patients with newly diagnosed glioblastoma. Cancer 2016;122:582-587. (c) 2015 American Cancer Society.

Neurosurgery

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Primitive neuroectodermal tumors of the central nervous system (CNS-PNETs) are highly aggressive, poorly differentiated embryonal tumors occurring predominantly in young children but also affecting adolescents and adults. Herein, we demonstrate that a significant proportion of institutionally diagnosed CNS-PNETs display molecular profiles indistinguishable from those of various other well-defined CNS tumor entities, facilitating diagnosis and appropriate therapy for patients with these tumors. From the remaining fraction of CNS-PNETs, we identify four new CNS tumor entities, each associated with a recurrent genetic alteration and distinct histopathological and clinical features. These new molecular entities, designated "CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2)," "CNS Ewing sarcoma family tumor with CIC alteration (CNS EFT-CIC)," "CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1)," and "CNS high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)," will enable meaningful clinical trials and the development of therapeutic strategies for patients affected by poorly differentiated CNS tumors.

Obstetrics, Gynecology and Women's Health Services

Schliep KC, Chen Z, Stanford JB, Xie Y, Mumford SL, **Hammoud AO**, Boiman Johnstone E, Dorais JK, Varner MW, Buck Louis GM, and Peterson CM. Endometriosis diagnosis and staging by operating surgeon and expert review using multiple diagnostic tools: an inter-rater agreement study *Bjog* 2015;PMID: 26435386. Full Text

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OBJECTIVE: To determine agreement on endometriosis diagnosis between real-time laparoscopy and subsequent expert review of digital images, operative reports, magnetic resonance imaging (MRI), and histopathology, viewed sequentially. DESIGN: Inter-rater agreement study. SETTING: Five urban surgical centres. POPULATION: Women, aged 18-44 years, who underwent a laparoscopy regardless of clinical indication. A random sample of 105 women with and 43 women without a postoperative endometriosis diagnosis was obtained from the ENDO study. METHODS: Laparoscopies were diagnosed, digitally recorded, and reassessed. MAIN OUTCOME MEASURES: Inter-observer agreement of endometriosis diagnosis and staging according to the revised American Society for Reproductive Medicine criteria. Prevalence and bias-adjusted kappa values (kappa) were calculated for diagnosis, and weighted kappa values were calculated for staging. RESULTS: Surgeons and expert reviewers had substantial agreement on diagnosis and staging after viewing digital images (n = 148; mean kappa = 0.67, range 0.61-0.69; mean kappa = 0.64, range 0.53-0.78, respectively) and after additionally viewing operative reports (n = 148; mean kappa = 0.88, range 0.85-0.89; mean kappa = 0.85, range 0.84-0.86, respectively). Although additionally viewing MRI findings (n = 36) did not greatly impact agreement, agreement substantially decreased after viewing histological findings (n = 67), with expert reviewers changing their assessment from a positive to a negative diagnosis in up to 20% of cases. CONCLUSION: Although these findings suggest that misclassification bias in the diagnosis or staging of endometriosis via visualised disease is minimal, they should alert gynaecologists who review operative images in order to make decisions on endometriosis treatment that operative reports/drawings and histopathology, but not necessarily MRI, will improve their ability to make sound judgments. TWEETABLE ABSTRACT: Endometriosis diagnosis and staging agreement between expert reviewers and operating surgeons was substantial.

Obstetrics, Gynecology and Women's Health Services

Adekola H, Gill N, Sakr S, Hobson D, Bryant D, Abramowicz JS, and Soto E. Outcomes following intra-amniotic instillation with indigo carmine to diagnose prelabor rupture of membranes in singleton pregnancies: a single center experience *J Matern Fetal Neonatal Med* 2016; 29(4):544-549. PMID: 25714481. Article Request Form

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OBJECTIVE: To evaluate clinical outcomes of women with singleton pregnancies that underwent intra-amniotic dye instillation (amniodye test) following equivocal diagnosis of prelabor rupture of membranes (PROM). METHOD: Records of 34 pregnant women who underwent amniodye test for equivocal PROM were reviewed. Comparisons of characteristics, amniotic fluid (AF) cultures, AF interleukin (IL)-6 concentrations, and placenta pathology results between women who tested positive and those who tested negative were performed. A sub-analysis of women who were amniodye test-negative was also performed. RESULTS: (1) Commonest indication for amniodye test was a typical history of PROM with positive conventional tests and persistently normal AF volume, (2) amniodye test-positive women had a shorter procedure-to-delivery interval (p = 0.008), and a greater proportion of histologic acute

chorioamnionitis (p = 0.04) and funisitis (p = 0.01) than amniodye-negative women, and (3) in addition to similarities to women with amniodye-positive test, amniodye test-negative women who delivered <34 weeks, had a greater proportion of women with risk for preterm birth (p = 0.04), than their counterparts who delivered between 34 0/7 and 36 6/7 weeks. CONCLUSION: Equivocal diagnosis of PPROM should warrant an amniodye test to avoid iatrogenic intervention in women with intact amniotic membranes. AF analysis should be performed in amniodye test-negative women.

Obstetrics, Gynecology and Women's Health Services

Allo G, **Chitale DA**, **Alford SH**, **Munkarah AR**, **Winer I**, and **Ratnam M**. Glucocorticoid receptor expression in ovarian tumors *Lab Invest* 2016; 96:274A-274A. PMID: Not assigned. Abstract

Henry Ford Hosp, Detroit, MI 48202 USA. Karmanos Canc Inst, Detroit, MI USA.

Background: Dexamethasone (Dex) is a synthetic glucocorticoid that is frequently coadministered with chemotherapy in ovarian and other cancers to alleviate side effects of chemotherapy on non-target tissues. However, in vitro and preclinical data show that Dex can induce stress response mechanisms in lung, breast and ovarian cancer cells, causing it to attenuate cytotoxicity of, and response to chemotherapeutic drugs when Dex is co-administered. This response has been suggested to be predicted by the expression status of glucocorticoid receptor (GR) in lung and breast cancers. Therefore, establishing GR as a predictive biomarker of tumor response to Dex-combined chemotherapy would potentially enable clinical decision making with respect to the use of Dex duringchemotherapy, particularly as alternative Dex-free treatments such as nab-paclitaxel are now available. We therefore undertook to examine the distribution of GR expressionwithin various subtypes of ovarian tumors as a first step toward exploring GR as a predictor of chemotherapy response in ovarian neoplasms. Design: Tissue microarrays of 286 ovarian tumors, each case represented in triplicate, were semi-quantitatively assessed for GR immunohistochemical expression using H-score (negative staining defined as weak to no staining H-score<50 while strong
diffuse staining as that with H-score≥200). Descriptive statistics and Fischer's exact tests were used for statistical analysis. Results: Of the 286 cases examined, 244 tumors (85%) showed GR expression (Table 1), 193 (79%) of which with strong diffuse positivity. Among ovarian epithelial carcinomas, type 2 cancers were more likely to be GR positive (190 of 205, 93% vs. 47 of 74, 64%; p< 0.0001), with more cases exhibiting strong diffuse positivity (149 of 205, 73% vs. 37 of 74, 50%; p= 0.0005). Conclusions: This is the first report of a comprehensive study of GR status in ovarian tumors, demonstrating highly variable GR expression profile both among subtypes of ovarian cancer and within each, subtype suggesting that tumor GR status may be a major determinant of the variability in response of ovarian cancer patients to chemotherapy. Pathologic subgroups of patients identified as expressing high GR may also be candidates for novel treatments that use GR antagonists

Obstetrics, Gynecology and Women's Health Services

Rauch K, Hicks M, **Adekola H**, and Abramowicz J. Aneuploidy screening: The ongoing role of first-trimester ultrasound *First-Trimester Ultrasound* 2016:131-152. PMID: Not assigned - Book chapter. Book Request Form

ACOG recommends that all women be offered aneuploidy screening prior to 20 weeks gestation. The landscape of prenatal aneuploidy screening has evolved from assessing a single parameter (maternal age) to incorporating a myriad of different ultrasound and serum markers, to the most current and direct method of analyzing fetal DNA within maternal circulation. Although the performance of aneuploidy screening has undoubtedly improved over the years, there continues to be discussion surrounding the best use of these technologies in clinical practice. With new technologies we can now screen for additional aneuploidies beyond trisomies 21, 18, and 13. While screening for aneuploidy via circulating cell free fetal DNA (ccffDNA) has become increasingly popular, the benefits of first-trimester ultrasound in the detection of genetic conditions and fetal anomalies cannot be understated. With the expansion in available screening methodologies, we must continue to evaluate the practical implications including

clinical utility, patient autonomy, and the ability to provide informed consent for an ever-growing number of chromosomal conditions.

Obstetrics, Gynecology and Women's Health Services
Toubia T, **Schiff L**, **Wegienka G**, and **Sangha R**. Extended length of stay after robotic-assisted hysterectomy: Association with uterine weight and other risk factors *J Gynecol Surg* 2016; 32(1):19-23. PMID: Not assigned. Article Request Form

T. Toubia, Department of Women's Health, Henry Ford Health System, Chapel Hill, United States

Background: Robotic-assisted hysterectomy (RH) has the same clinical benefits as laparoscopy and offers surgeons additional benefits. However, RH-related costs are high and its clinical benefits have not been shown to be better than those achieved with laparoscopy. A key cost factor is the length of (hospital) stay (LOS). Objective: The aim of this study was to identify the relationship between uterine weight and LOS following RH and potential risk factors for extended LOS. Materials and Methods: This study involved a retrospective cohort of all RHs performed in a midwestern tertiary-care teaching hospital and its suburban affiliates, from January 2011 to December 2012. Data were collected using Current Procedural Terminology codes. The current authors examined if any of several variables were associated with uterine weight, using Spearman's correlation for continuous variables and Wilcoxon's rank sum or Kruskal-Wallis test for categorical variables. Comparison of variables between patients who did and who did not have a LOS>1 day was performed using a Wilcoxon rank sum test for continuous variables and a Chi-square or Fisher's exact test for categorical variables. Those that were associated with both uterine weight and LOS were considered as potential confounders and were included in the logistic regression model. The adjusted odds ratio (OR) for a 100-g increase in uterine weight was calculated. Results: Of 239 patients who underwent RH, 48 (20%) had a LOS>1 day. Uterine weight was significantly greater among patients with LOS>1 day (483 g versus 337 g; p=0.008). Patients who had LOS>1 day had a greater estimated blood loss (EBL; means: 178 mL versus 95 mL; p=0.006) and a significantly longer procedure duration (means: 236 minutes versus 168 minutes; p<0.005), compared to patients with LOS=1. In addition, patients with LOS>1 day had higher baseline pain scores (4.5 versus 3.2; p=0.003). Number of ports and oophorectomy were both significantly associated with LOS. For a 100-g increase in uterine weight, there was 1.12 times the odds of having LOS>1 day (OR=1.12; 95% confidence interval: 1.02, 1.21). After controlling for procedure duration, EBL, number of ports, transfusion rates and oophorectomy, the adjusted OR (aOR) was not significant (aOR=1.0; CI: 0.89, 1.12). Conclusions: When adjusted for procedure duration, EBL, number of ports, transfusion rates, and oophorectomy, uterine weight was not associated with LOS after RH. Larger studies are needed to explore further the associations among procedure duration, EBL, baseline pain scores, oophorectomy, and number of ports used with prolonged LOS after RH. Pain management seemed to be the single greatest indication for increased LOS after RH. (J GYNECOL SURG 32:19)

Ophthalmology and Eye Care Services
Hessburg PC, Rizzo J, and **O'Malley ER**. Preface: The eye and the chip world research congress on visual neuro-prosthetics *J Neural Eng* 2016; 13(2):020401. PMID: 26904980. Article Request Form

Henry Ford Health System, Detroit Institute of Ophthalmology, USA.

Ophthalmology and Eye Care Services
Im M, and Fried SI. Temporal properties of network-mediated responses to repetitive stimuli are dependent upon retinal ganglion cell type *J Neural Eng* 2016; 13(2):025002. PMID: 26905231. Article Request Form

VA Boston Healthcare System, 150 South Huntington Avenue, Boston, MA 02130, USA. Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, 50 Blossom Street, Boston,

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OBJECTIVE: To provide artificially-elicited vision that is temporally dynamic, retinal prosthetic devices will need to repeatedly stimulate retinal neurons. However, given the diversity of physiological types of retinal ganglion cells (RGCs) as well as the heterogeneity of their responses to electric stimulation, temporal properties of RGC responses have not been adequately investigated. Here, we explored the cell type dependence of network-mediated RGC responses to repetitive electric stimulation at various stimulation rates. APPROACH: We examined responses of ON and OFF types of RGCs in the rabbit retinal explant to five consecutive stimuli with varying inter-stimulus intervals (10-1000 ms). Each stimulus was a 4 ms long monophasic sinusoidal cathodal current, which was applied epiretinally via a conical electrode. Spiking activity of targeted RGCs was recorded using a cell-attached patch electrode. MAIN RESULTS: ON and OFF cells had distinct responses to repetitive stimuli. Consistent with earlier studies, OFF cells always generated reduced responses to subsequent stimuli compared to responses to the first stimulus. In contrast, a new stimulus to ON cells suppressed all pending/ongoing responses from previous stimuli and initiated its own response that was remarkably similar to the response from a single stimulus in isolation. This previously unreported 'reset' behavior was observed exclusively and consistently in ON cells. These contrasts between ON and OFF cells created a range of stimulation rates (4-7 Hz) that maximized the ratio of the responses arising in ON versus OFF cells. SIGNIFICANCE: Previous clinical testing reported that subjects perceive bright phosphenes (ON responses) and also prefer stimulation rates of 5-7 Hz. Our results suggest that responses of ON cells are weak at high rates of stimulation (> approximately 7 Hz) due to the reset while responses of OFF cells are strong at low rates (< approximately 4 Hz) due to reduced desensitization, both reducing the ratio of ON to OFF responses. In combination with previous results indicating that responses in ON cells more closely match physiological patterns (Im and Fried 2015 J. Physiol. 593 3577-96), our results offer a potential reason for the user preference of intermediate rates (5-7 Hz).

Orthopaedics

Charters MA, **Frisch NB**, **Wessell NM**, Dobson C, **Les CM**, and **Silverton CD**. Rivaroxaban versus enoxaparin for venous thromboembolism prophylaxis after hip and knee arthroplasty *J Arthroplasty* 2015; 30(7):1277-1280. PMID: 25724111. Full Text

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The oral Factor Xa inhibitor rivaroxaban (Xarelto) has been the pharmacologic agent used for venous thromboembolism (VTE) prophylaxis after primary hip and knee arthroplasty (THA/TKA) at our institution since February 2012. The purpose of our study was to compare rates of VTE and major bleeding between rivaroxaban and our previous protocol of enoxaparin after THA/TKA. A retrospective cohort study was performed including 2406 consecutive patients at our institution between 1/1/11 and 9/30/13. Patients who did not have unilateral primary THA/TKA or who received other anticoagulants were excluded. Of the 1762 patients included, 1113 patients (63.2%) received enoxaparin and 649 patients (36.8%) received rivaroxaban. This study found no demonstrable differences between these two anticoagulants in rates of VTE, infection, reoperation, transfusion, or major bleeding. Therapeutic, Retrospective comparative study, Level III.

Orthopaedics

Li B, Singer NG, **Yeni YN**, **Haggins DG**, Barnboym E, **Oravec D**, Lewis S, and Akkus O. A point of care Raman spectroscopy based device to diagnose gout and pseudogout: Comparison with the clinical standard microscopic analysis *Arthritis Rheumatol* 2016;PMID: 26882173. Full Text

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Department of Orthopaedics, School of Medicine, Case Western Reserve University, Cleveland, OH, USA.
Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA.

OBJECTIVE: To demonstrate the usefulness of a novel medical device based on Raman spectroscopy for rapid point of care diagnosis of gout and pseudogout. METHODS: A shoebox sized point of care Raman (POCR) device was developed for gout and pseudogout diagnoses. The device included a disposable syringe microfiltration kit to collect arthropathic crystals from synovial fluid and a customized automated Raman spectrometry system to identify crystal species chemically. The POCR diagnosis was compared with the clinical standard compensated polarized light microscopic (CPLM) analysis of synovial fluid aspirates (N = 174) collected from symptomatic patients. Kappa coefficients were used to measure the agreement between POCR and CPLM. RESULT: Overall, POCR and CPLM analyses agreed in 89.7% of samples (156 out of 174). In diagnosing gout, the Kappa coefficient for POCR and CPLM was 0.84 (95% CI 0.75-0.94). In diagnosing pseudogout, the Kappa coefficient for POCR and CPLM was 0.61 (95% CI 0.42-0.81). CONCLUSION: Kappa coefficients indicated that POCR and CPLM had excellent agreement in diagnosing gout, and good agreement in diagnosing pseudogout. The POCR device holds the potential to standardize and expedite the time to clinical diagnosis of gout and pseudogout, especially in settings where certified operators trained for CPLM analysis are absent.

Orthopaedics

Vallier HA, Moore TA, and **Nahm NJ**. Re: Issues regarding patient assessment scores that focus on acid base changes in fracture patients *J Trauma Acute Care Surg* 2016;PMID: 26885999. Full Text

Clyde L. Nash, M.D. Professor of Orthopaedic Education Professor of Orthopaedic Surgery Case Western Reserve University The MetroHealth System Director of Spine Trauma Associate Professor of Orthopaedic Surgery Case Western Reserve University The MetroHealth System Resident in Orthopaedic Surgery Henry Ford Hospital.

Otolaryngology – Head and Neck Surgery

Asher BF, **Seidman MD**, Reddy WD, and Omole FS. Integrative medical approaches to allergic rhinitis *Curr Opin Otolaryngol Head Neck Surg* 2015; 23(3):221-225. PMID: 25943958. Full Text

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PURPOSE OF REVIEW: Complementary and integrative medicine (CIM), formerly known as alternative medicine, is now part of the mainstream management for patients with a host of medical issues. This current opinion focuses on the use of CIM, more specifically, the use of nutritional and herbal therapies and homeopathic medications for patients with allergic symptoms. RECENT FINDINGS: The literature review revealed that naturally occurring substances when compared with placebo more often than not resulted in significant improvement of the allergic rhinitis symptoms. SUMMARY: Despite encouraging results, additional studies with greater rigor are needed.

Otolaryngology – Head and Neck Surgery

Craig JR, Zhao K, Doan N, Khalili S, Lee JY, Adappa ND, and Palmer JN. Cadaveric validation study of computational fluid dynamics model of sinus irrigations before and after sinus surgery *Int Forum Allergy Rhinol* 2016;PMID: 26880742. Article Request Form

Department of Otolaryngology, Henry Ford Health System, Detroit, MI.
Department of Otolaryngology, Ohio State University, Columbus, OH.
Department of Engineering, Drexel University, Philadelphia, PA.
Department of Otolaryngology, University of Pennsylvania, Philadelphia, PA.

BACKGROUND: Investigations into the distribution of sinus irrigations have been limited by labor-intensive methodologies that do not capture the full dynamics of irrigation flow. The purpose of this study was to validate the accuracy of a computational fluid dynamics (CFD) model for sinonasal irrigations through a cadaveric experiment. METHODS: Endoscopic sinus surgery was performed on 2 fresh cadavers to open all 8 sinuses, including a Draf III procedure for cadaver 1, and Draf IIb frontal sinusotomies for cadaver 2. Computed tomography maxillofacial scans were obtained preoperatively and postoperatively, from which CFD models were created. Blue-dyed saline in a 240-mL squeeze bottle was used to irrigate cadaver sinuses at 60 mL/second (120 mL per side, over 2 seconds). These parameters were replicated in CFD simulations. Endoscopes were placed through trephinations drilled through the anterior walls of the maxillary and frontal sinuses, and sphenoid roofs. Irrigation flow into the maxillary, frontal, and sphenoid sinuses was graded both ipsilateral and contralateral to the side of nasal irrigation, and then compared with the CFD simulations. RESULTS: In both cadavers, preoperative and postoperative irrigation flow into maxillary, frontal, and sphenoid sinuses matched extremely well when comparing the CFD models and cadaver endoscopic videos. For cadaver 1, there was 100% concordance between the CFD model and cadaver videos, and 83% concordance for cadaver 2. CONCLUSION: This cadaveric experiment provided potential validation of the CFD model for simulating saline irrigation flow into the maxillary, frontal, and sphenoid sinuses before and after sinus surgery.

Pathology

Jiang F, **Cabrera Fernandez DF**, Church J, **Gulati R**, **Taylor A**, **Menon M**, and **Kuriakose P**. Correlation between peripheral blood counts and day 14 bone marrow biopsy in acute myeloid leukemia during induction chemotherapy *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

[Jiang, Feng; Kuriakose, Philip] Henry Ford Hosp, Hematol Oncol, Detroit, MI 48202 USA. [Fernandez, Diego Cabrera] Henry Ford Hosp, Internal Med, Detroit, MI 48202 USA. [Church, Julia] Michigan State Univ, Coll Osteopath Med, E Lansing, MI 48824 USA. [Gulati, Rohit; Menon, Madhu] Henry Ford Hosp, Pathol, Detroit, MI 48202 USA. [Taylor, Andrew] Henry Ford Hosp, Publ Hlth Sci, Detroit, MI 48202 USA.

