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Henry Ford Health System Publication List – August 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 September, and then imported into EndNote for formatting.There are 127 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
Frieder J, and **Younus M**. Autoimmune progesterone dermatitis with delayed intradermal skin reaction: A case report *Ann Allergy Asthma Immunol* 2016;PMID: 27566859. Full Text

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Allergy and Immunology
Levin AM, **Sitarik AR**, **Havstad SL**, Fujimura KE, **Wegienka G**, **Cassidy-Bushrow AE**, **Kim H**, **Zoratti EM**, Lukacs NW, Boushey HA, Ownby DR, Lynch SV, and **Johnson CC**. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity *Sci Rep* 2016; 6:31775. PMID: 27558272. Full Text

Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, 48202, USA.
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Division of Gastroenterology, Department of Medicine, University of California, San Francisco, CA, 94143, USA.
Division of Allergy and Clinical Immunology, Department of Medicine, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Pathology, University of Michigan, Ann Arbor, MI, 48109, USA.
Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco, CA, 94143, USA.
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The joint impact of pregnancy, environmental, and sociocultural exposures on early life gut microbiome is not yet well-characterized, especially in racially and socioeconomically diverse populations. Gut microbiota of 298 children from a Detroit-based birth cohort were profiled using 16S rRNA sequencing: 130 neonates (median age = 1.2 months) and 168 infants (median age = 6.6 months). Multiple factors were associated with neonatal gut microbiome composition in both single- and multi-factor models, with independent contributions of maternal race-ethnicity, breastfeeding, mode of delivery, marital status, exposure to environmental tobacco smoke, and indoor pets. These findings were consistent in the infants, and networks demonstrating the shared impact of factors on gut microbial composition also showed notable topological similarity between neonates and infants. Further, latent groups defined by these factors explained additional variation, highlighting the importance of combinatorial effects. Our findings also have implications for studies investigating the impact of the early life gut microbiota on disease.

Allergy and Immunology
Wegienka G, **Havstad S**, **Kim H**, **Zoratti E**, Ownby D, **Woodcroft KJ**, and **Johnson CC**. Subgroup differences in the associations between dog exposure during the first year of life and early life allergic outcomes *Clin Exp Allergy* 2016;PMID: 27562398. Full Text

Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI.
Division of Allergy and Clinical Immunology, Henry Ford Hospital, Detroit, MI.

Department of Pediatrics, Georgia Health Sciences University, Augusta, GA.

BACKGROUND: The effect of dog exposure on the risk of children developing allergic disease remains controversial. Many analyses have not considered that associations may vary within population subgroups. OBJECTIVE: Examine whether associations between living with a dog in the first year of life and allergic outcomes vary within subgroups selected a priori (race, gender and delivery mode). METHODS: Black (n=496) and White (n=196) children enrolled in the WHEALS birth cohort study had a clinical examination at age 2 years to assess eczema and allergen-specific IgE (sIgE) and perform skin prick testing (SPT). Whether the child lived with an indoor dog in the first year of life was assessed through interview, as was doctor diagnosis of asthma at ages 3-6 years. RESULTS: Living with a dog was associated with decreased odds of having >/=1 positive SPT (OR=0.56, 95%CI 0.34, 0.91) and having eczema (OR=0.34, 95%CI 0.20, 0.60). The association with SPT was stronger in those children born via cesarian-section versus vaginally (OR=0.29, 95%CI 0.12, 0.74 versus OR=0.76, 95%CI 0.43, 1.37, respectively, interaction p=0.087) and in those who were firstborn versus not (OR=0.27, 95%CI 0.11, 0.67 versus OR=0.82, 95%CI 0.45, 1.47, respectively, interaction p=0.044). The association with eczema was stronger in children born vaginally compared with those born via cesarian-section (OR=0.17, 95%CI 0.06, 0.43 versus OR=0.65, 95%CI 0.31, 1.35, respectively, interaction p=0.025) and was stronger in Black versus White children (OR=0.30, 95%CI 0.15, 0.61 versus OR=0.78, 95%CI 0.29, 2.11, respectively, interaction p=0.12). Dog keeping was not significantly inversely associated with having >/=1 elevated sIgE and only approached statistical significance with asthma.

Anesthesiology
Loomba V, **Kaveeshvar H**, and **Dwivedi S**. Paraplegia after thoracic epidural steroid injection *A A Case Rep* 2016;PMID: 27536909. Article Request Form

From the *Department of Anesthesiology, Henry Ford Hospital, Detroit, Michigan; and daggerDepartment of Neurology, Henry Ford Hospital, Detroit, Michigan.

Epidural steroid injections are a common procedure performed by pain physicians. The American Society of Regional Anesthesia along with several other groups recently provided guidelines for performing epidural injections in the setting of anticoagulants. We present a case of a patient who developed an epidural hematoma and subsequent paraplegia despite strict adherence to these guidelines. Although new guidelines serve to direct practice, risks of devastating neurologic complications remain as evidenced by our case.

Anesthesiology
Patel S, Weierstahl KL, **Shah S**, and **Fidkowski CW**. Anesthetic management for cesarean delivery in a patient with pulmonary emboli, pulmonary hypertension, and right ventricular failure *A A Case Rep* 2016;PMID: 27513968. Article Request Form

From the *Department of Anesthesiology, Henry Ford Hospital, Detroit, Michigan; and daggerWayne State University School of Medicine, Detroit, Michigan.

The maternal mortality rate for parturients with severe pulmonary hypertension is 30% to 50%. General, epidural, and combined low-dose spinal-epidural anesthesia have been used successfully for cesarean deliveries in patients with pulmonary hypertension. We describe a cesarean delivery performed using an intrathecal catheter in a 25-year-old morbidly obese (body mass index, 82 kg/m) woman (gravida 3, para 2 at 32 weeks of gestation) who had severe pulmonary hypertension, right ventricular failure, pulmonary emboli, and obstructive sleep apnea. We discuss the anesthetic considerations for parturients with severe pulmonary hypertension undergoing cesarean delivery including the selection of anesthetic technique, vasopressors, and uterotonic agents.

Cardiology
Adams KF, Jr., Butler J, Patterson JH, Gattis Stough W, Bauman JL, van Veldhuisen DJ, Schwartz TA, **Sabbah H**, Mackowiak JI, Ventura HO, and Ghali JK. Dose response characterization of the association of serum digoxin concentration with mortality outcomes in the Digitalis Investigation Group trial *Eur J Heart Fail* 2016; 18(8):1072-1081. PMID: 27492641. Full Text

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Department of Medicine, Division of Cardiology, Emory University, Atlanta, GA, USA.

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Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
Division of Cardiology, Wayne State University, Henry Ford Health System, Detroit, MI, USA.
Center for Outcomes Research, Nashville, TN, USA.
John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, USA.
Division of Cardiology, Mercer University School of Medicine, Macon, GA, USA.

AIMS: Many patients with heart failure and reduced EF remain at high risk for hospitalization despite evidence-based therapy. Digoxin may decrease hospitalization; however, uncertainty persists concerning its proper administration and effect on mortality. This study investigated whether using dose response concepts to re-evaluate the relationship between serum digoxin concentration and key mortality outcomes in patients with reduced EF in the Digitalis Investigation Group trial would help clarify efficacy and safety. METHODS AND RESULTS: Multivariable Cox proportional hazards modelling and propensity score adjustment assessed the relationship between serum digoxin concentration (>/=0.5 ng/mL) as a continuous variable and mortality outcomes. In patients treated with digoxin, a significant linear association was found between serum concentration and all-cause mortality [adjusted hazard ratio (HR) 1.25, 95% confidence interval (CI) 1.14-1.38, P < 0.001 per 0.5 ng/mL increase in serum concentration]. Based on this relationship, a bidirectional association was found between digoxin therapy and all-cause mortality when compared with placebo. The lowest serum concentrations (0.5-0.7 ng/mL) were associated with the lowest risk of all-cause mortality (adjusted HR 0.77, 95% CI 0.67-0.89, P < 0.001) while high serum concentrations (1.6-2.0 ng/mL) were associated with increased mortality (adjusted HR 1.33, 95% CI 1.12-1.58, P = 0.001). Consistent with this finding, lower serum concentrations (0.5-0.7 ng/mL) were associated with reduced death from worsening heart failure and a neutral effect on cardiovascular death not due to worsening heart failure. CONCLUSION: These findings favour targeting serum concentrations from 0.5 to 0.7 ng/mL when dosing digoxin in patients with heart failure and reduced EF.

Cardiology

Arbit B, Sharma S, Clopton P, Mueller C, **Nowak R**, **McCord J**, Mockel M, Filippatos G, Daniels L, Di Somma S, and Maisel A. Influence of gender and copeptin levels on clinical outcomes in patients with acute heart failure *J Card Fail* 2016; 22(8):S29-S29. PMID: Not assigned. Abstract

[Arbit, Boris; Sharma, Sumita; Clopton, Paul; Daniels, Lori; Maisel, Alan] UCSD, La Jolla, CA USA. [Mueller, Christian] Univ Basel Hosp, Basel, Switzerland. [Nowak, Richard; McCord, James] Henry Ford Hlth Syst, Detroit, MI USA. [Mockel, Martin] Campus Virchow Klinikum, Charite, Berlin, Germany. [Filippatos, Gerasimos] UCSD, Athens, Greece. [Di Somma, Salvatore] Univ Sapienza, San Andrea Hosp, Rome, Italy.

Background: Copeptin is a novel biomarker derived from the C-terminal fragment of arginine vasopressin precursor (AVP), also known as antidiuretic hormone. Copeptin is released in response to the same factors as AVP and is more readily isolated and measured than AVP. Some studies have suggested that it may be superior to BNP in predicting death in patients with acute heart failure (AHF). To our knowledge, we are presenting the first study of gender-related differences of copeptin in prediction of mortality, readmissions, and emergency department visits. Methods: Current anaylysis used data from the Biomarkers in Acute Heart Failure (BACH) trial. 1641 patients presenting to the ED with acute dyspnea were prospectively enrolled in the study. Patients with valid measurements of copeptin and sodium were included in the current analysis. Patients were followed for up to 90 days after initial evaluation for the end points of all-cause mortality, HF-related readmissions, and HF-related ED visits. For the prognostic evaluation of copeptin, we divided the cohort by gender and by copeptin quartiles (specific to each gender). We then performed Cox regression for the combined end-point of all-cause mortality, HF-related readmissions, and HF-related ED visits. Results: 1641 subjects were enrolled, of which 568 were diagnosed with AHF. Of these, 557 patients (347 male, 210 female) had valid measurements of sodium and copeptin. There were 64 deaths, 149 death- or HF-related readmission events, and 172 death- or HF-related readmission or HF related ED visit events. Patients with copeptin levels in the highest quartile (>61.4 pmol/L for men, >54.1 pmol/L for women) had significantly increased rates of the combined end-point, $\chi 2 = 19.4$, P < .0001. Interestingly, rates were very similar among men and women above the 75th percentile, but below, women had significantly less events. Conclusions: This is the first study of gender-related

differences of copeptin in prediction of clinical endpoints. Accounting for gender, copeptin may be a valuable tool in risk stratification of patients with AHF.

Cardiology

Blanke P, Naoum C, Ahmadi A, Cheruvu C, Soon J, Arepalli C, Gransar H, Achenbach S, Berman DS, Budoff MJ, Callister TQ, **Al-Mallah MH**, Cademartiri F, Chinnaiyan K, Rubinshtein R, Marquez H, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Shaw LJ, Kaufmann PA, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Chang HJ, Chow BW, Min J, and Leipsic J. Long-term prognostic utility of coronary ct angiography in stable patients with diabetes mellitus *JACC Cardiovasc Imaging* 2016;PMID: 27568114. Full Text

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OBJECTIVES: The goal of this study was to determine the long-term prognostic value of coronary computed tomography angiography (CTA) among patients with diabetes mellitus (DM) compared with nondiabetic subjects. BACKGROUND: The long-term prognostic value of coronary CTA in patients with DM is not well established. METHODS: Patients enrolled in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry with 5-year follow-up data were identified. The extent and severity of coronary artery disease (CAD) were analyzed at baseline coronary CTA and in relation to outcomes between diabetic and nondiabetic patients. CAD according to coronary CTA was defined as none (0% stenosis), nonobstructive (1% to 49% stenosis), or obstructive (>/=50% stenosis). Time to death (and in a subgroup, time to major adverse cardiovascular event) was estimated by using multivariable Cox proportional hazards models. RESULTS: A total of 1,823 patients were identified as having DM with 5-year clinical follow-up and were propensity-matched to 1,823 patients without DM (mean age 61.8 +/- 10.9 years; 54.4% male). Patients with DM did not exhibit a heightened risk of death compared with the propensity-matched nondiabetic subjects in the absence of CAD on coronary CTA (risk-adjusted hazard ratio [HR] of DM: 1.32; 95% confidence interval [CI]: 0.78 to 2.24; p = 0.296). Patients with DM were at increased risk of dying compared with nondiabetic subjects in the setting of nonobstructive CAD (in the propensity-matched cohort: HR, 2.10; 95% CI: 1.43 to 3.09; p < 0.001) with a mortality risk greater than nondiabetic subjects with obstructive disease (p < 0.001). In a risk-adjusted hazard analysis among patients with DM, both per-patient obstructive CAD and nonobstructive CAD conferred an increase in all-cause mortality risk compared with patients without atherosclerosis on coronary CTA (nonobstructive disease-HR: 2.07; 95% CI: 1.33 to 3.24; p = 0.001;

obstructive disease-HR: 2.22; 95% CI: 1.47 to 3.36; p < 0.001). CONCLUSIONS: Among patients with DM, nonobstructive and obstructive CAD according to coronary CTA were associated with higher rates of all-cause mortality and major adverse cardiovascular events at 5 years, and this risk was significantly higher than in nondiabetic subjects. Importantly, patients with DM without CAD according to coronary CTA were at a risk comparable to that of nondiabetic subjects.

Cardiology

Bryce K, **Pehote M**, and **Lanfear D**. Cognitive functioning and post-lvad outcomes:Influence of comorbidities and specific cognitive domains *J Card Fail* 2016; 22(8):S124-S124. PMID: Not assigned. Abstract

[Bryce, Kelly; Pehote, Melody; Lanfear, David] Henry Ford Hosp, Detroit, MI 48202 USA.

Introduction: Left ventricular assist devices (LVAD) are accepted therapy for end stage heart failure, but optimal patient selection remains challenging. Our group and others recently showed that baseline cognitive impairment is associated with worse outcomes post LVAD. We investigated whether this was impacted overall comorbidity burden, and which dimensions of cognitive function were most critical. Methods: A retrospective review was conducted on 100 consecutive patients who received continuous flow LVADs over a three year period (2011 and 2014) who were administered The Montreal Cognitive Assessment (MoCA) at the time of their pre-surgical psychological evaluation. Those who did not survive to discharge were excluded. Demographic information, MoCA scores and patient outcomes were collected. The primary endpoint of interest was time to hospital readmission tested using Cox regression models adjusted for potential confounders (age, race, gender, indication, and INTERMACS category). Comorbidity burden was assessed using the Charlson index. Standard MoCA subscores for Executive function, Attention, Naming, Abstraction, Language, and Orientation were tested as categorical variables (dichotomized at the median). Results: Average age was 55.6 (±12.29), 22% were female (n = 22), 42% were non-white race (n = 42), and 69% were destination therapy (n = 69). Charlson index was higher in patients with worse baseline MoCA (mean 4.5 vs 3.6, P = .021), but this did not impact the association of MoCA score with time to readmission (Charlson p = NS, MoCA category P = .005 HR = 2.0). When each subscore was tested in regression models only Attention was associated with risk of readmission (HR 2.5, P = .029). Conclusions: Among patients receiving LVADs, baseline cognitive dysfunction is associated with a greater burden of comorbidities, but this did not account for the increased hospital readmission rates among cognitively impaired patients. The cognitive domain that appears most important to post-LVAD outcomes is Attention/Concentration; the mechanism involved is unclear and deserves further investigation.

Cardiology

Gu X, **Xu J**, **Zhu L**, Bryson T, **Yang XP**, **Peterson E**, and **Harding P**. Prostaglandin e2 reduces cardiac contractility via ep3 receptor *Circ Heart Fail* 2016; 9(8)PMID: 27502370. Full Text

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BACKGROUND: Prostaglandin E2 (PGE2) EP receptors EP3 and EP4 signal via decreased and increased cAMP production, respectively. Previously, we reported that cardiomyocyte-specific EP4 knockout mice develop dilated cardiomyopathy with reduced ejection fraction. Thus, we hypothesized that PGE2 increases contractility via EP4 but decreases contractility via EP3. METHODS AND RESULTS: The effects of PGE2 and the EP1/EP3 agonist sulprostone on contractility were examined in the mouse Langendorff preparation and in adult mouse cardiomyocytes. Isolated hearts of adult male C57Bl/6 mice were perfused with PGE2 (10(-6) M) or sulprostone (10(-6) M) and compared with vehicle. Both PGE2 and sulprostone decreased +dp/dt (P<0.01) and left ventricular developed pressure (P<0.001) with reversal by an EP3 antagonist. In contrast, the EP4 agonist had the opposite effect. Adult mouse cardiomyocytes contractility was also reduced after treatment with either PGE2 or sulprostone for 10 minutes. We then examined the acute effects of PGE2, sulprostone, and the EP4 agonist on expression of phosphorylated phospholamban and sarcoendoplasmic reticulum Ca(2+)-ATPase 2a in adult mouse cardiomyocytes using Western blot. Treatment with either PGE2 or sulprostone decreased expression of phosphorylated phospholamban corrected to total phospholamban, whereas treatment with the EP4 agonist had the opposite effect. Sarcoendoplasmic reticulum Ca(2+)-ATPase 2a expression was unaffected. Finally, we examined the effect of these

compounds in vivo using pressure-volume loops. Both PGE2 and sulprostone decreased +dp/dt, whereas the EP4 agonist increased +dp/dt. CONCLUSIONS: Contractility is reduced via the EP3 receptor but increased via EP4. These effects may be mediated through changes in phospholamban phosphorylation and has relevance to detrimental effects of inflammation.

Cardiology

Kabbani L, **Munie S**, **Lin J**, **Velez M**, **Isseh I**, **Brooks S**, **Leix S**, and **Shepard A**. Flow patterns in the carotid arteries of patients with left ventricular assist devices *Ann Vasc Surg* 2016;PMID: 27531092. Full Text

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OBJECTIVE: To evaluate and define the expected flow pattern changes of carotid artery duplex ultrasound after LVAD placement. METHODS: Retrospective review of Henry Ford Hospital database of patients who had undergone LVAD placement between March 2008 and July 2012 was performed. All patients who had carotid artery duplex scanning before and after LVAD placement within two years of each other and showed less than 50% stenosis were included in this study. Type of waveform, carotid peak systolic velocity and end-diastolic velocities were analyzed, and the values were compared before and after LVAD placement. RESULTS: A total of 13 patients with LVAD had at least two carotid duplex studies before and after LVAD placement within two years of each other. Of those, 92% (n=12) were men, and 61% (n=8) were Caucasian. Mean age was 61 years old. The Heartware ventricular assist device (HVAD) was implanted in 4 patients and the HeartMate II left ventricular assist device was implanted in 9 patients. Post-LVAD Doppler imaging demonstrated parvus tardus waveform. Analysis of flow velocities revealed that peak systolic velocity was diminished after LVAD placement in both the internal and common carotid arteries ($p=0.006$ and $p<0.0001$ respectively). End-diastolic velocity, however, was noted to be increased post LVAD ($p<0.0001$). Interestingly, mean flow velocities in both the common and internal carotid arteries remained stable after LVAD placement. CONCLUSION: This study reveals changes in waveform morphology and peak systolic and diastolic velocities in the common and internal carotid arteries on carotid duplex after LVAD placement. Additionally, it shows that despite changes in post LVAD pulse pressure in the carotid arteries, the mean flow velocity remained unchanged.

Cardiology

Karacsonyi J, **Alaswad K**, Jaffer FA, Yeh RW, Patel M, Bahadorani J, Karatasakis A, Danek BA, Doing A, Grantham JA, Karmpaliotis D, Moses JW, Kirtane A, Parikh M, Ali Z, Lombardi WL, Kandzari DE, Lembo N, Garcia S, Wyman MR, Alame A, Nguyen-Trong PK, Resendes E, Kalsaria P, Rangan BV, Ungi I, Thompson CA, Banerjee S, and Brilakis ES. Use of intravascular imaging during chronic total occlusion percutaneous coronary intervention: Insights from a contemporary multicenter registry *J Am Heart Assoc* 2016; 5(8)PMID: 27543800. Full Text

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Medical Center of the Rockies, Loveland, CO.
Mid America Heart Institute, Kansas City, MO.
Columbia University, New York, NY.
University of Washington, Seattle, WA.
Piedmont Heart Institute, Atlanta, GA.
Minneapolis VA Healthcare System and University of Minnesota, Minneapolis, MN.
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BACKGROUND: Intravascular imaging can facilitate chronic total occlusion (CTO) percutaneous coronary intervention. METHODS AND RESULTS: We examined the frequency of use and outcomes of intravascular imaging among 619 CTO percutaneous coronary interventions performed between 2012 and 2015 at 7 US centers. Mean age was 65.4+/-10 years and 85% of the patients were men. Intravascular imaging was used in 38%: intravascular ultrasound in 36%, optical coherence tomography in 3%, and both in 1.45%. Intravascular imaging was used for stent sizing (26.3%), stent optimization (38.0%), and CTO crossing (35.7%, antegrade in 27.9%, and retrograde in 7.8%). Intravascular imaging to facilitate crossing was used more frequently in lesions with proximal cap ambiguity (49% versus 26%, P<0.0001) and with retrograde as compared with antegrade-only cases (67% versus 31%, P<0.0001). Despite higher complexity (Japanese CTO score: 2.86+/-1.19 versus 2.43+/-1.19, P=0.001), cases in which imaging was used for crossing had similar technical and procedural success (92.8% versus 89.6%, P=0.302 and 90.1% versus 88.3%, P=0.588, respectively) and similar incidence of major cardiac adverse events (2.7% versus 3.2%, P=0.772). Use of intravascular imaging was associated with longer procedure (192 minutes [interquartile range 130, 255] versus 131 minutes [90, 192], P<0.0001) and fluoroscopy (71 minutes [44, 93] versus 39 minutes [25, 69], P<0.0001) time. CONCLUSIONS: Intravascular imaging is frequently performed during CTO percutaneous coronary intervention both for crossing and for stent selection/optimization. Despite its use in more complex lesion subsets, intravascular imaging was associated with similar rates of technical and procedural success for CTO percutaneous coronary intervention. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02061436.