Background Current NCCN guideline recommends that a bone marrow sample be performed 7-10 days (day 14 bone marrow) after completion of induction therapy in newly diagnosed acute myeloid leukemia (AML). However, the value of day 14 bone marrow has been questioned due to the invasive nature of the procedure and lack of specificity pertaining to complete remission in cases of borderline blasts count and cellularity. We examined peripheral blood count and bone marrow from day 0 to day 14, to see if a reduction of peripheral blood correlated and predicted the day 14 bone marrow morphologic changes and complete remission (mCR). Methods We did 10 years retrospective review between year 2004 and 2013 at the Henry Ford Hospital, on patients who had newly diagnosed AML and day 14 bone marrow biopsy. The majority of patients underwent "7+3" or a "7+3"-like regimen for induction chemotherapy. Firstly, we evaluated the relationship of change of peripheral blood count from day 0 to day 14 with blast percentage and cellularity of bone marrow. Spearman correlations coefficients were computed for each pair of characteristics. Peripheral blood count includes neutrophil (ANC), monocyte, white blood cells (WBC), blast, hemoglobin and platelet. Secondly, we investigated the possible correlation of mCR to peripheral blood and bone marrow changes, using binary univariate logistic regression. mCR as defined by blast percentage <5, absolute neutrophil (ANC) >1000/mm3, platelets>100,000/mm3. Thirdly, we explored differences in peripheral blood counts on day 14 among three bone marrow groups, those with blast percentage <5, 5-20, >20. Results A total of 200 patients were reviewed and 56 patients met the inclusion

criteria. Decrease of ANC/WBC correlated with decrease of bone marrow blast/cellularity from day 0 to day 14 (ANC: Blast P ≤ 0.05; ANC: cellularity P ≤ 0.05; WBC: blast P ≤ 0.001, WBC: cellularity P ≤ 0.01). In other words, a larger reduction in ANC/WBC correlated with larger reduction in both blast and cellularity in bone marrow. However, this correlation with bone marrow change was not found in peripheral blast, monocyte, hemoglobin and platelet. We also found that with increasing age, there was less reduction from day 0 to day 14 in bone marrow blast and cellularity. Bone marrow blast and cellularity on day 14 is strongly associated with mCR (P<0.01), the reduction of blast (43.7 +/- 22.86, Odds ratio 1.03 (1.01, 1.06), P=0.012) and cellularity (66.21 +/- 29.98, Odds ratio 1.03 (1.01, 1.05), P=0.003) from day 0 to 14 is also predictive for mCR. Interestingly, there is a trending effect that the reduction of ANC from day 0 to 14 may predict mCR, but it is not statistically significant (Odds ratio 1.22 (1.02, 1.66), P=0.097). The reduction of WBC is not associated with mCR. Furthermore, peripheral blood counts on day 14 are similar among 3 bone marrow groups, those of blast percentage <5, 5-20, and >20% on day 14. Conclusion ANC/WBC decrease from day 0 to day 14 correlated with the decrease in bone marrow blast count and cellularity, and can be used as a predictor for bone marrow change on day 14, but the level of day 14 peripheral blood findings are similar among 3 bone marrow groups (blast percentage <5, 5-20, and >20% on day 14), so it could not be used to predict the level of bone marrow change. Our data confirmed that the significant decrease of bone marrow blast percentage and cellularity from day 0 to 14 predicts mCR. Decrease of ANC from day 0 to 14 may also predict mCR although it is not statistically significant. A larger sample size can be studied in the future to further explore the possibility of using peripheral blood to predict bone marrow changes and mCR. Summary Our data demonstrates a significant reduction of ANC on day 14 after induction therapy in newly diagnosed AML, which correlates with a decrease in bone marrow cellularity and blast percentage. However, a statistically significant association with blast percentage pertaining to mCR was not obtained. In conclusion, while the current findings do not justify replacement of day 14 bone marrow for predicting mCR, further large scale studies are indicated.

Pathology

Adwar W, **Gadde R**, **Chitale DA**, **Allo G**, **Schultz D**, **Gaba AR**, and **Zhang ZY**. Management of insufficient endometrial biopsy for women with abnormal uterine bleeding: To further investigate or reassure? *Lab Invest* 2016; 96:273A-273A. PMID: Not assigned. Abstract

[Adwar, Wamidh; Gadde, Ramya; Chitale, Dhananjay A.; Allo, Ghassan; Schultz, Daniel; Gaba, Arthur R.; Zhang, Ziying] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Endometrial biopsy (EB) is an essential part of investigation performed in women having AUB and is recommended for all women over the age of 45 years with abnormal uterine bleeding (AUB). Frequently, EB contains only scant strips of endometrial surface epithelium, creating a dilemma for pathologists and cliniciansjudging adequacy for management. There are no published guidelines for endometrial biopsy adequacy. There is considerable disagreement among clinicians regarding furthermanagement. The current recommendation is that endometrial thickness of <4 mm is considered as reassuring. To investigate this recommendation, we correlated EB with ultrasound (US) findings and available follow up data. Design: Electronic medical records were used to retrieve EB performed on women older than 50 years presenting with AUB and for whom US and follow up data were available. Patients who didn't have endometrial pathology or gynecologic complaints within 12 months of follow up were considered as having no evidence of endometrial disease. We categorized EB results into 3 groups: group I: had only strips of endometrial surface epithelium; group II: had intact benign endometrium (proliferative/secretory); and group III: had endometrial pathology (polyp/hyperplasia/cancer).Results: 183 patients were retrieved, age ranging 50-85 years. The follow up period is from 1 month to 9 years. There were 79 (43%) patients in group I: 42/79 with ET ≥4 mm, 4 (9.5%) of them had endometrial carcinoma (EMC) upon follow up, while 25/79 patients with ET< 4 mm, 1 (4%) patient had EMC upon follow up. In12/79 patients, EM could not be visualized by US and all had no evidence of disease (EOD) upon follow up. In group II, there were 83 (45%) patients: 58/83 with ET ≥4 mm, 1 (1.7%)
patient had serous carcinoma upon follow up and 11/83 with ET< 4 mm, all had no EOD upon follow up. In 14/83 patients, EM could not be visualized by US and all had no EOD upon follow up. In group III, there were 21 (12%) patients, 5 had polyps, 6 had hyperplasia and 10 had EMC, all with ET≥4 mm except 1 polyp with ET <4 mm. Conclusions: Based on this preliminary data from our cohort, for clinical

management, it is essential to correlate with US findings if the EB only contains strips of surfaceepithelium (group I) because 9.5% of such patients with thickened EM were found to have cancer upon follow up. Noteworthy, in this group, ET <4mm did not guarantee no cancer. In addition, the presence of intact benign endometrium (group II) can't entirely exclude cancer especially when ET ≥ 4 mm.

Pathology

Allo G, **Chitale DA**, **Alford SH**, **Munkarah AR**, **Winer I**, and **Ratnam M**. Glucocorticoid receptor expression in ovarian tumors *Lab Invest* 2016; 96:274A-274A. PMID: Not assigned. Abstract

Henry Ford Hosp, Detroit, MI 48202 USA. Karmanos Canc Inst, Detroit, MI USA.

Background: Dexamethasone (Dex) is a synthetic glucocorticoid that is frequently coadministered with chemotherapy in ovarian and other cancers to alleviate side effects of chemotherapy on non-target tissues. However, in vitro and preclinical data show that Dex can induce stress response mechanisms in lung, breast and ovarian cancer cells, causing it to attenuate cytotoxicity of, and response to chemotherapeutic drugs when Dex is co-administered. This response has been suggested to be predicted by the expression status of glucocorticoid receptor (GR) in lung and breast cancers. Therefore, establishing GR as a predictive biomarker of tumor response to Dex-combined chemotherapy would potentially enable clinical decision making with respect to the use of Dex duringchemotherapy, particularly as alternative Dex-free treatments such as nab-paclitaxel are now available. We therefore undertook to examine the distribution of GR expressionwithin various subtypes of ovarian tumors as a first step toward exploring GR as a predictor of chemotherapy response in ovarian neoplasms. Design: Tissue microarrays of 286 ovarian tumors, each case represented in triplicate, were semi-quantitatively assessed for GR immunohistochemical expression using H-score (negative staining defined as weak to no staining H-score<50 while strong diffuse staining as that with H-score≥200). Descriptive statistics and Fischer's exact tests were used for statistical analysis. Results: Of the 286 cases examined, 244 tumors (85%) showed GR expression (Table 1), 193 (79%) of which with strong diffuse positivity. Among ovarian epithelial carcinomas, type 2 cancers were more likely to be GR positive (190 of 205, 93% vs. 47 of 74, 64%; p< 0.0001), with more cases exhibiting strong diffuse positivity (149 of 205, 73% vs. 37 of 74, 50%; p= 0.0005). Conclusions: This is the first report of a comprehensive study of GR status in ovarian tumors, demonstrating highly variable GR expression profile both among subtypes of ovarian cancer and within each, subtype suggesting that tumor GR status may be a major determinant of the variability in response of ovarian cancer patients to chemotherapy. Pathologic subgroups of patients identified as expressing high GR may also be candidates for novel treatments that use GR antagonists

Pathology

Arias-Stella J, **Shah AB**, **Gupta NS**, and **Williamson SR**. Ck20 and p53 immunohistochemistry: Staining patterns and follow up in urinary bladder specimens with urothelial atypia *Lab Invest* 2016; 96:215A-215A. PMID: Not assigned. Abstract

[Arias-Stella, Javier; Shah, Alpa B.; Gupta, Nilesh S.; Williamson, Sean R.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Urinary bladder carcinoma in situ (CIS) is associated with a considerable risk of progression to invasive bladder cancer, and refractory disease may necessitate radical surgery. Therefore, distinction from reactive urothelium is critical. CK20 and p53 are among the most common immunohistochemical (IHC) antibodies used for this purpose. However, to date, most studies have investigated specimens with established benign or malignant diagnoses. In contrast, we studied the use of CK20 and p53 in bladder specimens with borderline or suspicious features for CIS and correlated with subsequent or prior cancer diagnoses. Design: Specimens with equivocal urothelial atypia from 2008-2015 were retrieved. CK20 and p53 IHC was performed to analyze staining pattern and intensity. Staining was classified as CIS pattern (both stains yielding strong uniform labeling of the area

of concern), discordant (only 1 yielding CIS pattern), indeterminate (1 or both yielding partial or equivocal labeling), or benign (both stains yielding a benign pattern). Prior and subsequent bladder specimen diagnoses were reviewed. Results: A total of 69 specimens from 65 patients with equivocal atypia were retrieved. Nine (13%) had a CIS staining pattern, 18 (26%) were discordant, 31 (45%) were indeterminate, and 11 (16%) showed a benign staining pattern. Of the discordant specimens, 13 labeled for CK20 but not p53, whereas 5 showed the opposite. Most patients (n=43; 65%) had a known history of bladder cancer, of whom 26 had recurrence with an average interval of 37 months (2-216). A subset of patients (n=23; 35%) had no prior history of bladder cancer. Of these, only 1 patient with CK20+ staining later developed diagnostic carcinoma.Conclusions: IHC for CK20 and p53 is commonly used for discrimination of urothelial CIS from benign or reactive urothelium, and has been previously studied in specimens with established morphology. In our cohort of specimens with equivocal urothelial atypia, very few patients without a prior diagnosis of bladder cancer progressed to diagnostic cancer (1/23), suggesting that an inconclusive staining pattern is similar to a diagnosis of “atypia of unknown significance”. Patients with a known history of
bladder cancer had a substantial rate of recurrence, independent of staining pattern.

Pathology

Calio A, Eble JN, Hes O, Martignoni G, **Williamson SR**, Brunelli M, Osunkoya AO, Wang LS, Comperat E, Wang MS, Zhang SB, Curless K, Post K, Chang HY, Baldridge LA, MacLennan G, Montironi R, Grignon DJ, and Cheng L. Distinct clinicopathological features in metanephric adenoma harboring BRAF mutation *Lab Invest* 2016; 96:220A-220A. PMID: Not assigned. Abstract

Univ Verona, I-37100 Verona, Italy. Indiana Univ, Indianapolis, IN 46204 USA. Charles Univ Prague, Hosp Plzen, Plzen, Czech Republic. Henry Ford Hlth Syst, Detroit, MI USA. Emory Univ, Atlanta, GA 30322 USA. Fudan Univ, Shangai Canc Ctr, Shanghai, Peoples R China. Grp Hosp Pitie Salpetriere, F-75634 Paris, France. Case Western Reserve Univ, Cleveland, OH 44106 USA. Polytech Univ Marche Reg, Ancona, Italy.

Background: BRAF mutation has been recently reported in metanephric adenoma. We sought to determine the clinical and morphologic features of BRAF mutated metanephric adenoma and correlate BRAF mutation with BRAF V600E immunohistochemical staining results. Design: A series of 45 metanephric adenomas were analyzed for the occurrence of BRAF mutation (BRAF V600E, BRAF V600D, BRAF V600K and BRAF V600R) using the BRAF RGQ PCR kit (Qiagen). Immunohistochemistry was performed using monoclonal mouse antibody VE1 (Spring Bioscience), recognizing the BRAF V600E mutant protein. Results: Thirty-eight of 45 cases (84%) showed BRAF V600E mutation; none of the other BRAF variants were detected. Of 38 BRAF mutated neoplasms, 34 cases showed positive VE1 immunostainings (sensitivity 89%, specificity 100%). The following features were associated with BRAF V600E mutation: older patients (p=0.001), female predominance (p=0.005), the presence of a predominant acinar component (p=0.02), and the presence of edematous stroma (p=0.05). Conclusions: BRAF mutated metanephric adenomas were associated with older age, female predominance, and the presence of a predominant acinar component and edematous stroma. A subset of BRAF mutated metanephric adenomas was not detected by VE1 immunostaining

Pathology

Chitale DA, **Wozniak J**, **Main N**, **Varney R**, **Tuthill M**, and **Zarbo RJ**. Image documented surgical pathology (ID-SP) to enhance patient safety - lean redesign of the value stream steps from gross examination to signout *Lab Invest* 2016; 96:493A-493A. PMID: Not assigned. Abstract

[Chitale, Dhananjay A.; Wozniak, Jason; Main, Nelson; Varney, Ruan; Tuthill, Mark; Zarbo, Richard J.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Mis-identification (Mis-ID) and Mis-communication (Mis-COM) defects are requent causes of potentially significant medical errors that threaten patient safety. The hand-off nature of surgical pathology processes from specimen collection to signout affords opportunities for Mis-ID/Mis-COM

failures. To further enhance safer surgical pathology, we have explored process and technologic innovations that leverage the maxim “a picture is worth a thousand words” by integrating ID-SP digital workstation employing images attached in the lab information system that visually document all required information at gross examination to be used by downstream workstations. Design: Times to perform all steps of grossing and documentation were assessed comparing 25 biopsies grossed by a single pathology assistant with our traditional grossing protocol (TGP), dictationless & wordless, to ID-SP protocol developed for the LeanSTATION Bx digital macro-imaging system (Milestone Medical, Kalamazoo, MI). ID-SP documentation gross protocol consisted of sequential digital image recordings: 1-requisition, 2- specimen container label as received and barcoded cassette, 3-container contents as received, 4- tissue placed in cassette with superimposed 1 mm electronic measuring grid. Results: Average time required for ID-SP gross was 76 seconds per specimen vs. 37 seconds for TGP. Histology personnel could refer to gross specimen descriptions at time of embedding whereas actual images of submitted tissues in cassettes were available attached to the case in Pathology PACS system (Apollo PACS, Inc, Falls Church, VA). These images were also available to downstream histology personnel at cutting stations. Pathologists at the time of signout had additional visual quality control checks to confirm patient identification of requisitions, container and cassette labels and submitted tissue. Conclusions: Grossing time of ID-SP protocol was double TGP, but the image protocol provided additional assurance of catching Mis_ID and Mis-COM errors with prospective visual quality control tracking of requisitions and specimens at each workstation from gross to pathologist. In our experience the time difference expended is more than
recouped in the average rework time of 8 man-hours wasted in resolving a MIS-ID case searching for empty specimen containers, interviewing clinical & pathology personnel, performing DNA profiling and amending reports. Further efficiencies in some practices may be obtained with ID-SP work design by eliminating time & bottlenecks in transcription and report correction

Pathology

Fontugne J, Davis K, **Palanisamy N**, Udager A, Mehra R, McDaniel AS, Siddiqui J, Rubin MA, Mosquera JM, and Tomlins SA. Clonal evaluation of prostate cancer foci in biopsies with discontinuous tumor involvement by dual ERG/SPINK1 immunohistochemistry *Mod Pathol* 2016; 29(2):157-165. PMID: 26743468. Full Text

Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, NY, USA.
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The presence of two or more prostate cancer foci separated by intervening benign tissue in a single core is a well-recognized finding on prostate biopsy. Cancer involvement can be measured by including intervening benign tissue or only including the actual cancer involved area. Importantly, this parameter is a common enrollment criterion for active surveillance protocols. We hypothesized that spatially distinct prostate cancer foci in biopsies may arise from separate clones, impacting cancer involvement assessment. Hence, we used dual ERG/SPINK1 immunohistochemistry to determine the frequency of separate clones-when separate tumor foci showed discordant ERG and/or SPINK1 status-in discontinuously involved prostate biopsy cores from two academic institutions. In our cohort of 97 prostate biopsy cores with spatially discrete tumor foci (from 80 patients), discontinuous cancer involvement including intervening tissue ranged from 20 to 100% and Gleason scores ranged from 6 to 9. Twenty-four (25%) of 97 discontinuously involved cores harbored clonally distinct cancer foci by discordant ERG and/or SPINK1 expression status: 58% (14/24) had one ERG(+) focus, and one ERG(-)/SPINK1(-) focus; 29% (7/24) had one SPINK1(+) focus and one ERG(-)/SPINK1(-) focus; and 13% (3/24) had one ERG(+) focus and one SPINK1(+) focus. ERG and SPINK1 overexpression were mutually exclusive in all tumor foci. In summary, our results show that ~25% of discontinuously involved prostate biopsy cores showed tumor foci with discordant ERG/SPINK1 status, consistent with multiclonal disease.

The relatively frequent presence of multiclonality in discontinuously involved prostate biopsy cores warrants studies on the potential clinical impact of clonality assessment, particularly in cases where tumor volume in a discontinuous core may impact active surveillance eligibility.

Pathology

Gadde R, **Barod R**, **Rogers CG**, **Gupta NS**, and **Williamson SR**. The spectrum of oncocytic renal tumors from oncocytoma to eosinophilic variant chromophobe renal cell carcinoma - is there a need to sub-classify and what is the malignant potential? *Lab Invest* 2016; 96:231A-231A. PMID: Not assigned. Abstract

[Gadde, Ramya; Barod, Ravi; Rogers, Craig G.; Gupta, Nilesh S.; Williamson, Sean R.] Henry Ford Hlth Syst, Detroit, MI USA.

Background: Oncocytoma is well-recognized as a benign renal neoplasm, and chromophobe renal cell carcinoma (RCC), whether classic or eosinophilic variant, is generally regarded as having less aggressive behavior than other RCC subtypes. We analyzed oncologic outcomes in our patients with such renal tumors, including oncocytoma, eosinophilic variant chromophobe RCC, classic chromophobe RCC, and tumors with oncocytic morphology that evaded definitive classification. Design: Our pathology database was queried for oncocytomas, chromophobe RCCs, and other oncocytic renal neoplasms (unclassified, hybrid, and borderline tumors) diagnosed between 2006 and 2013. Other tumor subtypes, such as clear cell or papillary RCC with variant oncocytic morphology, were excluded Results: A total of 126 cases were retrieved, including 38 oncocytomas, 31 eosinophilic variant chromophobe RCCs, and 14 oncocytic tumors with inconclusive morphology. These were compared to 43 chromophobe RCC with classic (non-eosinophilic) histology. Follow-up for 83 patients with oncocytic renal tumors, ranged from 1 month to 102 months (median 44), and revealed no adverse events (recurrence or metastasis), including 14 oncocytic tumors that were difficult to definitively classify As a control group, classic chromophobe RCCs were variably larger (0.8 to 23.0 cm, mean 4.9cm), with a subset (10/43) being pT3a, due to vein invasion (1), renal sinus and perinephric fat invasion (1), and perinephric fat invasion (8). Conclusions: Our findings support the benign behavior of oncocytoma and nonaggressive behavior of eosinophilic variant chromophobe RCC and related borderline oncocytic neoplasms. Despite that some tumors exhibit oncocytic morphology that evade definitive classification, outcomes in these patients are generally good, with no disease recurrence or metastasis in this study. Taking into account the indolent behavior of these tumors may aid in designing clinical follow-up strategies and patient counseling, even when features are not perfect for diagnosis of oncocytoma.

Pathology

Gulavita P, Zhou M, Amin MB, Sirohi D, Garcia E, Dal Cin P, **Williamson SR**, and Hirsch M. Morphologic and molecular evaluation of thyroid-like follicular carcinoma of the kidney *Lab Invest* 2016; 96:235A-235A. PMID: Not assigned. Abstract

Brigham & Womens Hosp, 75 Francis St, Boston, MA 02115 USA. NYU, New York, NY USA. Cedars Sinai Med Ctr, Irvine, CA USA. Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Thyroid-like follicular carcinoma of the kidney (TLFCK) is a rare yet emerging subtype of renal cell carcinoma (RCC) that has morphologic resemblance with thyroid neoplasms. Some believe that TLFCK is a variant of papillary RCC, but there is limited supporting evidence for this association. Additionally, morphologic similarity to mesonephric carcinoma of the gynecologic tract (gyn-MC) raises thepossibility that TLFCK may be of mesonephric origin. Design: 10 renal neoplasms, plus 1 renal mesonephric remnant (MR), with morphologicfeatures similar to that seen in thyroid or gyn-MCs were evaluated morphologically, immunophenotypically, and with next generation sequencing (NGSeq) to gain a better understanding of the morphologic features and genetic/molecular alterations. Results: Tumors presented in patients ranging 15-77 years old (1:1 M:F), and ranged from 1 to 16.5 cm (median 3.2 cm). 8 cases were pT1a, 2 pT3. All 10 tumors appeared well circumscribed and had at minimum a tubular architecture, 9 including micro and macrofollicular formation with luminal eosinophilic material. 4 cases

also had papillary features. 9 cases demonstrated nuclear grooves; one had prominent nuclear clearing and pseudoinclusions. All 10 cases were PAX8 and EMA positive, and TTF1 negative. Similar to gyn-MCs and 1 MR, 3 cases were positive for GATA3, CD10 and calretinin; 2 of these were CK7 and AMACR negative. 6 GATA3 negative cases were CK7 and AMACR positive; CD10 and calretinin were also negative. 1 case was negative for all markers except CD10. NGSeq was performed on 7 cases. A total of 40 gene mutations were identified (range 5-11 per case); 6 mutations recurred in 2 cases each. Copy number variation (CNV) was present in 5 cases, including 2 cases with +7/+17. Other chromosomal gains included +2, +8, +12 and +16. No chromosomal loss was seen. 2 cases demonstrated focal copy number gain at the region of SOX9, BCL2, and MET. One pT3a case presented with LN metastases. All patients are negative for active disease (up to 36 months follow-up). Conclusions: These findings demonstrate that RCCs with thyroid-like morphology demonstrate immunoprofiles and chromosomal alterations that overlap with mesonephric and papillary RCC. Interestingly, trisomy 7, 12, 16 and 17 has been previously reported in presumed TLFCK. Additional investigation of the molecular alterations in TLFCK may help gain a better understanding of the pathophysiology of these relatively indolent tumors.

Pathology

Hwang C, Sethi S, Heilbrun LK, **Gupta NS**, **Chitale DA**, Sakr WA, **Menon M**, **Peabody JO**, Smith DW, Sarkar FH, and Heath EI. Anti-androgenic activity of absorption-enhanced 3, 3'-diindolylmethane in prostatectomy patients *Am J Transl Res* 2016; 8(1):166-176. PMID: Not assigned. Full Text

E.I. Heath, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, United States

Consumption of cruciferous vegetables is associated with a decreased risk of developing prostate cancer. Antineoplastic effects of cruciferous vegetables are attributable to bioactive indoles, most prominently, 3, 3'-diindolylmethane (DIM). In addition to effects on proliferation and apoptosis, DIM acts as an antiandrogen in prostate cancer cell lines. This study characterized the effects of prostatic DIM on the androgen receptor (AR) in patients with prostate cancer. Men with localized prostate cancer were treated with a specially formulated DIM capsule designed for enhanced bioavailability (BR-DIM) at a dose of 225 mg orally twice daily for a minimum of 14 days. DIM levels and AR activity were assessed at the time of prostatectomy. Out of 28 evaluable patients, 26 (93%) had detectable prostatic DIM levels, with a mean concentration of 14.2 ng/gm. The mean DIM plasma level on BR-DIM therapy was 9.0 ng/mL; levels were undetectable at baseline and in follow-up samples. AR localization in the prostate was assessed with immunohistochemistry. After BR-DIM therapy, 96% of patients exhibited exclusion of the AR from the cell nucleus. In contrast, in prostate biopsy samples obtained prior to BR-DIM therapy, no patient exhibited AR nuclear exclusion. Declines in PSA were observed in a majority of patients (71%). Compliance was excellent and toxicity was minimal. In summary, BR-DIM treatment resulted in reliable prostatic DIM levels and anti-androgenic biologic effects at well tolerated doses. These results support further investigation of BR-DIM as a chemopreventive and therapeutic agent in prostate cancer.

Pathology

Jamal M, **Williamson SR**, **Diaz-Insua M**, **Menon M**, **Stricker H**, **Peabody J**, **Rogers CG**, and **Gupta NS**. Significance of percentage of gleason pattern 4 at needle biopsy in predicting final gleason score and correlation with pathologic outcomes at radical prostatectomy *Lab Invest* 2016; 96:240A-240A. PMID: Not assigned. Abstract

[Jamal, Mohsin; Williamson, Sean R.; Diaz-Insua, Mireya; Menon, Mani; Stricker, Hans; Peabody, James; Rogers, Craig G.; Gupta, Nilesh S.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: The 2005 ISUP modified Gleason grading scheme resulted in upgrade of some Gleason score (GS) 6 tumors to GS7. Most practices currently provide percentage of higher Gleason patterns in prostate needle biopsies (PNB), with the most common scenario being percentage of Gleason pattern 4 (%G4). The aim of our study was to evaluate the clinical significance of reporting this finding. Design: We analyzed PNBs between 2011 - 2013 with diagnosis of GS7 and 8 prostatic adenocarcinoma (PCa) and

corresponding robotic radical prostatectomy (RRP) specimens. Results: A total of 162 cases with both PNB and RRP specimens were selected. Mean age of these patients was 62 years. The %G4 on biopsy correlated significantly with percentage of positive cores (rho=0.60, p<0.001) and tumor volume (rho=0.52, p<0.001). We stratified the patients into four quartiles based on %G4 on PNB . Q1: %G 4 <=10, Q2: >10% - 20%, Q3: >20% - 50%, Q4: >50%. Correlation of the %G4 quartiles with the GS on RRP is listed in Table 1.For quartiles Q1, Q2 and Q3, there was a significant increase of upgrading in the RRP specimen to 4+3=7 with increase of %G4 on biopsy (p-v=0.005). Likewise, within Q4, there was a significant upgrade of GS in the RRP specimen (from 4+3=7 to 4+4=8 and 4+5=9). Q1 was associated with greater percentage of organ confined disease, and negative lymph nodes (LN). In contrast, Q3 and Q4 were associated with high percentage of established extraprostatic extension, seminal vesicle invasion, angio invasion and positive LN (Table 2). Conclusions: %G4 is a clinically significant parameter that provides valuable information in management of patients with PCa. GS7 PCa with minor %G4 shows favorable pathologic outcome, whereas there is an increase in upgrading and adverse pathologic outcomes with increase in %G4 reported on PNB.

Pathology

Jamal M, **Williamson SR**, **Diaz-Insua M**, **Menon M**, **Stricker H**, **Peabody J**, **Rogers CG**, and **Gupta NS**. Clinical significance of percentage of gleason pattern 4 in gleason score 7 prostate cancer at radical prostatectomy *Lab Invest* 2016; 96:240A-240A. PMID: Not assigned. Abstract

[Jamal, Mohsin; Williamson, Sean R.; Diaz-Insua, Mireya; Menon, Mani; Stricker, Hans; Peabody, James; Rogers, Craig G.; Gupta, Nilesh S.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: We sought to determine the prognostic value of percentage Gleason pattern 4 in radical prostatectomy specimens. Design: We selected 400 patients who underwent robotic radical prostatectomy (RRP) between 2010 and 2011 with Gleason score 7. Data collected included pT stage, tumor volume, margin status, angiolymphatic invasion and lymph node involvement and biochemical recurrence (BCR) at 2 years after surgery. Results: Mean age of the patients was 62 years. We stratified the patients into four quartiles based on percentage of Gleason pattern 4 (GP4). Q1: percent of Gleason 4 <=20, Q2: >20% - 35%, Q3: >35% - 65%, Q4: >65%. Table 1 shows these quartiles correlated with multiple pathological outcomes. Percentage of GP4 was associated with BCR when other pathologic features were accounted for. A percent greater than 65 (i.e. fourth quartile) was significantly different from a percent of 20 or less in providing a greater likelihood for recurrence OR=6.53 (95% CI 2.43, 17.56). The other factors that were also significant were margins, positive lymph nodes and angiolymphatic invasion. These four variables yielded a c-statistic of 0.82. If percentage of GP4 is considered as a continuous measure, it is also independently related with PSA recurrence within 2 years of surgery. A unit increase in the percent of GP4 increases the likelihood of recurrence by 3 percent, OR=1.03 (1.01, 1.04). Conclusions: 1. Gleason 7 prostatic adenocarcinoma represents a heterogenous group of tumors. A subgroup of tumors with Gleason score 3+4=7 with low percentage of GP4 (<=20%) carry favorable prognosis compared to Gleason score 3+4=7 tumors with higher percentage (>20%) of pattern 4. 2. Percentage of GP4 is an important parameter that should be reported on all radical prostatectomies with Gleason score 7, given its independent prognostic value. 3. Additional studies are needed to determine the role of higher Gleason pattern percentages in tumors other than Gleason score 7.

Pathology

Kezlarian B, Cheng L, **Gupta NS**, and **Williamson SR**. Vasitis nodosa and related lesions: A modern immunohistochemical staining profile with special emphasis on diagnostic dilemmas *Lab Invest* 2016; 96:242A-242A. PMID: Not assigned. Abstract

Henry Ford Hlth Syst, Detroit, MI USA. Indiana Univ, Indianapolis, IN 46204 USA.

Background: Vasitis nodosa is a benign proliferation of vas deferens epithelium, thought to be a response to trauma, obstruction, or previous surgical intervention, usually vasectomy. Although diagnosis is usually

straightforward, worrisome histologic features are well-known, such as prominent nucleoli, pseudoinvasive growth pattern, and perineural invasion. We sought to characterize the immunohistochemical staining pattern with a modern antibody panel, with particular emphasis on cases occurring in worrisome clinical scenarios. Design: We queried our database for cases of vasitis or epididymitis nodosa or sperm granuloma, yielding a cohort of 28 specimens. Ultimately, 21 were confirmed to have vasitis nodosa and were included in the final cohort. These, in addition to two posttreatment prostate and bladder carcinomas mimicking vasitis nodosa were stained with antibodies to PAX-8, CD10, p63, racemase (AMACR), prostein and prostate-specific antigen (PSA). Results: Two diagnostically problematic cases of vasitis nodosa included 1) bladder muscle and florid soft tissue involvement in a cystectomy specimen after prostatectomy and 2) involvement of the ampulla and ejaculatory duct in a radical prostatectomy specimen. PAX-8 yielded consistent positive (100%) nuclear staining in the lesional glands, often stronger and more uniform than native vas deferens. CD10 similarly labeled the proliferative glands, in addition to luminal and extra-cellular secretions, and the basement membranes and apical surfaces of native and proliferative glands. Labeling for p63 was basally located, but often markedly attenuated or lacking in the proliferative glands compared to native epithelium. Racemase positivity was variable but often present (18/21). PSA and prostein were consistently (100%) negative. Conclusions: In addition to characterizing the immunohistochemical signature of vasitis nodosa, this study unearthed novel diagnostic pitfalls. Rare problematic lesions include “invasion” of the ejaculatory duct at the prostate and involvement of bladder muscle after prostatectomy. The proliferative vasitis nodosa glands often have a prostate cancer-like staining pattern with variable racemase positivity and negative or patchy p63, in contrast to the native vas deferens. However, reliable positivity for PAX-8 and negative staining for PSA and prostein aid in distinguishing from prostate cancer.

Pathology

Kezlarian B, **Favazza L**, **Arias-Stella J**, **Schultz D**, and **Chitale DA**. Does tumor infiltrating lymphocyte (TIL) count influence oncotype DxTM recurrence score and magee equation scores? *Lab Invest* 2016; 96:49A-49A. PMID: Not assigned. Abstract

[Kezlarian, Brie; Favazza, Laura; Arias-Stella, Javier; Schultz, Daniel; Chitale, Dhananjay A.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Genomic health Inc. -Oncotype DxTM assay (GHI), a RT-PCR based genomic test analyzes the expression of 21 genes to give a distant breast cancer Recurrence Score (RS), stratifying ER+, node negative breast cancer patients for or against chemotherapy. The Magee equations (ME) use standard pathologic and immunohistochemical parameters [estrogen receptor (ER), progesterone receptor (PR), MIB1 proliferation index (PI) and tumor size] to estimate the RS. Proliferation group of genes are heavily weighted in most of these mathematical equations and correlates with PI. TILs generally have high PI. High TIL count is known to indicate good prognosis in breast cancer and is reported to predict sensitivity for chemotherapy. Our aim of this study was to investigate the correlation between TIL, PI, RS, and ME in estrogen receptor positive (ER+) invasive breast cancers (BC). Design: Cases of ER+BC that had GHI-RS results available were identified, tissue microarrays (TMAs) with a 1.0 mm diameter, each case represented in triplicate, were constructed. Multiple clinical and morphologic parameters including histologic features, hormonal status and TMN stage were recorded from electronic pathology report. TMAs were stained with different T lymphocyte markers (CD3, CD4, CD8) and leukocyte common antigen (LCA) to score all the lymphocytes. The average number of positive cells per case was counted. ER+BC were subclassified as Luminal A (ER+/PR+/HER- 2-/Low MIB1), Luminal B (ER+/PR+/HER-2+ or high MIB1 labeling >15%). Pearson correlation was performed to compare clinicopathologic parameters, GHI-RS and ME. Results: A total of 160 cases of breast carcinomas were identified. The average tumor size was 1.7 cm (SD: 1.0, range: 0.4-8.5 cm, median: 1.5 cm). There were 52/160 (32.5%) grade 1, 88/160 (55%) grade 2, 20/160 (12.5%) grade 3 tumors. There were 160/160 (100%) ER+, 139/160 (87%) PR+, 21/160 (13%) PR-, 152/160 (95%) HER2-and 8/160 (5%) HER2+ tumors. The GHI-RS included 94/160 (59%) low RS, 59/160 (37%) intermediate RS, 7/160 (4%) high RS. Pearson correlation between TIL count vs GHI-RS & ME were: GHI-RS : 0.169412 (p=0.0339), ME1=0.298713 (p=0.000226); ME2: 0.235647 (p=0.002974), ME3: 0.339557 (p<0.00002).Conclusions: In this study, the high TIL count in

ER+BC was associated with an elevation of both GHI-RS and ME. More studies to support this observation are necessary for confirmation.

Pathology

Kouba E, Simper N, Eble JN, Grignon DJ, Wang MS, Zhang SB, Wang LS, Martignoni G, **Williamson SR**, Brunelli M, Luchini C, Calio A, and Cheng L. High fidelity of driver chromosomal alterations among primary and metastatic renal cell carcinomas: Implications for disease evolution and treatment *Lab Invest* 2016; 96:243A-243A. PMID: Not assigned. Abstract

Indiana Univ Sch Med, Indianapolis, IN 46202 USA. Fudan Univ, Shanghai Canc Ctr, Shanghai 200433, Peoples R China. Univ Verona, I-37100 Verona, Italy. Henry Ford Hlth Syst, Detroit, MI USA.

Background: Recent studies have demonstrated considerable genomic heterogeneity in both primary and metastatic renal cell carcinomas (RCCs). This mutational diversity has serious implications for the development and implementation of targeted molecular therapies. We evaluated 32 cases of primary RCC with their associated metastatic tumors to determine if the hallmark chromosomal anomalies of these tumors are preserved over the course of disease progression. Design: Thirty two matched pairs of primary and metastatic renal cell carcinomas (21 clear cell RCC, 11 papillary RCC) were analyzed. All tumors were evaluated for chromosome 3p deletion and trisomy 7 and 17 using fluorescence in situ hybridization (FISH).Results: Of the 21 clear cell RCCs, 17 primary tumors (81%) showed a deletion of chromosome 3p. All 17 of the corresponding metastatic tumors displayed the same abnormality. Two additional tumors developed 3p deletion in the metastasis. All clear cell RCCs were disomic for chromosomes 7 and 17. In contrast, 9 of the 11 papillary RCCs (82%) showed trisomy for both chromosomes 7 and 17. These molecular aberrations were conserved in the paired metastatic tumors. Conclusions: Our results demonstrated a high degree of genomic fidelity among the primary and metastatic lesions in renal cell carcinomas. These findings may have important clinical and diagnostic implications.

Pathology

Lindquist KJ, Paris PL, Hoffmann TJ, Cardin NJ, Kazma R, Mefford JA, Simko JP, Ngo V, **Chen Y**, **Levin AM**, **Chitale D**, Helfand BT, Catalona WJ, **Rybicki BA**, and Witte JS. Mutational landscape of aggressive prostate tumors in African American men *Cancer Res* 2016;PMID: 26921337. Full Text

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Prostate cancer is the most frequently diagnosed and second most fatal non-skin cancer among men in the United States. African American men are two times more likely to develop and die of prostate cancer compared with men of other ancestries. Previous whole genome or exome tumor sequencing studies of prostate cancer have primarily focused on men of European ancestry. In this study, we sequenced and characterized somatic mutations in aggressive (Gleason {greater than or equal to}7, stage {greater than or equal to}T2b) prostate tumors from 24 African American patients. We describe the locations and prevalence of small somatic mutations (up to 50 bases in length), copy number aberrations, and structural

rearrangements in the tumor genomes compared with patient-matched normal genomes. We observed several mutation patterns consistent with previous studies, such as large copy number aberrations in chromosome 8 and complex rearrangement chains. However, TMPRSS2-ERG gene fusions and PTEN losses occurred in only 21% and 8% of the African American patients, respectively, far less common than in patients of European ancestry. We also identified mutations that appeared specific to or more common in African American patients, including a novel CDC27-OAT gene fusion occurring in 17% of patients. The genomic aberrations reported in this study warrant further investigation of their biological significance in the incidence and clinical outcomes of prostate cancer in African Americans.

Pathology

Lu ZC, **Williamson SR**, **Diaz-Insua M**, **Stricker H**, **Menon M**, and **Gupta NS**. Pathologic outcomes and biochemical recurrence (BCR) free survival in men younger than 45 years with prostate cancer (PCa) treated with robotic radical prostatectomy (RRP) *Lab Invest* 2016; 96:247A-247A. PMID: Not assigned. Abstract

[Lu, Zhichun; Williamson, Sean R.; Diaz-Insua, Mireya; Stricker, Hans; Menon, Mani; Gupta, Nilesh S.] Henry Ford Hosp, Detroit, MI 48202 USA.

Pathology

Priemer DS, Montironi R, Wang L, **Williamson SR**, Lopez-Beltran A, and Cheng L. Neuroendocrine tumors of the prostate: Emerging insights from molecular data and updates to the 2016 world health organization classification *Endocr Pathol* 2016;PMID: 26885643. Full Text

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Neuroendocrine neoplasms of the prostate represent a multifarious group of tumors that exist both in pure forms and associated with prostatic adenocarcinoma. Morphologically, neuroendocrine cells in prostate neoplasms can range from being indistinguishable from surrounding prostate adenocarcinoma cells to having high-grade neuroendocrine appearances similar to neuroendocrine malignancies of other organs. On the molecular level, neuroendocrine malignancies arising in the setting of prostate adenocarcinoma have been the subject of a large amount of recent research, most of which has supported the conclusion that neuroendocrine malignancy within the prostate develops as a transdifferentiation from prostate adenocarcinoma. There has not, however, been substantial investigation into rare, pure neuroendocrine malignancies and the possibility that these tumors may have a different cell of origin and molecular genesis. Here, we discuss the morphologic spectrum of malignant neuroendocrine prostate neoplasms and review the most recent molecular data on the subject of malignant neuroendocrine differentiation in prostatic adenocarcinoma. In reflection of the most recent data, we also discuss diagnostic classification of prostate neuroendocrine tumors with reference to the 2016 World Health Organization (WHO) classification. We discuss the reporting of these tumors, placing emphasis on the differentiation between pure and mixed neuroendocrine malignancies so that, in the least, they can be easily identified for the

purposes of future clinical and laboratory-based investigation. Finally, we suggest a designation for an unclassifiable (or not otherwise specified) high-grade neuroendocrine prostate malignancy whose features do not easily place it into one of the WHO diagnostic entities.