Cardiology

Kirtane AJ, Doshi D, Leon MB, Lasala JM, Ohman EM, **O'Neill WW**, Shroff A, Cohen MG, Palacios IF, Beohar N, Uriel N, Kapur NK, Karmpaliotis D, Lombardi W, Dangas GD, Parikh MA, Stone GW, and Moses JW. Treatment of higher-risk patients with an indication for revascularization: Evolution within the field of contemporary percutaneous coronary intervention *Circulation* 2016; 134(5):422-431. PMID: 27482004. Full Text

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Patients with severe coronary artery disease with a clinical indication for revascularization but who are at high procedural risk because of patient comorbidities, complexity of coronary anatomy, and/or poor hemodynamics represent an understudied and potentially underserved patient population. Through advances in percutaneous interventional techniques and technologies and improvements in patient selection, current percutaneous coronary intervention may allow appropriate patients to benefit safely from revascularization procedures that might not have been offered in the past. The burgeoning interest in these procedures in some respects reflects an evolutionary step within the field of percutaneous coronary intervention. However, because of the clinical complexity of many of these patients and procedures, it is critical to develop dedicated specialists within interventional cardiology who are trained with the cognitive and technical skills to select these patients appropriately and to perform these procedures safely. Preprocedural issues such as multidisciplinary risk and treatment assessments are highly relevant to the successful treatment of these patients, and knowledge gaps and future directions to improve outcomes in this emerging area are discussed. Ultimately, an evolution of contemporary interventional cardiology is necessary to treat the increasingly higher-risk patients with whom we are confronted.

Cardiology

Luo N, Merrill P, Whellan DJ, Pina IL, Fiuzat M, Kraus WE, Kitzman DW, **Keteyian SJ**, O'Connor CM, and Mentz RJ. Exercise training in patients with chronic heart failure and atrial fibrillation: Results from the hf-action trial *J Card Fail* 2016; 22(8):S71-S71. PMID: Not assigned. Abstract

[Luo, Nancy; Merrill, Peter; Fiuzat, Mona; Kraus, William E.; O'Connor, Christopher M.; Mentz, Robert J.] Duke Clin Res Inst, Durham, NC USA. [Luo, Nancy; Kraus, William E.; Mentz, Robert J.] Duke Univ, Med Ctr, Durham, NC USA. [Whellan, David J.] Thomas Jefferson Univ, Phhiladelphia, PA USA. [Pina, Ileana L.] Montefiore Einstein Med Ctr, New York, NY USA. [Kitzman, Dalane W.] Wake Forest Sch Med, Winston Salem, NC USA. [Keteyian, Steven J.] Henry Ford Hosp, Detroit, MI 48202 USA. [O'Connor, Christopher M.] Inova Heart & Vasc Inst, Falls Church, VA USA.

Background: Moderate physical activity has been reported to reduce atrial fibrillation (AF). However, few data are available regarding the safety and efficacy of physical activity in heart failure patients with atrial fibrillation. Purpose: This study seeks to examine if outcomes with exercise training in HF vary according to AF status. Methods: Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) randomized 2331 ambulatory HF patients with reduced systolic function (ejection fraction [EF] ≤ 35%) to exercise training or usual care. We examined clinical characteristics and outcomes (mortality/hospitalization) by baseline AF status (past history of AF or AF on baseline CPX vs. no AF) using adjusted Cox models and explored an interaction with exercise training. In the overall population as well as by AF status, we assessed post-randomization AF events (new or recurrent) through 12 months diagnosed through 12-lead ECGs, hospitalizations for AF, or report of serious adverse arrhythmia caused by AF. RESULTS: Of 2292 patients with baseline rhythm data, 382 (17%) had AF, 1602 (70%) had sinus rhythm, and 308 (13%) had “other” rhythm. Patients with AF were older, more likely to be men, and had lower EF than those with sinus rhythm. AF patients reported similar baseline quality of life but exhibited lower baseline peak VO 2 . Over a median follow-up of 2.6 years, AF was associated with a 24% per year higher rate of mortality/hospitalization (hazard ratio [HR], 1.53 [95% confidence interval {CI}, 1.34–1.74; P < .001) in unadjusted analysis but did not remain significant when adjusted for other predictors of outcome (HR, 1.15 [95% CI, 0.98–1.35]; P = .09). There was no significant difference in AF events through 12 months by randomized treatment assignment in the overall population or by baseline AF status (all P > .1). There was no interaction between AF status and exercise training on outcomes (all P > .1). Conclusions: AF in patients with chronic HF was associated with older age and reduced exercise capacity but not a differential response to exercise training. We did not observe a reduction in AF events with exercise training as compared to usual care. (Exercise Training Program to Improve Clinical Outcomes in Individuals with Congestive Heart Failure; NCT00047437).

Cardiology

Luzum JA, and **Lanfear DE**. Pharmacogenetic risk scores for perindopril clinical and cost effectiveness in stable coronary artery disease: When are we ready to implement? *J Am Heart Assoc* 2016; 5(3):e003440. PMID: 27021567. Full Text

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Cardiology

Mark DB, Federspiel JJ, Cowper PA, Anstrom KJ, Hoffmann U, Patel MR, Davidson-Ray L, Daniels MR, Cooper LS, Knight JD, Lee KL, Douglas PS, Bonow R, Anderson G, Bertoni A, Carr JJ, Min JK, Proschan M, Spertus JA, Ulrich CM, Al-Khalidi HR, Bonds D, Cook N, Dolor RJ, Go A, Fordyce C, Harding T, Hayden S, Kosinski A, Krucoff MW, Leifer E, Martinez B, Mudrick DW, Picard MH, Rubin G, Salvaggio K, Schneider RM, Shen A, Tardif JC, Tate W, Udelson JE, Vavalle J, Velazquez EJ, Garg J, Huang M, Wu S, Yang Q, Yow E, Zhang A, Apgar C, Achenbach S, Corsini E, Ghoshhajra BB, Lu M, Truong Q, Kinan D, Carlos E, Cole J, Johnson M, Krista M, Ridner M, Abidov A, Barker B, Bies R, Jones D, Weathers L, Albert T, Ariani K, Banerjee S, Budoff M, Chang D, Forman S, Foster G, Hsu J, Jang J, Kahn A, Karlsberg R, Krishnam M, Lee M, Lepor N, Loh I, Lurie M, McConnell M, Ruehm S, Vorobiof G, Abramson S, Friedrich S, Moloo J, Treat S, Keller A, Yang C, Bramlet D, Braun E, Foucauld J, Ghai A, Guzman P, Hendel R, Javier J, Schmalfuss C, Sotolongo C, Tannenbaum A, Weinstock B, Champney K, Frohwein S, Jenkins L, Koganti D, Litwin S, Shapiro P, Leung C, Hinchman D, Clark S, Danciu S, Hines J, Patel A, Sullivan D, Trivedi D, Vidovich M, Mahenthiran J, Shaikh S, Teague S, Clark C, Martin E, Sigurdsson G, Bloom S, Hagley M, Schmidt W, Sorrell V, Turner M, Weiss R, Hearne S, Jerome S, Morss A, Ruberg R, **Abdul-Nour K**, Chinnaiyan K, Goraya T, Heath J, Meengs M, Nahhas G, Nounou M, Saba S, Sallach S, Ginete W, Helmer G, McLaurin M, Pellikka P, Pelzel J, Carroll W, Martin A, Rivard A, Ciaramita J, Hawa Z, Woodard P, Jehle A, Delcore M, Porter T, Van De Graaff E, Budhwani N, Bullock-Palmer R, Espinoza A, Kostis J, Mustafa M, Cavanaugh B, Cohen R, Donnino R, Garcia M,

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Background: PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) found that initial use of at least 64-slice multidetector computed tomography angiography (CTA) versus functional diagnostic testing strategies did not improve clinical outcomes in stable symptomatic patients with suspected coronary artery disease (CAD) requiring noninvasive testing. Objective: To conduct an economic analysis for PROMISE (a major secondary aim of the study). Design: Prospective economic study from the U.S. perspective. Comparisons were made according to the intention-to-treat principle, and CIs were calculated using bootstrap methods. (ClinicalTrials.gov: NCT01174550) Setting: 190 U.S. centers. Patients: 9649 U.S. patients enrolled in PROMISE between July 2010 and September 2013. Median follow-up was 25 months. Measurements: Technical costs of the initial (outpatient) testing strategy were estimated from Premier Research Database data. Hospital-based costs were estimated using hospital bills and Medicare cost-charge ratios. Physician fees were taken from the Medicare Physician Fee Schedule. Costs were expressed in 2014 U.S. dollars, discounted at 3% annually, and estimated out to 3 years using inverse probability weighting methods. Results: The mean initial testing costs were $174 for exercise electrocardiography; $404 for CTA; $501 to $514 for pharmacologic and exercise stress echocardiography, respectively; and $946 to $1132 for exercise and pharmacologic stress nuclear testing, respectively. Mean costs at 90 days were $2494 for the CTA strategy versus $2240 for the functional strategy (mean difference, $254 [95% CI, $634 to $906]). The difference was associated with more revascularizations and catheterizations (4.25 per 100 patients) with CTA use. After 90 days, the mean cost difference between the groups out to 3 years remained small. Limitation: Cost weights for test strategies were obtained from sources outside PROMISE. Conclusion: Computed tomography angiography and functional diagnostic testing strategies in patients with suspected CAD have similar costs through 3 years of follow-up.

Cardiology

Michaels AT, **Radjef R**, **She RC**, **Liu B**, **Peterson E**, Pinto Y, **Williams K**, **Sabbah H**, and **Lanfear D**. Improving risk prediction in heart failure: MAGGIC plus natriuretic peptides *J Card Fail* 2016; 22(8):S99-S99. PMID: Not assigned. Abstract

Background: Risk stratification of patients with heart failure (HF) remains challenging but is a critical need. The MAGGIC score is a clinical risk model derived from meta-analysis of nearly 40k patients. Natriuretic peptides (NP) have consistently shown powerful risk prediction in HF patients, but the incremental value in addition to MAGGIC score is not known. Methods: In this single center study 4264 patients were analyzed from two cohorts; a prospective ambulatory registry of HF patients (n = 1314) who had baseline NTproBNP levels measured, and a retrospective cohort collected utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015; n = 2503) with clinical BNP levels measured at or near discharge. The hospital discharge cohort were all assigned NYHA class IV. The primary end-point was all cause mortality. Performance of the MAGGIC score and NP levels was assessed within each cohort utilizing Cox regression and receiver operating curves (ROC) analysis (MAGGIC alone vs. MAGGIC+NP) with the net reclassification improvement (NRI) also calculated. Results: The overall cohort had an average age of 71.2 years, was 47.8% females, and 41% self-identified African Americans. Median follow up was 1.52 years during which there were 1139 deaths (27%). The MAGGIC score was a strong predictor of outcome in both cohorts (P < .001). In ROC analysis of the ambulatory registry, NP significantly improved area under the curve (AUC) compared to MAGGIC alone from 0.74 to 0.79 (P = .002) and had a NRI of 0.354 (Figure). In contrast, within the hospital discharge cohort NP levels did not significantly add to MAGGIC score (AUC 0.681 vs. 0.676, NRI = 0.033, P = .284) (Figure). Conclusion: In our study, NP levels in the ambulatory setting significantly improved risk stratification provided by the MAGGIC score, but discharge NP levels did not improve MAGGIC prediction of post-hospital survival. Overall risk stratification and particularly NP utility is much better in the ambulatory setting.

Cardiology

Michaels AT, **Radjef R**, **She RC**, **Peterson E**, **Liu B**, and **Lanfear DE**. Predicting mortality at discharge following hospitalization for acute heart failure *J Card Fail* 2016; 22(8):S21-S22. PMID: Not assigned. Abstract

Background : Risk stratification for heart failure (HF) patients remains a critical need, particularly among those hospitalized where many clinical decisions are being made at discharge. Recently a robust risk model, the MAGGIC score, was derived from data on nearly 40k patients. This provides 1 year mortality estimates and is available as an online clinical tool. Whether it is useful to risk-stratify patients being discharged from the hospital is unknown. Methods : This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. For the hospital discharge subjects, when tabulating MAGGIC all patients were assigned NYHA class IV. The primary endpoint was all-cause mortality. Vital status was assessed utilizing system administrative data and the social security death master file. Performance of the MAGGIC score was evaluated within cohorts and compared across the two groups using Cox models stratified by cohort and then with an interaction term (MAGGIC*Cohort). Calibration was assessed by comparing observed vs. MAGGIC-predicted 1 year mortality. Results : Overall the study patients had an average age of 71.2 years, 47.8% were female and 41% were self-identified African Americans, and there were 1139 deaths (27%) over a median follow up of 1.52 years. The hospital discharge cohort was overall much higher risk than the ambulatory cohort (figure). The MAGGIC score was a strong predictor of outcomes in both groups (both P < .001). With a HR (per MAGGIC point) of 1.13 in the ambulatory registry and 1.10 in the hospital discharge patients. In ROC analysis MAGGIC showed an area under the curve (AUC) of 0.74, but an AUC in the hospital discharge cohort of 0.67. When modeled using an interaction term, MAGGIC did appear to be more predictive in the ambulatory group with an interaction coefficient of 0.03 (P = .004). Although calibration appeared suboptimal in both cohorts (Figure), with MAGGIC underestimating the true risk, this appeared similar in both cohorts. Discussion : The MAGGIC score is able to provide important prognostic information on patients being discharged from the hospital for HF, though the performance was somewhat inferior than in a comparable ambulatory cohort. MAGGIC underestimated risk in both ambulatory and hospital cohorts, suggesting calibration may need to be reassessed in more real-world patient data sets.

Cardiology

Parikh KS, Coles A, Schulte PJ, Kraus WE, Fleg JL, **Keteyian SJ**, Pina IL, Fiuzat M, Whellan DJ, O'Connor CM, and Mentz RJ. Relation of angina pectoris to outcomes, quality of life, and response to exercise training in patients with chronic heart failure (from HF-ACTION) *Am J Cardiol* 2016;PMID: 27561194. Full Text

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Angina pectoris (AP) is associated with worse outcomes in heart failure (HF). We investigated the association of AP with health-related quality of life (HRQoL), exercise capacity, and clinical outcomes and its interaction with exercise training in an HF population. We grouped 2,331 patients with HF with reduced ejection fraction in the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial of usual care +/- exercise training according to whether they had self-reported AP by Canadian classification score. HRQoL and clinical outcomes were assessed by AP status. In HF-ACTION, 406 patients (17%) had AP at baseline (44% with Canadian classification score >/=II) with HF severity similar to those without AP. Patients with AP had similar baseline exercise capacity but worse depressive symptoms and HRQoL. AP was associated with 22% greater adjusted risk for all-cause mortality/hospitalizations, driven by hospitalizations. There was significant interaction between baseline AP and exercise training peak VO2 change (p = 0.019) but not other end points. Exercise training was associated with greater peak VO2 improvement after 3 months in patients with AP (treatment effect = 1.25 ml/kg/min, 95% CI 0.6 to

1.9). In conclusion, AP was associated with worse HRQoL and depressive symptoms. Despite greater peak VO2 improvement with exercise training, patients with AP experienced more adverse outcomes.

Cardiology
Radjef R, **Michaels A**, **Peterson E**, **She R**, **Liu B**, **Williams K**, **Sabbah H**, and **Lanfear D**. Performance of MAGGIC score in african americans compared to whites *J Card Fail* 2016; 22(8):S101-S101. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Cardiology
Sabbah HN, **Gupta RC**, **Sing-Gupta V**, **Zhang KF**, and **Xu J**. Long-Term Therapy with Elamipretide Normalizes ATP Synthase Activity in Left Ventricular *J Card Fail* 2016; 22(8):S23-S23. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Cardiology
Singh V, Damluji AA, Mendirichaga R, Alfonso CE, Martinez CA, Williams D, Heldman AW, de Marchena EJ, **O'Neill WW**, and Cohen MG. Elective or emergency use of mechanical circulatory support devices during transcatheter aortic valve replacement *J Interv Cardiol* 2016;PMID: 27550213. Full Text

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OBJECTIVE: Evaluate the use of mechanical circulatory support (MCS) devices in high-risk patients undergoing transcatheter aortic valve replacement (TAVR). BACKGROUND: The use of MCS devices in elderly patients with multiple comorbidities undergoing TAVR is underexplored. METHODS: All patients undergoing TAVR at a single tertiary academic center who required MCS during index procedure between 2008 and 2015 were included in a prospective database. RESULTS: MCS was used in 9.4% (54/577) of all TAVRs (n = 52 Edwards Sapien and n = 2 CoreValves) of which 68.5% (n = 37) were used as part of a planned strategy, and 31.5% (n = 17) were used in emergency "bail-out" situations. IABP was the most commonly used device (87%) followed by Impella and ECMO (6% each). Among the MCS group, 22% required cardiopulmonary resuscitation during the procedure (n = 4 elective [11%] vs. n = 8 emergent [47%]) and 15% upgrade to a second device (Impella or CPB after IABP; n = 5 elective [14%] vs. n = 3 emergent [18%]). Median duration of support was 1-day. Device related complications were low (4%). In-hospital mortality in this extremely high-risk population was 24% (13/54) (11% [4/37] for elective cases and 53% [9/17] for emergency cases). Cardiogenic shock (50%) was the most common cause of in-hospital death. Cumulative all-cause 1-year mortality was 35% (19/54) (19% 97/370 for elective and 71% [12/17] for emergency cases). CONCLUSION: Emergent use of MCS during TAVR in extremely high-risk population is associated with high short and long-term mortality rates. Early identification of patients at risk for hemodynamic compromise may rationalize elective utilization of MCS during TAVR.

Center for Health Policy and Health Services Research

Cajigal S, **Wells KE**, **Peterson EL**, **Ahmedani BK**, Yang JJ, Kumar R, Burchard EG, and **Williams LK**. Predictive properties of the asthma control test and its component questions for severe asthma exacerbations *J Allergy Clin Immunol Pract* 2016;PMID: 27544712. Full Text

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BACKGROUND: Current US guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. OBJECTIVE: The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting the risk of severe asthma exacerbations. METHODS: Individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity, and those included in the current analysis had the following characteristics: age 18 years or more, physician-diagnosed asthma, and longitudinal care received at a large health system in southeastern Michigan. Study participants underwent a baseline evaluation, which included answering the ACT. A severe asthma exacerbation was defined as one requiring oral steroids, an emergency department visit, or inpatient admission. Receiver-operator characteristic curves were used to measure and compare the predictive utility of the ACT and its component questions for severe asthma exacerbations. RESULTS: Of 1180 participants, 354 (30.0%) experienced a severe asthma exacerbation within 6 months of their baseline evaluation. When compared with the individual questions that composed the ACT, the composite score was significantly better at predicting severe exacerbations with 1 exception; the composite ACT score and the question assessing rescue medication use were not significantly different (P = .580). Pharmacy-based records of metered-dose inhaler short-acting beta-agonist use and asthma severity were also not significantly different from the composite ACT score. CONCLUSIONS: Our study demonstrates that although the ACT is modestly predictive for exacerbations, the composite score may not be superior to assessing rescue medication use alone for predicting the risk of severe asthma exacerbations.

Center for Health Policy and Health Services Research

Foster MA, Xing J, Moorman AC, Boscarino J, **Gordon SC**, **Lu M**, **Rupp L**, Schmidt MA, Trinacty CM, Xu F, Holmberg SD, and Spradling PR. Frequency of and factors associated with receipt of liver-related specialty care among patients with hepatitis c in the chronic hepatitis cohort study *Dig Dis Sci* 2016;PMID: 27510752. Full Text

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BACKGROUND: Linking persons with hepatitis C virus (HCV) to care and treatment is critical to reduction in disease burden; typically, this entailed referral to a specialist. However, data regarding the frequency and factors associated with referral among patients in healthcare organizations (HCOs) are lacking. METHODS: Among persons in four US HCOs with newly diagnosed HCV during 2006-2011, we determined the frequency of liver-related specialist care after diagnosis. We also identified sociodemographic and clinical characteristics associated with such care by multivariate analysis, adjusted for all variables. RESULTS: Among 3592 patients with newly diagnosed HCV, 57 % (range among sites 45-90 %) received specialist care; of these, 57 % received care within 90 days of diagnosis. Patient characteristics associated with receipt of specialist care included: affiliation with one of the study sites [adjusted odds ratio (aOR) 4.8 vs. the referent site); having Medicare plus private insurance (aOR 1.6 vs. Medicaid); and having elevated alanine aminotransferase (ALT) (aOR 1.6 vs. normal ALT) or lower platelet values (aOR 1.4 vs. normal platelet level). Specialist care within 90 days of diagnosis was associated with private insurance (aOR 1.5 vs. Medicaid), elevated ALT levels (aOR 1.3-2.3 vs. normal), and having >/=2 comorbid conditions (aOR 1.4 vs. no comorbid conditions). Compared to patients not referred, those referred were more likely to be treated (aOR 3.5). CONCLUSIONS: Receipt of specialist care among persons with newly diagnosed HCV varied among HCOs. Clinical evidence of liver disease and having private insurance were associated with prompt receipt of specialist care and HCV treatment.

Center for Health Policy and Health Services Research
Luzum JA, and **Lanfear DE**. Pharmacogenetic risk scores for perindopril clinical and cost effectiveness in stable coronary artery disease: When are we ready to implement? *J Am Heart Assoc* 2016; 5(3):e003440. PMID: 27021567. Full Text

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Center for Health Policy and Health Services Research
Michaels AT, **Radjef R**, **She RC**, **Liu B**, **Peterson E**, Pinto Y, **Williams K**, **Sabbah H**, and **Lanfear D**. Improving risk prediction in heart failure: MAGGIC plus natriuretic peptides *J Card Fail* 2016; 22(8):S99-S99. PMID: Not assigned. Abstract

Background: Risk stratification of patients with heart failure (HF) remains challenging but is a critical need. The MAGGIC score is a clinical risk model derived from meta-analysis of nearly 40k patients. Natriuretic peptides (NP) have consistently shown powerful risk prediction in HF patients, but the incremental value in addition to MAGGIC score is not known. Methods: In this single center study 4264 patients were analyzed from two cohorts; a prospective ambulatory registry of HF patients (n = 1314) who had baseline NTproBNP levels measured, and a retrospective cohort collected utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015; n = 2503) with clinical BNP levels measured at or near discharge. The hospital discharge cohort were all assigned NYHA class IV. The primary end-point was all cause mortality. Performance of the MAGGIC score and NP levels was assessed within each cohort utilizing Cox regression and receiver operating curves (ROC) analysis (MAGGIC alone vs. MAGGIC+NP) with the net reclassification improvement (NRI) also calculated. Results: The overall cohort had an average age of 71.2 years, was 47.8% females, and 41% self-identified African Americans. Median follow up was 1.52 years during which there were 1139 deaths (27%). The MAGGIC score was a strong predictor of outcome in both cohorts (P < .001). In ROC analysis of the ambulatory registry, NP significantly improved area under the curve (AUC) compared to MAGGIC alone from 0.74 to 0.79 (P = .002) and had a NRI of 0.354 (Figure). In contrast, within the hospital discharge cohort NP levels did not significantly add to MAGGIC score (AUC 0.681 vs. 0.676, NRI = 0.033, P = .284) (Figure). Conclusion: In our study, NP levels in the ambulatory setting significantly improved risk stratification provided by the MAGGIC score, but discharge NP levels did not improve MAGGIC prediction of post-hospital survival. Overall risk stratification and particularly NP utility is much better in the ambulatory setting.

Center for Health Policy and Health Services Research

Radjef R, **Michaels A**, **Peterson E**, **She R**, **Liu B**, **Williams K**, **Sabbah H**, and **Lanfear D**. Performance of MAGGIC score in african americans compared to whites *J Card Fail* 2016; 22(8):S101-S101. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Center for Health Policy and Health Services Research

Rundell SD, Goode AP, Suri P, Heagerty PJ, Comstock BA, Friedly JL, Gold LS, Bauer Z, Avins AL, Nedeljkovic SS, **Nerenz DR**, Kessler L, and Jarvik JG. The impact of comorbid knee and hip osteoarthritis on longitudinal clinical and health care use outcomes in older adults with new visits for back pain *Arch Phys Med Rehabil* 2016;PMID: 27519927. Full Text

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OBJECTIVE: To examine if a comorbid diagnosis of knee or hip osteoarthritis (OA) in older adults with new back pain visits is associated with long-term patient-reported outcomes (PROs) and back-related healthcare use. DESIGN: Prospective cohort study SETTING: Three integrated health systems forming the Back pain Outcomes using Longitudinal Data cohort. PARTICIPANTS: 5,155 of 5,239 older adults (>/=65 years old) with a new visit for back pain and complete electronic health record data. INTERVENTIONS: Not applicable. We obtained OA diagnoses using diagnostic codes in the electronic health record 12 months prior to the new back pain visit. MAIN OUTCOME MEASURES: The Roland Morris Disability Questionnaire (RDQ) and the EQ-5D were key PROs. Health care use, measured by Relative Value Units (RVUs), was summed for the 12 months after the initial visit. We used generalized estimating equations to model PROs. We also used generalized linear models to test the association between comorbid knee or hip OA and total back-related RVUs. RESULTS: 368 (7.1%) of 5155 participants had a comorbid knee OA diagnosis and 94 (1.8%) had a hip OA diagnosis. 4711 (91.4%) had neither knee nor hip OA. In adjusted models, 12-month RDQ was 1.29 points higher (95% CI: 0.78, 1.80) for patients with knee OA and 1.20 points higher

(95% CI: 0.18, 2.22) for those with hip OA compared to those without knee or hip OA, respectively. Lower EQ-5D was found among participants with knee OA (0.02 lower ((95% CI: -0.04, -0.01)) and hip OA diagnoses (0.03 lower (95% CI: -0.06, -0.01)) compared to those without knee or hip OA, respectively. Comorbid knee or hip OA was not significantly associated with total 12-month back-related resource use. CONCLUSION: Comorbid knee or hip OA in older adults with a new back pain visit was associated with modestly worse long-term disability and health-related quality-of-life.

Center for Health Policy and Health Services Research
Scherrer JF, Salas J, Sullivan MD, Schneider FD, Bucholz KK, Burroughs T, Copeland L, **Ahmedani B**, and Lustman PJ. The influence of prescription opioid use duration and dose on development of treatment resistant depression *Prev Med* 2016;PMID: 27497660. Full Text

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Long-term prescription opioid use is associated both with new-onset and recurrence of depression. Whether chronic opioid use interferes with depression management has not been reported, therefore we determined whether patients' longer duration of opioid use and higher opioid dose are associated with new-onset treatment resistant depression (TRD) after controlling for confounding from pain and other variables. Data was obtained from Veteran Health Administration (VHA) de-identified patient medical records. We used a retrospective cohort design from 2000-2012. Eligible subjects (n=6,169) were 18-80 years of age, free of cancer and HIV, diagnosed with depression and opioid-free for the 24-month interval prior to the observation period. Duration of a new prescription for opioid analgesic was categorized as 1-30 days, 31-90 days and >90 days. Morphine-equivalent dose (MED) during follow-up categorized as </=50 mg versus >50 mg per day. Pain and other sources of confounding were controlled by propensity scores and inverse probability of treatment weighting. Cox proportional hazard models were computed to estimate the association between duration and dose of opioid and onset of TRD. After removing confounding by weighting data, opioid use for 31-90 days and for >90 days, compared to 1-30 days, was significantly associated with new onset TRD (HR=1.25; 95%CI: 1.09-1.45 and HR=1.52; 95%CI: 1.32-1.74, respectively). MED was not associated with new onset TRD. The risk of developing TRD increased as time spent on opioid analgesics increased. Long-term opioid treatment of chronic pain may interfere with treatment of depression.

Center for Health Policy and Health Services Research
Zhou K, Yee SW, Seiser EL, van Leeuwen N, Tavendale R, Bennett AJ, Groves CJ, Coleman RL, van der Heijden AA, Beulens JW, de Keyser CE, Zaharenko L, Rotroff DM, Out M, Jablonski KA, Chen L, Javorsky M, Zidzik J, **Levin AM**, **Williams LK**, Dujic T, Semiz S, Kubo M, Chien HC, Maeda S, Witte JS, Wu L, Tkac I, Kooy A, van Schaik RH, Stehouwer CD, Logie L, Sutherland C, Klovins J, Pirags V, Hofman A, Stricker BH, Motsinger-Reif AA, Wagner MJ, Innocenti F, Hart LM, Holman RR, McCarthy MI, Hedderson MM, Palmer CN, Florez JC, Giacomini KM, and Pearson ER. Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin *Nat Genet* 2016;PMID: 27500523. Full Text

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Metformin is the first-line antidiabetic drug with over 100 million users worldwide, yet its mechanism of action remains unclear. Here the Metformin Genetics (MetGen) Consortium reports a three-stage genome-wide association study (GWAS), consisting of 13,123 participants of different ancestries. The C allele of rs8192675 in the intron of SLC2A2, which encodes the facilitated glucose transporter GLUT2, was associated with a 0.17% ($P = 6.6 \times 10^{-14}$) greater metformin-induced reduction in hemoglobin A1c (HbA1c) in 10,577 participants of European ancestry. rs8192675 was the top cis expression quantitative trait locus (cis-eQTL) for SLC2A2 in 1,226 human liver samples, suggesting a key role for hepatic GLUT2 in regulation of metformin action. Among obese individuals, C-allele homozygotes at rs8192675 had a 0.33% (3.6 mmol/mol) greater absolute HbA1c reduction than T-allele homozygotes. This was about half the effect seen with the addition of a DPP-4 inhibitor, and equated to a dose difference of 550 mg of metformin, suggesting rs8192675 as a potential biomarker for stratified medicine.

Dermatology

Chen WB, Gao L, **Wang J**, Wang YG, Dong Z, Zhao J, **Mi QS**, and **Zhou L**. Conditional ablation of HDAC3 in islet beta cells results in glucose intolerance and enhanced susceptibility to STZ-induced diabetes *Oncotarget* 2016;PMID: 27542279. Full Text

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Histone deacetylases (HDACs) are enzymes that regulate gene expression by modifying chromatin structure through removal of acetyl groups from target histones or non-histone proteins. Previous in vitro studies suggest that HDACs may be novel pharmacological targets in immune-mediated islet beta-cell destruction. However, the role of specific HDAC in islet beta-cell development and function remain unclear. Here, we generated a conditional islet beta-cells specific HDAC3 deletion mouse model to determine the consequences of HDAC3 depletion on islet beta-cell differentiation, maintenance and function. Islet morphology, insulin secretion, glucose tolerance, and multiple low-dose streptozotocin (STZ)-induced diabetes incidence were evaluated and compared between HDAC3 knockout and wild type littermate controls. Mice with beta-cell-specific HDAC3 deletion displayed decreased pancreatic insulin content, disrupted glucose-stimulated insulin secretion, with intermittent spontaneous diabetes and dramatically enhanced susceptibility to STZ-induced diabetes. Furthermore, islet beta-cell line, MIN6 cells with siRNA-mediated HDAC3 silence, showed decreased insulin gene transcription, which was mediated, at least partially, through the upregulation of suppressors of cytokine signaling 3 (SOCS3). These results indicate the critical role of HDAC3 in normal beta-cell differentiation, maintenance and function.

Dermatology

Gold LS, Baldwin H, Rueda MJ, Kerrouche N, and Dréno B. Adapalene-benzoyl peroxide gel is efficacious and safe in adult female acne, with a profile comparable to that seen in teen-aged females *J Clin Aesthet Dermatol* 2016; 9(7):23-29. PMID: Not assigned. Article Request Form

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Objectives: To evaluate the efficacy and safety of adapalene 0.1% benzoyl peroxide 2.5% gel in women aged 25 years or older via subgroup analysis of existing Phase 2 and 3 study data. Methods: Meta-analysis of pooled data from three multicenter, randomized, double-blind, vehicle-controlled, parallel-group, clinical trials compared results of treatment with either adapalene 0.1% benzoyl peroxide 2.5% gel or vehicle gel in adult females and teen-aged females. Efficacy assessments included investigator's global assessment and median percent change in acne lesions. Safety assessments included skin tolerability and adverse events. Results: Two hundred fifty-four adult females and 488 teen-aged females were included in the analyses, and baseline characteristics were comparable between subjects receiving adapalene 0.1% benzoyl peroxide 2.5% or vehicle. Both adult females and teen-aged females in the adapalene 0.1% benzoyl peroxide 2.5% arm were significantly more often rated clear/almost clear compared with those in the vehicle arm at Weeks 8 (P=0.016) and 12 (P<0.001); at endpoint, success was achieved in 39.2 percent with adapalene 0.1% benzoyl peroxide 2.5% and 18.5 percent with vehicle. Comparison of the amount of difference between active and vehicle reductions in investigator's global assessment showed that efficacy was similar for adult females versus teen-aged females (20.7% vs. 19.9%, respectively). Adapalene 0.1% benzoyl peroxide 2.5% had a rapid onset of action, with statistically significant reductions in all acne lesion types versus vehicle observed by Week 1. Adapalene 0.1% benzoyl peroxide 2.5% was safe and well-tolerated by adult females with a tolerability profile consistent with that seen in teen-aged females. Conclusions: The once-daily fixed-dose combination product adapalene 0.1% benzoyl peroxide 2.5% is an efficacious, safe, and well-tolerated treatment for adult female acne, with a profile similar to that in teen-aged females.

Dermatology

Paul C, **Gold LS**, Cambazard F, Kalb RE, Lowson D, Moller AH, and Griffiths CEM. More rapid improvement in quality of life with fixed-combination calcipotriene plus betamethasone dipropionate aerosol foam vs. topical suspension (PSO-ABLE study in patients with psoriasis vulgaris) *Br J Dermatol* 2016; 175:213-214. PMID: Not assigned. Abstract

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Background and objective: The Phase III, PSO-ABLE study (NCT02132936) demonstrated superior efficacy with fixed combination calcipotriene 0.005% l)/betamethasone dipropionate 0.064% (BD) aerosol foam at wk 4 vs Cal/BD topical suspension (susp) at wk 8, with comparable safety up to wk 12, in patients (pts) with mild-to-severe psoriasis of the body. Changes in health-related quality of life (HRQoL) are presented here.Methods: Pts assessed HRQoL using dermatology life-quality index (DLQI) and generic EQ-5D questionnaires at baseline, wks 4, 8, 12. A DLQI score of 0 (range 0 to 30) and EQ-5D utility score of 1 (weighted range –0.594 to 1) indicate perfect health. The proportion of pts who achieved a DLQI score of 0/1 (no/low impairment) was also determined.Results: 463 pts were randomized (4:4:1:1) to treatment with once-daily Cal/BD foam (n=185), Cal/BD susp (n=188), foam vehicle (n=47) or susp vehicle (n=43). Mean baseline DLQI scores were 7.0 (Cal/BD foam), 7.9 (Cal/BD susp), 7.0 (foam vehicle) and 9.3 (susp vehicle), indicating moderate impact on HRQoL. DLQI scores improved by wk 12 in all groups; mean change in DLQI at wk 4 was significantly greater with Cal/BD foam than Cal/BD susp (–4.3 vs –3.8; adj diff –1.0; P=0.005); differences were not significant at wks 8 (–4.5 vs –4.4; adj diff –0.7; P=0.075), and 12 (–4.6 vs –4.3; adj diff –0.8; P=0.069). DLQI score improvements were significantly greater with both active treatments vs their respective vehicles at each time point (P< 0.05). Significantly more pts using Cal/BD foam than Cal/BD susp achieved DLQI scores of 0/1 at wks 4 (46 vs 32%; P=0.013) and 12 (61 vs 44%; P=0.003), with a non-significant difference at wk 8 (54 vs 43%; P=0.060). Mean baseline EQ-5D utility scores were 0.80 (Cal/BD foam), 0.82 (Cal/BD susp), 0.82 (foam vehicle) and 0.77 (susp vehicle). At wk 4, a significantly greater improvement in mean EQ-5D utility score was seen with Cal/BD foam vs Cal/BD susp (0.09 vs 0.03; adj diff 0.05; P< 0.001). From wk 8, improvements in utility scores for both Cal/BD formulations were comparable (wk 8: 0.08 vs 0.05; adj diff 0.03; P=0.06; wk 12: 0.07 vs 0.05; adj diff 0.02; P=0.21). Both active treatments had significantly greater wk 4 improvements in EQ-5D utility scores vs their respective vehicles (P< 0.05).Conclusion: In PSO-ABLE, Cal/BD aerosol foam improved HRQoL more rapidly than Cal/BD topical suspension, in pts with psoriasis vulgaris.

Dermatology

Paul C, **Stein Gold L**, Cambazard F, Kalb RE, Lowson D, Bang B, and Griffiths CE. Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis vulgaris: randomized, controlled PSO-ABLE study *J Eur Acad Dermatol Venereol* 2016;PMID: 27531752. Full Text

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BACKGROUND: Fixed combination calcipotriol 50 mug/g (Cal) plus betamethasone 0.5 mg/g (BD) foam has been developed as a new treatment option for patients with psoriasis. METHODS: The randomized, parallel-group, investigator-blinded Phase III, 12-week PSO-ABLE study compared the efficacy and safety of Cal/BD foam with Cal/BD gel. Patients aged >/=18 years with mild-to-severe psoriasis were randomized 4:4:1:1 to once-daily Cal/BD foam, Cal/BD gel, foam vehicle or gel vehicle (NCT02132936). The primary efficacy endpoint was the proportion of patients who were clear/almost clear with a >/= 2 grade improvement according to the physician's global assessment of disease severity (i.e. treatment success) at week 4 for Cal/BD foam vs. week 8 for Cal/BD gel. Secondary efficacy endpoints included: proportion of patients achieving at least a 75% reduction in modified psoriasis area and severity index (mPASI75), and time to treatment success (TTTS). Safety was monitored throughout. RESULTS: A total of 463 patients were randomized: Cal/BD foam (n = 185), Cal/BD gel (n = 188), foam vehicle (n = 47), gel vehicle (n = 43); overall completion rate was 90%. Cal/BD foam achieved higher treatment success rates (38% vs. 22%; P < 0.001) and mPASI75 (52% vs. 35%; P < 0.001) by week 4 than Cal/BD gel by week 8. Median TTTS with Cal/BD foam was 6 weeks; this could not be determined for Cal/BD gel as 50% treatment success was not achieved (P < 0.001). Adverse drug reactions were reported in 14 (7.6%) Cal/BD aerosol foam patients and 7 (3.7%) Cal/BD gel patients; all were single events except for itch with Cal/BD aerosol foam (n = 5; 2.7%) and worsening psoriasis with Cal/BD gel (n = 3; 1.6%). CONCLUSION: Cal/BD aerosol foam showed significantly greater efficacy after 4 weeks, than 8 weeks of treatment with Cal/BD gel, with similar tolerability.

Dermatology
Siddiqui K, **Stein Gold L**, and Gill J. The efficacy, safety, and tolerability of ivermectin compared with current topical treatments for the inflammatory lesions of rosacea: a network meta-analysis *Springerplus* 2016; 5(1):1151. PMID: 27504249. Full Text

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BACKGROUND: Rosacea is a common chronic skin condition that manifests as recurrent inflammatory lesions. Long-term treatment is required to control symptoms and disease progression, with topical treatments being the first-line choice. Ivermectin 1 % cream is a new once-daily (QD) topical treatment for the inflammatory lesions of rosacea, and it is important to compare the efficacy, safety, and tolerability of ivermectin with other currently available topical treatments. METHODS: A systematic literature review was performed from January 2011 to June 2015, with articles published prior to 2011 retrieved from a Cochrane review on rosacea. Randomized controlled trials of the topical treatment of adult patients with moderate-to-severe papulopustular rosacea were identified from electronic databases and trial registers, and supplemented with data from clinical study reports. Mixed treatment comparisons (MTCs) were conducted to compare different treatments according to Bayesian methodology. RESULTS: 57 studies were identified, with 19 providing data suitable for MTC. Ivermectin 1 % cream QD led to a significantly greater likelihood of success compared with azelaic acid 15 % gel twice-daily (BID) [relative risk (95 % credible interval): 1.25 (1.14-1.37)], and metronidazole 0.75 % cream BID [1.17 (1.08-1.29)] at 12 weeks. Ivermectin 1 % cream QD also demonstrated a significant reduction in inflammatory lesion count compared with azelaic acid 15 % gel BID [-8.04 (-12.69 to -3.43)] and metronidazole 0.75 % cream BID [-9.92 (-13.58 to -6.35)] at 12 weeks. Ivermectin 1 % cream QD led to a significantly lower risk of developing any AE or TRAE compared with azelaic acid 15 % gel BID [0.83 (0.71-0.97) and 0.47 (0.32-0.67), respectively]. CONCLUSIONS: Ivermectin 1 % cream QD appears to be a more effective topical treatment than other current options for the inflammatory lesions of rosacea, with at least an equivalent safety and tolerability profile, and could provide physicians and dermatologists with an alternative first-line treatment option.

Dermatology
Stein Gold LF. Acne: What's new *Semin Cutan Med Surg* 2016; 35(6 Suppl):S114-116. PMID: 27538054. Article Request Form

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Acne vulgaris is one of the most prevalent skin conditions. Antibiotics, when considered, are most effective in combination with other therapies, and limited evidence suggests that submicrobial doses of antibiotics may improve acne without increasing the risk for antibiotic resistance. A small but significant risk for inflammatory bowel disease has also been identified in children treated with multiple courses of antibiotics. New topical agents are expanding therapeutic options for acne. Semin Cutan Med Surg 35(supp6):S114-S116.

Dermatology
Zarbo A, Ouerfelli O, Klang M, and Lacouture ME. Increased airport scrutiny by the transportation security administration of a patient-passenger carrying ammonium lactate-containing moisturizer *JAMA Dermatol* 2016;PMID: 27486908. Full Text

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Emergency Medicine
Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Family Medicine

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Gastroenterology

Foster MA, Xing J, Moorman AC, Boscarino J, **Gordon SC**, **Lu M**, **Rupp L**, Schmidt MA, Trinacty CM, Xu F, Holmberg SD, and Spradling PR. Frequency of and factors associated with receipt of liver-related specialty care among patients with hepatitis c in the chronic hepatitis cohort study *Dig Dis Sci* 2016;PMID: 27510752. Full Text

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BACKGROUND: Linking persons with hepatitis C virus (HCV) to care and treatment is critical to reduction in disease burden; typically, this entailed referral to a specialist. However, data regarding the frequency and factors associated with referral among patients in healthcare organizations (HCOs) are lacking. METHODS: Among persons in four US HCOs with newly diagnosed HCV during 2006-2011, we determined the frequency of liver-related specialist care after diagnosis. We also identified sociodemographic and clinical characteristics associated with such care by multivariate

analysis, adjusted for all variables. RESULTS: Among 3592 patients with newly diagnosed HCV, 57 % (range among sites 45-90 %) received specialist care; of these, 57 % received care within 90 days of diagnosis. Patient characteristics associated with receipt of specialist care included: affiliation with one of the study sites [adjusted odds ratio (aOR) 4.8 vs. the referent site); having Medicare plus private insurance (aOR 1.6 vs. Medicaid); and having elevated alanine aminotransferase (ALT) (aOR 1.6 vs. normal ALT) or lower platelet values (aOR 1.4 vs. normal platelet level). Specialist care within 90 days of diagnosis was associated with private insurance (aOR 1.5 vs. Medicaid), elevated ALT levels (aOR 1.3-2.3 vs. normal), and having >/=2 comorbid conditions (aOR 1.4 vs. no comorbid conditions). Compared to patients not referred, those referred were more likely to be treated (aOR 3.5). CONCLUSIONS: Receipt of specialist care among persons with newly diagnosed HCV varied among HCOs. Clinical evidence of liver disease and having private insurance were associated with prompt receipt of specialist care and HCV treatment.