Pathology

Roquiz W, Pardeshi V, Hassan O, Abdulfatah E, **Modh A**, Salem N, Daaboul M, **Schultz D**, **Elshaikh MA**, Bandyopadhyay S, and Ali-Fehmi R. The impact of androgen receptor expression on endometrial carcinoma *Lab Invest* 2016; 96:306A-307A. PMID: Not assigned. Abstract

Wayne State Univ, Detroit Med Ctr, Detroit, MI USA. Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Endometrial carcinomas (EC) are the most common gynecological cancers. The impact of androgen receptor (AR) on EC is not well studied. The aim of our study is to assess the role of AR expression in endometrial carcinomas.Design: A retrospective review of 261 EC was conducted. H&E slides were reviewed and clinicopathologic parameters were analyzed. Immunohistochemical stains for AR, ER and PR was performed on tissue microarray. The hormonal expression was evaluated using a clinically validated cut-off established by ASCO/CAP. The data was analyzed using the Fisher exact test and Kaplan-Meier survival analysis. Results: Patients age ranged from 31 to 91 (median = 65 years). Type I EC included 202 endometrioid and 7 mucinous carcinoma, whereas Type II included 34 serous, 16 MMMT and 2 clear cell carcinoma. Although not significant, AR expression showed more frequent association with Type I, early FIGO stage (I-II), and low FIGO grade (1- 2) EC. AR expression significantly correlated with absence of lymphovascular invasion (P=0.041) and decreased LN involvement (P=0.048). Patients with AR expression showed increased disease free survival (208 vs 165 months, P=0.008). AR expression had a positive significant correlation with PR (P<0.001) and ER (P=0.037) expression.

Pathology

Rybicki BA, Rundle A, Kryvenko ON, **Mitrache N**, Do KC, **Jankowski M**, **Chitale DA**, **Trudeau S**, Belinsky SA, and Tang D. Methylation in benign prostate and risk of disease progression in men subsequently diagnosed with prostate cancer *Int J Cancer* 2016;PMID: 26860439. Full Text

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In DNA from prostate tumors, methylation patterns in gene promoter regions can be a biomarker for disease progression. It remains unclear whether methylation patterns in benign prostate tissue-prior to malignant transformation-may provide similar prognostic information. To determine whether early methylation events predict prostate cancer outcomes, we evaluated histologically benign prostate specimens from 353 men who eventually developed prostate cancer and received "definitive" treatment (radical prostatectomy [58%] or radiation therapy [42%]). Cases were drawn from a large hospital-based cohort of men with benign prostate biopsy specimens collected between 1990 and 2002. Risk of disease progression associated with methylation was estimated using time-to-event analyses. Average follow-up was over 5 years; biochemical recurrence (BCR) occurred in 91 cases (26%). In White men, methylation of the APC gene was associated with increased risk of BCR, even after adjusting for standard clinical risk factors for prostate cancer progression (adjusted hazard ratio (aHR)=2.26; 95%CI 1.23-4.16). APC methylation was most strongly associated with a significant increased risk of BCR in White men with low prostate specific antigen at cohort entry (HR=3.66; 95%CI 1.51-8.85). In additional stratified analyses, we found that methylation of the RARB gene significantly increased risk of BCR in African American cases who demonstrated methylation of at least one of the other four genes under study (HR=3.80; 95%CI 1.07-13.53). These findings may have implications in the early identification of aggressive prostate cancer as

well as reducing unnecessary medical procedures and emotional distress for men who present with markers of indolent disease.

Pathology

Samuel LP, Balada-Llasat JM, Harrington A, and Cavagnolo R. Multicenter assessment of gram stain error rates *J Clin Microbiol* 2016;PMID: 26888900. Article Request Form

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BACKGROUND: Gram stains remain the cornerstone of diagnostic testing in the microbiology laboratory for the guidance of empiric treatment prior to availability of culture results. Incorrectly interpreted Gram stains may adversely impact patient care and yet there are no comprehensive studies evaluating the reliability of the technique, and no established standards for performance. In this study, clinical microbiology laboratories at four major tertiary medical care centers evaluated Gram stain error rates across all non-blood specimen types using standardized criteria. The study focused on several factors that primarily contribute to errors in the process, including poor specimen quality, smear preparation, and interpretation of the smears. RESULTS: Number of specimens during the evaluation period ranged from 976 to 1864 specimens per site with a total of 6115 specimens. Gram stain results were discrepant from culture for 5% of all specimens. Fifty eight percent of discrepant results were specimens with no organisms reported on Gram stain but significant growth on culture while 42% of discrepant results had reported organisms on Gram stain that were not recovered in culture. Upon review of available slides, 24% (63/263) of discrepant results were due to reader error, which varied significantly based on site (9%-45%). The Gram stain error rate also varied between sites, ranging from 0.4% to 2.7%. CONCLUSIONS: The data demonstrate a significant variability between laboratories in Gram stain performance and affirm the need for ongoing quality assessment by laboratories. Standardized monitoring of Gram stains is an essential quality tool for laboratories and is necessary for the establishment of a quality benchmark across laboratories.

Pathology

Shah A, **Gadde R**, **Arias-Stella J**, **Williamson SR**, and **Gupta NS**. Radical prostatectomy outcomes of prostatic adenocarcinoma diagnosed after initial diagnosis of atypical glands on prostate needle biopsy *Lab Invest* 2016; 96:261A-262A. PMID: Not assigned. Abstract

[Shah, Alpa; Gadde, Ramya; Arias-Stella, Javier; Williamson, Sean R.; Gupta, Nilesh S.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Few studies have reviewed radical prostatectomy (RP) outcomes of prostate adenocarcinoma (PCa) detected on repeat biopsy after initial diagnosis of atypical glands (ATYP). The aim of this study is to review the location, tumor volume, grade, stage, margin and lymph node status of these tumors based on review of PNB and RP parameters. Design: Between 2009-2013, all cases of first-time diagnosis of ATYP on PNB were reviewed. Patients with previous or synchronous biopsy diagnosis of PCa and patients without follow-up biopsy data were excluded. Presence or absence of HGPIN and location of ATYP and HGPIN were noted. Number of positive cores, location, grade, and percentage of PCa was noted on all PNB. All staging and grading parameters of the tumor were recorded on RP.Results: 2471 PNBs were performed during the study period. 283 of these were diagnosed as ATYP. After applying exclusion criteria our final study population consisted of 128 patients with a first-time diagnosis of ATYP. 42 (33%) of these patients developed PCa on repeat biopsy. Vast majority 37/42 (88%) of post-ATYP PCa were within favorable prognostic groups of I and II (see Table 1). Few cases fell in Group III/GS 7 (3+4)—4 (10%), and a rare case in Group V/10 (5+5)—1 (2%).36 cases (85.7%) of PCa on repeat PNB were present at a contiguous location to a previous ATYP diagnosis. Six cases (14.3%) showed PCa in discontiguous location. 14/42 PCa diagnosed on PNB underwent RP at our institution. RP

parameters are listed in Table 2.Conclusions: PCa after initial ATYP diagnosis are low Gleason grade (Prognostic groups I and II) with excellent RP outcomes. It is rare to find low volume high grade PCa within the ATYP group and may be related to sampling on initial PNB. Location of ATYP highly correlates with the final location of PCa both on repeat PNB and RP.

Pathology

Williamson SR, **Chitale DA**, **Favazza L**, **Barod R**, **Rogers CG**, **Palanisamy N**, and **Gupta NS**. Clear cell renal cell tumors with intact VHL and chromosome 3p: how many entities exist? *Lab Invest* 2016; 96:271A-271A. PMID: Not assigned. Abstract

[Williamson, Sean R.; Chitale, Dhananjay A.; Favazza, Laura; Barod, Ravi; Rogers, Craig G.; Palanisamy, Nallasivam; Gupta, Nilesh S.] Henry Ford Hlth Syst, Detroit, MI USA.

Background: Clear cell renal cell carcinoma (RCC) is the most common adult renal cancer. However, there is increasing recognition that other tumors with morphologic similarity are genetically and likely behaviorally distinct, as exemplified by clear cell papillary RCC. We hypothesize that there may be yet other renal tumors currently classified as clear cell RCC that have distinct genetic underpinnings and possibly unique histologic features.
Design: The Cancer Genome Atlas (TCGA) published dataset was queried (cbioportal. org) for clear cell RCC tumors lacking VHL gene mutation and chromosome 3p loss. Genetic alterations were correlated with whole-slide images. Results: Of 418 tumors in the published TCGA clear cell RCC database, 387 had VHL mutation, copy number loss for chromosome 3p, or both (93%). Of the remaining 31 tumors, 27 had whole-slide images for review. Of these, 3 were shown in another study to be translocation RCC, all of which had suggestive histology, including large nests with calcifications, eosinophilic cells, papillae, and sclerotic stroma. Notably, one SFPQ-TFE3 tumor identified by the same study also had VHL mutation, copy number loss for chromosome 3p, and morphology indistinguishable from clear cell RCC. Two tumors had highly vacuolated cell morphology, of which 1 had copy number gain for chromosome 17, suggesting these may represent papillary RCC with florid cytoplasmic vacuolization. One had morphology of clear cell papillary RCC, and 3 had TCEB1 mutation, the features of which have recently been published. Four were high-grade RCC with rhabdoid morphology, and 5 had prominent fibromuscular stroma. The remaining 9 tumors lacked a unifying histologic pattern; however, these exhibited minor unusual
findings, including foamy rather than empty-appearing cytoplasm (n=4), widespread nuclear alignment (n=1), intranuclear cytoplasmic invaginations (n=1), and hyalinized stroma (n=1). Of all 27 tumors, only 6 had other mutations recently recognized in clear cell RCC, including SMARCA4 (n=2), SETD2 (n=2), PBRM1 (n=1), and BAP1 (n=1). Conclusions: The vast majority of clear cell RCC harbor VHL mutation, 3p copy number loss, or both. Of tumors with clear cell histology that lack these alterations, a subset can likely be reclassified as other established or emerging tumor entities. The remaining tumors, such as those with de novo high-grade morphology, fibromuscular stroma, and other subtle histologic variations suggest that a “clear cell” appearance may be a common phenotype of several genetic pathways, for which improved understanding may define new entities and guide prognostication and treatment.

Pathology

Williamson SR, **Gadde R**, Trpkov K, Hirsch M, Srigley JR, Reuter VE, Cheng L, Kunju LP, Barod R, Rogers CG, Delahunt B, Hes O, Eble JN, Zhou M, McKenney JK, Martignoni G, Fleming S, Grignon DJ, Moch H, and **Gupta NS**. Diagnostic criteria for oncocytic renal neoplasms: A survey of specialist renal tumor pathologists *Lab Invest* 2016; 96:270A-270A. PMID: Not assigned. Abstract

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Boston, MA 02115 USA. Univ Dundee, Dundee, Scotland. Univ Zurich Hosp, CH-8091 Zurich, Switzerland.

Background: Renal oncocytoma and chromophobe renal cell carcinoma (RCC) have been long recognized as distinct tumor subtypes; however, it remains unclear if uniform histologic, immunohistochemical, and genetic diagnostic criteria are used in practice. Design: Urologic pathologists with subspeciality interest in the kidney were invited to participate in a survey of diagnostic criteria for oncocytic renal tumors.Results: Responses were received from 17/26 invitees. Histologically, >1 mitotic figure was regarded as most uniformly worrisome (n=10) or incompatible with oncocytoma diagnosis (n=6), whereas focal nuclear wrinkling, focal perinuclear clearing, and multinucleation did not necessarily exclude this diagnosis but may, dependent on extent. Staining techniques most commonly used included: CK7 (94%), KIT (71%), vimentin (65%), colloidal iron (59%), CD10 (53%), and AMACR (41%). Rare CK7-positive cells (≤5%) was regarded as most supportive of oncocytoma, although a staining threshold excluding this diagnosis was not universal. Multiple chromosomal loss was most strongly supportive for chromophobe RCC diagnosis (65%); however, less certainty was reported for gains or a single loss. For tumors with mixed or inconclusive features, many participants use an intermediate diagnostic category (82%) that does not label the tumor as unequivocally benign or malignant, typically “oncocytic neoplasm” or “tumor” with a description. Some (65%), but not all, report outright diagnosis of oncocytoma in needle biopsies. A small minority (3/17) reported having seen oncocytoma-like tumors that metastasized.
Conclusions: The morphologic, immunohistochemical, and genetic characteristics that define oncocytic renal tumors remain incompletely understood. Further studies correlating genetics, outcome, and histology are needed to define which tumors truly warrant classification as carcinomas for patient counseling and follow-up strategies.

Pathology
Williamson SR, Grignon DJ, **Favazza L**, **Gupta NS**, **Chitale DA**, and **Palanisamy N**. Chromosome 6p amplification including the TFEB gene: a novel mechanism of renal cell carcinoma pathogenesis? *Lab Invest* 2016; 96:270A-271A. PMID: Not assigned. Abstract

Henry Ford Hlth Syst, Detroit, MI USA. Indiana Univ, Indianapolis, IN 46204 USA.

Background: Amplification of part of chromosome 6p, which includes almost half of the genes from chromosome 6, has been implicated in aggressive behavior in multiple cancers, although not to our knowledge in renal cell carcinoma. In this study, we report on a cohort of 3 renal cell carcinomas with 6p amplification including the TFEB gene, a member of the microphthalmia transcription factor (MITF) family of genes. Design: Three renal cell carcinomas were identified as having amplification of chromosome 6p including the TFEB gene, 1 via fluorescence in situ hybridization (FISH), and 2 from the Cancer Genome Atlas (TCGA) database. We studied morphology, immunohistochemical staining characteristics, and other genetic alterations in this
cohort. Results: The patients were 2 women and 1 man, ages 28, 61, and 57, respectively. All 3 tumors were infiltrative (pT3a) tubulopapillary neoplasms with variable infiltration of renal sinus fat, renal parenchyma, or vessels (A-B). The youngest patient had regional nodal metastasis at presentation. Amplification of the TFEB region was observed by FISH (C) in 1 tumor, without TFEB or TFE3 rearrangement or loss of chromosome 3p (D). The two TCGA specimens showed selective amplification of a region of chromosome 6p including the TFEB gene, without corresponding amplification of the MALAT1 (Alpha) gene region, the known fusion partner in TFEB translocation. VHL mutation and chromosome 3p loss were not observed, although the young patient had somatic mutation in FH (germline status unknown). FH mutation was lacking in the other TCGA tumor. The 2 tumors with immunohistochemical results were positive for CD10, AMACR, and PAX-2 or PAX-8. One demonstrated patchy positivity for melan-A and cathepsin K, whereas the other was negative for HMB45 and melan-A. Conclusions: In this cohort, 6p amplification was associated with aggressive tubulopapillary histology and lack of genetic alterations of other tumor types. One patient had FH gene mutation in the tumor, although it remains to be studied whether this is exclusively somatic or a manifestation of the hereditary

leiomyomatosis syndrome. Further studies will define whether this represents a unique entity related to MITF gene family alteration.

Pathology

Zarbo RJ, **Felicella M**, and **Gaba AR**. Validation of placental preservation for pathologic examination using the tissueSAFE formalin-free vacuum-sealing system *Lab Invest* 2016; 96:527A-527A. PMID: Not assigned. Abstract

[Zarbo, Richard J.; Felicella, Michelle; Gaba, Arthur R.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: Placentas are the unloved specimens of Labor and Delivery (L&D) and Pathology. Most are normal and not seen in Pathology but require safe systems for storage and disposal. Placentas that require pathologic evaluation present numerous challenges of non-standardized ex vivo time, tissue preservation conditions, timed exposure to formalin-fixation, consumption of high volumes of formalin for proper fixation and expensive disposal of the specimen and associated bucket of bloody formalin as hazardous waste. To address these issues, we have validated a vacuumsealed, formalin-free tissue handling system designed to originate from L&D with intent to control placenta preservation and transport to Pathology for histologic examination.
Design: 8 placentas were transported fresh from L&D to Henry Ford Hospital Pathology. Each was dissected according to protocol with 3 standard sections for immediate formalin fixation. Placentas were then sealed under low vacuum with the TissueSAFE system (Milestone Medical, Kalamazoo, MI) and retrieved for dissection and formalin fixation after storage in vacuum-sealed bags at 4 degrees for 24 hours (8 cases), 48 hours (4 cases) and 72 hours (4 cases). H&E stained slides were independently assessed by 2 placental pathologists using a 3 part scheme of 1) Adequate, 2) Less than optimal, or 3) Inadequate for histologic evaluation. This study was IRB-exempt. Results: All 102 H&E slides were assessed adequate for histologic evaluation. No
degradation of histologic detail was noted between fresh, formalin fixed to delayed fixation after 72 hours of vacuum-sealed cold storage. Conclusions: This histologic validation of vacuum-sealed human placentas allows consideration of differently designed processes for tissue handling by caregivers and pathologists. Potential advantages are controlled preanalytic placenta preservation up to 3 days at refrigerator temperature. Controlled fixation of fresh sections from each preserved placenta markedly reduces the amount of formalin (approximately 1 gallon/placenta) ordinarily used to fix the entire placenta before gross examination. Reduction of formalin at the front-end process of initial fixation translates to reducedback-end disposal of formalin as expensive hazardous waste. Both reductions translate to financial savings to the healthcare system. In L&D practices, this may eliminate formalin from the unit. Additionally, most placentas require disposal and vacuumsealing of individual specimens provides for a safe isolation and disposal avoiding a
fetid waste receptacle in L&D.

Pharmacy

Farhan SY, **Divine G**, **Neme K**, **Pelland D**, **Wautelet S**, **Mikulandric N**, **Ruemenapp K**, **Peres E**, and **Janakiraman N**. Cytomegalovirus and effect on early chimerism in patients with myeloid disorders undergoing stem cell transplantation using reduced toxicity ablative conditioning regimen *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

[Farhan, Shatha Y.; Neme, Klodiana; Pelland, Danielle; Wautelet, Susan; Mikulandric, Nancy; Ruemenapp, Kenneth; Peres, Edward; Janakiraman, Nalini] Henry Ford Hosp, Stem Cell Transplantat Josephine Ford Canc Inst, Hematol Oncol, Detroit, MI 48202 USA. [Divine, George] Henry Ford Hosp, Detroit, MI 48202 USA.

Cytomegalovirus (CMV) remains a significant cause of morbidity after allogeneic hematopoietic stem cell transplantation (SCT). The influence of CMV on the chimerism in reduced toxicity ablative conditioning SCT in myeloid disorders is ill defined. A recent report published in Blood by Sellar et al showed that in patients who received alemtuzumab-based regimen, the group of patients who were recipient positive

(R+)/ Donor negative (D-) had CMV-specific T cells that are exclusively of recipient origin and significantly influenced the chimerism status toward recipients. To explore the impact of seropositivity and seronegativity of CMV in recipients and donors on early chimerism, we undertook a retrospective analysis of patients with myeloid disorders who received four days of fludarabine and busulfan with or without anti-thymocyte globulin (ATG) at our center in the last 10 years. Methods: Chimerism assay was performed using a quantitative fluorescence-based short tandem repeat-polymerase chain reaction (STR-PCR) with capillary electrophoresis for PCR product resolution. Results: 42 patients were identified and included in the study. All patients received fludarabine (40 mg/m2/day x 4 doses), busulfan (3.2mg/kg/dose IV x 4 doses). Of these 42 patients, 25 had anti-thymocyte globulin. There were 28 male and 14 female patients with a median age of 62 years (range 48-74yrs). Median time to follow up was 8 months (0.8-54 months). Disease risk was considered advanced in 21 patients, intermediate in 4 and early in 17. Median blast number at time of SCT was 5%. Stem cell source included peripheral blood in all patients. There were no primary graft failures. Total recipient cell chimerism showed increase or persistence of recipient chimerism in 5/11 (45%) of R+D- vs 2/6 (33.3%) of R-D- in the group of patients who received ATG, p=1.0, with a mean of recipient chimerism at day 100 of 20.4% in the R+D- group compared to a mean of 17% in the R-D- group. In the group who did not get ATG, recipient chimerism persistence or increase was not that different between the R+D- patients 3/4 (75%) compared to 4/4 (100%) in patients who were seronegative for CMV (R-), p=1.0. The mean of recipient chimerism at day 100 in the R+D- no ATG group was 23.25% with a median of 12% while the mean and median at day 100 in the R- no ATG group were 35.25% and 19.5% respectively (p=0.573).When looking at the persistence or increase in recipient chimerism in the group of patients who were R+D-, in those who got ATG it was 45% increase vs 75% increase in those who did not get ATG (p=0.569) with a median of 12% vs 0% respectively (p=0.49). Also increase or persistence of recipient chimerism was 33.3 % in patients who were R- and got ATG vs 100% in R- no ATG patients (p=0.076)with median at day 100 of 0 vs 19.5% (p=0.098). Conclusion: In this small cohort from a single center, we found that in patients with myeloid disorders who received reduced toxicity ablative conditioning regimen, the group of patients who received ATG, there was no statistically significant increase in recipient chimersim in the R+D- group compared to R-D- group. This is different from what Sellar et al found in a small group of patients who received alemtuzumab. These results may indicate a difference between ATG and alemtuzumab in the effect of CMV seropositivity and negativity on the recipient chimerism, which need to be studied further in a larger retrospective or prospective study. This is especially important in myeloid disorders since persistent or increase in recipient chimerism may identify high-risk patient cohorts who may benefit from additional therapeutic interventions.