Gastroenterology

Gane E, Kowdley KV, Pound D, Stedman CA, Davis M, Etzkorn K, **Gordon SC**, Bernstein D, Everson G, Rodriguez-Torres M, Tsai N, Khalid O, Yang JC, Lu S, Dvory-Sobol H, Stamm LM, Brainard DM, McHutchison JG, Tong M, Chung RT, Beavers K, Poulos JE, Kwo PY, and Nguyen MH. Efficacy of Sofosbuvir, Velpatasvir, and GS-9857 in Patients with HCV Genotype 2, 3, 4, or 6 Infections in an Open-label, Phase 2 Trial *Gastroenterology* 2016;PMID: 27486033. Full Text

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Gilead Sciences, Foster City, CA, USA.
Huntington Medical Research Institutes Liver Center, Pasadena, CA, USA.
Massachusetts General Hospital, Boston, MA, USA.
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Stanford University Medical Center, Palo Alto, CA, USA.

BACKGROUND & AIMS: Studies are needed to determine the optimal regimen for patients with chronic hepatitis C virus (HCV) genotype 2, 3, 4, or 6 infections who have failed by a prior course of antiviral therapy, and the feasibility of further shortening treatment duration. We performed a phase 2 study to determine the efficacy and safety of the combination of the nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the NS3/4A protease inhibitor GS-9857 in these patients. METHODS: We performed a multicenter, open-label trial at 32 sites in the United States and 2 sites in New Zealand, from March 3, 2015 to April 27, 2015. Our study included 128 treatment-naive and treatment-experienced patients (1 with HCV genotype 1b, 33 with HCV genotype 2, 74 with HCV genotype 3, 17 with genotype HCV 4, and 3 with HCV genotype 6), with or without compensated cirrhosis. All patients received sofosbuvir-velpatasvir (400 mg/100 mg fixed-dose combination tablet) and GS-9857 (100 mg) once daily for 6-12 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). RESULTS: Following 6 weeks of treatment, SVR12s were achieved by 88% of treatment-naive patients without cirrhosis (29/33; 95% CI, 72%-97%). Following 8 weeks of treatment, SVR12s were achieved by 93% of treatment-naive patients with cirrhosis (28/30; 95% CI, 78%-99%). After 12 weeks of treatment, SVR12s were achieved by all treatment-experienced patients without cirrhosis (36/36; 95% CI, 90%-100%) and 97% of treatment-experienced patients with cirrhosis (28/29; 95% CI, 82%-100%). The most common adverse events were headache, diarrhea, fatigue, and nausea. Three patients (1%) discontinued treatment due to adverse events. CONCLUSIONS: In a phase 2 open-label trial, we found sofosbuvir-velpatasvir plus GS-9857 (8 weeks in treatment-naive patients or 12 weeks in treatment-experienced patients) to be safe and effective for patients with HCV genotype 2, 3, 4, or 6 infections, with or without compensated cirrhosis. ClinicalTrials.gov no: NCT02378961.

Gastroenterology
Kruger DL, Rein DB, Kil N, Jordan C, **Brown KA**, Yartel A, and Smith BD. Implementation of birth-cohort testing for hepatitis c virus: Lessons learned from three primary care sites *Health Promot Pract* 2016;PMID: 27496859. Full Text

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Hepatitis C virus infection affects approximately 2.2 to 3.2 million Americans. In 2012, the Centers for Disease Control and Prevention recommended a one-time antibody test of all persons belonging to the 1945-1965 birth cohort. Efforts to implement this recommendation in clinical settings are in their infancy; this case study report therefore seeks to share the experiences of three sites that implemented interventions to increase birth-cohort testing through participation in the Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C. At each site, project managers completed standardized questionnaires about their implementation experiences, and a qualitative analysis was conducted of the responses. The testing interventions used in-person recruitment, mail recruitment, and an electronic health record prompt. Sites reported that early efforts to obtain stakeholder buy-in were critical to effectively implement and sustain interventions and that the intervention required additional staffing resources beyond those being used for risk-based testing. In each case, administrative barriers were more extensive than anticipated. For the electronic health record-based intervention, technological support was critical in achieving study goals. Despite these barriers, interventions in all sites were successful in increasing rates of testing and case identification, although future studies will need to evaluate the relative costs and benefits of each intervention.

Gastroenterology
Parekh R, **Segovia M**, and **Kaur N**. Tumor-necrosis-factor-α antagonist therapy for inflammatory bowel disease after liver transplantation *Am J Transplant* 2016; 16:666-667. PMID: Not assigned. Abstract

R. Parekh, Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, United States

Background: The safety and effectiveness of tumor-necrosis-factor-α antagonist (anti-TNF-α) therapy for inflammatory bowel disease (IBD) has not been well-established in patients after liver transplantation (LT). We aimed to evaluate the safety and efficacy of anti-TNF-α agents in the treatment of IBD in patients after LT for primary sclerosing cholangitis (PSC). Methods: We performed a chart review on patients with a diagnosis of IBD who underwent LT for PSC between 1993 and 2015 at Henry Ford Hospital. Five patients received anti-TNF-α therapy after LT for treatment of IBD. Various clinical and demographic data, hospital admissions, prednisone escalation for IBD, surgeries, endoscopy findings and infectious complications were recorded. Results: Three males and 2 females received anti-TNF-α agents for IBD after LT. One out of the 5 patients received a living donor LT. Prior to LT, 1 patient had received an anti-TNF-α agent and the other 4 patients were treated with 5 Amino-Salicylic Acid derivatives and/or immunomodulators. Clinical response was achieved in 1 out of 5 patients. Infections were seen in 2 patients. Two patients underwent total colectomy for severe uncontrolled IBD. Two patients developed post-transplant lymphoproliferative disorder (PTLD). One patient died due to complications secondary to PTLD. Conclusion: In our study, anti-TNF-α agents were found to be both ineffective and unsafe in patients after LT for PSC. Rates of infection were increased when given in combination with immunosuppressive agents for LT. PTLD occurred at a greater rate in these patients. Given these complications, in patients with severe UC post LT, early colectomy should be considered rather than medical therapy. Further studies are needed to evaluate the safety and efficacy profile of these therapies in post-LT patients on a larger scale. (Table Presented).

Gastroenterology
Rao B, **Yoshida A**, **Ibrahim M**, and **Jafri SM**. The use of perioperative lactate values as markers for adverse outcomes in liver transplantation *Am J Transplant* 2016; 16:672. PMID: Not assigned. Abstract

B. Rao, Internal Medicine, Henry Ford Hospital, Detroit, United States

Introduction: We examined the utility of perioperative lactate values for the prediction of multiple post-transplant outcomes including length of hospital stay (LOS), acute cellular rejection (ACR), and mortality in a single center liver transplant population. Methods: Retrospective chart review of all patients undergoing primary orthotopic liver transplant at a large urban tertiary care center from 2008-2010. Data was obtained on recipient demographics, donor age, donor gender, surgical time points, cold ischemia time (CIT), preoperative lactate, peak intraoperative lactate,

and peak postoperative lactate (maximum lactate value within 48 hours post-surgery). We examined outcomes of postoperative LOS, history of moderate or severe ACR, and mortality. Analysis was performed using multivariate linear and logistic regression models. Results: 273 patients were included for analysis. Mean recipient age was 52 (range 17-72) with 66% males. Mean donor age was 43 (range 7-83) with 40% males. Mean CIT was 312 minutes (range 12-699). Mean MELD was 22 (range 6-53). For every one unit increase in peak intraoperative lactate there was a 1.64 day increase in LOS ($p < 0.001$). For every one unit increase in peak intraoperative lactate the odds of death was significantly increased at one month (OR = 1.37, $p = 0.001$) and one year (OR = 1.14; $p = 0.021$). For every one unit increase in peak postoperative lactate there was a 1.76 day increase in LOS ($p < 0.001$). The odds of death was significantly increased for every one unit increase in peak postoperative lactate at one month (OR = 1.28; $p = 0.004$) and one year (OR = 1.13; $p = 0.003$). Preoperative lactate was not associated with any significant adverse outcomes. None of the perioperative lactate values were associated with developing an episode of moderate or severe ACR after transplant. Conclusion: Our results create a better understanding and interpretation of perioperative lactate values in liver transplantation. Findings clearly show an association between perioperative lactate values and mortality up to one year after transplant.

Gastroenterology

Verna E, Levitsky J, O'Leary J, Bzowej N, **Moonka D**, Hyland R, Brainard D, McHutchison J, and Terrault N. Short duration perioperative administration of ledipasvir/sofosbuvir is safe and effective in preventing HCV recurrence after liver transplant *Am J Transplant* 2016; 16:333-334. PMID: Not assigned. Abstract

E. Verna, Columbia Univ., United States

Background: The optimal timing and duration of DAA therapy in HCV patients undergoing liver transplant(LT) is unknown. CRUSH-C is an open-label, Phase 2 study evaluating the safety and efficacy of short, perioperative ledipasvir(LDV)/ sofosbuvir(SOF) for 4 weeks in HCV genotype(GT) 1 or 4 patients to prevent HCV recurrence post-LT. Methods:25 patients, with chronic HCV GT 1 or 4, listed for LT, not receiving antiviral therapy, were enrolled to receive a single dose of LDV/SOF the day before LT followed by LDV/SOF for an additional 28 days post-LT. Patients were required to have a baseline EGFR ≥40 mL/min at screening and day of LT. Receipt of a liver from an anti-HCV positive donor was an exclusion criterion. Immunosuppression management was at investigator discretion. Results: Interim data on the first 11 transplanted patients are available. Most patients were female(55%), Caucasian(82%), IL28B non-CC(64%). Four (36%) were treatment-experienced, all were GT 1. Baseline CTP class: A(27%), B(36%), and C(36%). The median MELD score was 13(range 7-16). 4/11 patients received a liver from a living donor. One patient met CrCl stopping rules (eGFR <30 mL/ min) at Day 7, and discontinued. All other patients completed the planned therapy, 9/10(90%) have achieved SVR4; the patient with relapse has initiated protocoldefined retreatment with LDV/SOF for 12 weeks. Treatment was safe and well tolerated. 9/11(82%) patients had an AE, the majority being mild or moderate. One grade 2 AE (dry eyes) was considered related to study drug. Three patients had SAEs: bile duct stenosis; acute kidney injury, elevated creatinine, and post-operative peri-incisional wound cellulitis; and decreased hepatic artery flow. All were assessed by the investigator as unrelated to study medication. No subjects have died or experienced graft loss. Updated results will be presented. Conclusions: These preliminary data support the safe use of LDV/SOF in the immediate pre- and perioperative transplant period. Preemptive use of LDV/SOF administered as a single dose pre-LT and for 4 weeks following transplant may represent an effective strategy to prevent HCV recurrence.

Gastroenterology

Weick A, **Sadiq O**, **Jafri SM**, and **Moonka D**. Initial experience with ledipasvir-sofosbuvir based therapy for recurrent hepatitis C after liver transplantation *Am J Transplant* 2016; 16:793. PMID: Not assigned. Abstract

A. Weick, Henry Ford Hospital, Detroit, United States

Objectives: Evaluate outcomes of Ledipasvir-Sofosbuvir based hepatitis C therapy in liver transplant patients at a single center. Methods: All post-liver transplant patients started on Ledipasvir-Sofosbuvir therapy between January 1 and October 1 2015 were evaluated for treatment response using HCV RNA levels at initiation of treatment, 4 weeks, 12 weeks, and end of treatment. Sustained viral response (SVR) was evaluated at weeks 4 (SVR4) and 12 (SVR12) post-treatment. Peak total bilirubin, HCV genotype, initial laboratory parameters, and hemoglobin nadir were collected. Results: 85 patients started treatment, 29 reached the 12 week post-treatment timepoint. Treatment started an average of 4.5 years post-transplant (range 1 mo to 11 yrs). 23 were male, mean age was 62 years (49-72), and average BMI was 28.2 (19.7-38.9). 62% of the patients were white and 34% were African American. 17 (59%) patients had genotype 1a, 9 (31%) patients had genotype 1b. Four patients (14%) had Ishak score of 4 or greater. 19 (66%) patients were treated for 12 weeks using Ledipasvir- Sofosbuvir with ribavirin, 10 (34%) were treated for 24 weeks using only Ledipasvir- Sofosbuvir. Mean ribavirin starting dose was 800 mg/daily (range 200-1200 mg). 28/29

patients (96%) achieved SVR12. The single failure had HIV co-infection, Ishak score of 6, previously failed sofosbuvir/ribavirin therapy, was on PPI, and developed rejection while on treatment. This was the only rejection episode among those who completed therapy. Average hemoglobin drop with ribavirin used was 2.58, compared to 0.96 without ribavirin. Five of 19 patients with ribavirin (26%) required ribavirin dose reduction. Three patients had pre-existing hyperbilirubinemia (total bilirubin 32.5), none of whom experienced increased bilirubin levels on treatment. Three patients had new onset hyperbilirubinemia, one did not resolve by end of treatment. Discussion: Combination therapy of Ledipasvir-Sofosbuvir seems to be well tolerated in our post-transplant population. Twelve weeks of treatment seems to be adequate when using ribavirin. We saw only one episode of rejection and five instances of ribavirin dose reduction, with no treatment discontinuation. This regimen was 96% effective at achieving SVR12 in our experience. (Table Presented).

Graduate Medical Education

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

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Hematology, Oncology and the Josephine Ford Cancer Institute

Aljundi L, Miller N, **Taylor A**, **Hung J**, and **Hwang C**. Time to castration-resistance and docetaxel outcomes in metastatic prostate cancer *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

L. Aljundi

Background: Castration resistant prostate cancer (CRPC) continues to present a challenge for oncologists. There is renewed interest in the use of docetaxel in advanced prostate cancer; however, a significant portion of patients do not respond and eventually all patients develop resistance. Androgen receptor (AR) variants have been hypothesized to be a common resistance mechanism to both androgen deprivation therapy (ADT) and docetaxel. We thus proposed that initial response to ADT might predict future response to docetaxel. Methods: A set of Cox regressions was computed to investigate the time to progression while on ADT and other factors on time to progression and overall survival while on docetaxel. Hazard ratios and pvalues for each factor were calculated. Patients were stratified according to their time to progression while on ADT into three groups by tertiles. Rapid progressors were patients who progressed within less than a year while on ADT, intermediate progressors progressed within 1 and 2.6 years and slow progressors progressed after more than 2.6 years. Survival for each of these three categories was plotted using the Kaplan-Meier method and differences were assessed with the log-rank test. Results: Time to prostate specific antigen (PSA) progression while on ADT predicted future docetaxel response (HR = 0.8, p = 0.03) in univariate analysis. A difference in time to PSA progression was noted between rapid and fast progressors on ADT (p = 0.009, log-rank test). Overall survival for rapidly progressing patients was significantly inferior to intermediate and slow progressors (p = < 0.001, logrank). However, multivariate analysis did not meet criteria for statistical significance between time to progression while on ADT and time to progression while on docetaxel (p = 0.062). Conclusions: Although time to CRPC was correlated with docetaxel outcomes, the relationship was not statistically significant on multivariate analysis. Further research is required to identify molecular characteristics in patients with CRPC that will predict response and outcomes with more precision.

Hematology, Oncology and the Josephine Ford Cancer Institute
Apolo AB, Infante JR, Hamid O, Patel MR, **Wang D**, Kelly K, Mega AE, Britten CD, Ravaud A, Mita AC, Safran H, Stinchcombe T, Grote HJ, V on Heydebreck A, Cuillerot JM, and Gulley JL. Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic urothelial carcinoma from the JAVELIN solid tumor phase 1b trial: Analysis of safety, clinical activity, and PD-L1 expression *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A.B. Apolo

Background: Avelumab∗ is a fully human anti-PD-L1 IgG1 antibody under clinical investigation in multiple cancers. We report updated safety and efficacy associated with avelumab as a 2nd-line therapy in patients (pts) with metastatic urothelial carcinoma (mUC; NCT01772004). Methods: Pts with mUC unselected for PD-L1 expression received avelumab 10 mg/kg IV Q2W until progression, unacceptable toxicity, or withdrawal. Tumors were assessed every 6 wks (RECIST 1.1). Unconfirmed objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were evaluated. Adverse events (AEs) were graded by NCI-CTCAE v4.0. PD-L1 expression was assessed by IHC. Results: As of Oct 7, 2015, 44 pts (27 [61.4%] with visceral metastasis) were treated with avelumab (median 14 wks [range 2-56]) and followed for a median of 11 mos (range 10- 13). Median age was 68 y (range 30-84), ECOG PS was 0 (43.2%) or 1 (56.8%), and median number of prior therapies was 2 (range 1-6). Treatment-related (TR) AEs occurred in 30 pts (68.2%); the most common (≥10%) were infusion-related reaction (20.5%), fatigue (20.5%), asthenia (11.4%), and nausea (11.4%). Grade ≥3 TRAEs were asthenia, myositis, decreased appetite, and elevated CPK or AST (each 1 event) and no treatment- related deaths occurred. ORR was 18.2% (8 pts; 95% CI: 8.2, 32.7) with 2 CRs and 6 PRs; 4 were ongoing. SD was observed in 17 pts (38.6%); disease-control rate was 56.8%. PD- L1 expression was evaluable in 35 pts. Using a ≥5% cutoff for tumor cell staining, 12/35 [34.3%] were PD-L1+; ORR was 50.0% in PD-L1+ pts (6/12; 95% CI: 21.1, 78.9) vs 4.3% in PD-L1- pts (1/23; 95% CI: 0.1, 21.9). PFS rate at 24 wks was 58.3% (95% CI: 27.0, 80.1) in PD-L1+ pts vs 16.6% (95% CI: 4.2, 36.0) in PD-L1-. ORR in pts +/- baseline visceral metastasis was 18.5% (5/27) and 17.6% (3/17), respectively. OS at 12 mos was 50.9% (95% CI: 32.6, 66.6) for the overall population. Conclusions: Avelumab showed an acceptable safety profile and promising clinical activity in pts with mUC. Greater activity in pts with PD-L1+ tumors was observed. A randomized phase 3 trial of avelumab in pts with mUC is underway.

Hematology, Oncology and the Josephine Ford Cancer Institute
Bardia A, Dacosta NA, Gabrail NY, Lemon S, Danso MA, **Ali HY**, Fleming RA, Kurman MR, Eisner JR, Moore WR, Gucalp A, and Traina TA. Phase (Ph) 1 study of oral seviteronel (VT-464), a dual CYP17- Lyase (L) inhibitor and androgen receptor (AR) antagonist, in patients (pts) with advanced AR+ triple negative (TNBC) or estrogen receptor (ER)+ breast cancer (BC) *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A. Bardia

Background: Seviteronel (Sevi), a CYP17-L inhibitor (reduces androgen and estrogen biosynthesis) and AR antagonist, has activity in castration resistant prostate cancer (CRPC) at a dose of 750 mg nightly. Sevi potently and dose-dependently inhibits the growth of ER(+)/AR(+) tamoxifen-resistant (TAMR) MCF7 and ER(-)/AR(+) MDA-MB-453 cells. In a TAMR xenograft BC model, Sevi decreases tumor growth > enzalutamide, an AR antagonist (Ellison et al. SABCS 2015). Approximately 80% of BCs, including a subset of TNBC that expresses AR, are potential targets for Sevi based on its mechanism of action (MOA). The primary objective of this Ph 1 study is to establish the recommended Ph 2 dose (RP2D) in women with BC (NCT02580448). Methods: Eligible pts have AR(+) TNBC or ER(+)/HER2-normal metastatic BC. ER(+) pts must have had ≥ 1 prior line of endocrine therapy; no limit to prior treatment for TNBC. Sevi start dose was 750 mg, administered nightly with dinner (28 d cycle) (n = 6/cohort). AR(+) status was confirmed using central IHC analysis with ≥ 10% staining used for evaluable TNBC pts. Tumor samples and blood for CTC, ctDNA and steroid biomarker analysis were collected. Scans were performed every 2-3 mo to estimate 16 and 24 wk clinical benefit rate. Results: As of 1/28/14, 13 pts received Sevi with 5 in screening. 8 pts are on study between Cycle 1 and 6 (median Cycle 2). Sevi systemic exposure appears inversely dependent on body mass in women and is greater than historical data in men. Exploratory lower dose cohorts were enrolled at 600 and 450 mg. Single dose Cmax was 17.4±4.4 vs. 14.9±4.3 pM and AUC 0-8h was 99.8±17.9 vs. 78.9±14.1 pM∗h at 750 and 600 mg. Most adverse events (AEs) were Grade 1 or 2, including fatigue (31%), tremor (31%) and vomiting (23%). One Grade 3 related AE was reported (confusion at 750 mg and was a DLT). Conclusions: Sevi is overall welltolerated in women with an AE profile similar to that in men. With higher exposures, the RP2D in women is likely to be lower than in men. The dual Sevi MOA (reduced sex-steroid production and AR antagonism) may provide a new novel treatment option for AR(+) TNBC or ER(+) BC.

Hematology, Oncology and the Josephine Ford Cancer Institute
Cristea MC, Miao J, Argiris A, Chen AM, Daly ME, Decker RH, Garland LL, **Wang D**, Koczywas M, Moon J, Kelly K, and Gandara DR. SWOG S1206: A dose-finding study of veliparib (ABT-888) added to chemoradiotherapy (CRT) with carboplatin (C) and paclitaxel (P) for unresectable stage III non-small cell lung cancer (NSCLC) *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

M.C. Cristea

Background: Preclinical studies of the PARP inhibitor velaparib (V) demonstrated synergistic effects when combined with various cytotoxic agents and radiation (RT). S1206 is a phase I trial of V given concurrently with standard CRT in stage III NSCLC. Methods: Newly diagnosed pts with unresectable stage III NSCLC, performance status 0-1 and adequate organ function were eligible. A standard 3+3 design was used with 3 V dose levels, 40 mg, 80 mg and 120 mg orally, twice a day. Pts received weekly C (AUC 2) and P (45 mg/m2) during concurrent thoracic RT (2 Gy fractions/day, total dose 60 Gy) and V throughout RT duration. Pts without progression received 2 cycles (every 21 days) of consolidation C (AUC 6), P (200 mg/m2) and V 80 mg twice daily on days 1-7 of each cycle. Dose-limiting toxicity (DLT) was assessed during the first 9 weeks of treatment. Results: From January 2013 to December 2015, a total of 21 pts were enrolled of whom15 (6/8 at 40 mg cohort, 6/7 at 80 mg, 3/6 at 120 mg) are evaluable for DLT. Three pts. at the 120 mg dose level are currently in the DLT evaluation period. Fifteen pts were enrolled to V dose levels 40 mg and 80 mg (median age 67, male 60%, stg. IIIA 67%, stg IIIB 33%, ECOG 0 47%, non-squamous histology 60%). Two pts developed a DLT: grade (G) 3 esophagitis with dysphagia (at the 40 mg cohort) and G 3 esophagitis with dehydration (at 80 mg). Other G 3/4 AEs during CRT, on the 40 mg and 80 mg cohorts, not meeting DLT definition included: neutropenia (6 pts), leukopenia (5 pts) and esophagitis less than 7 days duration (3 pts). One pt had G 3 neutropenic fever during CRT (DLT included G 4 neutropenic fever). One treatment-related death due to sepsis occurred after consolidation chemotherapy. Conclusions: V in combination with CRT with weekly C and P is well tolerated with expected toxicities that relate to the backbone CRT regimen. At completion of this phase I trial a randomized phase II trial comparing CRT with or without V will be initiated.

Hematology, Oncology and the Josephine Ford Cancer Institute
Fisher KW, Zhang S, Wang M, Montironi R, Wang L, Baldrige LA, Wang JY, MacLennan GT, **Williamson SR**, Lopez-Beltran A, and Cheng L. TMPRSS2-ERG gene fusion is rare compared to PTEN deletions in stage T1a prostate cancer *Mol Carcinog* 2016;PMID: 27500376. Full Text

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T1a prostate cancers (cancer found incidentally in transurethral resection, <5% of the tissue) are indolent tumors of the transition zone. The overexpression of ERG and the inactivation of PTEN have been shown to be important drivers of carcinogenesis in large series of prostate cancer, but the genetics of transition zone tumors have not been well characterized. We evaluated the status of ERG and PTEN in formalin-fixed paraffin-embedded tissue using immunohistochemical and FISH analysis in 54 T1a transition zone tumors. The protein expression of ERG was determined using a rabbit monoclonal antibody and nuclear staining was scored as positive or negative. The genomic status of ERG was determined using 3 colored FISH using an ERG-TMPRSS2 tri-color probe set. The protein expression of PTEN was determined using a rabbit monoclonal antibody and cytoplasmic and nuclear staining was scored as positive or negative. The genomic status of PTEN was determined using dual color FISH with a PTEN probe and a CEP10 probe. We found ERG rearrangement in 2 of 54 tumors (4%), one with protein overexpression by immunohistochemistry. PTEN inactivation was seen in 13 of 54 tumors (24%). Nine of the 13 PTEN alleles were inactivated by hemizygous deletion. No homozygous PTEN deletion was observed. PTEN deletion and ERG rearrangement were mutually exclusive. ERG rearrangement was rare compared to peripheral zone tumors and to PTEN inactivation in T1a transition zone tumors.

Hematology, Oncology and the Josephine Ford Cancer Institute
Geary M, **Kachalsky E**, Pennick L, Johnson M, Hatcher N, Rosenblatt K, Dunn L, and Stolfi A. Perceived ideal roles of hemophilia treatment center social workers in the United States and barriers to those roles *Haemophilia* 2016; 22:113-113. PMID: Not assigned. Abstract

Hematology, Oncology and the Josephine Ford Cancer Institute
Geary M, **Kachalsky E**, Pennick L, Rosenblatt K, Hatcher N, Johnson M, Dunn L, and Stolfi A. Social work caseloads in hemophilia treatment centers in the United States *Haemophilia* 2016; 22:117-117. PMID: Not assigned. Abstract

Hematology, Oncology and the Josephine Ford Cancer Institute
Johnson M, **Kachalsky E**, Geary M, Pennick L, Dunn L, Hatcher N, Stolfi A, and Rosenblatt K. The role of the Hemophilia Treatment Center (HTC) social worker in the United States *Haemophilia* 2016; 22:117-117. PMID: Not assigned. Abstract

Hematology, Oncology and the Josephine Ford Cancer Institute
Kelly K, Heery CR, Patel MR, Infante JR, Iannotti N, Leach JW, **Wang D**, Chandler JC, Arkenau HT, Taylor MH, Gordon MS, Wong DJL, Safran H, Kaufman H, Keilholz U, Bajars M, V on Heydebreck A, Speit I, Cuillerot JM, and Gulley JL. Avelumab (MSB0010718C; anti-PD-LI) in patients with advanced cancer: Safety data from 1300 patients enrolled in the phase 1b JAVELIN Solid Tumor trial *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

K. Kelly

Background: Avelumab∗ is a fully human anti-PD-L1 IgG1 antibody showing preliminary efficacy in multiple tumor types. We report updated safety data of single-agent avelumab in patients (pts) with locally advanced or metastatic (LA/M) solid tumors from a phase 1b trial (NCT01772004). Methods: Pts from 16 different expansion cohorts (including NSCLC, gastric, ovarian, urothelial, mesothelioma, and breast), all unselected for PD-L1 expression, received avelumab 10 mg/kg IV Q2W until progression, unacceptable toxicity, or withdrawal. Treatment-emergent adverse events (AEs) were graded by NCI-CTCAE v4.0. Results: As of Nov 5, 2015, 1,300 pts received avelumab and were followed for ≥ 4 wks. Median age was 63 y (range 20-91), ECOG PS was 0 (37.7%), 1 (62.1%), or 2-3 (0.2%), and median number of prior lines of anticancer therapy was 2 (range 1-13). Median duration of treatment with avelumab and number of administrations were 11.5 wks (range 2-104) and 5 infusions (range 1-50), respectively. Treatment-related (TR) AEs occurred in 813 pts (62.5%), and the most common (≥ 5%) were fatigue (n = 212, 16.3%), infusionrelated reaction (IRR; n = 209, 16.1%), nausea (n = 108, 8.3%), chills (n = 102, 7.8%), diarrhea (n = 79, 6.1%), and pyrexia (n = 72, 5.5%). Grade ≥ 3 TRAEs occurred in 124 pts (9.5%). The most frequent (≥ 0.5%) grade ≥ 3 TRAEs were GGT elevation (n = 9, 0.7%), IRR (n = 9, 0.7%), fatigue (n = 8, 0.6%), lipase elevation (n = 8, 0.6%), anemia (n = 7, 0.5%), and dyspnea (n = 6, 0.5%). Potential immune-related (ir) TRAEs were reported for 93 pts (7.2%); the most frequent (≥ 1.0%) were hypothyroidism (n = 45; 3.5%) and pneumonitis (n = 13; 1.0%). TRAEs resulted in permanent discontinuation for 79 pts (6.1%): 25 (1.9%) due to an IRR and 14 (1.1%) due to a potential irTRAE. TRAEs were considered the primary cause of death by the investigator for 5 pts (0.4%): radiation pneumonitis (1), pneumonitis (1), autoimmune hepatitis/liver failure (2), and respiratory distress/sepsis (1). Conclusions: Single-agent avelumab showed an acceptable safety profile in a heavily pretreated population and large dataset of pts with LA/M malignancies. Additional analyses and phase 3 trials are ongoing.

Hematology, Oncology and the Josephine Ford Cancer Institute
Kuriakose J, John J, Hanagavadi S, Balar M, Pillai V, and **Kuriakose P**. Impact of twinning between HTC's: Incremental gain with longitudinal experience *Haemophilia* 2016; 22:54-54. PMID: Not assigned. Abstract

[Kuriakose, Jonathan] Univ Michigan, Ann Arbor, MI 48109 USA. [John, Joseph] Christian Med Coll & Hosp, Dept Clin Haematol Haematooncol & Bone Marrow Ste, Ludhiana, Punjab, India. [Hanagavadi, Suresh; Balar, Mahendra] Karnataka Hemophilia Soc, Dept Hematopathol, Davanagere, India. [Pillai, Vijayakumar] Dist Hosp Aluva, Hemophilia Treatment Ctr, Ernakulam, India. [Kuriakose, Philip] Henry Ford Hlth Syst, Dept Internal Med, Div Hematol Oncol, Detroit, MI USA.

Hematology, Oncology and the Josephine Ford Cancer Institute
Malik D, **Kuriakose P**, **Ivins DB**, and Church J. Single center clinical and pharmacokinetic experience with long-acting recombinant factor VIII (rFVIIIFx) and IX (rFIXFc) *Haemophilia* 2016; 22:101-101. PMID: Not assinged. Abstract

Hematology, Oncology and the Josephine Ford Cancer Institute

Mattour AH, **Walbert T**, **Lee I**, and **Wang D**. A revisit of the devastating outcome of leptomeningeal disease *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A.H. Mattour

Background: Leptomeningeal metastasis (LM) represents a devastating complication of malignancies by forming tumor deposits on the leptomeninges at about 5% to 8% of cancer patients (Pts). Standard therapies include radiotherapy (RT) to focal involved areas, systemic and/or intrathecal (IT) chemotherapies which have been recommended for palliation but with unclear benefit toward survival. This study is to review the pattern of the clinical practice and outcomes on Pts with LM who have received care at Henry Ford Hospital between 2004 and 2014 Methods: A retrospective study targeted all Pts of LM (icd-9 code 198.4) between 01/01/2004 and 01/01/2014. Pts with primary brain, orbital and spinal lesions as well as Pts with cord compressions were excluded from this study. LM Pts were included based on MRI images, cerebral spinal fluid (CSF) cytology and/or dural biopsy. Data from onset of primary tumor, therapeutic interventions, methods of LM diagnosis, duration (days) from initial cancer onset to LM diagnosis, then from LM diagnosis to death were collected and analyzed as shown Results: 328 Pts with LM (icd-9: 198.4) were identified, but 58 Pts fulfilled inclusions. Of 58 Pts, 22 (38%) had breast cancer (38%), 12 (21%) NSCLC. LM was diagnosed in 34 Pts (59%) based on MRI findings, 4 (6%) by CSF cytology and 19 (33%) by both. Majority (37 Pts, 64%) received therapy after LM diagnosis: 16 (27%) received IT chemotherapy, 15 (26%) received RT while 6 (10%) received both. Twenty-one of LM Pts (36%) received no treatment under various circumstances. Of 58 Pts, the median time from cancer onset to LM diagnosis was 686 days while median overall survival (OS) was 1038 days, and median OS from LM to death was 95 days. Survival difference was observed for Pts (37, 64%) received LM-directed treatment as 113 days but only 61 days for those received no therapies Conclusions: LM is a prognostic complication in malignancies. It poses a grave challenge due to limited therapeutics that only carry modest survival benefit. Data from these 58 Pts shown a benchmarks of survival from LM diagnosis was 4 months with treatment, and 2 months without. These are consistent with published data over last decades without improvement. Therefore, more clinical researches in LM diagnosis and therapies are needed.

Hematology, Oncology and the Josephine Ford Cancer Institute

Michael Bauer T, Adkins D, Schwartz GK, Werner TL, Alva AS, Hong DS, Carvajal RD, Saleh MN, Bazhenova L, Goel S, Eaton KD, Siegel RD, **Wang D**, Lauer RC, Neuteboom STC, Faltaos D, Chen I, Christensen J, Chao RC, and Heist RS. A first in human phase I study of receptor tyrosine kinase (RTK) inhibitor MGCD516 in patients with advanced solid tumors *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

T. Michael Bauer

Background: MGCD516 is an oral, potent small molecule inhibitor of a closely related spectrum of RTKs including RET, TRK family, DDR2, MET, AXL and split RTKs (VEGFR, PDGFR and KIT). MGCD516 has demonstrated antitumor activity in nonclinical cancer models harboring genetic alterations of MGCD516 targets including rearrangement of RET or NTRK or CHR4q12 amplification. Methods: Study objectives include evaluation for safety, pharmacokinetics (PK), pharmacodynamics (PD), the maximum tolerated dose (MTD) and clinical activity of MGCD516 in patients (pts) with advanced solid tumors. Eligible pts received a single dose for PK profiling followed by continuous daily dosing (QD) in 21 day cycles. Results: 32 unselected pts (14 men/18 women; median age 62 years; range 27-85) with advanced solid tumors were treated in escalating dose cohorts of 10, 20, 40, 80, 110, 150 or 200mg MGCD516. At 80mg, 1 of 6 evaluable pts experienced a DLT (Grade 3 palmar plantar erythrodysesthesia). At 200mg, 3 DLTs were observed among 3 evaluable pts (intolerable Grade 2 neuropathy, fatigue and stomatitis in 1 pt each), demonstrating 200mg exceeded the MTD. Treatment-related AEs (> 15% of pts; Grade1- 3) included hypertension, fatigue, diarrhea, nausea and decreased appetite. One treatment-related Grade 4 AE (febrile neutropenia) was reported. Prolonged stable disease (SD) has been observed in multiple pts including 3 pts with at least 17 weeks SD and 1 pt with 35 weeks SD. Preliminary PK data show that exposure increased dose proportionally with doses up to 200mg. At 150mg, the Cavg and AUC0-24 values at steady state (90.7 ng/mL and 2.18 µg h/mL, resp.) exceed plasma exposure projections required for inhibition of key RTK targets and antitumor efficacy in nonclinical tumor models. Preliminary clinical PD data indicate dose dependent inhibition of the VEGF and MET pathways. Conclusions: The Phase 1b dose for MGCD516 was established at 150mg QD. MGCD516 shows favorable PK characteristics, on-target PD effects and is associated primarily with constitutional or GI-related AEs. Phase 1b enrollment began November 2015. Pts with NSCLC or other solid tumors with specific genetic alterations in MGCD516 target RTK genes are being enrolled.

Hematology, Oncology and the Josephine Ford Cancer Institute
Patel MR, Fakih M, Olszanski AJ, Lockhart AC, Drilon AE, Fu S, Bazhenova L, Patel R, Oliver JW, Multani PS, and **Wang D**. A phase 1 dose escalation study of RXDX-105, an oral RET and BRAF inhibitor, in patients with advanced solid tumors *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

M.R. Patel

Background: RXDX-105 is a multikinase inhibitor that has demonstrated potent inhibition of RET. RXDX-105 is also active against BRAF. RET alterations are associated with the development of various types of cancer. Acquired BRAF mutations can result in constitutive activation of the MEK/ERK signaling pathway, which fuels cancer growth. Methods: Pts with advanced solid tumors were enrolled in a Phase 1 dose escalation study with a standard 3 + 3 design to determine the recommended Phase 2 dose (RP2D) of RXDX-105, administered once daily on a continuous dosing schedule. Tumor response was assessed every 8 wks (RECIST v1.1). Treatment-emergent adverse events (AEs) were recorded according to NCI CTC v4.03. Pharmacokinetic (PK) analysis was performed. Results: To date, 45 pts (21 m and 24 F) received RXDX-105 across 8 dose levels (20 to 350 mg QD). Median age was 60 years (range 27-81). Median number of cycles was 2 (range 1 to 30). The PK data demonstrate an RXDX-105 half-life of 28 to 42 hrs. At 275 mg fed state, exposure reached the predicted efficacious concentration (Ceff) based on preclinical data of RET and BRAF inhibition. The most common AEs were: fatigue (19 pts; 42%), vomiting (16 pts; 36%), nausea (16 pts; 36%), rash (15 pts; 33%), and constipation (12 pts; 27%). 4 DLTs occurred: G3 maculopapular rash (n = 1; 200 mg), G3 fatigue (n = 1; 275 mg), G3 diarrhea (n = 1; 275 mg fed state), and G3 hyperbilirubinemia (n = 1; 350 mg fed state). All DLTs resolved with dose hold. 2 SAEs were considered treatment-related: G2 headache, which occurred during hospitalization for disease progression, and G3 hyperbilirubinemia. No treatment-related deaths occurred. 1 durable PR was observed and disease shrinkage was noted in another 3 patients, 1 of whom has BRAF V600E-mutant papillary thyroid cancer and continues on study after over 2 years with SD. Conclusions: In this ongoing study, the predicted efficacious exposure has been achieved and several patients have experienced clinical benefit. The safety profile to date indicates that RXDX- 105 is tolerable at doses above the projected Ceff threshold. Dose escalation is ongoing. A Ph 1b basket study in pts with RET or BRAF alterations will commence after RP2D selection.

Hematology, Oncology and the Josephine Ford Cancer Institute
Rybkin II, Kio EA, Masood A, Shum MK, Halmos B, Blakely CM, Eaton KD, Sharma N, Nemunaitis JJ, Saccaro SJ, Boumber Y, Mena RR, Mirshahidi HR, Janne PA, Christensen J, Chao RC, Tassell VR, Faltaos D, and Schreeder MT. Amethyst NSCLC trial: Phase 2, parallel-arm study of receptor tyrosine kinase (RTK) inhibitor, MGCD265, in patients (pts) with advanced or metastatic non-small cell lung cancer (NSCLC) with activating genetic alterations in mesenchymal-epithelial transition factor (MET) *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

I.I. Rybkin

Background: MGCD265 is an oral, potent, small molecule RTK inhibitor of MET and Axl, which are important for mediating signals for cell growth, survival, and migration. M≤Tmutations and/or gene amplification have been reported in approximately 7% of NSCLC and function as oncogenic drivers that promote cancer development and progression. AffiTsplice site mutations that result in the deletion of exon 14 (METex14del) represent a novel class of genetic alterations that have been implicated as oncogenic drivers in a subset of NSCLC. METex14del contains the Y1003 CBL ubiquitin ligase regulatory binding site that mediates CBL-dependent MET degradation and signal attenuation. Deletion of this region results in sustained activation of MET and its downstream signaling pathways. MGCD265 has demonstrated anti-tumor efficacy with robust tumor regression in xenograft models ofMETex14del and MET amplification. Additionally, confirmed partial responses have been observed in pts with MET-altered NSCLC treated with MGCD265 in the Phase 1 setting. Methods: This global Phase 2 trial is enrolling pts with NSCLC characterized by activating genetic MET alterations in tumor tissue or blood and who have received at least one prior platinum-containing regimen for advanced disease. Pts will be enrolled to one of four study arms based on the type of MET dysregulation: 1) mutations in tissue, 2) amplification in tissue, 3) mutations in blood, and 4) amplification in blood. The primary endpoint is Obj ective Response Rate (ORR) in accordance with RECIST 1.1; a Bayesian Predictive Probability Design is applied independently to each treatment arm. Secondary objectives are safety and tolerability, response duration, survival, correlations between tissue and blood testing, and PK/PD. Pts are treated with MGCD265 in 21-day cycles until RECIST-defined progression or unacceptable toxicity. The study is open for enrollment and recruitment is ongoing. (Table Presented).

Hematology, Oncology and the Josephine Ford Cancer Institute
Saste AB, **Gulati R**, **Kuriakose P**, **Inamdar K**, **Karner K**, **Carey J**, and **Menon M**. Prognostic impact of aberrant t/NK cell marker expression in AML *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A.B. Saste

Background: Aberrant expression of NK and T cell antigens (NK/T) in AML blasts is well known.However,their influence on EFS(after standard first line AML induction) & OS has not been well studied.We conducted such an analysis in AML with normal cytogenetics.We also studied the prognostic significance of NK/T expression in FLT3 & NPM1 negative cases. Methods: A retrospective analysis of 266 cases of AML over 10 years was conducted. Flow cytometry done at the time of initial diagnosis was available for 201 of the 266 cases.NK/T cell markers such as CD2,CD3,CD5,CD7 & CD56,available in 83 cases,were analyzed.NK/T positivity threshold was set at > 20% of the gated blast population. EFS and OS were compared between NK/T+ and NK/T- groups using log-rank tests/Kaplan-Meier curves.FLT3 and NPM1 proportions in NK/T+ and NK/T- cases were compared using Fisher's exact test. Results: NK/T+ and NK/T- frequencies were 46% (38/83) and 54% (45/83) respectively. Amongst NK/T+ cases CD56 (67%) was the most commonly expressed marker and “AML with myelodysplasia related changes” (47%) was the most common subtype. Amongst AML cases in which cytogenetic analysis was performed (n = 198), 72 cases had normal cytogenetics (AML CyNO).Within this group 41(71.9%) were NK/T+ and 16(28.1%) were NK/T-.While trends demonstrated an inferior EFS and OS in NK/T+ cases,given our small sample size,statistical significance was not reached. EFS of NK/T+ was 0 weeks (95% CI:0-20) versus 15.6 weeks (95% CI:0-36) in NK/T- (p = 0.515).Median EFS for NK/T+ and NK/T- was 3.6 weeks (95% CI:0-24).OS for NK/T+ was 32 weeks (95% CI: 12-96) versus 112 weeks (95% CI: 28-163.2) in NK/T- (p = 0.077).Median OS for NK/T+ and NK/T- was 47.9 weeks (95% CI:28-112). In FLT3- and NPM- AML CyNO cases both EFS(0 versus 3.6 weeks) and OS(24 versus 120 weeks) showed a statitically insignificant trend toward inferior survivals in NK/T+ arm.FLT3 or NPM1 distribution was not statistically different between NK/T+ and NK/T- cases in AML CyNO. Conclusions: When known confounding low/high risk cytogenetic abnormalities affecting survival in AML were eliminated, trends suggested worse survivals for AML CyNO NK/T+; however they failed to reach statistical significance. We are therefore currently analyzing a larger cohort.