Public Health Sciences

El-Refai M, **Hrobowski T**, **Peterson EL**, **Wells K**, Spertus JA, **Williams LK**, and **Lanfear DE**. Race and association of angiotensin converting enzyme/angiotensin receptor blocker exposure with outcome in heart failure *J Cardiovasc Med (Hagerstown)* 2015; 16(9):591-596. PMID: 24842464. Full Text

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PURPOSE: Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been established as a mainstay of heart failure treatment. Current data are limited and conflicting regarding the consistency of ACE/ARB benefit across race groups in heart failure. This study aims to clarify this point. METHODS: This was a retrospective study of insured patients with a documented ejection fraction of less than 50%, hospitalized for heart failure between January 2000 and June 2008. Pharmacy claims data were used to estimate ACE/ARB exposure over 6-month rolling windows. The association between ACE/ARB exposure and all-cause hospitalization or death was assessed by proportional hazards regression, with adjustment for baseline covariates and beta-blocker exposure. Further analyses were stratified by race, and included an ACE/ARB x Race interaction term. RESULTS: A total of 1095 patients met inclusion criteria (619 African-American individuals). Median follow-up was 2.1 years. In adjusted models, ACE/ARB exposure was associated with lower risk of death or hospitalization in both groups (African-Americans hazard ratio 0.47, $P < 0.001$; whites hazard ratio 0.55, $P < 0.001$). A formal test for interaction was consistent with similar effects in each group ($P = 0.861$, beta = 0.04).

CONCLUSION: ACE/ARB exposure was equally associated with a protective effect in preventing death or rehospitalization among heart failure patients with systolic dysfunction in both African-American patients and whites.

Public Health Sciences

Farhan SY, **Divine G**, **Neme K**, **Pelland D**, **Wautelet S**, **Mikulandric N**, **Ruemenapp K**, **Peres E**, and **Janakiraman N**. Cytomegalovirus and effect on early chimerism in patients with myeloid disorders undergoing stem cell transplantation using reduced toxicity ablative conditioning regimen *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

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Cytomegalovirus (CMV) remains a significant cause of morbidity after allogeneic hematopoietic stem cell transplantation (SCT). The influence of CMV on the chimerism in reduced toxicity ablative conditioning SCT in myeloid disorders is ill defined. A recent report published in Blood by Sellar et al showed that in patients who received alemtuzumab-based regimen, the group of patients who were recipient positive (R+)/ Donor negative (D-) had CMV-specific T cells that are exclusively of recipient origin and significantly influenced the chimerism status toward recipients. To explore the impact of seropositivity and seronegativity of CMV in recipients and donors on early chimerism, we undertook a retrospective analysis of patients with myeloid disorders who received four days of fludarabine and busulfan with or without anti-thymocyte globulin (ATG) at our center in the last 10 years. Methods: Chimerism assay was performed using a quantitative fluorescence-based short tandem repeat-polymerase chain reaction (STR-PCR) with capillary electrophoresis for PCR product resolution. Results: 42 patients were identified and included in the study. All patients received fludarabine (40 mg/m2/day x 4 doses), busulfan (3.2mg/kg/dose IV x 4 doses). Of these 42 patients, 25 had anti-thymocyte globulin. There were 28 male and 14 female patients with a median age of 62 years (range 48-74yrs). Median time to follow up was 8 months (0.8-54 months). Disease risk was considered advanced in 21 patients, intermediate in 4 and early in 17. Median blast number at time of SCT was 5%. Stem cell source included peripheral blood in all patients. There were no primary graft failures. Total recipient cell chimerism showed increase or persistence of recipient chimerism in 5/11 (45%) of R+D- vs 2/6 (33.3%) of R-D- in the group of patients who received ATG, p=1.0, with a mean of recipient chimerism at day 100 of 20.4% in the R+D- group compared to a mean of 17% in the R-D- group. In the group who did not get ATG, recipient chimerism persistence or increase was not that different between the R+D- patients 3/4 (75%) compared to 4/4 (100%) in patients who were seronegative for CMV (R-), p=1.0. The mean of recipient chimerism at day 100 in the R+D- no ATG group was 23.25% with a median of 12% while the mean and median at day 100 in the R- no ATG group were 35.25% and 19.5% respectively (p=0.573).When looking at the persistence or increase in recipient chimerism in the group of patients who were R+D-, in those who got ATG it was 45% increase vs 75% increase in those who did not get ATG (p=0.569) with a median of 12% vs 0% respectively (p=0.49). Also increase or persistence of recipient chimerism was 33.3 % in patients who were R- and got ATG vs 100% in R- no ATG patients (p=0.076)with median at day 100 of 0 vs 19.5% (p=0.098). Conclusion: In this small cohort from a single center, we found that in patients with myeloid disorders who received reduced toxicity ablative conditioning regimen, the group of patients who received ATG, there was no statistically significant increase in recipient chimersim in the R+D- group compared to R-D- group. This is different from what Sellar et al found in a small group of patients who received alemtuzumab. These results may indicate a difference between ATG and alemtuzumab in the effect of CMV seropositivity and negativity on the recipient chimerism, which need to be studied further in a larger retrospective or prospective study. This is especially important in myeloid disorders since persistent or increase in recipient chimerism may identify high-risk patient cohorts who may benefit from additional therapeutic interventions.

Public Health Sciences

Haque R, Xu XQ, Yood MU, **Cassidy-Bushrow AE**, Van den Eeden SK, and Potosky AL. Cardiovascular disease risk and androgen deprivation therapy in patients with localized prostate cancer *Pharmacoepidemiol Drug Saf* 2015; 24:323-324. PMID: Not assigned. Abstract

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Background: Scant information exists regarding the adverse effects of ADT (androgen deprivation therapy) on cardiovascular disease (CVD) risk among men with localized prostate cancer. As ADT is increasingly being used as primary mono-therapy in such men who undergo conservative treatment, information on adverse cardiac events is critically needed for optimal treatment decision-making. Objectives: Our goal was to examine the association between primary ADT use and the risk of incident CVD among patients with localized prostate cancer. Methods: We conducted a population-based cohort study using comprehensive electronic health records and cancer registry data from the Kaiser Permanente Southern California health plan. All men with newly diagnosed localized prostate cancer (1995–2008), who were not treated with curative intent therapy, and without evidence of CVD at baseline were followed for up to 16 years, through December 2010 (n = 7587). We examined 10 individual CVD events as our primary outcomes, as well as a composite of these outcomes. Cox proportional hazard models with time-varying treatment variables and other covariates were used to assess the direct effect of primary ADT use (administered within 12 months of initial diagnosis) on the time to developing each incident CVD event and the composite CVD events. Race/ethnicity, age, and tumor characteristics, CVD medication use, and CVD risk factors were captured and adjusted to account for confounding by indication. Results: Of the 7587 prostate cancer survivors, nearly 40% of men who did not receive any curative intent therapy initiated ADT within 12 months following initial diagnosis. Rates for each of the 10 individual outcomes were higher for men treated with ADT than for men not exposed to ADT. ADT was associated with increased risk of heart failure (adjusted HR = 1.30, 95%CI: 1.09–1.54, p = 0.0034) and composite CVD events (adjusted HR = 1.24, 95%CI: 1.12–1.38, p < 0.0001). Conclusions: Among men with clinically localized prostate cancer not receiving curative intent therapy, we found increased risk of non-fatal cardiovascular disease with primary ADT use as mono-therapy.

Public Health Sciences

Jiang F, **Cabrera Fernandez DF**, Church J, **Gulati R**, **Taylor A**, **Menon M**, and **Kuriakose P**. Correlation between peripheral blood counts and day 14 bone marrow biopsy in acute myeloid leukemia during induction chemotherapy *Blood* 2015; 126(23):3. PMID: Not assigned. Abstract

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Background Current NCCN guideline recommends that a bone marrow sample be performed 7-10 days (day 14 bone marrow) after completion of induction therapy in newly diagnosed acute myeloid leukemia (AML). However, the value of day 14 bone marrow has been questioned due to the invasive nature of the procedure and lack of specificity pertaining to complete remission in cases of borderline blasts count and cellularity. We examined peripheral blood count and bone marrow from day 0 to day 14, to see if a reduction of peripheral blood correlated and predicted the day 14 bone marrow morphologic changes and complete remission (mCR). Methods We did 10 years retrospective review between year 2004 and 2013 at the Henry Ford Hospital, on patients who had newly diagnosed AML and day 14 bone marrow biopsy. The majority of patients underwent "7+3" or a "7+3"-like regimen for induction chemotherapy. Firstly, we evaluated the relationship of change of peripheral blood count from day 0 to day 14 with blast percentage and cellularity of bone marrow. Spearman correlations coefficients were computed for each pair of

characteristics. Peripheral blood count includes neutrophil (ANC), monocyte, white blood cells (WBC), blast, hemoglobin and platelet. Secondly, we investigated the possible correlation of mCR to peripheral blood and bone marrow changes, using binary univariate logistic regression. mCR as defined by blast percentage <5, absolute neutrophil (ANC) >1000/mm3, platelets>100,000/mm3. Thirdly, we explored differences in peripheral blood counts on day 14 among three bone marrow groups, those with blast percentage <5, 5-20, >20. Results A total of 200 patients were reviewed and 56 patients met the inclusion criteria. Decrease of ANC/WBC correlated with decrease of bone marrow blast/cellularity from day 0 to day 14 (ANC: Blast P ≤ 0.05; ANC: cellularity P ≤ 0.05; WBC: blast P ≤ 0.001, WBC: cellularity P ≤ 0.01). In other words, a larger reduction in ANC/WBC correlated with larger reduction in both blast and cellularity in bone marrow. However, this correlation with bone marrow change was not found in peripheral blast, monocyte, hemoglobin and platelet. We also found that with increasing age, there was less reduction from day 0 to day 14 in bone marrow blast and cellularity. Bone marrow blast and cellularity on day 14 is strongly associated with mCR (P<0.01), the reduction of blast (43.7 +/- 22.86, Odds ratio 1.03 (1.01, 1.06), P=0.012) and cellularity (66.21 +/- 29.98, Odds ratio 1.03 (1.01, 1.05), P=0.003) from day 0 to 14 is also predictive for mCR. Interestingly, there is a trending effect that the reduction of ANC from day 0 to 14 may predict mCR, but it is not statistically significant (Odds ratio 1.22 (1.02, 1.66), P=0.097). The reduction of WBC is not associated with mCR. Furthermore, peripheral blood counts on day 14 are similar among 3 bone marrow groups, those of blast percentage <5, 5-20, and >20% on day 14. Conclusion ANC/WBC decrease from day 0 to day 14 correlated with the decrease in bone marrow blast count and cellularity, and can be used as a predictor for bone marrow change on day 14, but the level of day 14 peripheral blood findings are similar among 3 bone marrow groups (blast percentage <5, 5-20, and >20% on day 14), so it could not be used to predict the level of bone marrow change. Our data confirmed that the significant decrease of bone marrow blast percentage and cellularity from day 0 to 14 predicts mCR. Decrease of ANC from day 0 to 14 may also predict mCR although it is not statistically significant. A larger sample size can be studied in the future to further explore the possibility of using peripheral blood to predict bone marrow changes and mCR. Summary Our data demonstrates a significant reduction of ANC on day 14 after induction therapy in newly diagnosed AML, which correlates with a decrease in bone marrow cellularity and blast percentage. However, a statistically significant association with blast percentage pertaining to mCR was not obtained. In conclusion, while the current findings do not justify replacement of day 14 bone marrow for predicting mCR, further large scale studies are indicated.

Public Health Sciences

Wells KE, **Kim H**, **Havstad S**, and **Woodcroft KJ**. Trends in asthma-related pharmacy fills *Pharmacoepidemiol Drug Saf* 2015; 24:139-140. PMID: Not assigned. Abstract

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Background: National Asthma Education and Prevention Program guidelines recommend inhaled corticosteroids (ICS) plus a long-acting beta-agonist (LABA) as step-up therapy for the management of persistent asthma when ICS alone offers inadequate control of asthma symptoms. The advent of ICS/LABA in a single inhaler may have influenced prescribing trends over time. Objectives: The aim of the study was to investigate the trends in asthma-related pharmacy fills and asthma exacerbations pre- and post-availability of ICS/LABA in a single inhaler. Methods: Detailed longitudinal data on healthcare and medication use from a large covered patient population were used to assess rates of ICS ± LABA, short-acting beta-agonist (SABA), oral corticosteroid (OC) pharmacy fills, and asthma-related exacerbations. Analyses were limited to patients aged 12–56 years with a diagnosis of asthma between 1 January 1999 and 31 December 2011. Patients with a recorded diagnosis of chronic obstructive pulmonary disease were excluded from rate calculations. Time trend analysis was used to identify changes in these rates over time. Results: The analysis comprised 441 867 individuals and 199 797 filled prescriptions for asthma medications from 1 January 1999 to 31 December 2011. The rate of LABA as add-on therapy to ICS in separate inhalers peaked at 117 fills per 100 000 individuals in December of 1999. Within 2.5 years of FDA approval, the fill rate for ICS/LABA in a single inhaler surpassed the monthly rate of ICS fills. Since then, the average fill rate of ICS/LABA more than doubled that of ICS monotherapy (307 vs. 145 fills per 100 000). Rates of SABA fills dropped significantly ($p < 0.0001$) during

the same period. Time trend analysis did not show a statistically significant change in rates of OC fills and asthma-related hospitalizations during the observation period (p = 0.0545, 0.3633 respectively), while asthma-related emergency department visits significantly increased over time (p = 0.0018). Conclusions: ICS/LABA in a single inhaler is the most commonly prescribed asthma controller therapy since 2003. The symptom relief that the addition of LABA provides may motivate regular use, thereby reducing the need for SABAs. There was no reduction in the rate of asthma exacerbations over time.

Public Health Sciences

Lin JC, **Kabbani LS**, **Peterson EL**, **Masabni K**, **Morgan JA**, **Brooks S**, **Wertella KP**, and **Paone G**. Clinical utility of carotid duplex ultrasound prior to cardiac surgery *J Vasc Surg* 2016; 63(3):710-714. PMID: 26916583. Full Text

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OBJECTIVE: Clinical utility and cost-effectiveness of carotid duplex examination prior to cardiac surgery have been questioned by the multidisciplinary committee creating the 2012 Appropriate Use Criteria for Peripheral Vascular Laboratory Testing. We report the clinical outcomes and postoperative neurologic symptoms in patients who underwent carotid duplex ultrasound prior to open heart surgery at a tertiary institution. METHODS: Using the combined databases from our clinical vascular laboratory and the Society of Thoracic Surgery, a retrospective analysis of all patients who underwent carotid duplex ultrasound within 13 months prior to open heart surgery from March 2005 to March 2013 was performed. The outcomes between those who underwent carotid duplex scanning (group A) and those who did not (group B) were compared. RESULTS: Among 3233 patients in the cohort who underwent cardiac surgery, 515 (15.9%) patients underwent a carotid duplex ultrasound preoperatively, and 2718 patients did not (84.1%). Among the patients who underwent carotid screening vs no screening, there was no statistically significant difference in the risk factors of cerebrovascular disease (10.9% vs 12.7%; P = .26), prior stroke (8.2% vs 7.2%; P = .41), and prior transient ischemic attack (2.9% vs 3.3%; P = .24). For those undergoing isolated coronary artery bypass grafting (CABG), 306 (17.8%) of 1723 patients underwent preoperative carotid duplex ultrasound. Among patients who had carotid screening prior to CABG, the incidence of carotid disease was low: 249 (81.4%) had minimal or mild stenosis (<50%); 25 (8.2%) had unilateral moderate stenosis (50%-69%); 10 (3.3%) had bilateral moderate stenosis; 9 (2.9%) had unilateral severe stenosis (70%-99%); 5 (1.6%) had contralateral moderate stenosis; 2 (0.7%) had bilateral severe stenosis; 4 (1.3%) had unilateral occluded with contralateral less than 50% stenosis, 1 (0.3%) had unilateral occluded with contralateral (70%-99%) stenosis; and 1 had bilateral occluded carotid arteries. Primary outcomes of patients who underwent isolated CABG showed no difference in the perioperative mortality (2.9% vs 4.3%; P = .27) and stroke (2.9% vs 2.6%; P = .70) between patients undergoing preoperative duplex scanning and those who did not. Primary outcomes of patients who underwent open heart surgery also showed no difference in the perioperative mortality (5.1% vs 6.9%; P = .14) and stroke (2.6% vs 2.4%; P = .85) between patients undergoing preoperative duplex scanning and those who did not. Operative intervention of severe carotid stenosis prior to isolated CABG occurred in 2 of the 17 patients (11.8%) identified who underwent carotid endarterectomy with CABG. CONCLUSIONS: In this study, the correlation between preoperative duplex-documented high-grade carotid stenosis and postoperative stroke was low. Prudent use of preoperative carotid duplex ultrasound should be based on the presence of cerebrovascular symptoms and the type of open heart surgery.

Public Health Sciences

Lindquist KJ, Paris PL, Hoffmann TJ, Cardin NJ, Kazma R, Mefford JA, Simko JP, Ngo V, **Chen Y**, **Levin AM**, **Chitale D**, Helfand BT, Catalona WJ, **Rybicki BA**, and Witte JS. Mutational landscape of aggressive prostate tumors in African American men *Cancer Res* 2016;PMID: 26921337. Full Text

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Prostate cancer is the most frequently diagnosed and second most fatal non-skin cancer among men in the United States. African American men are two times more likely to develop and die of prostate cancer compared with men of other ancestries. Previous whole genome or exome tumor sequencing studies of prostate cancer have primarily focused on men of European ancestry. In this study, we sequenced and characterized somatic mutations in aggressive (Gleason {greater than or equal to}7, stage {greater than or equal to}T2b) prostate tumors from 24 African American patients. We describe the locations and prevalence of small somatic mutations (up to 50 bases in length), copy number aberrations, and structural rearrangements in the tumor genomes compared with patient-matched normal genomes. We observed several mutation patterns consistent with previous studies, such as large copy number aberrations in chromosome 8 and complex rearrangement chains. However, TMPRSS2-ERG gene fusions and PTEN losses occurred in only 21% and 8% of the African American patients, respectively, far less common than in patients of European ancestry. We also identified mutations that appeared specific to or more common in African American patients, including a novel CDC27-OAT gene fusion occurring in 17% of patients. The genomic aberrations reported in this study warrant further investigation of their biological significance in the incidence and clinical outcomes of prostate cancer in African Americans.

Public Health Sciences

Mawri S, **Michaels A**, **Gibbs J**, **Shah S**, Rao S, Kugelmass A, Lingam N, Arida M, **Jacobsen G**, Rowlandson I, Iyer K, **Khandelwal A**, and **McCord J**. The comparison of physician to computer interpreted electrocardiograms on ST-elevation myocardial infarction door-to-balloon times *Crit Pathw Cardiol* 2016; 15(1):22-25. PMID: 26881816. Full Text

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OBJECTIVE: The purpose of the project was to study the impact that immediate physician electrocardiogram (ECG) interpretation would have on door-to-balloon times in ST-elevation myocardial infarction (STEMI) as compared with computer-interpreted ECGs. METHODS: This was a retrospective cohort study of 340 consecutive patients from September 2003 to December 2009 with STEMI who underwent emergent cardiac catheterization and percutaneous coronary intervention. Patients were stratified into 2 groups based on the computer-interpreted ECG interpretation: those with acute myocardial infarction identified by the computer interpretation and those not identified as acute myocardial infarction. Patients (n = 173) from September 2003 to June 2006 had their initial ECG reviewed by the triage nurse, while patients from July 2006 to December 2009 (n = 167) had their ECG reviewed by the emergency department physician within 10 minutes. Times for catheterization laboratory activation and percutaneous coronary intervention were recorded in all patients. RESULTS: Of the 340

patients with confirmed STEMI, 102 (30%) patients were not identified by computer interpretation. Comparing the prior protocol of computer ECG to physician interpretation, the latter resulted in significant improvements in median catheterization laboratory activation time {19 minutes [interquartile range (IQR): 10-37] vs. 16 minutes [IQR: 8-29]; P < 0.029} and in median door-to-balloon time [113 minutes (IQR: 86-143) vs. 85 minutes (IQR: 62-106); P < 0.001]. CONCLUSION: The computer-interpreted ECG failed to identify a significant number of patients with STEMI. The immediate review of ECGs by an emergency physician led to faster activation of the catheterization laboratory, and door-to-balloon times in patients with STEMI.