Hematology, Oncology and the Josephine Ford Cancer Institute
Smit EF, Kopp HG, Kim DW, Tortora G, Spira AI, Berruti A, Lee DH, Reguart N, **Rybkin II**, Akimov M, Schumacher KM, Upalawanna A, Xu C, Squires M, and Tan DSW. GEOMETRY duo-1: A phase (Ph) Ib/II, multicenter trial of oral cMET inhibitor capmatinib (INC280) ± erlotinib vs platinum + pemetrexed in adult patients (pts) with epidermal growth factor receptor (EGFR)-mutated, cMET-amplified, locally advanced/metastatic non-small cell lung cancer (NSCLC) with acquired resistance to prior EGFR tyrosine kinase inhibitor (TKI) therapy *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

E.F. Smit

Background: Despite high overall response rates (ORR) to EGFR TKIs, most pts with EGFR-mutated NSCLC develop acquired resistance; secondary activation of cMET as gene amplification, occurs in ~20% of cases. Capmatinib (INC280) is a potent and selective cMET inhibitor. Preliminary clinical activity of INC280 + gefitinib was reported in pts with EGFR-mutated, cMET-amplified, EGFR TKI-resistant NSCLC. Methods: This multicenter, Ph Ib/II study (NCT02468661) will commence with a dose-escalation safety phase of INC280 + erlotinib. This will be followed by a randomized Ph II part, which will study the safety and efficacy of INC280 ± erlotinib compared with platinum + pemetrexed, in pts with EGFR TKI-resistant advanced NSCLC due to cMET amplification (EGFR T790M-negative). cMET gene copy number will be determined by fluorescence in situ hybridization. Eligible pts (≥ 18 years of age; ECOG PS 0-1) must have had prior therapy with a 1st/2nd-generation EGFR TKI (≥ 1 in Ph Ib: only 1 in Ph II). Pts in Ph II must be chemo therapy-naive. In Ph Ib (N≈O-15), erlotinib 150 mg tablets once daily (QD), and increasing doses of rNC280 with a starting dose of 200 mg tablets twice daily (BID), will be administered on a continuous dosing schedule. In Ph II (N ≈120), pts will undergo central testing for cMET and T790M, and be randomized 1:1:1 in 3 arms: 1. INC280 (400 mg BID); 2. INC280 (recommended Ph II dose [RP2D]) + erlotinib (150 mg QD); 3. Cisplatin (75 mg/m2)/carboplatin (AUC 5 or 6) + pemetrexed (500 mg/m2; every 21 days). The primary objectives are to determine the maximum tolerated dose/RP2D of INC280 + erlotinib (Ph Ib), and to compare the investigator-assessed antitumor activity of INC280 ± erlotinib vs platinum + pemetrexed therapy, measured by progression-free survival (Ph II). Secondary objectives include investigator-assessed ORR, disease control rate, duration of response, overall survival, safety, and pharmacokinetics. Enrollment is ongoing. (Table Presented).

Hematology, Oncology and the Josephine Ford Cancer Institute
Wang D, Braiteh F, Lee JJ, Denlinger CS, Shepard DR, Chaudhary A, Lin Y, Gao L, Asakiewicz C, Nasroulah F, and LoRusso P. Lack of pharmacokinetic drug-drug interaction between ramucirumab and irinotecan in patients with advanced solid tumors *Cancer Chemother Pharmacol* 2016;PMID: 27507037. Full Text

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Fox Chase Cancer Center, Philadelphia, PA, USA.
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Eli Lilly and Company, Indianapolis, IN, USA.
Eli Lilly and Company, Bridgewater, NJ, USA.
Yale Cancer Center, New Haven, CT, USA.

PURPOSE: The objective of this phase II study was to evaluate the potential of pharmacokinetic (PK) drug-drug interactions between ramucirumab and irinotecan or its metabolite, SN-38, when administered with folinic acid and 5-fluorouracil (FOLFIRI). METHODS: Patients received intravenous infusions of FOLFIRI and ramucirumab 8 mg/kg on Day 1 of a 2-week cycle. FOLFIRI was administered alone in Cycle 1; ramucirumab followed by FOLFIRI was administered in all subsequent cycles. Blood was collected at regular intervals after infusions in Cycles 1 and 2 to determine irinotecan, SN-38, and ramucirumab concentrations. PK parameters were derived by noncompartmental analysis. RESULTS: Twenty-nine patients received treatment. The dose-normalized area under the concentration versus time curve from zero to infinity [AUC(0-infinity)] and the maximum observed concentration (C max) of irinotecan and SN-38 were comparable between Cycle 1 (FOLFIRI alone) and Cycle 2 (ramucirumab + FOLFIRI). The ratios of geometric least squares (LS) means for irinotecan were 0.93 (90 % CI 0.83-1.05) for AUC(0-infinity) and 1.04 (90 % CI 0.97-1.12) for C max. The ratios of geometric LS means for SN-38 were 0.95 (90 % CI 0.88-1.04) for AUC(0-infinity) and 0.97 (90 % CI 0.85-1.12) for C max. The most common treatment-emergent adverse events, regardless of grade, were fatigue (19 patients, 65.5 %), diarrhea, (16 patients, 55.2 %), and neutropenia (15 patients, 51.7 %). Grade >/=3 neutropenia was reported in 7 (24.1 %) patients. CONCLUSIONS: There was no PK drug-drug interaction between ramucirumab and irinotecan or its metabolite, SN-38. Ramucirumab with FOLFIRI was well tolerated in this study, with no new safety concerns.

Hypertension Research
Cerrato BD, **Carretero OA**, **Janic B**, Grecco HE, and Gironacci MM. Heteromerization between the bradykinin b2 receptor and the angiotensin-(1-7) mas receptor: Functional consequences *Hypertension* 2016;PMID: 27550920. Full Text

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Bradykinin B2 receptor (B2R) and angiotensin-(1-7) Mas receptor (MasR)-mediated effects are physiologically interconnected. The molecular basis for such cross talk is unknown. It is hypothesized that the cross talk occurs at the receptor level. We investigated B2R-MasR heteromerization and the functional consequences of such interaction. B2R fused to the cyan fluorescent protein and MasR fused to the yellow fluorescent protein were transiently coexpressed in human embryonic kidney293T cells. Fluorescence resonance energy transfer analysis showed that B2R and MasR formed a constitutive heteromer, which was not modified by their agonists. B2R or MasR antagonists decreased fluorescence resonance energy transfer efficiency, suggesting that the antagonist promoted heteromer dissociation. B2R-MasR heteromerization induced an 8-fold increase in the MasR ligand-binding affinity. On agonist stimulation, the heteromer was internalized into early endosomes with a slower sequestration rate from the plasma membrane, compared with single receptors. B2R-MasR heteromerization induced a greater increase in arachidonic acid release and extracellular signal-regulated kinase phosphorylation after angiotensin-(1-7) stimulation, and this effect was blocked by the B2R antagonist. Concerning serine/threonine kinase Akt activity, a significant bradykinin-promoted activation was detected in B2R-MasR but not in B2R-expressing cells. Angiotensin-(1-7) and bradykinin elicited antiproliferative effects only in cells expressing B2R-MasR heteromers, but not in cells expressing each receptor alone. Proximity ligation assay confirmed B2R-MasR interaction in human glomerular endothelial cells supporting the interaction between both receptors in vivo. Our findings provide an explanation for the cross talk between bradykinin B2R and angiotensin-(1-7) MasR-mediated effects. B2R-MasR heteromerization induces functional changes in the receptor that may lead to long-lasting protective properties.

Hypertension Research
Gonzalez GE, **Rhaleb NE**, D'Ambrosio MA, **Nakagawa P**, **Liao TD**, **Peterson EL**, **Leung P**, **Dai X**, **Janic B**, **Liu YH**, **Yang XP**, and **Carretero OA**. Cardiac-deleterious role of Galectin-3 in Angiotension II-induced Hypertension *Am J Physiol Heart Circ Physiol* 2016;PMID: 27496875. Full Text

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The lectin Galectin-3 (Gal-3) is important in immune regulation. In both hypertensive rats and heart-failure patients, Gal-3 is also a marker for unfavorable prognosis. Nevertheless, the mechanism of Gal-3 action in hypertension-induced target organ damage is unknown. We hypothesized that in Ang II-induced hypertension, Gal-3 deficiency prevents left ventricular (LV) adverse remodeling and LV dysfunction by reducing immune responses and myocardial fibrosis. Male C57BL/6J and Gal-3 knockout (KO) mice were infused with Ang II for 8 weeks. We assessed: 1) systolic blood pressure (SBP) by plethysmography; 2) LV function and remodeling by echocardiography, 3) myocardial fibrosis by histology, 4) cardiac macrophage infiltration by histology, 5) ICAM-1 and VCAM-1 expression by Western blotting, 6) plasma cytokines by enzyme-linked immunosorbent assay, and 7) regulatory T cells (Treg) by flow cytometry detected by their combined expression of CD4, CD25, and FOXP3. SBP and cardiac hypertrophy increased similarly in both mouse strains when infused with Ang II. However, hypertensive C57BL/6J mice suffered impaired ejection and shortening fractions. These mice also had higher myocardial fibrosis and macrophage infiltration, higher cardiac ICAM-1 expression, as well as plasma IL-6. However, all these parameters were blunted in Gal-3KO mice. Hypertensive Gal-3KO mice also had a higher percentage splenic Treg lymphocytes. In conclusion, in Ang II-induced hypertension, Gal-3 genetic deletion prevented LV dysfunction without affecting the blood pressure or LV hypertrophy. This study indicates that the Ang II effects are partially mediated or triggered by Gal-3 together with related intercellular signaling, leading to cardiac inflammation and fibrosis.

Hypertension Research
Gu X, **Xu J**, **Zhu L**, Bryson T, **Yang XP**, **Peterson E**, and **Harding P**. Prostaglandin e2 reduces cardiac contractility via ep3 receptor *Circ Heart Fail* 2016; 9(8)PMID: 27502370. Full Text

From the Hypertension and Vascular Research Division, Department of Internal Medicine (X.G., J.X., L.Z., T.B., X.-P.Y., P.H.) and Department of Physiology (T.B., P.H.), Wayne State University School of Medicine, Detroit, MI; Department of Public Health Sciences (E.P.), Henry Ford Hospital, Detroit, MI; and Department of Cardiology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China (X.G.).
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BACKGROUND: Prostaglandin E2 (PGE2) EP receptors EP3 and EP4 signal via decreased and increased cAMP production, respectively. Previously, we reported that cardiomyocyte-specific EP4 knockout mice develop dilated cardiomyopathy with reduced ejection fraction. Thus, we hypothesized that PGE2 increases contractility via EP4 but decreases contractility via EP3. METHODS AND RESULTS: The effects of PGE2 and the EP1/EP3 agonist sulprostone on contractility were examined in the mouse Langendorff preparation and in adult mouse cardiomyocytes. Isolated hearts of adult male C57Bl/6 mice were perfused with PGE2 (10(-6) M) or sulprostone (10(-6) M) and compared with vehicle. Both PGE2 and sulprostone decreased +dp/dt ($P<0.01$) and left ventricular developed pressure ($P<0.001$) with reversal by an EP3 antagonist. In contrast, the EP4 agonist had the opposite effect. Adult mouse cardiomyocytes contractility was also reduced after treatment with either PGE2 or sulprostone for 10 minutes. We then examined the acute effects of PGE2, sulprostone, and the EP4 agonist on expression of phosphorylated phospholamban and sarcoendoplasmic reticulum Ca(2+)-ATPase 2a in adult mouse cardiomyocytes using Western blot. Treatment with either PGE2 or sulprostone decreased expression of phosphorylated phospholamban corrected to total phospholamban, whereas treatment with the EP4 agonist had the opposite effect. Sarcoendoplasmic reticulum Ca(2+)-ATPase 2a expression was unaffected. Finally, we examined the effect of these compounds in vivo using pressure-volume loops. Both PGE2 and sulprostone decreased +dp/dt, whereas the EP4 agonist increased +dp/dt. CONCLUSIONS: Contractility is reduced via the EP3 receptor but increased via EP4. These effects may be mediated through changes in phospholamban phosphorylation and has relevance to detrimental effects of inflammation.

Infectious Diseases

Bardossy AC, **Zervos J**, and **Zervos M**. Preventing hospital-acquired infections in low-income and middle-income countries: Impact, gaps, and opportunities *Infect Dis Clin North Am* 2016; 30(3):805-818. PMID: 27515149. Full Text

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In low-income and middle-income countries (LMIC) health care-associated infections (HAIs) are a serious concern. Many factors contribute to the impact in LMIC, including lack of infrastructure, inconsistent surveillance, deficiency in trained personnel and infection control programs, and poverty- related factors. In LMIC the risk of HAIs may be up to 25% of hospitalized patients. Building infection control capacity in LMIC is possible where strategies are tailored to the specific needs of LMIC. Strategies must start with simple, cost-effective measures then expand to include more complicated measures. Goals for short-term, medium-term, and long-term actions should be planned and resources prioritized.

Infectious Diseases

Bourgi K, **Brar I**, and **Baker-Genaw K**. Health disparities in hepatitis c screening and linkage to care at an integrated health system in southeast michigan *PLoS One* 2016; 11(8):e0161241. PMID: 27525983. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, United States of America.
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With recommended screening for hepatitis C among the 1945-1965 birth cohort and advent of novel highly effective therapies, little is known about health disparities in the Hepatitis C care cascade. Our objective was to evaluate hepatitis C screening rates and linkage to care, among patients who test positive, at our large integrated health system. We used electronic medical records to retrospectively identify patients, in the birth cohort, who were seen in 21 Internal Medicine clinics from July 2014 to June 2015. Patients previously screened for hepatitis C and those with established disease were excluded. We studied patients' sociodemographic and medical conditions along with provider-specific factors associated with likelihood of screening. Patients who tested positive for HCV antibody were reviewed to assess appropriate linkage to care and treatment. Of 40,561 patients who met inclusion criteria, 21.3% (8657) were screened, 1.3% (109) tested positive, and 30% (30/100) completed treatment. Multivariate logistic regression showed that African American race, male gender, electronic health engagement, residency teaching clinic visit, and having more than one clinic visit were associated with higher odds of screening. Patients had a significant decrease in the likelihood of screening with sequential interval increase in their Charlson comorbidity index. When evaluating hepatitis C treatment in patients who screened positive, electronic health engagement was associated with higher odds of treatment whereas Medicaid insurance was associated with significantly lower odds. This study shows that hepatitis C screening rates and linkage to care continue to be suboptimal with a significant impact of multiple sociodemographic and insurance factors. Electronic health engagement emerges as a tool in linking patients to the hepatitis C care cascade.

Infectious Diseases

Bourgi K, **Choi W**, **Nakhle A**, **Abdel-Rahman Z**, **Abreu-Lanfranco O**, **Ramesh M**, **Patel A**, **Del Busto R**, and **Alangaden G**. Risk factors for single and recurrent symptomatic urinary tract infections within the first year after kidney transplantation *Am J Transplant* 2016; 16:778-779. PMID: Not assigned. Abstract

K. Bourgi, Henry Ford Hospital, Detroit, United States

Urinary Tract Infection (UTI) is the most common infection after kidney transplantation (KT). However studies have been incongruent regarding risk factors associated with incidence and recurrence of symptomatic UTIs in this population. We identified patients who underwent KT between 01/2012 to 12/2013 and developed symptomatic single or recurrent UTI within the first year of transplant. Recurrent infection was defined as having at least 2 UTIs in 6 months or 3 UTIs in one year. Demographic information, medical comorbidities and transplant variables were assessed for association with single and recurrent UTIs. 190 patients underwent KT during the study period. After excluding asymptomatic bacteriuria, a total of 36 patients developed a UTI within the first year of which 18 had recurrent UTIs. Factors associated with developing UTI (single or recurrent) were female gender∗ and repeat KT∗. Patients with recurrent UTIs (vs. single) were significantly more likely to be diabetics∗ , to have higher comorbidity

index∗. KT recipients with recurrent UTI had significantly higher incidence of adverse renal outcomes, defined as increase in serum creatinine by 50% during the first year of transplant∗. Interestingly there was a significant association between isolation of Klebsiella pneumoniae in the index urine culture and the likelihood of recurrent UTI ∗. UTI is a frequent problem after KT and has high likelihood of recurrence. Multiple demographic, transplant and microbiological factors interplay as significant predisposing factors. (Table Presented).

Infectious Diseases

Huprikar S, Casner L, Camera Pierrotti L, Nellore A, Madan R, Garcia-Diaz J, Jacobs S, Lee D, Trindade Clemente W, **Alangaden G**, La Hoz R, Theodoropoulos N, Miceli M, Santoro-Lopes G, Banach D, Simon D, and Patel G. Outcomes associated with carbapenem-resistant enterobacteriaceae infection after solid organ transplantation in a multicenter study *Am J Transplant* 2016; 16:403. PMID: Not assigned. Abstract

S. Huprikar, Mount Sinai, United States

Background Carbapenem-resistant Enterobacteriaceae infection (CREI) is associated with poor outcomes in solid organ transplant (SOT) recipients but most reports are single center experiences. Methods Patients who underwent SOT between 1/1/2007 and 7/31/2013 and later developed CREI were eligible for chart review. The primary outcome was one-year mortality in SOT recipients with CREI within one year of SOT. Results Our cohort consists of 164 SOT recipients from 15 sites. The median age was 56; 61% were male. The transplanted organs were as follows: kidney (72), liver (62), liver-kidney (14), other (16). There were 170 CRE isolates: Klebsiella (129), Enterobacter (26) and other (15). 196 sites of CREI were observed: urinary tract (62), bloodstream (40), abdomen (36), lung (26), surgical site (25) and other (7). Surgical complications prior to CREI occurred in 83 (51%). In the entire cohort, the median intervals from SOT to CREI and from CREI to death were 51 days and 71 days, respectively. CREI occurred within one year of SOT in 140 (85%). The one-year mortality rate was 39/140 (28%) with a median interval from CREI to death of 30 days. The median interval from SOT to CREI in the 24 patients who developed CREI after one year was 812 days. The mortality rate in this group was 10/24 (42%). The median interval from CREI to death in this group was 50 days. Conclusions To our knowledge, this is the largest multicenter series of post-SOT CREI and confirms that CREI is usually an early complication. The one-year survival rate of 72% in SOT recipients with CREI in the first year is better than previously described in the literature. Analyses to identify factors associated with mortality and survival are in progress.

Infectious Diseases

Huprikar S, Casner L, Pouch S, Pinheiro Freire M, Madan R, Kwak E, Satlin M, **Hartman P**, Pisney L, Henrique Mourão P, La Hoz R, and Patel G. Prior infection or colonization with carbapenem-resistant enterobacteriaceae is not an absolute contraindication for solid organ transplantation *Am J Transplant* 2016; 16:260. PMID: Not assigned. Abstract

S. Huprikar, Mount Sinai, New York, United States

Background Carbapenem-resistant Enterobacteriaceae (CRE) infection is associated with poor outcomes after solid organ transplantation (SOT). The significance of CRE colonization or infection prior to SOT is not known. Methods Patients who underwent SOT between 1/1/2007 and 7/31/2013 and had pre-SOT cultures positive for CRE were identified for chart review. The primary outcome was one-year mortality. Results 57 SOT recipients from 10 sites were identified. The median age was 54 and 68% were male. 59 pre-SOT CRE isolates were identified: Klebsiella pneumoniae (n=45), Escherichia coli (5), Enterobacter (4), Klebsiella oxytoca (2), Serratia marcescens (2) and Citrobacter freundii (1). The culture sources of pre-SOT CRE were as follows: urine (22), rectal swab (21), blood (16), respiratory (9), others (10). The date of the most recent CRE culture was a median of 54 days (range: 1-2064) prior to SOT. The transplanted organs were as follows: liver (27), heart (17), kidney (7), liver-kidney (3), lung (2), and intestine (1). 22 (39%) patients developed CRE infection a median of 7.5 days (range: 2-151) after SOT. There was a surgical complication prior to CRE infection in 11/22 (50%) patients. The CRE causing infections were K. pneumoniae (19), Enterobacter (2), and Serratia (1) and matched the pre-SOT CRE in all patients except one. The sites of infection were as follows: bloodstream (11), surgical site or intra-abdominal (11), urinary tract (6), and pneumonia (5). One-year mortality was 21% (12/57) in the entire cohort; 27% (6/22) in patients with post-SOT CRE infection; and 17% (6/35) in patients without post-SOT CRE infection. Conclusions CRE colonization/infection should not be considered an absolute contraindication for SOT since one-year survival is nearly 80%. Strategies to prevent post-CRE infection may further improve survival. Analyses to identify risk factors associated with post-CRE infection and mortality are in progress.