Public Health Sciences

Ownby D, and **Johnson CC**. Recent understandings of pet allergies *F1000Res* 2016; 5PMID: 26918180. Full Text

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Allergic reactions to pets have been recognized for at least a hundred years. Yet our understanding of the effects of all of the interactions between pet exposures and human immune responses continues to grow. Allergists, epidemiologists, and immunologists have spent years trying to better understand how exposures to pet allergens lead to allergic sensitization (the production of allergen-specific immunoglobulin class E [IgE] antibodies) and subsequent allergic disease. A major new development in this understanding is the recognition that pet exposures consist of not only allergen exposures but also changes in microbial exposures. Exposures to certain pet-associated microbes, especially in the neonatal period, appear to be able to dramatically alter how a child's immune system develops and this in turn reduces the risk of allergic sensitization and disease. An exciting challenge in the next few years will be to see whether these changes can be developed into a realistic preventative strategy with the expectation of significantly reducing allergic disease, especially asthma.

Public Health Sciences

Petraszko A, **Siegal D**, **Flynn M**, **Rao SD**, **Peterson E**, and **van Holsbeeck M**. The advantages of tomosynthesis for evaluating bisphosphonate-related atypical femur fractures compared to radiography *Skeletal Radiol* 2016;PMID: 26861160. Full Text

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OBJECTIVE: To investigate the advantages of using tomosynthesis (TS) compared to radiographs in the detection, characterization, and follow-up of bisphosphonate-related atypical femur fractures (BP-AFF). SUBJECTS AND METHODS: Eight patients were identified retrospectively who underwent TS for radiographic findings suspicious for BP-AFF. Two radiologists independently interpreted 15 radiographs and 16 TS examinations, indicating the presence or absence of the following: (1) cortical "beaking" on radiographs, (2) radiolucent fracture line on radiographs, and (3) fracture lucency on TS corresponding to the site of radiographic abnormality. Radiation dose data were calculated for radiographs and TS using Monte Carlo analysis. RESULTS: There was agreement on 100 % of radiographs regarding the presence

or absence of a cortical beak. Regarding the presence or absence of a fracture lucency, there was agreement on 100 % of TS examinations (Kappa = 1.0) and 73 % of radiographs (Kappa = 0.40 +/- 0.24). For the 46 % of radiographs in which one or both radiologists did not visualize a fracture line, there was 100 % agreement for the presence of a fracture line on the corresponding TS. The interobserver agreement for fracture line detection was significantly higher for TS than for radiographs (p = 0.012). The effective radiation dose using TS was approximately 96 % lower compared to radiography. CONCLUSION: TS outperformed radiographs in the detection and characterization of BP-AFF. TS may also have advantages over radiography for BP-AFF follow-up through its unique ability to visualize fracture healing with lower effective radiation doses to the patient.

Public Health Sciences

Petraszko A, **Siegal D**, **Flynn M**, **Rao SD**, **Peterson E**, and **van Holsbeeck M**. Erratum to: The advantages of tomosynthesis for evaluating bisphosphonate-related atypical femur fractures compared to radiography *Skeletal Radiol* 2016;PMID: 26899141. Full Text

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Public Health Sciences

Rybicki BA, Rundle A, Kryvenko ON, **Mitrache N**, Do KC, **Jankowski M**, **Chitale DA**, **Trudeau S**, Belinsky SA, and Tang D. Methylation in benign prostate and risk of disease progression in men subsequently diagnosed with prostate cancer *Int J Cancer* 2016;PMID: 26860439. Full Text

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In DNA from prostate tumors, methylation patterns in gene promoter regions can be a biomarker for disease progression. It remains unclear whether methylation patterns in benign prostate tissue-prior to malignant transformation-may provide similar prognostic information. To determine whether early methylation events predict prostate cancer outcomes, we evaluated histologically benign prostate specimens from 353 men who eventually developed prostate cancer and received "definitive" treatment (radical prostatectomy [58%] or radiation therapy [42%]). Cases were drawn from a large hospital-based cohort of men with benign prostate biopsy specimens collected between 1990 and 2002. Risk of disease progression associated with methylation was estimated using time-to-event analyses. Average follow-up was over 5 years; biochemical recurrence (BCR) occurred in 91 cases (26%). In White men, methylation of the APC gene was associated with increased risk of BCR, even after adjusting for standard clinical risk factors for prostate cancer progression (adjusted hazard ratio (aHR)=2.26; 95%CI 1.23-4.16). APC methylation was most strongly associated with a significant increased risk of BCR in White men with low prostate specific antigen at cohort entry (HR=3.66; 95%CI 1.51-8.85). In additional stratified analyses, we

found that methylation of the RARB gene significantly increased risk of BCR in African American cases who demonstrated methylation of at least one of the other four genes under study (HR=3.80; 95%CI 1.07-13.53). These findings may have implications in the early identification of aggressive prostate cancer as well as reducing unnecessary medical procedures and emotional distress for men who present with markers of indolent disease.

Public Health Sciences

Toubia T, **Schiff L**, **Wegienka G**, and **Sangha R**. Extended length of stay after robotic-assisted hysterectomy: Association with uterine weight and other risk factors *J Gynecol Surg* 2016; 32(1):19-23. PMID: Not assigned. Article Request Form

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Background: Robotic-assisted hysterectomy (RH) has the same clinical benefits as laparoscopy and offers surgeons additional benefits. However, RH-related costs are high and its clinical benefits have not been shown to be better than those achieved with laparoscopy. A key cost factor is the length of (hospital) stay (LOS). Objective: The aim of this study was to identify the relationship between uterine weight and LOS following RH and potential risk factors for extended LOS. Materials and Methods: This study involved a retrospective cohort of all RHs performed in a midwestern tertiary-care teaching hospital and its suburban affiliates, from January 2011 to December 2012. Data were collected using Current Procedural Terminology codes. The current authors examined if any of several variables were associated with uterine weight, using Spearman's correlation for continuous variables and Wilcoxon's rank sum or Kruskal-Wallis test for categorical variables. Comparison of variables between patients who did and who did not have a LOS>1 day was performed using a Wilcoxon rank sum test for continuous variables and a Chi-square or Fisher's exact test for categorical variables. Those that were associated with both uterine weight and LOS were considered as potential confounders and were included in the logistic regression model. The adjusted odds ratio (OR) for a 100-g increase in uterine weight was calculated. Results: Of 239 patients who underwent RH, 48 (20%) had a LOS>1 day. Uterine weight was significantly greater among patients with LOS>1 day (483 g versus 337 g; p=0.008). Patients who had LOS>1 day had a greater estimated blood loss (EBL; means: 178 mL versus 95 mL; p=0.006) and a significantly longer procedure duration (means: 236 minutes versus 168 minutes; p<0.005), compared to patients with LOS=1. In addition, patients with LOS>1 day had higher baseline pain scores (4.5 versus 3.2; p=0.003). Number of ports and oophorectomy were both significantly associated with LOS. For a 100-g increase in uterine weight, there was 1.12 times the odds of having LOS>1 day (OR=1.12; 95% confidence interval: 1.02, 1.21). After controlling for procedure duration, EBL, number of ports, transfusion rates and oophorectomy, the adjusted OR (aOR) was not significant (aOR=1.0; CI: 0.89, 1.12). Conclusions: When adjusted for procedure duration, EBL, number of ports, transfusion rates, and oophorectomy, uterine weight was not associated with LOS after RH. Larger studies are needed to explore further the associations among procedure duration, EBL, baseline pain scores, oophorectomy, and number of ports used with prolonged LOS after RH. Pain management seemed to be the single greatest indication for increased LOS after RH. (J GYNECOL SURG 32:19)

Pulmonary

Hohenforst-Schmidt W, Zarogoulidis P, Pitsiou G, Linsmeier B, Tsavlis D, Kioumis I, Papadaki E, Freitag L, Tsiouda T, Turner JF, Browning R, **Simoff M**, Sachpekidis N, Tsakiridis K, Zaric B, Yarmus L, Baka S, Stratakos G, and Rittger H. Drug eluting stents for malignant airway obstruction: A critical review of the literature *J Cancer* 2016; 7(4):377-390. PMID: 26918052. Full Text

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Lung cancer being the most prevalent malignancy in men and the 3(rd) most frequent in women is still associated with dismal prognosis due to advanced disease at the time of diagnosis. Novel targeted therapies are already on the market and several others are under investigation. However non-specific cytotoxic agents still remain the cornerstone of treatment for many patients. Central airways stenosis or obstruction may often complicate and decrease quality of life and survival of these patients. Interventional pulmonology modalities (mainly debulking and stent placement) can alleviate symptoms related to airways stenosis and improve the quality of life of patients. Mitomycin C and sirolimus have been observed to assist a successful stent placement by reducing granuloma tissue formation. Additionally, these drugs enhance the normal tissue ability against cancer cell infiltration. In this mini review we will concentrate on mitomycin C and sirolimus and their use in stent placement.

Pulmonary

Ost DE, Ernst A, Lei XD, Kovitz KL, Benzaquen S, **Diaz-Mendoza J**, **Greenhill S**, Toth J, Feller-Kopman D, Puchalski J, Baram D, Karunakara R, Jimenez CA, Filner JJ, Morice RC, Eapen GA, Michaud GC, Estrada-Y-Martin RM, Rafeq S, Grosu HB, **Ray C**, Gilbert CR, Yarmus LB, **Simoff M**, and Registry AQB. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions results of the AQuIRE registry *Am J Respir Crit Care Med* 2016; 193(1):68-77. PMID: 26367186. Full Text

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Rationale: Advanced bronchoscopy techniques such as electromagnetic navigation (EMN) have been studied in clinical trials, but there are no randomized studies comparing EMN with standard bronchoscopy. Objectives: To measure and identify the determinants of diagnostic yield for bronchoscopy in patients with peripheral lung lesions. Secondary outcomes included diagnostic yield of different sampling techniques, complications, and practice pattern variations. Methods: We used the AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) registry to conduct a multicenter study

of consecutive patients who underwent transbronchial biopsy (TBBx) for evaluation of peripheral lesions. Measurements and Main Results: Fifteen centers with 22 physicians enrolled 581 patients. Of the 581 patients, 312 (53.7%) had a diagnostic bronchoscopy. Unadjusted for other factors, the diagnostic yield was 63.7% when no radial endobronchial ultrasound (r-EBUS) and no EMN were used, 57.0% with r-EBUS alone, 38.5% with EMN alone, and 47.1% with EMN combined with r-EBUS. In multivariate analysis, peripheral transbronchial needle aspiration (TBNA), larger lesion size, nonupper lobe location, and tobacco use were associated with increased diagnostic yield, whereas EMN was associated with lower diagnostic yield. Peripheral TBNA was used in 16.4% of cases. TBNA was diagnostic, whereas TBBx was nondiagnostic in 9.5% of cases in which both were performed. Complications occurred in 13 (2.2%) patients, and pneumothorax occurred in 10 (1.7%) patients. There were significant differences between centers and physicians in terms of case selection, sampling methods, and anesthesia. Medical center diagnostic yields ranged from 33 to 73% (P = 0.16). Conclusions: Peripheral TBNA improved diagnostic yield for peripheral lesions but was underused. The diagnostic yields of EMN and r-EBUS were lower than expected, even after adjustment.

Radiation Oncology

Roquiz W, Pardeshi V, Hassan O, Abdulfatah E, **Modh A**, Salem N, Daaboul M, **Schultz D**, **Elshaikh MA**, Bandyopadhyay S, and Ali-Fehmi R. The impact of androgen receptor expression on endometrial carcinoma *Lab Invest* 2016; 96:306A-307A. PMID: Not assigned. Abstract

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Background: Endometrial carcinomas (EC) are the most common gynecological cancers. The impact of androgen receptor (AR) on EC is not well studied. The aim of our study is to assess the role of AR expression in endometrial carcinomas.Design: A retrospective review of 261 EC was conducted. H&E slides were reviewed and clinicopathologic parameters were analyzed. Immunohistochemical stains for AR, ER and PR was performed on tissue microarray. The hormonal expression was evaluated using a clinically validated cut-off established by ASCO/CAP. The data was analyzed using the Fisher exact test and Kaplan-Meier survival analysis. Results: Patients age ranged from 31 to 91 (median = 65 years). Type I EC included 202 endometrioid and 7 mucinous carcinoma, whereas Type II included 34 serous, 16 MMMT and 2 clear cell carcinoma. Although not significant, AR expression showed more frequent association with Type I, early FIGO stage (I-II), and low FIGO grade (1- 2) EC. AR expression significantly correlated with absence of lymphovascular invasion (P=0.041) and decreased LN involvement (P=0.048). Patients with AR expression showed increased disease free survival (208 vs 165 months, P=0.008). AR expression had a positive significant correlation with PR (P<0.001) and ER (P=0.037) expression.

Radiology

Petraszko A, **Siegal D**, **Flynn M**, **Rao SD**, **Peterson E**, and **van Holsbeeck M**. The advantages of tomosynthesis for evaluating bisphosphonate-related atypical femur fractures compared to radiography *Skeletal Radiol* 2016;PMID: 26861160. Full Text

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OBJECTIVE: To investigate the advantages of using tomosynthesis (TS) compared to radiographs in the detection, characterization, and follow-up of bisphosphonate-related atypical femur fractures (BP-AFF). SUBJECTS AND METHODS: Eight patients were identified retrospectively who underwent TS for radiographic findings suspicious for BP-AFF. Two radiologists independently interpreted 15 radiographs and 16 TS examinations, indicating the presence or absence of the following: (1) cortical "beaking" on radiographs, (2) radiolucent fracture line on radiographs, and (3) fracture lucency on TS corresponding to the site of radiographic abnormality. Radiation dose data were calculated for radiographs and TS using Monte Carlo analysis. RESULTS: There was agreement on 100 % of radiographs regarding the presence or absence of a cortical beak. Regarding the presence or absence of a fracture lucency, there was agreement on 100 % of TS examinations (Kappa = 1.0) and 73 % of radiographs (Kappa = 0.40 +/- 0.24). For the 46 % of radiographs in which one or both radiologists did not visualize a fracture line, there was 100 % agreement for the presence of a fracture line on the corresponding TS. The interobserver agreement for fracture line detection was significantly higher for TS than for radiographs (p = 0.012). The effective radiation dose using TS was approximately 96 % lower compared to radiography. CONCLUSION: TS outperformed radiographs in the detection and characterization of BP-AFF. TS may also have advantages over radiography for BP-AFF follow-up through its unique ability to visualize fracture healing with lower effective radiation doses to the patient.

Radiology

Petraszko A, **Siegal D**, **Flynn M**, **Rao SD**, **Peterson E**, and **van Holsbeeck M**. Erratum to: The advantages of tomosynthesis for evaluating bisphosphonate-related atypical femur fractures compared to radiography *Skeletal Radiol* 2016;PMID: 26899141. Full Text

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Rheumatology

Li B, Singer NG, **Yeni YN**, **Haggins DG**, Barnboym E, **Oravec D**, Lewis S, and Akkus O. A point of care Raman spectroscopy based device to diagnose gout and pseudogout: Comparison with the clinical standard microscopic analysis *Arthritis Rheumatol* 2016;PMID: 26882173. Full Text

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OBJECTIVE: To demonstrate the usefulness of a novel medical device based on Raman spectroscopy for rapid point of care diagnosis of gout and pseudogout. METHODS: A shoebox sized point of care

Raman (POCR) device was developed for gout and pseudogout diagnoses. The device included a disposable syringe microfiltration kit to collect arthropathic crystals from synovial fluid and a customized automated Raman spectrometry system to identify crystal species chemically. The POCR diagnosis was compared with the clinical standard compensated polarized light microscopic (CPLM) analysis of synovial fluid aspirates (N = 174) collected from symptomatic patients. Kappa coefficients were used to measure the agreement between POCR and CPLM. RESULT: Overall, POCR and CPLM analyses agreed in 89.7% of samples (156 out of 174). In diagnosing gout, the Kappa coefficient for POCR and CPLM was 0.84 (95% CI 0.75-0.94). In diagnosing pseudogout, the Kappa coefficient for POCR and CPLM was 0.61 (95% CI 0.42-0.81). CONCLUSION: Kappa coefficients indicated that POCR and CPLM had excellent agreement in diagnosing gout, and good agreement in diagnosing pseudogout. The POCR device holds the potential to standardize and expedite the time to clinical diagnosis of gout and pseudogout, especially in settings where certified operators trained for CPLM analysis are absent.

Sleep Medicine
Kalmbach DA, **Pillai V**, Arnedt JT, and **Drake CL**. Identifying at-risk individuals for insomnia using the ford insomnia response to stress test *Sleep* 2016; 39(2):449-456. PMID: 26446111. Full Text

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Study Objectives: A primary focus of the National Institute of Mental Health's current strategic plan is "predicting" who is at risk for disease. As such, the current investigation examined the utility of premorbid sleep reactivity in identifying a specific and manageable population at elevated risk for future insomnia. Methods: A community-based sample of adults (n = 2,892; 59.3% female; 47.9 +/- 13.3 y old) with no lifetime history of insomnia or depression completed web-based surveys across three annual assessments. Participants reported parental history of insomnia, demographic characteristics, sleep reactivity on the Ford Insomnia in Response to Stress Test (FIRST), and insomnia symptoms. DSM-IV diagnostic criteria were used to determine insomnia classification. Results: Baseline FIRST scores were used to predict incident insomnia at 1-y follow-up. Two clinically meaningful FIRST cutoff values were identified: FIRST = 16 (sensitivity 77%; specificity 50%; odds ratio [OR] = 2.88, P < 0.001); and FIRST = 18 (sensitivity 62%; specificity 67%; OR = 3.32, P < 0.001). Notably, both FIRST cut-points outperformed known maternal (OR = 1.49-1.59, P < 0.01) and paternal history (P = NS) in predicting insomnia onset, even after controlling for stress exposure and demographic characteristics. Of the incident cases, insomniacs with highly reactive sleep systems reported longer sleep onset latencies (FIRST = 16: 65 min; FIRST = 18: 68 min) than participants with nonreactive insomnia (FIRST < 16: 37 min; FIRST < 18: 44 min); these groups did not differ on any other sleep parameters. Conclusions: The current study established a cost-and time-effective strategy for identifying individuals at elevated risk for insomnia based on trait sleep reactivity. The FIRST accurately identifies a focused target population in which the psychobiological processes complicit in insomnia onset and progression can be better investigated, thus improving future preventive efforts.

Sleep Medicine
Ondo WG, Grieger F, Moran K, Kohnen R, and **Roth T**. Post hoc analysis of data from two clinical trials evaluating the minimal clinically important change in international restless legs syndrome sum score in patients with restless legs syndrome (Willis-Ekbom Disease) *J Clin Sleep Med* 2016; 12(1):63-70. PMID: 26446245. Full Text

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STUDY OBJECTIVES: Determine the minimal clinically important change (MCIC), a measure determining the minimum change in scale score perceived as clinically beneficial, for the international restless legs syndrome (IRLS) and restless legs syndrome 6-item questionnaire (RLS-6) in patients with moderate to severe restless legs syndrome (RLS/Willis-Ekbom disease) treated with the rotigotine transdermal system. METHODS: This post hoc analysis analyzed data from two 6-mo randomized, double-blind, placebo-controlled studies (SP790 [NCT00136045]; SP792 [NCT00135993]) individually and as a pooled analysis in rotigotine-treated patients, with baseline and end of maintenance IRLS and Clinical Global Impressions of change (CGI Item 2) scores available for analysis. An anchor-based approach and receiver operating characteristic (ROC) curves were used to determine the MCIC for the IRLS and RLS-6. We specifically compared "much improved vs minimally improved," "much improved/very much improved vs minimally improved or worse," and "minimally improved or better vs no change or worse" on the CGI-2 using the full analysis set (data as observed). RESULTS: The MCIC IRLS cut-off scores for SP790 and SP792 were similar. Using the pooled SP790+SP792 analysis, the MCIC total IRLS cut-off score (sensitivity, specificity) for "much improved vs minimally improved" was -9 (0.69, 0.66), for "much improved/very much improved vs minimally improved or worse" was -11 (0.81, 0.84), and for "minimally improved or better vs no change or worse" was -9 (0.79, 0.88). MCIC ROC cut-offs were also calculated for each RLS-6 item. CONCLUSIONS: In patients with RLS, the MCIC values derived in the current analysis provide a basis for defining meaningful clinical improvement based on changes in the IRLS and RLS-6 following treatment with rotigotine.