Infectious Diseases
Ordaya EE, and **Alangaden GJ**. Real-life use of isavuconazole in patients intolerant to other azoles *Clin Infect Dis* 2016;PMID: 27553376. Full Text

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Internal Medicine
Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Internal Medicine
Bourgi K, **Brar I**, and **Baker-Genaw K**. Health disparities in hepatitis c screening and linkage to care at an integrated health system in southeast michigan *PLoS One* 2016; 11(8):e0161241. PMID: 27525983. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, United States of America.
Division of Infectious Diseases, Henry Ford Hospital, Detroit, MI, United States of America.

With recommended screening for hepatitis C among the 1945-1965 birth cohort and advent of novel highly effective therapies, little is known about health disparities in the Hepatitis C care cascade. Our objective was to evaluate hepatitis C screening rates and linkage to care, among patients who test positive, at our large integrated health system. We used electronic medical records to retrospectively identify patients, in the birth cohort, who were seen in 21 Internal Medicine clinics from July 2014 to June 2015. Patients previously screened for hepatitis C and those with established disease were excluded. We studied patients' sociodemographic and medical conditions along with provider-specific factors associated with likelihood of screening. Patients who tested positive for HCV antibody were reviewed to assess appropriate linkage to care and treatment. Of 40,561 patients who met inclusion criteria, 21.3% (8657) were screened, 1.3% (109) tested positive, and 30% (30/100) completed treatment. Multivariate logistic regression showed that African American race, male gender, electronic health engagement, residency teaching clinic visit, and having more than one clinic visit were associated with higher odds of screening. Patients had a significant decrease in the likelihood of screening with sequential interval increase in their Charlson comorbidity index. When evaluating hepatitis C treatment in patients who screened positive, electronic health engagement was associated with higher odds of treatment whereas Medicaid insurance was associated with significantly lower odds. This study shows that hepatitis C screening rates and linkage to care continue to be suboptimal with a significant impact of multiple sociodemographic and insurance factors. Electronic health engagement emerges as a tool in linking patients to the hepatitis C care cascade.

Internal Medicine
Bourgi K, **Choi W**, **Nakhle A**, **Abdel-Rahman Z**, **Abreu-Lanfranco O**, **Ramesh M**, **Patel A**, **Del Busto R**, and **Alangaden G**. Risk factors for single and recurrent symptomatic urinary tract infections within the first year after kidney transplantation *Am J Transplant* 2016; 16:778-779. PMID: Not assigned. Abstract

K. Bourgi, Henry Ford Hospital, Detroit, United States

Urinary Tract Infection (UTI) is the most common infection after kidney transplantation (KT). However studies have been incongruent regarding risk factors associated with incidence and recurrence of symptomatic UTIs in this population. We identified patients who underwent KT between 01/2012 to 12/2013 and developed symptomatic single or recurrent UTI within the first year of transplant. Recurrent infection was defined as having at least 2 UTIs in 6 months or 3 UTIs in one year. Demographic information, medical comorbidities and transplant variables were assessed for association with single and recurrent UTIs. 190 patients underwent KT during the study period. After excluding asymptomatic bacteriuria, a total of 36 patients developed a UTI within the first year of which 18 had recurrent UTIs. Factors associated with developing UTI (single or recurrent) were female gender∗ and repeat KT∗. Patients with recurrent UTIs (vs. single) were significantly more likely to be diabetics∗ , to have higher comorbidity index∗. KT recipients with recurrent UTI had significantly higher incidence of adverse renal outcomes, defined as increase in serum creatinine by 50% during the first year of transplant∗. Interestingly there was a significant association between isolation of Klebsiella pneumoniae in the index urine culture and the likelihood of recurrent UTI ∗. UTI is a frequent problem after KT and has high likelihood of recurrence. Multiple demographic, transplant and microbiological factors interplay as significant predisposing factors. (Table Presented).

Internal Medicine
Caceres PS, **Mendez M**, **Haque MZ**, and **Ortiz PA**. Vesicle associated membrane protein 3 (vamp3) mediates constitutive trafficking of the renal co-transporter nkcc2 in thick ascending limbs: Role in renal function and blood pressure *J Biol Chem* 2016;PMID: 27551042. Full Text

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Renal cells of the thick ascending limb (TAL) reabsorb NaCl via the apical Na+/K+/2Cl- co-transporter NKCC2. Trafficking of NKCC2 to the apical surface regulates NKCC2-mediated NaCl absorption and blood pressure. The molecular mechanisms by which NKCC2 reaches the apical surface and their role in renal function and maintenance of blood pressure are poorly characterized. Here we report that NKCC2 interacts with the vesicle fusion protein VAMP3 and they co-localize at the TAL apical surface. We observed that silencing VAMP3 in vivo blocks constitutive NKCC2 exocytic delivery, decreasing the amount of NKCC2 at the TAL apical surface. VAMP3 is not required for cAMP-stimulated NKCC2 exocytic delivery. Additionally, genetic deletion of VAMP3 in mice decreased total expression of NKCC2 in the TAL and lowered blood pressure. Consistent with these results, urinary excretion of water and electrolytes was higher in VAMP3 knockout mice, which produced more diluted urine. We conclude that VAMP3 interacts with NKCC2 and mediates its constitutive exocytic delivery to the apical surface. Additionally, VAMP3 is required for normal NKCC2 expression, renal function and blood pressure.

Internal Medicine
Cajigal S, **Wells KE**, **Peterson EL**, **Ahmedani BK**, Yang JJ, Kumar R, Burchard EG, and **Williams LK**. Predictive properties of the asthma control test and its component questions for severe asthma exacerbations *J Allergy Clin Immunol Pract* 2016;PMID: 27544712. Full Text

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BACKGROUND: Current US guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. OBJECTIVE: The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting the risk of severe asthma exacerbations. METHODS: Individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity, and those included in the current analysis had the following characteristics: age 18 years or more, physician-diagnosed asthma, and longitudinal care received at a large health system in southeastern Michigan. Study participants underwent a baseline evaluation, which included answering the ACT. A severe asthma exacerbation was defined as one requiring oral steroids, an emergency department visit, or inpatient admission. Receiver-operator characteristic curves were used to measure and compare the predictive utility of the ACT and its component questions for severe asthma exacerbations. RESULTS: Of 1180 participants, 354 (30.0%) experienced a severe asthma exacerbation within 6 months of their baseline evaluation. When compared with the individual questions that composed the ACT, the composite score was significantly better at predicting severe exacerbations with 1 exception; the composite ACT score and the question assessing rescue medication use were not significantly different (P = .580). Pharmacy-based records of metered-dose inhaler short-acting beta-agonist use and asthma severity were also not significantly different from the composite ACT score. CONCLUSIONS: Our study demonstrates that although the ACT is modestly predictive for exacerbations, the composite score may not be superior to assessing rescue medication use alone for predicting the risk of severe asthma exacerbations.

Internal Medicine

Chen WB, Gao L, **Wang J**, Wang YG, Dong Z, Zhao J, **Mi QS**, and **Zhou L**. Conditional ablation of HDAC3 in islet beta cells results in glucose intolerance and enhanced susceptibility to STZ-induced diabetes *Oncotarget* 2016;PMID: 27542279. Full Text

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Histone deacetylases (HDACs) are enzymes that regulate gene expression by modifying chromatin structure through removal of acetyl groups from target histones or non-histone proteins. Previous in vitro studies suggest that HDACs may be novel pharmacological targets in immune-mediated islet beta-cell destruction. However, the role of specific HDAC in islet beta-cell development and function remain unclear. Here, we generated a conditional islet beta-cells specific HDAC3 deletion mouse model to determine the consequences of HDAC3 depletion on islet beta-cell differentiation, maintenance and function. Islet morphology, insulin secretion, glucose tolerance, and multiple low-dose streptozotocin (STZ)-induced diabetes incidence were evaluated and compared between HDAC3 knockout and wild type littermate controls. Mice with beta-cell-specific HDAC3 deletion displayed decreased pancreatic insulin content, disrupted glucose-stimulated insulin secretion, with intermittent spontaneous diabetes and dramatically enhanced susceptibility to STZ-induced diabetes. Furthermore, islet beta-cell line, MIN6 cells with siRNA-mediated HDAC3 silence, showed decreased insulin gene transcription, which was mediated, at least partially, through the upregulation of suppressors of cytokine signaling 3 (SOCS3). These results indicate the critical role of HDAC3 in normal beta-cell differentiation, maintenance and function.

Internal Medicine

Connolly MD, **Zervos MJ**, **Barone CJ, 2nd**, **Johnson CC**, and **Joseph CL**. The mental health of transgender youth: Advances in understanding *J Adolesc Health* 2016;PMID: 27544457. Full Text

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This review provides an update on the growing body of research related to the mental health of transgender youth that has emerged since the 2011 publication of the Institute of Medicine report on the health of lesbian, gay, bisexual, and transgender people. The databases PubMed and Ovid Medline were searched for studies that were published from January 2011 to March 2016 in English. The following search terms were used: transgender, gender nonconforming, gender minority, gender queer, and gender dysphoria. Age limits included the terms youth, child,

children, teenager*, and adolescen*. The combined search produced 654 articles of potential relevance. The resulting abstracts went through a tiered elimination system, and the remaining 15 articles, which presented quantitative data related to the prevalence of transgender youth and their mental health, were included in the present review. In addition to providing new estimates of the number of young people who identify as transgender (.17%-1.3%), studies since 2011 have shown that transgender youth have higher rates of depression, suicidality and self-harm, and eating disorders when compared with their peers. Gender-affirming medical therapy and supported social transition in childhood have been shown to correlate with improved psychological functioning for gender-variant children and adolescents. Recent research has demonstrated increased rates of psychiatric morbidity among transgender youth compared to their peers. Future work is needed to understand those youth who identify as gender nonbinary, improve methods to capture and understand diverse gender identities and related health disparities, and delineate the social determinants of such disparities.

Internal Medicine

Danek BA, Karatasakis A, **Karmpaliotis D**, Alaswad K, Jaffer FA, Yeh RW, Patel MP, Bahadorani J, Lombardi WL, Wyman RM, Grantham JA, Kandzari DE, Lembo NJ, Doing AH, Toma C, **Moses JW**, **Kirtane AJ**, **Ali ZA**, **Parikh M**, Garcia S, Nguyen-Trong PK, Karacsonyi J, Alame AJ, Kalsaria P, Thompson C, Banerjee S, and Brilakis ES. Effect of lesion age on outcomes of chronic total occlusion percutaneous coronary intervention: Insights from a contemporary US multicenter registry *Can J Cardiol* 2016;PMID: 27476986. Full Text

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BACKGROUND: We sought to determine the effect of lesion age on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). METHODS: We examined the characteristics and outcomes of 394 CTO PCIs with data on lesion age, performed between 2012 and 2016 at 11 experienced US centres. RESULTS: Mean patient age was 66 +/- 10 years and 85.6% of the patients were men. Overall technical and procedural success rates were 90.1% and 87.5%, respectively. A major adverse cardiovascular event (MACE) occurred in 16 patients (4.1%). Mean and median lesion ages were 43 +/- 62 months and 12 months (interquartile range, 3-64 months), respectively. Patients were stratified into tertiles according to lesion age (3-5, 5-36.3, and > 36.3 months). Older lesion age was associated with older patient age (68 +/- 8 vs 65 +/- 10 vs 64 +/- 11 years; P = 0.009), previous coronary artery bypass grafting (62% vs 42% vs 30%; P < 0.001), and moderate/severe calcification (75% vs 53% vs 59%; P = 0.001). Older lesions more often required use of the retrograde approach and antegrade dissection/re-entry for successful lesion crossing. There was no difference in technical (87.8% vs 89.6% vs 93.0%; P = 0.37) or procedural (86.3% vs 87.4% vs 89.0%; P = 0.80) success, or the incidence of MACE (3.1% vs 3.0% vs 6.3%; P = 0.31) for older vs younger occlusions. CONCLUSIONS: Older CTO lesions exhibit angiographic complexity and more frequently necessitate the retrograde approach or antegrade dissection/re-entry. Older CTOs can be recanalized with high technical and procedural success and acceptable MACE rates. Lesion age appears unlikely to be a significant determinant of CTO PCI success.

Internal Medicine

Deeb D, **Gao X**, **Liu Y**, **Zhang Y**, **Shaw J**, **Valeriote FA**, and **Gautam SC**. The inhibition of cell proliferation and induction of apoptosis in pancreatic ductal adenocarcinoma cells by verrucarin A, a macrocyclic trichothecene, is associated with the inhibition of Akt/NF-small ka, CyrillicB/mTOR prosurvival signaling *Int J Oncol* 2016; 49(3):1139-1147. PMID: 27573873. Article Request Form

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Pancreatic ductal adenocarcinoma (PDA) remains one of the most difficult to treat of all malignancies. Multimodality regimens provide only short-term symptomatic improvement with minor impact on survival, underscoring the urgent need for novel therapeutics and treatment strategies for PDA. Trichothecenes are powerful mycotoxins that inhibit protein synthesis and induce ribotoxic stress response in mammalian cells. Verrucarin A (VC-A) is a Type D macrocyclic mycotoxin which inhibited cell proliferation and induced apoptosis in breast cancer cells. However, the antitumor activity of VC-A for PDA cells has not been investigated. Here we show potent antitumor activity and the mechanism of action of VC-A in PDA cell lines. VC-A strongly inhibited the proliferation and arrested cells in the S phase of the cell cycle. The blocking of cell cycle progression by VC-A was associated with the inhibition of cell cycle regulatory proteins cyclin D1, cyclin E, cyclin-dependent kinases (cdks) cdk2, cdk4 and cdk inhibitor WAF1/21. VC-A induced apoptosis in PDA cells as indicated by the increased Annexin V FITC-binding, cleavage of poly(ADP-ribose) polymerase1 (PARP-1) and procaspases-3, -8 and -9. VC-A also induced mitochondrial depolarization and release of cytochrome c and it inhibited Bcl-2 family proteins that regulate apoptosis (Bcl-2, Bcl-xL, Bax and Bad). In addition, VC-A reduced the levels of inhibitors of apoptosis survivin and c-IAP-2. Finally, VC-A downregulated the expression of prosurvival phospho-Akt (p-Akt), nuclear factor kappaB (NF-kappaB) (p65) and mammalian target of rapamycin (p-mTOR) signaling proteins and their downstream mediators. Together, these results demonstrated strong antiproliferative and apoptosis-inducing activity of verrucarin A for PDA cells through cell cycle arrest and inhibition of the prosurvival (antiapoptotic) AKT/NF-kappaB/mTOR signaling.

Internal Medicine

Heidemann DL, **Thompson E**, and **Drake SM**. Does timing of internal medicine residency interview affect likelihood of matching? *South Med J* 2016; 109(8):466-470. PMID: 27490656. Full Text

From the Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.

OBJECTIVES: Applicants to our internal medicine (IM) residency program consistently have shared concerns about whether the interview date influences their ability to match via the National Residency Matching Program. We performed a retrospective study to assess whether interview timing was associated with successful matching at our IM program. METHODS: We identified all of the applicants who interviewed for a first-year position with our IM residency program from 2010 to 2014. Each year's interview dates were totaled and divided equally into three categories: early, middle, or late. Baseline demographics, United States Medical Licensing Examination scores, and type of medical school (American or international) were compared among the interview date groups and between those who did and did not match at our program. RESULTS: Of 914 interviewees, 311 interviewed early (October/November), 299 interviewed in the middle (December), and 304 interviewed late (January). The proportion to match at our program was similar in each interview group (12.5%, 18.4%, 15.1%, respectively; P = 0.133). Logistic regression analysis showed that the middle interview group had increased odds to match compared with the early group (odds ratio 1.590; P = 0.044). The late-versus-early group showed no difference (P = 0.362). No significant differences were found with type of medical school or United States Medical Licensing Examination scores. Of all of the interviewees participating in the match, nearly all matched into a program somewhere, with no significant difference based on interview timing. CONCLUSIONS: When considering all of the interviewees, interview date showed no major influence on matching. Only the middle interview time period showed a slight increased chance of matching to our IM program, but the significance was marginal.

Internal Medicine

Kabbani L, **Munie S**, **Lin J**, **Velez M**, **Isseh I**, **Brooks S**, **Leix S**, and **Shepard A**. Flow patterns in the carotid arteries of patients with left ventricular assist devices *Ann Vasc Surg* 2016;PMID: 27531092. Full Text

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OBJECTIVE: To evaluate and define the expected flow pattern changes of carotid artery duplex ultrasound after LVAD placement. METHODS: Retrospective review of Henry Ford Hospital database of patients who had undergone LVAD placement between March 2008 and July 2012 was performed. All patients who had carotid artery duplex scanning before and after LVAD placement within two years of each other and showed less than 50% stenosis were included in this study. Type of waveform, carotid peak systolic velocity and end-diastolic velocities were analyzed, and the values were compared before and after LVAD placement. RESULTS: A total of 13 patients with LVAD had at least two carotid duplex studies before and after LVAD placement within two years of each other. Of those, 92% (n=12) were men, and 61% (n=8) were Caucasian. Mean age was 61 years old. The Heartware ventricular assist device (HVAD) was implanted in 4 patients and the HeartMate II left ventricular assist device was implanted in 9 patients. Post-LVAD Doppler imaging demonstrated parvus tardus waveform. Analysis of flow velocities revealed that peak systolic velocity was diminished after LVAD placement in both the internal and common carotid arteries ($p=0.006$ and $p<0.0001$ respectively). End-diastolic velocity, however, was noted to be increased post LVAD ($p<0.0001$). Interestingly, mean flow velocities in both the common and internal carotid arteries remained stable after LVAD placement. CONCLUSION: This study reveals changes in waveform morphology and peak systolic and diastolic velocities in the common and internal carotid arteries on carotid duplex after LVAD placement. Additionally, it shows that despite changes in post LVAD pulse pressure in the carotid arteries, the mean flow velocity remained unchanged.

Internal Medicine

Michaels AT, **Radjef R**, **She RC**, **Liu B**, **Peterson E**, Pinto Y, **Williams K**, **Sabbah H**, and **Lanfear D**. Improving risk prediction in heart failure: MAGGIC plus natriuretic peptides *J Card Fail* 2016; 22(8):S99-S99. PMID: Not assigned. Abstract

Background: Risk stratification of patients with heart failure (HF) remains challenging but is a critical need. The MAGGIC score is a clinical risk model derived from meta-analysis of nearly 40k patients. Natriuretic peptides (NP) have consistently shown powerful risk prediction in HF patients, but the incremental value in addition to MAGGIC score is not known. Methods: In this single center study 4264 patients were analyzed from two cohorts; a prospective ambulatory registry of HF patients (n = 1314) who had baseline NTproBNP levels measured, and a retrospective cohort collected utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015; n = 2503) with clinical BNP levels measured at or near discharge. The hospital discharge cohort were all assigned NYHA class IV. The primary end-point was all cause mortality. Performance of the MAGGIC score and NP levels was assessed within each cohort utilizing Cox regression and receiver operating curves (ROC) analysis (MAGGIC alone vs. MAGGIC+NP) with the net reclassification improvement (NRI) also calculated. Results: The overall cohort had an average age of 71.2 years, was 47.8% females, and 41% self-identified African Americans. Median follow up was 1.52 years during which there were 1139 deaths (27%). The MAGGIC score was a strong predictor of outcome in both cohorts ($P < .001$). In ROC analysis of the ambulatory registry, NP significantly improved area under the curve (AUC) compared to MAGGIC alone from 0.74 to 0.79 ($P = .002$) and had a NRI of 0.354 (Figure). In contrast, within the hospital discharge cohort NP levels did not significantly add to MAGGIC score (AUC 0.681 vs. 0.676, NRI = 0.033, $P = .284$) (Figure). Conclusion: In our study, NP levels in the ambulatory setting significantly improved risk stratification provided by the MAGGIC score, but discharge NP levels did not improve MAGGIC prediction of post-hospital survival. Overall risk stratification and particularly NP utility is much better in the ambulatory setting.

Internal Medicine

Michaels AT, **Radjef R**, **She RC**, **Peterson E**, **Liu B**, and **Lanfear DE**. Predicting mortality at discharge following hospitalization for acute heart failure *J Card Fail* 2016; 22(8):S21-S22. PMID: Not assigned. Abstract

Background : Risk stratification for heart failure (HF) patients remains a critical need, particularly among those hospitalized where many clinical decisions are being made at discharge. Recently a robust risk model, the MAGGIC score, was derived from data on nearly 40k patients. This provides 1 year mortality estimates and is available as an online clinical tool. Whether it is useful to risk-stratify patients being discharged from the hospital is unknown. Methods : This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. For the hospital discharge subjects, when tabulating MAGGIC all patients were assigned NYHA class IV. The primary endpoint was all-cause mortality. Vital status was assessed utilizing system administrative data and the social security death master file. Performance of the MAGGIC score was evaluated within cohorts and compared across the two groups using Cox models stratified by cohort and then with an interaction term (MAGGIC*Cohort). Calibration was assessed by comparing observed vs. MAGGIC-predicted 1 year mortality. Results : Overall the study patients had an average age of 71.2 years, 47.8%

were female and 41% were self-identified African Americans, and there were 1139 deaths (27%) over a median follow up of 1.52 years. The hospital discharge cohort was overall much higher risk than the ambulatory cohort (figure). The MAGGIC score was a strong predictor of outcomes in both groups (both P < .001). With a HR (per MAGGIC point) of 1.13 in the ambulatory registry and 1.10 in the hospital discharge patients. In ROC analysis MAGGIC showed an area under the curve (AUC) of 0.74, but an AUC in the hospital discharge cohort of 0.67. When modeled using an interaction term, MAGGIC did appear to be more predictive in the ambulatory group with an interaction coefficient of 0.03 (P = .004). Although calibration appeared suboptimal in both cohorts (Figure), with MAGGIC underestimating the true risk, this appeared similar in both cohorts. Discussion : The MAGGIC score is able to provide important prognostic information on patients being discharged from the hospital for HF, though the performance was somewhat inferior than in a comparable ambulatory cohort. MAGGIC underestimated risk in both ambulatory and hospital cohorts, suggesting calibration may need to be reassessed in more real-world patient data sets.