Surgery

Bisleri G, Tononi L, **Morgan JA**, Bordonali T, Cheema FH, Siddiqui OT, Repossini A, Rosati F, and Muneretto C. Separation of mediastinal shed blood during aortic valve surgery elicits a reduced inflammatory response *J Cardiovasc Med (Hagerstown)* 2016; 17(1):62-68. PMID: 24933196. Full Text

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AIMS: The detrimental effects of inflammation following cardiopulmonary bypass (CPB) could negatively affect the postoperative outcome in a specific subset of high-risk patients. We therefore investigated the impact of a CPB circuit (Admiral, Eurosets, Italy) that allows separation of intracavitary and mediastinal blood on the release of biochemical markers and clinical outcome when compared with a conventional circuit. METHODS: Thirty patients undergoing aortic valve surgery were prospectively enrolled and assigned to Admiral group (Group 1, G1, n = 15) or conventional CPB group (Group 2, G2, n = 15). The Admiral oxygenator allows for a separate collection of mediastinal blood processed through a cell-saver before retransfusion. Clinical data and biochemical parameters were measured preoperatively, during CPB and at different time-points postoperatively. RESULTS: Preoperative demographics, intraoperative data (as CPB and aortic cross-clamping time) and perioperative complications did not differ between groups. Inflammatory response was significantly decreased in G1, as assessed by means of D-dimer (G1 = 1332.3 +/- 953.9 vs. G2 = 2791.9 +/- 1740.7 ng/ml, P = 0.02), C-reactive protein (G1 = 169.1 +/- 164.8 vs. G2 = 57.1 +/- 39.3 mg/l, P = 0.04), interleukin-6 (G1 = 11.8 +/- 12.5 vs. G2 = 26.5 +/- 24.9 pg/ml, P = 0.02) and tumour necrosis factor-alpha (G1 = 29 +/- 28.7 vs. G2 = 45.5 +/- 23.6 pg/ml, P = 0.03). CONCLUSION: Although no considerable difference was detected in terms of perioperative outcomes, the Admiral oxygenator did result in a significant reduction of inflammatory markers during the early postoperative course.

Surgery

Fontana RJ, Brown RS, Moreno-Zamora A, Prieto M, Joshi S, Londono MC, Herzer K, Chacko KR, Stauber RE, Knop V, **Jafri SM**, Castells L, Ferenci P, Torti C, Durand CM, Loiacono L, Lionetti R, Bahirwani R, Weiland O, Mubarak A, ElSharkawy AM, Stadler B, Montalbano M, Berg C, Pellicelli AM, Stenmark S, Vekeman F, Ionescu-Ittu R, Emond B, and Reddy KR. Daclatasvir combined with sofosbuvir or simeprevir in liver transplant recipients with severe recurrent hepatitis C infection *Liver Transpl* 2016;PMID: 26890629. Article Request Form

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Daclatasvir is a potent, pangenotypic NS5A inhibitor with demonstrated antiviral efficacy when combined with sofosbuvir or simeprevir with or without ribavirin in patients with chronic hepatitis C virus (HCV) infection. Herein, we report efficacy and safety data for daclatasvir-based all-oral antiviral therapy in liver transplant (LT) recipients with severe recurrent HCV. Daclatasvir 60 mg/day was administered for up to 24 weeks as part of a compassionate use protocol. The study included 97 LT recipients with a mean age of 59.3 +/- 8.2 years; 93% had genotype 1 HCV and 31% had biopsy-proven cirrhosis between the time of LT and the initiation of daclatasvir. The mean MELD score was 13.0 +/- 6.0, and the proportion with CTP A/B/C was 51%/31%/12%, respectively. Mean HCV RNA at daclatasvir initiation was 14.3 x 6 log10 IU/mL, and 37% had severe cholestatic HCV infection. Antiviral regimens were selected by the local investigator and included daclatasvir/sofosbuvir (n = 77), daclatasvir/simeprevir (n = 18), and daclatasvir/simeprevir/sofosbuvir (n = 2); 35% overall received ribavirin. At the end of treatment (EOT) and 12 weeks after EOT, 88 (91%) and 84 patients (87%), respectively, were HCV-RNA negative or had levels < 43 IU/mL. CTP and MELD scores significantly improved between daclatasvir-based treatment initiation and last contact. Three virological breakthroughs and 2 relapses occurred in patients treated with daclatasvir/simeprevir with or without ribavirin. None of the 8 patient deaths (6 during and 2 after

therapy) were attributed to therapy. CONCLUSION: Daclatasvir-based all-oral antiviral therapy was well tolerated and resulted in a high SVR in LT recipients with severe recurrent HCV infection. Most treated patients experienced stabilization or improvement in their clinical status.

Surgery
Go PH, **Nemeh HW**, **Borgi J**, **Paone G**, and **Morgan JA**. Effect of body mass index on outcomes in left ventricular assist device recipients *J Card Surg* 2016;PMID: 26856974. Full Text

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BACKGROUND AND AIM: Obesity is associated with higher mortality following heart transplantation, but there remains no consensus regarding outcomes in left ventricular assist device (LVAD) recipients. We sought to determine the impact of body mass index (BMI) on outcomes in patients undergoing LVAD implantation. METHODS: This was a single-institution retrospective review, including all patients who received a HeartMate II LVAD or HeartWare HVAD between March 2006 and June 2014. Patients were stratified into three groups based on normal (<25 kg/m2), overweight (25-30 kg/m2), and obese (>30 kg/m2) BMI. RESULTS: Two hundred patients were included in the analysis. Mean BMI was 28.3 kg/m2 , (27% normal, 36% overweight, and 36.5% obese). Obese patients were younger (51.9 years, p = 0.03) and had higher incidence of diabetes (58.9% vs. 24.1%; p < 0.001) and peripheral vascular disease (16.4% vs. 1.9%; p = 0.03). Normal BMI patients were more likely to undergo LVAD implantation as destination therapy compared to the overweight and obese groups (67% vs. 39% vs. 51%; p = 0.01) and had higher incidence of postoperative stroke/transient ischemic attack (22.2% vs. 6.9% vs. 12.3%; p = 0.04) and postoperative bleeding requiring reoperation (27.8% vs. 12.5% vs. 9.6%; p = 0.01). Survival at one, three, and five years was similar across all BMI groups. BMI was not an independent predictor of overall survival. CONCLUSIONS: Appropriately-selected patients at the extremes of BMI can safely undergo LVAD implantation with no difference in survival. BMI should not in itself be considered a contraindication to LVAD placement.

Surgery
Hammoud Z. The 5 most important recent publications regarding robotic esophageal surgery *Semin Thorac Cardiovasc Surg* 2016; ePub ahead of printPMID: Not assigned. Full Text

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Robotic-assisted minimally invasive esophagectomy is gaining acceptance as a safe and effective alternative to open esophagectomy.

Surgery
Kolbe N, Sisson K, and Albaran R. Abdominal pain and hematuria: duodenal perforation from ingested foreign body causing ureteral obstruction and hydronephrosis *J Surg Case Rep* 2016; 2016(2)PMID: 26903557. Full Text

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Foreign body (FB) ingestion is a relatively common reason for visits to the emergency room. If the FB is symptomatic or damaging to the patient, either endoscopic or surgical intervention should ensue. We present a case of abdominal pain and hematuria beginning approximately 24 h after an incidental FB ingestion. Initial CT imaging defined a linear opacity perforating through the posterior duodenal wall abutting the ureter causing inflammation and hydronephrosis. After two unsuccessful endoscopic attempts at retrieval, we were able to identify the object with the aid of intraoperative fluoroscopy and surgically remove the FB. The patient recovered uneventfully and was discharged home. Posterior

duodenal perforation by an FB may not manifest with obvious localized or systemic symptoms unless the perforation involves surrounding structures such as the aorta, vena cava or ureter. In such cases, surgical intervention is required for FB removal.

Surgery

Lin JC, **Kabbani LS**, **Peterson EL**, **Masabni K**, **Morgan JA**, **Brooks S**, **Wertella KP**, and **Paone G**. Clinical utility of carotid duplex ultrasound prior to cardiac surgery *J Vasc Surg* 2016; 63(3):710-714. PMID: 26916583. Full Text

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OBJECTIVE: Clinical utility and cost-effectiveness of carotid duplex examination prior to cardiac surgery have been questioned by the multidisciplinary committee creating the 2012 Appropriate Use Criteria for Peripheral Vascular Laboratory Testing. We report the clinical outcomes and postoperative neurologic symptoms in patients who underwent carotid duplex ultrasound prior to open heart surgery at a tertiary institution. METHODS: Using the combined databases from our clinical vascular laboratory and the Society of Thoracic Surgery, a retrospective analysis of all patients who underwent carotid duplex ultrasound within 13 months prior to open heart surgery from March 2005 to March 2013 was performed. The outcomes between those who underwent carotid duplex scanning (group A) and those who did not (group B) were compared. RESULTS: Among 3233 patients in the cohort who underwent cardiac surgery, 515 (15.9%) patients underwent a carotid duplex ultrasound preoperatively, and 2718 patients did not (84.1%). Among the patients who underwent carotid screening vs no screening, there was no statistically significant difference in the risk factors of cerebrovascular disease (10.9% vs 12.7%; P = .26), prior stroke (8.2% vs 7.2%; P = .41), and prior transient ischemic attack (2.9% vs 3.3%; P = .24). For those undergoing isolated coronary artery bypass grafting (CABG), 306 (17.8%) of 1723 patients underwent preoperative carotid duplex ultrasound. Among patients who had carotid screening prior to CABG, the incidence of carotid disease was low: 249 (81.4%) had minimal or mild stenosis (<50%); 25 (8.2%) had unilateral moderate stenosis (50%-69%); 10 (3.3%) had bilateral moderate stenosis; 9 (2.9%) had unilateral severe stenosis (70%-99%); 5 (1.6%) had contralateral moderate stenosis; 2 (0.7%) had bilateral severe stenosis; 4 (1.3%) had unilateral occluded with contralateral less than 50% stenosis, 1 (0.3%) had unilateral occluded with contralateral (70%-99%) stenosis; and 1 had bilateral occluded carotid arteries. Primary outcomes of patients who underwent isolated CABG showed no difference in the perioperative mortality (2.9% vs 4.3%; P = .27) and stroke (2.9% vs 2.6%; P = .70) between patients undergoing preoperative duplex scanning and those who did not. Primary outcomes of patients who underwent open heart surgery also showed no difference in the perioperative mortality (5.1% vs 6.9%; P = .14) and stroke (2.6% vs 2.4%; P = .85) between patients undergoing preoperative duplex scanning and those who did not. Operative intervention of severe carotid stenosis prior to isolated CABG occurred in 2 of the 17 patients (11.8%) identified who underwent carotid endarterectomy with CABG. CONCLUSIONS: In this study, the correlation between preoperative duplex-documented high-grade carotid stenosis and postoperative stroke was low. Prudent use of preoperative carotid duplex ultrasound should be based on the presence of cerebrovascular symptoms and the type of open heart surgery.

Surgery

Nagai S, Mangus RS, Anderson E, Ekser B, Kubal CA, Fridell JA, and Tector AJ. Intestinal graft failure: Should we perform the allograft enterectomy before or with retransplantation? *Transplantation* 2016;PMID: 26901076. Full Text

1 Division of Transplant Surgery, Department of Surgery, Indiana University School of Medicine, Indianapolis, IN. 2 Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI.

BACKGROUND: Intestinal graft dysfunction is sometimes irreversible and requires allograft enterectomy with or without retransplantation. There is no comprehensive assessment of allograft enterectomy regarding indications and outcomes. The aim of this study was to evaluate management of patients with intestinal graft failure with special reference to indications and outcomes of allograft enterectomy and the procedure's validity as a bridge to retransplantation. METHODS: Graft and patient survivals, reason for graft failure, and rejection episodes were evaluated in 221 intestinal recipients (primary transplantation [n = 201], retransplantation [n = 20]). Indications, surgical factors, and outcomes of allograft enterectomy were investigated. RESULTS: Reasons for isolated enterectomy included systemic infection in 11, gastrointestinal bleeding in 1, and severe electrolyte imbalance in 1, all of which were associated with rejection. One isolated intestinal transplantation patient underwent isolated enterectomy due to cytomegalovirus enteritis. One multivisceral transplantation patient underwent isolated allograft enterectomy due to bowel necrosis. Of these 15 patients, 3 died from persistent infection postoperatively, whereas 8 underwent retransplantation with median interval of 74 days (42-252 days). Allosensitization occurred between isolated enterectomy and retransplantation in 2, one of whom lost the second graft due to rejection. Simultaneous allograft enterectomy and retransplantation was performed in 3 isolated intestinal transplantation and 9 multivisceral transplantation patients. Patient survival after retransplantation was similar between patients who underwent isolated allograft enterectomy and those who did simultaneous enterectomy with retransplantation (P = 0.82). CONCLUSIONS: In cases of irreversible intestinal graft dysfunction, isolated allograft enterectomy successfully provides recovery from comorbidities as a lifesaving procedure and does not compromise outcomes of retransplantation.

Urology

Dangle PP, Akhavan A, Odeleye M, Avery D, Lendvay T, Koh CJ, **Elder JS**, Noh PH, Bansal D, Schulte M, MacDonald J, Shukla A, Kim C, Herbst K, Corbett S, Kearns J, Kunnavakkam R, and Gundeti MS. Ninety-day perioperative complications of pediatric robotic urological surgery: A multi-institutional study *J Pediatr Urol* 2015;PMID: 26897324. Full Text

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BACKGROUND: Robotic technology is the newest tool in the armamentarium for minimally invasive surgery. Individual centers have reported on both the outcomes and complications associated with this technology, but the numbers in these studies remain small, and it has been difficult to extrapolate meaningful information. OBJECTIVES: The intention was to evaluate a large cohort of pediatric robotic patients through a multi-center database in order to determine the frequency and types of complications associated with robotic surgery for pediatric reconstructive and ablative procedures in the United States. STUDY DESIGN: After institutional review board approvals at the participating centers, data were retrospectively collected (2007-2011) by each institute and entered into a RedCap(R) database. Available demographic and complication data that were assigned Clavien grading scores were analyzed. RESULTS: From a cohort of 858 patients (880 RAL procedures), Grade IIIa and Grade IIIb complications were seen in 41 (4.8%); and one patient (0.1%) had a grade IVa complication. Intraoperative visceral injuries secondary to robotic instrument exchange and traction injury were seen in four (0.5%) patients, with subsequent conversion to an open procedure. Grade I and II complications were seen in 59 (6.9%) and 70 (8.2%) patients, respectively; they were all managed conservatively. A total of 14 (1.6%) were converted to an open or pure laparoscopic procedure, of which, 12 (86%) were secondary to mechanical challenges. DISCUSSION: It is believed that this study represents the largest and most comprehensive description of pediatric RAL urological complications to date. The results demonstrate a 4.7% rate of Clavien Grade IIIa and Grade IIIb complications in a total of 880 cases. While small numbers make it difficult to draw conclusions regarding the most complex reconstructive cases (bladder diverticulectomy, bladder neck revision, etc.), the data on the more commonly performed procedures, such as the RAL pyeloplasty and ureteral reimplantation, are robust and more likely represent the true complication rate for these procedures when performed by highly experienced robotic surgeons. CONCLUSION: Pediatric robotic urologic procedures are technically feasible and safe. The overall 90-day complication rate is similar to reports of laparoscopic and open surgical procedures. COMPLICATIONS: n (%) Life threatening (IVa): 1 (0.1%) Requiring radiologic and or surgical intervention (IIIa and IIIb): 41 (4.8%) Secondary to robotic system: 4 (0.5%) Mechanical failure leading to conversion: 14 (1.6%).

Urology

Abdollah F, **Dalela D**, **Sood A**, **Sammon J**, **Jeong W**, Beyer B, Fossati N, **Rogers CG**, **Diaz-Insua M**, **Peabody J**, Haese A, Montorsi F, Graefen M, Briganti A, and **Menon M**. Intermediate-term cancer control outcomes in prostate cancer patients treated with robotic-assisted laparoscopic radical prostatectomy: a multi-institutional analysis *World J Urol* 2016;PMID: 26873596. Full Text

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PURPOSE: Cancer control outcomes following robot-assisted radical prostatectomy (RARP) for prostate cancer (PCa) remain inadequately addressed over intermediate-term (>/=5-year) follow-up. We examined biochemical recurrence-free survival (BCRFS), clinical recurrence-free survival (CRFS), and cancer-specific survival (CSS) in a multi-institutional cohort of men undergoing RARP for localized PCa. MATERIALS AND METHODS: A total of 5670 PCa patients undergoing RARP +/- pelvic lymph node dissection as primary treatment modality at three tertiary care centers between 2001 and 2010 were analyzed. BCRFS, CRFS, and CSS were estimated using the Kaplan-Meier method. Cox proportional hazards model tested their association with available preoperative and postoperative parameters. RESULTS: 43.6 and 15.1 % of patients had D'Amico intermediate- and high-risk disease, respectively. Over a mean (median) follow-up of 56 (50.4) months, 797 men had a BCR, 78 men had CR, and 32 men died of PCa. Actuarial BCRFS, CRFS, and CSS, respectively, were 83.3, 98.6, and 99.5 % at 5-year; 76.5, 97.5, and 98.7 % at 8-year; and 73.3, 96.7, and 98.4 % at 10-year follow-ups. Only 1.7 % of patients received any adjuvant treatment. Preoperative prostate-specific antigen (PSA) and biopsy Gleason score

(GS) were independent clinical predictors of BCRFS, CRFS, and CSS, while postoperatively positive surgical margin, pathological GS, pathological stage, and lymph node invasion were significantly associated with BCR and CR (all $p < 0.05$). CONCLUSIONS: Cancer control outcomes of RARP appear comparable to those reported for open and laparoscopic RP in previous literature, despite low overall rate of adjuvant treatment. Disease severity and preoperative PSA may aid in risk prognostication and defining postoperative follow-up protocols.

Urology
Abdollah F, Klett DE, **Sammon JD**, **Dalela D**, **Sood A**, Hsu L, **Diaz M**, **Gupta N**, **Peabody JO**, Trinh QD, and **Menon M**. Predicting lymph node invasion in patients treated with robot-assisted radical prostatectomy *Can J Urol* 2016; 23(1):8141-8150. PMID: 26892054. Article Request Form

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

INTRODUCTION: To develop a nomogram to predict lymph node invasion (LNI) in the contemporary North American patient treated with robot-assisted radical prostatectomy (RARP). MATERIALS AND METHODS: We included 2,007 patients treated with RARP and pelvic lymph node dissection (PLND) at a single institution between 2008 and 2012. D'Amico low risk patients underwent an obturator and hypogastric PLND, while extended PLND was reserved for intermediate/high risk patients. Logistic regression analysis tested the relationship between LNI and all available predictors. Independent predictors of LNI were used to develop a novel nomogram. Discrimination, calibration and decision-curve analysis were used to analyze the performance of our novel nomogram, and compare it to open radical prostatectomy (ORP)-based models, namely the Godoy nomogram. RESULTS: Overall, 5.3% of our patients harbored LNI. Median number of lymph nodes removed was 6.0 (interquartile range: 4-11). The most parsimonious multivariable model to predict LNI consisted of the following independent predictors: PSA value, clinical stage, and primary and secondary Gleason scores (all $p </= 0.02$). The discrimination of our novel model was 86.2%, and its calibration was virtually optimal. Using a 2% nomogram cut off, 58% of patients would be spared PLND, while missing only 9.4% of individuals with LNI. The novel nomogram compared favorably to the Godoy nomogram, when discrimination, calibration and net-benefit were used as benchmarks. CONCLUSIONS: Approximately 5% of contemporary North American patients harbor LNI at RARP. Our novel nomogram can accurately identify these patients, and this may help to improve patient selection, and avoid unnecessary PLND in the majority of patients.

Urology
Dabaja AA, and Goldstein M. When is a varicocele repair indicated: the dilemma of hypogonadism and erectile dysfunction? *Asian J Androl* 2016; 18(2):213-216. PMID: 26696437. Full Text

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In the past, the indications for varicocelectomy are primarily for infertility with abnormal semen parameters, testicular hypotrophy/atrophy in adolescents, and/or pain. The surgical treatment of varicocele for hypogonadism is controversial and debated. Recently, multiple reports in the literature have suggested that varicocele is associated with hypogonadism and varicocele repair can increase testosterone levels. Men with hypogonadal symptoms should have at least two serum testosterone levels. Microsurgical varicocelectomy may be beneficial for men with clinically palpable varicoceles with documented hypogonadism. In this review, we summarize the most recent literature linking varicocele to hypogonadism and sexual dysfunction and the impact of repair on serum testosterone levels. We performed a search of the published English literature. The key words used were "varicocele and hypogonadism" and "varicocele surgery and testosterone." We included published studies after 1998. We, also, evaluated the effect of surgery on the changes in the serum testosterone level regardless of the indication for the varicocele repair.

Urology

Gadde R, **Gulati R**, **Inamdar KV**, **Michalowski S**, and **Menon M**. Cytogenetic analysis is crucial in the early diagnosis of indolent t-cell prolymphocytic leukemia *Lab Invest* 2016; 96:345A-345A. PMID: Not assigned. Abstract

Background: T cell prolymphocytic leukemia (T-PLL) is a rare and aggresive T-cell leukemia with prominent lymphocytosis. Most T-PLLs demonstrate either inv (14) (q11q32), t(14;14)(q11q32), t(7;14)(q35q32) or t(X;14)(q28q11) abnormalities. Indolent T-PLLs are even rarer, challenging to diagnose, detected incidentally and demonstrate only mild lymphocytosis but progress rapidly after the initial latent phase. The goal of this study was to establish the specificity of the cytogenetic abnormalities seen in T-PLL and to compare clinicopathologic-cytogenetic features of indolent vs. typical T-PLLs. Design: A search from 2003 to 2015 revealed 150,000 cytogenetics samples with 30,000 bone marrows (BM). BM, peripheral blood and lymph node (when available) slides were morphologically examined and cells were characterized as prolymphocytic, sezary, cleaved, floret, atypical (small, medium or large). Flow cytometric data was reviewed for T/NK- antigen markers and chromosomal analysis for karyotyping. Results: 26/150000 (0.02%) cases had T-PLL like chromosome 14 abnormalities; Inv 14 (14 cases), t (7; 14) (7 cases), t(X; 14) (4 cases) and add (14) in 1 case. 11/14 cases of inv 14 were T-PLLs of which 6 were indolent. 3/14 had other diagnoses including 1) Adult T-cell leukemia/lymphoma (ATLL) 2) Acute myeloid leukemia (AML) and 3) Mycosis Fungoides (MF). In ATLL, the inv 14 breakpoints were same as T-PLL whereas AML and MF cases had different breakpoints. Of the t(7;14)(q35q32.1) and t(X;14)(q28q11) cases, 0/7 and 1/4 were T-PLL respectively. t (7;14) and t (X;14) were found in other entities including CLL (1 case), lymphoplasmacytic lymphoma (1 case), soft tissue tumor (1 case), AML (2 cases), large B-cell lymphoma (1 case) and multiple myeloma (4 cases) albeit with different breakpoints. Clinically, all cases with indolent T-PLL had varying levels of bone marrow involvement, borderline to prominent lymphadenopathy but no splenomegaly. Lymphocytes in both typical and indolent T-PLL cases showed diverse morphology and were not always necessarily of prolymphocytic morphology. Immunophenotypically, 6 T-PLL cases were CD4+, 3 were CD4+CD8+ and 1 case was CD8+. Interestingly, all CD4+CD8+ cases were indolent whereas the CD8+ case was a typical T-PLL. Conclusions: Inv(14) involving the TCL1 locus or t (X;14) (q28q11) is specific for T-PLL (indolent or typical) or ATLL and thus cytogenetic assessment for this abnormality should be considered on every case of T-lymphoproliferation in blood regardless of clinical presentation in order to detect indolent T-PLLs which progress rapidly after initial phase. [Gadde, Ramya; Gulati, Rohit; Inamdar, Kedar V.; Michalowski, Susan; Menon, Madhu] Henry Ford Hosp, Detroit, MI 48202 USA.

Urology

Griffin M, **Diaz-Insua M**, **ElShatanoufy S**, and **Atiemo H**. Medical student robotic simulator performance does not correlate with their usmle scores *Neurourol Urodyn* 2016; 35:S14-S15. PMID: Not assigned. Abstract

[Griffin, Meghan; Diaz-Insua, Mireya; ElShatanoufy, Solafa; Atiemo, Humphrey] Henry Ford Hosp, Detroit, MI 48202 USA.

Introduction: Studies have shown a correlation between visuospatial and surgical ability, as well as a between visuospatial ability and performance on the da Vinci Skills Simulator (Intuitive Surgical, CA). We aimed to detect a correlation between USMLE scores, and perfomance on the robotic simulator. Methods: We enrolled 29 3rd and 4th year medical students naïve to the robotic simulator during Ob/Gyn rotation. Twenty-two completed USMLE step one and two. Demographic data including age, gender, interest in a surgical specialty and intended medical field were collected. Students were asked to complete three exercises repeating each three times. Metrics were measured and a score for each repetition of each exercise calculated. Computer-generated feedback was recorded and revealed to the student between repetitions. An overall score calculated. The students' medical school provided USMLE scores. The Pearson correlation coefficient was used to evaluate for correlations between USMLE and robotic simulator scores, and tested using the t-distribution. ANOVA and t-test were used to detect differences in scores among students interested in a surgical, non-surgical or an undecided discipline.

Results: Of the 22 students, 17 were male with an average age of 25 years. The mean step 1 and step 2 scores were 232.0 ± 19.2 and 242.1 ± 14.4 respectively. The mean overall robotic score was 74.3% ± 8.1. The USMLE scores did not correlate with the robotic score (r = 0.02, -0.13 respectively). With repetition robotic scores improved on average 40% and was weakly associated with step 1 scores (r = 0.12, P = 0.54). The mean change from step 1 to step 2 was 10.2 ± 10.7 and was not associated with the robot score. When categorized based on intended medical field the mean robot scores were 78.2% ± 7.6, 70.4% ± 10.2, and 72.8% ± 6.6 for a surgical, non-surgical, and undecided discipline, respectively (P = 0.51). There was a trend towards significance between scores of those interested in a surgical discipline (mean = 78.2%) vs. those interested in a non-surgical discipline (mean = 70.4%, P = 0.07). Students who intend a surgical field showed better economy of motion (157.8 ± 24.2 cm and 214.9 ± 53.7 cm, P = 0.031) and performed the skills in less time (97.3 ± 19.2 s and 160.4 ± 48.9 s, P = 0.013) than those who do not.Conclusion: Performance on the simulator does not correlate with USMLE scores but improvement with repetition is weakly associated with USMLE scores. Students who intend a surgical field performed the da Vinci skills simulator exercises more quickly.

Urology

Hwang C, Sethi S, Heilbrun LK, **Gupta NS**, **Chitale DA**, Sakr WA, **Menon M**, **Peabody JO**, Smith DW, Sarkar FH, and Heath EI. Anti-androgenic activity of absorption-enhanced 3, 3'-diindolylmethane in prostatectomy patients *Am J Transl Res* 2016; 8(1):166-176. PMID: Not assigned. Full Text

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Consumption of cruciferous vegetables is associated with a decreased risk of developing prostate cancer. Antineoplastic effects of cruciferous vegetables are attributable to bioactive indoles, most prominently, 3, 3'-diindolylmethane (DIM). In addition to effects on proliferation and apoptosis, DIM acts as an antiandrogen in prostate cancer cell lines. This study characterized the effects of prostatic DIM on the androgen receptor (AR) in patients with prostate cancer. Men with localized prostate cancer were treated with a specially formulated DIM capsule designed for enhanced bioavailability (BR-DIM) at a dose of 225 mg orally twice daily for a minimum of 14 days. DIM levels and AR activity were assessed at the time of prostatectomy. Out of 28 evaluable patients, 26 (93%) had detectable prostatic DIM levels, with a mean concentration of 14.2 ng/gm. The mean DIM plasma level on BR-DIM therapy was 9.0 ng/mL; levels were undetectable at baseline and in follow-up samples. AR localization in the prostate was assessed with immunohistochemistry. After BR-DIM therapy, 96% of patients exhibited exclusion of the AR from the cell nucleus. In contrast, in prostate biopsy samples obtained prior to BR-DIM therapy, no patient exhibited AR nuclear exclusion. Declines in PSA were observed in a majority of patients (71%). Compliance was excellent and toxicity was minimal. In summary, BR-DIM treatment resulted in reliable prostatic DIM levels and anti-androgenic biologic effects at well tolerated doses. These results support further investigation of BR-DIM as a chemopreventive and therapeutic agent in prostate cancer.

Urology

Jamal M, **Williamson SR**, **Diaz-Insua M**, **Menon M**, **Stricker H**, **Peabody J**, **Rogers CG**, and **Gupta NS**. Significance of percentage of gleason pattern 4 at needle biopsy in predicting final gleason score and correlation with pathologic outcomes at radical prostatectomy *Lab Invest* 2016; 96:240A-240A. PMID: Not assigned. Abstract

[Jamal, Mohsin; Williamson, Sean R.; Diaz-Insua, Mireya; Menon, Mani; Stricker, Hans; Peabody, James; Rogers, Craig G.; Gupta, Nilesh S.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: The 2005 ISUP modified Gleason grading scheme resulted in upgrade of some Gleason score (GS) 6 tumors to GS7. Most practices currently provide percentage of higher Gleason patterns in prostate needle biopsies (PNB), with the most common scenario being percentage of Gleason pattern 4 (%G4). The aim of our study was to evaluate the clinical significance of reporting this finding. Design: We analyzed PNBs between 2011 - 2013 with diagnosis of GS7 and 8 prostatic adenocarcinoma (PCa) and corresponding robotic radical prostatectomy (RRP) specimens. Results: A total of 162 cases with both

PNB and RRP specimens were selected. Mean age of these patients was 62 years. The %G4 on biopsy correlated significantly with percentage of positive cores (rho=0.60, p<0.001) and tumor volume (rho=0.52, p<0.001). We stratified the patients into four quartiles based on %G4 on PNB . Q1: %G 4 <=10, Q2: >10% - 20%, Q3: >20% - 50%, Q4: >50%. Correlation of the %G4 quartiles with the GS on RRP is listed in Table 1.For quartiles Q1, Q2 and Q3, there was a significant increase of upgrading in the RRP specimen to 4+3=7 with increase of %G4 on biopsy (p-v=0.005). Likewise, within Q4, there was a significant upgrade of GS in the RRP specimen (from 4+3=7 to 4+4=8 and 4+5=9). Q1 was associated with greater percentage of organ confined disease, and negative lymph nodes (LN). In contrast, Q3 and Q4 were associated with high percentage of established extraprostatic extension, seminal vesicle invasion, angio invasion and positive LN (Table 2). Conclusions: %G4 is a clinically significant parameter that provides valuable information in management of patients with PCa. GS7 PCa with minor %G4 shows favorable pathologic outcome, whereas there is an increase in upgrading and adverse pathologic outcomes with increase in %G4 reported on PNB.

Urology

Jamal M, **Williamson SR**, **Diaz-Insua M**, **Menon M**, **Stricker H**, **Peabody J**, **Rogers CG**, and **Gupta NS**. Clinical significance of percentage of gleason pattern 4 in gleason score 7 prostate cancer at radical prostatectomy *Lab Invest* 2016; 96:240A-240A. PMID: Not assigned. Abstract

[Jamal, Mohsin; Williamson, Sean R.; Diaz-Insua, Mireya; Menon, Mani; Stricker, Hans; Peabody, James; Rogers, Craig G.; Gupta, Nilesh S.] Henry Ford Hosp, Detroit, MI 48202 USA.

Background: We sought to determine the prognostic value of percentage Gleason pattern 4 in radical prostatectomy specimens. Design: We selected 400 patients who underwent robotic radical prostatectomy (RRP) between 2010 and 2011 with Gleason score 7. Data collected included pT stage, tumor volume, margin status, angiolymphatic invasion and lymph node involvement and biochemical recurrence (BCR) at 2 years after surgery. Results: Mean age of the patients was 62 years. We stratified the patients into four quartiles based on percentage of Gleason pattern 4 (GP4). Q1: percent of Gleason 4 <=20, Q2: >20% - 35%, Q3: >35% - 65%, Q4: >65%. Table 1 shows these quartiles correlated with multiple pathological outcomes. Percentage of GP4 was associated with BCR when other pathologic features were accounted for. A percent greater than 65 (i.e. fourth quartile) was significantly different from a percent of 20 or less in providing a greater likelihood for recurrence OR=6.53 (95% CI 2.43, 17.56). The other factors that were also significant were margins, positive lymph nodes and angiolymphatic invasion. These four variables yielded a c-statistic of 0.82. If percentage of GP4 is considered as a continuous measure, it is also independently related with PSA recurrence within 2 years of surgery. A unit increase in the percent of GP4 increases the likelihood of recurrence by 3 percent, OR=1.03 (1.01, 1.04). Conclusions: 1. Gleason 7 prostatic adenocarcinoma represents a heterogenous group of tumors. A subgroup of tumors with Gleason score 3+4=7 with low percentage of GP4 (<=20%) carry favorable prognosis compared to Gleason score 3+4=7 tumors with higher percentage (>20%) of pattern 4. 2. Percentage of GP4 is an important parameter that should be reported on all radical prostatectomies with Gleason score 7, given its independent prognostic value. 3. Additional studies are needed to determine the role of higher Gleason pattern percentages in tumors other than Gleason score 7.

Urology

Leow JJ, Chang SL, Meyer CP, Wang Y, Hanske J, **Sammon JD**, Cole AP, Preston MA, Dasgupta P, **Menon M**, Chung BI, and Trinh QD. Robot-assisted versus open radical prostatectomy: A contemporary analysis of an all-payer discharge database *Eur Urol* 2016;PMID: 26874806. Full Text

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BACKGROUND: More than a decade since its inception, the benefits and cost efficiency of robot-assisted radical prostatectomy (RARP) continue to elicit controversy. OBJECTIVE: To compare outcomes and costs between RARP and open RP (ORP). DESIGN, SETTING, AND PARTICIPANTS: A cohort study of 629 593 men who underwent RP for localized prostate cancer at 449 hospitals in the USA from 2003 to 2013, using the Premier Hospital Database. INTERVENTION: RARP was ascertained through a review of the hospital charge description master for robotic supplies. OUTCOME MEASURES AND STATISTICAL ANALYSIS: Outcomes were 90-d postoperative complications (Clavien), blood product transfusions, operating room time (ORT), length of stay (LOS), and direct hospital costs. Propensity-weighted regression analyses accounting for clustering by hospitals and survey weighting ensured nationally representative estimates. RESULTS AND LIMITATIONS: RARP utilization rapidly increased from 1.8% in 2003 to 85% in 2013 (p<0.001). RARP patients (n=311 135) were less likely to experience any complications (odds ratio [OR] 0.68, p<0.001) or prolonged LOS (OR 0.28, p<0.001), or to receive blood products (OR 0.33, p=0.002) compared to ORP patients (n=318 458). The adjusted mean ORT was 131min longer for RARP (p=0.002). The 90-d direct hospital costs were higher for RARP (+$4528, p<0.001), primarily attributed to operating room and supplies costs. Costs were no longer signficantly different between ORP and RARP among the highest-volume surgeons (>/=104 cases/yr; +$1990, p=0.40) and highest-volume hospitals (>/=318 cases/yr; +$1225, p=0.39). Limitations include the lack of oncologic characteristics and the retrospective nature of the study. CONCLUSIONS: Our contemporary analysis reveals that RARP confers a perioperative morbidity advantage at higher cost. In the absence of large randomized trials because of the widespread adoption of RARP, this retrospective study represents the best available evidence for the morbidity and cost profile of RARP versus ORP. PATIENT SUMMARY: In this large study of men with prostate cancer who underwent either open or robotic radical prostatectomy, we found that robotic surgery has a better morbidity profile but costs more.

Urology

Li HH, **Borchert A**, and **Atiemo H**. Contemporary treatment of detrusor sphincter dyssynergia: A systematic review *Neurourol Urodyn* 2016; 35:S54-S55. PMID: Not assigned. Abstract

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Introduction: Detrusor sphincter dyssynergia (DSD) can present in patients with neurogenic bladder due to spinal cord disease but no treatment guidelines currently exist. We sought to systematically review the contemporary literature to determine outcomes of treatments for DSD. Methods: Ovid Medline, Embase, Pubmed, and Web of Science were searched within the last 10 years for “detrusor sphincter dyssynergia”. Results were independently reviewed by two co-authors for inclusion using the PRISMA guidelines. Exclusion criteria were: pediatric populations, no full text availability, reviews, non-clinical focus, non-English language and case reports. Papers were included only if DSD was described in the methods or results section. Results: 515 articles were screened to yield 22 full text articles. The majority were retrospective studies (15), five were prospective non-randomized studies, and two studies were prospective, randomized trials. Twelve studies (55%) defined DSD and 11 (50%) described electromyography in the diagnosis of DSD. A total of 830 patients (527 male, 104 female, 199 not specified) had DSD from spinal cord injury (413), multiple sclerosis (104), multiple system atrophy (33), and not specified (280). Treatments included Botulinum A injections into the external sphincter (7 studies, mean follow-up time: 1–6 months, reported success rates: 64–100%) or bladder (3, 3–6 months, 44–76%), urethral stents (4, 10–240 months, 9–91%), sphincterotomy (2,12–76 months, 48–85%), other

surgical interventions (2, 3–60 months, 81–87%), alpha-blockers (2, 21–60 months, 44–76%), anticholinergics (1, 3 months, success rates not described), sacral neuromodulation (1, 49 months, 60%), and anal stretch (1). Conclusion: There is a lack of standardization in the diagnosis and treatment outcomes of DSD. Intrasphincteric or detrusor Botulinum toxin type A injection appears to be a primary intervention strategy after failed conservative therapies such as intermittent catherization or medications. More invasive treatments such as sacral neuromodulation and sphincterotomy have also shown relatively high success rates while urethral stent placement has associated high complication and failure rates.

Urology
Lu ZC, **Williamson SR**, **Diaz-Insua M**, **Stricker H**, **Menon M**, and **Gupta NS**. Pathologic outcomes and biochemical recurrence (BCR) free survival in men younger than 45 years with prostate cancer (PCa) treated with robotic radical prostatectomy (RRP) *Lab Invest* 2016; 96:247A-247A. PMID: Not assigned. Abstract

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Urology
Pennell CP, Hirst AD, Campbell WB, **Sood A**, Agha RA, Barkun JS, and McCulloch P. Practical guide to the idea, development and exploration stages of the IDEAL framework and recommendations *Br J Surg* 2016;PMID: 26865013. Full Text

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BACKGROUND: Evaluation of new surgical procedures is a complex process challenged by evolution of technique, operator learning curves, the possibility of variable procedural quality, and strong treatment preferences among patients and clinicians. Preliminary studies that address these issues are needed to prepare for a successful randomized trial. The IDEAL (Idea, Development, Exploration, Assessment and Long-term follow-up) Framework and Recommendations provide an integrated step-by-step evaluation pathway that can help investigators achieve this. METHODS: A practical guide was developed for investigators evaluating new surgical interventions in the earlier phases before a randomized trial (corresponding to stages 1, 2a and 2b of the IDEAL Framework). The examples and practical tips included were chosen and agreed upon by consensus among authors with experience either in designing and conducting IDEAL format studies, or in helping others to design such studies. They address the most common challenges encountered by authors attempting to follow the IDEAL Recommendations. RESULTS: A decision aid has been created to help identify the IDEAL stage of an innovation from literature reports, with advice on how to design and report the IDEAL study formats discussed, along with the ethical and scientific rationale for specific recommendations. CONCLUSION: The guide helps readers and researchers to understand and implement the IDEAL Framework and Recommendations to improve the quality of evidence supporting surgical innovation.

Urology
Williamson SR, Grignon DJ, **Favazza L**, **Gupta NS**, **Chitale DA**, and **Palanisamy N**. Chromosome 6p amplification including the TFEB gene: a novel mechanism of renal cell carcinoma pathogenesis? *Lab Invest* 2016; 96:270A-271A. PMID: Not assigned. Abstract

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Background: Amplification of part of chromosome 6p, which includes almost half of the genes from chromosome 6, has been implicated in aggressive behavior in multiple cancers, although not to our knowledge in renal cell carcinoma. In this study, we report on a cohort of 3 renal cell carcinomas with 6p amplification including the TFEB gene, a member of the microphthalmia transcription factor (MITF) family of genes. Design: Three renal cell carcinomas were identified as having amplification of chromosome 6p including the TFEB gene, 1 via fluorescence in situ hybridization (FISH), and 2 from the Cancer Genome Atlas (TCGA) database. We studied morphology, immunohistochemical staining characteristics, and other genetic alterations in this cohort. Results: The patients were 2 women and 1 man, ages 28, 61, and 57, respectively. All 3 tumors were infiltrative (pT3a) tubulopapillary neoplasms with variable infiltration of renal sinus fat, renal parenchyma, or vessels (A-B). The youngest patient had regional nodal metastasis at presentation. Amplification of the TFEB region was observed by FISH (C) in 1 tumor, without TFEB or TFE3 rearrangement or loss of chromosome 3p (D). The two TCGA specimens showed selective amplification of a region of chromosome 6p including the TFEB gene, without corresponding amplification of the MALAT1 (Alpha) gene region, the known fusion partner in TFEB translocation. VHL mutation and chromosome 3p loss were not observed, although the young patient had somatic mutation in FH (germline status unknown). FH mutation was lacking in the other TCGA tumor. The 2 tumors with immunohistochemical results were positive for CD10, AMACR, and PAX-2 or PAX-8. One demonstrated patchy positivity for melan-A and cathepsin K, whereas the other was negative for HMB45 and melan-A. Conclusions: In this cohort, 6p amplification was associated with aggressive tubulopapillary histology and lack of genetic alterations of other tumor types. One patient had FH gene mutation in the tumor, although it remains to be studied whether this is exclusively somatic or a manifestation of the hereditary leiomyomatosis syndrome. Further studies will define whether this represents a unique entity related to MITF gene family alteration.