Internal Medicine

Qureshi W, Ali Z, Amjad W, **Alirhayim Z**, Farooq H, Qadir S, Khalid F, and Al-Mallah MH. Venous thromboembolism in cancer: An update of treatment and prevention in the era of newer anticoagulants *Front Cardiovasc Med* 2016; 3:24. PMID: 27517038. Full Text

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Cancer patients are at major risk of developing venous thromboembolism (VTE), resulting in increased morbidity and economic burden. While a number of theories try to explain its pathophysiology, its risk stratification can be broadly done in cancer-related, treatment-related, and patient-related factors. Studies report the prophylactic use of thrombolytic agents to be safe and effective in decreasing VTE-related mortality/morbidity especially in postoperative cancer patients. Recent data also suggest the prophylactic use of low molecular weight Heparins (LMWHs) and Warfarin to be effective in reducing VTEs related to long-term central venous catheter use. In a double-blind, multicenter trial, a new ultra-LMWH Semuloparin has shown to be efficacious in preventing chemotherapy-associated VTE's along with other drugs, such as Certoparin and Nadoparin. LMWHs are reported to be very useful in preventing recurrent VTEs in advanced cancers and should be preferred over full dose Warfarin. However, their long-term safety beyond 6 months has not been established yet. Furthermore, this paper discusses the safety and efficacy of different drugs used in the treatment and prevention of recurrent VTEs, including Bemiparin, Semuloparin, oral direct thrombin inhibitors, parenteral and direct oral factor Xa inhibitors.

Internal Medicine

Radjef R, **Michaels A**, **Peterson E**, **She R**, **Liu B**, **Williams K**, **Sabbah H**, and **Lanfear D**. Performance of MAGGIC score in african americans compared to whites *J Card Fail* 2016; 22(8):S101-S101. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans

showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Internal Medicine

Rao B, **Yoshida A**, **Ibrahim M**, and **Jafri SM**. The use of perioperative lactate values as markers for adverse outcomes in liver transplantation *Am J Transplant* 2016; 16:672. PMID: Not assigned. Abstract

B. Rao, Internal Medicine, Henry Ford Hospital, Detroit, United States

Introduction: We examined the utility of perioperative lactate values for the prediction of multiple post-transplant outcomes including length of hospital stay (LOS), acute cellular rejection (ACR), and mortality in a single center liver transplant population. Methods: Retrospective chart review of all patients undergoing primary orthotopic liver transplant at a large urban tertiary care center from 2008-2010. Data was obtained on recipient demographics, donor age, donor gender, surgical time points, cold ischemia time (CIT), preoperative lactate, peak intraoperative lactate, and peak postoperative lactate (maximum lactate value within 48 hours post-surgery). We examined outcomes of postoperative LOS, history of moderate or severe ACR, and mortality. Analysis was performed using multivariate linear and logistic regression models. Results: 273 patients were included for analysis. Mean recipient age was 52 (range 17-72) with 66% males. Mean donor age was 43 (range 7-83) with 40% males. Mean CIT was 312 minutes (range 12-699). Mean MELD was 22 (range 6-53). For every one unit increase in peak intraoperative lactate there was a 1.64 day increase in LOS ($p < 0.001$). For every one unit increase in peak intraoperative lactate the odds of death was significantly increased at one month (OR = 1.37, $p = 0.001$) and one year (OR = 1.14; $p = 0.021$). For every one unit increase in peak postoperative lactate there was a 1.76 day increase in LOS ($p < 0.001$). The odds of death was significantly increased for every one unit increase in peak postoperative lactate at one month (OR = 1.28; $p = 0.004$) and one year (OR = 1.13; $p = 0.003$). Preoperative lactate was not associated with any significant adverse outcomes. None of the perioperative lactate values were associated with developing an episode of moderate or severe ACR after transplant. Conclusion: Our results create a better understanding and interpretation of perioperative lactate values in liver transplantation. Findings clearly show an association between perioperative lactate values and mortality up to one year after transplant.

Internal Medicine

Rodriguez J, **Patel A**, and **Goggins M**. Age gap analysis between live donor and recipients in kidney transplantation: Opportunities to improve voluntary exchange programs and kidney paired donation *Am J Transplant* 2016; 16:450. PMID: Not assigned. Abstract

J. Rodriguez, Internal Medicine, Henry Ford Hospital, Detroit, United States

Graft survival(GS) perception is that, with a smaller age gap between the donor(D) and recipient(R), better the outcome. It is unclear if there is an age-gap limit at which the benefit in GS disappears. We chose to analyze graft failure(GF)rates among R of living donors(LD) with an incremental D minus R age gap. We compared such groups to standard criteria deceased donors(SCD)transplants. Methods: Using the UNOS database from 1995 to 2013, we evaluated GF involving LD with R ages 18-79 from 1995 onward. We compared GF among R from LD with an age-gap, D minus R, of <10, 10-14, 15-19, 20-24, 25-30 and 30+. These age-gap groups were compared to SCD R. D and R demographic and transplant data were used to allow Cox regression analysis. Endpoints were plotted using Kaplan-Meir analysis. Results: When D are older than R, Cox regression analysis(n=13,930)showed no statistical difference in GF comparing a D-R age-gap less than 10 vs age-gap 10-14(p 0.636).There was a significant increase in GF in age-gap 15-19 (n=3,127)compared to 10-14 (P<0.001, HR 1.55).There was no GF difference comparing remaining age-gap groups.Kaplan-Meier curve confirmed findings.Fig1 Comparing LD R of same age-gap groups with R of SCD(n=29,058) a statistical significance decreased in GF was found between age-gap<15 (p<0.001, HR 0.67). There was no statistical difference between the wider age-gap groups and SCD R. When R are older than D, Cox regression analysis(n=41,881) showed that age-gap of <10 had statistically significant improved GF compared to age gap>10(p<0.001, HR 1.18)however, it was not significant when compared to age gap >15 (p=0.1). Conclusions: There appears to be a statistical significant benefit on GF within LD R if the age-gap is <15 compared to age gap>15. Within age gap groups of >15, there was no difference in GF. LD R had decreased GF when compared to SCD R, if age gap was <15, but not if gap was>15.For R older than D,there is no GF benefit with an age gap of >15 compared to <15. (Figure Presented).

Internal Medicine

Sabbah HN, **Gupta RC**, **Sing-Gupta V**, **Zhang KF**, and **Xu J**. Long-Term Therapy with Elamipretide Normalizes ATP Synthase Activity in Left Ventricular *J Card Fail* 2016; 22(8):S23-S23. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Internal Medicine

Takahashi K, **Patel AK**, **Putchakayala KG**, **Denny JE**, **Kim DY**, and **Malinzak LE**. Arterioenteric fistula 12 years after kidney transplant *Kidney Int* 2016; 90(3):710. PMID: 27521122. Full Text

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Internal Medicine

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Metformin is the first-line antidiabetic drug with over 100 million users worldwide, yet its mechanism of action remains unclear. Here the Metformin Genetics (MetGen) Consortium reports a three-stage genome-wide association study (GWAS), consisting of 13,123 participants of different ancestries. The C allele of rs8192675 in the intron of SLC2A2, which encodes the facilitated glucose transporter GLUT2, was associated with a 0.17% (P = 6.6 x 10-14) greater metformin-induced reduction in hemoglobin A1c (HbA1c) in 10,577 participants of European ancestry. rs8192675 was the top cis expression quantitative trait locus (cis-eQTL) for SLC2A2 in 1,226 human liver samples, suggesting a key role for hepatic GLUT2 in regulation of metformin action. Among obese individuals, C-allele homozygotes at rs8192675 had a 0.33% (3.6 mmol/mol) greater absolute HbA1c reduction than T-allele homozygotes. This was about half the effect seen with the addition of a DPP-4 inhibitor, and equated to a dose difference of 550 mg of metformin, suggesting rs8192675 as a potential biomarker for stratified medicine.

Nephrology

Moza A, Khan A, **Prashar R**, Khan S, Khouri S, Vetteth S, Malhotra D, Rees M, Moukarbel G, and Ortiz J. Pulmonary hypertension in renal transplant candidates: A systematic review and meta-analysis of the available evidence *Am J Transplant* 2016; 16:573. PMID: Not assigned. Abstract

A. Moza, Cardiovascular Medicine, University of Toledo Medical Center, Toledo, United States

Background: Pulmonary hypertension (PHT) is common in patients with end stage renal disease (ESRD). Moderate to severe PHT is a strong independent predictor of mortality in hemodialysis (HD) patients, and in those undergoing noncardiac surgery. The studies which have evaluated the association of PHT with renal transplant outcomes have shown conflicting results. We performed a systematic review and meta-analysis of the current available evidence examining the effect of existing PHT on relevant clinical outcomes following renal transplantation. Materials and Methods: Major databases (Pubmed, Embase, Cochrane, Web of Science, and Scopus) were searched for studies of

patients undergoing renal transplantation that reported pulmonary pressures and transplantation outcomes. Data were extracted from the original publications. Results: Out of 259 publications, only 3 (with a total of 502 patients) were eligible for inclusion in the current analysis. Our meta-analysis of these three studies suggests a three-fold increase in mortality after renal transplantation in patients with PHT compared to those without PHT (OR 3.15, 95% confidence interval 1.42-6.97; p = 0.005). A qualitative review indicates that PHT is associated with both early graft dysfunction and worse renal function at 12 months post-transplant. Conclusions: There is paucity of clinical trial data examining the effect of pulmonary hypertension and its management on renal transplant outcomes. In this meta-analysis we found that there is an increased risk of mortality in patients with pulmonary hypertension who undergo renal transplantation. (Figure Presented).

Nephrology
Takahashi K, **Patel AK**, **Putchakayala KG**, **Denny JE**, **Kim DY**, and **Malinzak LE**. Arterioenteric fistula 12 years after kidney transplant *Kidney Int* 2016; 90(3):710. PMID: 27521122. Full Text

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Nephrology
Tinney F, **Yessayan L**, **Abouljoud M**, and **Patel A**. Characterization of vascular lesions in living donor renal transplant implant biopsies *Am J Transplant* 2016; 16:646. PMID: Not assigned. Abstract

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INTRODUCTION: Nephrosclerosis is often associated with pathological injury to kidneys resulting from chronic high blood pressure and/or aging, and may predict the progression of decline in renal function. We sought to evaluate pathological features of implant biopsies, such as arteriolosclerosis (AS), arteriolar hyalinosis (AH), microthrombi, and glomerulosclerosis (GS), and to correlate this pathology with renal function in living transplant donors. METHODS: A retrospective review of 100 living donor renal transplants was conducted, from June 2012 to June 2015. All recipient biopsies were obtained intra-operatively, and evaluated for pathological abnormalities. The impact of the presence of arterial abnormalities on donor serum creatinine at five different time points was evaluated (pre-operative, and at 2, 26, 52, and 104 weeks post-donation). Arterial changes were defined as the presence of at least one of the following: AS, AH or microthrombi. RESULTS: Donors' (N=100) mean age was 43 years (range 20-67), 66 were female and 80 were white. Of the recipient biopsies done intra-operatively, 55/100 reported abnormal pathology (31% GS, 17% AS, and 13% AH). Donors with age greater than 50 years were more likely to have arterial changes (OR 3.35; 95% CI [1.31-8.59]). In a multivariate model adjusting for race, gender, body mass index (BMI), and baseline kidney function, arterial hyalinosis was associated with age (OR 1.10; 95% CI [1.03-1.17]). However, age was not associated with neither AS, microthrombi or GS. Arterial changes were not significantly associated with race, BMI, or pre/post-operative serum creatinine values. CONCLUSIONS: These results suggest that despite all donors meeting preoperative criteria, older donors demonstrated more pathological arterial changes, especially AH. Of additional concern, the shear number of healthy donors who displayed pathological changes at the time of transplant suggests that the evaluation of donor candidates may not be entirely adequate. Further research into the longterm outcomes of donor populations, as well as the recovery of renal function in recipients, is underway. (Table Presented).

Neurology
Chopp M. Treatment of stroke and neural injury with exosomes and miRNA cargo *Journal of Cerebral Blood Flow and Metabolism* 2016; 36:8. PMID: Not assigned. Abstract

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Traditionally, treatment of neural injury (e.g. stroke, traumatic brain injury neurodegenerative disease) has focused on reduction of the lesion, with, as of now, little translational benefit to humans. A more effective and viable translational approach for the effective treatment of neural injury may reside in stimulating and amplifying endogenous restorative mechanism. Thus, we redirect the focus of therapy from the lesion (i.e. neuroprotection) to the intact central nervous system (CNS) (neurorestoration), to remodel the CNS. In this presentation, data will be presented illustrating robust post neural injury plasticity, and coupling of neurovascular restorative processes. I will describe ways by which we may amplify these processes by both cellular and pharmacological means to promote neurological recovery. Molecular underpinnings of these restorative events will be described, e.g., where the developmental morphogen,

sonic hedgehog (Shh) is activated by effective neurorestorative treatments of neural injury. Delving deeper into the molecular targets of recovery, I discuss how restorative therapies, such as cell-based therapies, which amplify neurological recovery and stimulate remodeling of tissues, communicate with and alter their environment. I will describe the essential roles of microRNAs, master molecular switches-that regulate gene translation and subsequently many biological processes, in promoting neurological recovery. I will demonstrate that stem-like cells act as “factories” to produce tiny lipid particles, exosomes (~40-100nm). Exosomes encapsulate proteins, mRNAs, and miRNAs within. Stem-like cells, and many others, generate these exosomes, and thereby transfer key genetic regulatory instructions to tissue adjacent to and remote from the administered stem cells. These exosomes may be employed without their mother-cells as a monotherapy for the treatment of stroke and neural injury. In addition, I will describe how the cargo of the cell generated exosomes may be tailored to contain specific miRNA to promote neurite outgrowth. This exosome/miRNA communication network underlies a vast arena of biological processes and may be employed to promote recovery post stroke and neural injury.

Neurology
Espay AJ, **LeWitt PA**, Hauser RA, Merola A, Masellis M, and Lang AE. Neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease and related synucleinopathies: prioritisation of treatment targets *Lancet Neurol* 2016; 15(9):954-966. PMID: 27478953. Full Text

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Neurogenic orthostatic hypotension and supine hypertension are common manifestations of cardiovascular dysautonomia in Parkinson's disease and related synucleinopathies. Because these disorders are haemodynamic opposites, improvement in one might be achieved at the expense of worsening of the other. Thus, management decisions necessitate assessment of the individual risks for patients with coexistent neurogenic orthostatic hypotension and supine hypertension. Whereas neurogenic orthostatic hypotension poses risks for falls and can be associated with cognitive impairment in the short term, chronic supine hypertension can be associated with stroke and myocardial infarction in the long term. Because few clinical trial data exist for outcomes in patients with coexistent neurogenic orthostatic hypotension and supine hypertension, clinicians need to balance, on the basis of comorbidities and disease staging, the potential immediate benefits of treatment for neurogenic orthostatic hypotension and the long-term risks of supine hypertension treatment in each patient. Future research needs to focus on ascertaining a safe degree of supine hypertension when treating neurogenic orthostatic hypotension; the effectiveness of nocturnal antihypertensive therapy in patients with coexistent neurogenic orthostatic hypotension and supine hypertension; and the prevalence, scope, and therapeutic requirements for managing neurogenic orthostatic hypotension that manifests with falls or cognitive impairment, but without postural lightheadedness or near syncope.

Neurology
Loeffler DA, Klaver AC, Coffey MP, Aasly JO, and **LeWitt PA**. Age-related decrease in heat shock 70-kda protein 8 in cerebrospinal fluid is associated with increased oxidative stress *Front Aging Neurosci* 2016; 8:178. PMID: 27507943. Full Text

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Age-associated declines in protein homeostasis mechanisms ("proteostasis") are thought to contribute to age-related neurodegenerative disorders. The increased oxidative stress which occurs with aging can activate a key proteostatic process, chaperone-mediated autophagy. This study investigated age-related alteration in cerebrospinal fluid (CSF) concentrations of heat shock 70-kDa protein 8 (HSPA8), a molecular chaperone involved in proteostatic mechanisms including chaperone-mediated autophagy, and its associations with indicators of oxidative stress (8-hydroxy-2'

deoxyguanosine [8-OHdG] and 8-isoprostane) and total anti-oxidant capacity. We examined correlations between age, HSPA8, 8-OHdG, 8-isoprostane, and total antioxidant capacity (TAC) in CSF samples from 34 healthy subjects ranging from 20 to 75 years of age. Age was negatively associated with HSPA8 (rho = -0.47; p = 0.005). An age-related increase in oxidative stress was indicated by a positive association between age and 8-OHdG (rho = 0.61; p = 0.0001). HSPA8 was moderately negatively associated with 8-OHdG (rho = -0.58; p = 0.0004). Age and HSPA8 were weakly associated with 8-isoprostane and TAC (range of rho values: -0.15 to 0.16). Our findings in this exploratory study suggest that during healthy aging, CSF HSPA8 may decrease, perhaps due in part to an increase in oxidative stress. Our results also suggest that 8-OHdG may be more sensitive than 8-isoprostane for measuring oxidative stress in CSF. Further studies are indicated to determine if our findings can be replicated with a larger cohort, and if the age-related decrease in HSPA8 in CSF is reflected by a similar change in the brain.

Neurology
Loomba V, **Kaveeshvar H**, and **Dwivedi S**. Paraplegia after thoracic epidural steroid injection *A A Case Rep* 2016;PMID: 27536909. Article Request Form

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Epidural steroid injections are a common procedure performed by pain physicians. The American Society of Regional Anesthesia along with several other groups recently provided guidelines for performing epidural injections in the setting of anticoagulants. We present a case of a patient who developed an epidural hematoma and subsequent paraplegia despite strict adherence to these guidelines. Although new guidelines serve to direct practice, risks of devastating neurologic complications remain as evidenced by our case.

Neurology
Patel N. Review of medication-induced movement disorders *JAMA Neurol* 2016; 73(8):1034. PMID: 27533355. Full Text

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Neurology
Tsivgoulis G, Katsanos AH, Magoufis G, Kargiotis O, Papadimitropoulos G, Vadikolias K, Karapanayiotides T, Ellul J, Alexandrov AW, **Mitsias PD**, and Alexandrov AV. Percutaneous transluminal angioplasty and stenting for symptomatic intracranial arterial stenosis: a systematic review and meta-analysis *Ther Adv Neurol Disord* 2016; 9(5):351-358. PMID: 27582890. Full Text

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OBJECTIVES: The cumulative safety and efficacy measures of percutaneous transluminal angioplasty and stenting (PTAS) for secondary stroke prevention in patients with symptomatic intracranial arterial stenosis (sICAS) have not previously been evaluated using a meta-analytical approach. METHODS: We conducted a systematic review and random effects meta-analysis of all available randomized controlled trials (RCTs) evaluating the safety and efficacy of PTAS (in comparison with medical therapy) for sICAS. RESULTS: Three RCTs (678 total patients) were included in the quantitative analysis. PTAS was associated with a higher risk of recurrent ischemic stroke in the territory of qualifying artery both within 30 days [risk ratio (RR) = 2.21, 95% confidence interval (CI) 1.10-4.43] and 1 year (RR = 1.92, 95% CI 1.10-3.36). PTAS was also related to a higher risk of any ischemic stroke within 30 days from the index event (RR = 2.08, 95% CI 1.17-3.71). The risk for intracranial hemorrhage was found to be higher in PTAS patients

both within 30 days (RR = 10.60, 95% CI 1.98-56.62) and 1 year (RR = 8.15, 95% CI 1.50-44.34). The composite outcome of any stroke or death within 1 year (RR = 2.29, 95% CI 1.13-4.66) and 2 years (RR = 1.52, 95% CI 1.04-2.21) was higher in PTAS than in medical therapy. PTAS was associated with a higher risk of any stroke or death within 2 years in the sICAS subgroup located in posterior circulation (RR = 2.37, 95% CI 1.27-4.42). CONCLUSIONS: PTAS is associated with adverse early and long-term outcomes and should not be recommended in patients with sICAS. Further research to identify subgroups of patients who could also serve as candidates for future interventional trials along with efforts to reduce procedure-related complications are needed.

Neurology

Van Den Bent MJ, Gan HK, Lassman AB, Kumthekar P, Merrell R, Butowski NA, Lwin Z, **Mikkelsen T**, Nabors LB, Papadopoulos KP, Penas-Prado M, Simes J, Wheeler H, Gomez EJ, Lee HJ, Roberts-Rapp L, Xiong H, Bain EE, Holen KD, and Reardon DA. Efficacy of a novel antibody-drug conjugate (ADC), ABT-414, as monotherapy in epidermal growth factor receptor (EGFR) amplified, recurrent glioblastoma (GBM) *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

M.J. Van Den Bent

Background: Recurrent GBM (rGBM) has dismal prognosis. Almost 50% GBM tumors harbor amplified (amp) EGFR. ABT-414 is a tumor specific ADC combining an antibody targeting a unique conformation of EGFR (ABT-806) to a microtubule cytotoxin, monomethyl auristatin F (MMAF). Here we report the safety and efficacy of ABT-414 monotherapy at recommended phase 2 dose (RPTD) in EGFR amp, rGBM. Methods: M12-356 (NCT01800695) is an open-label, phase 1, 3-arm study: Arm A (ABT- 414+radiation/temozolomide (TMZ) in newly diagnosed GBM (nGBM)), Arm B (ABT- 414+TMZ in nGBM as adjuvant therapy, or in rGBM) and Arm C (ABT-414 monotherapy in rGBM). Each arm had an escalation cohort to determine the RPTD and an expansion cohort to establish the safety and preliminary efficacy at RPTD. Results of Arm C expansion cohort at 1.25 mg/kg RPTD (IV infusion) are shown here. Eligible patients (pts) were adults with KPS score ≥ 70, EGFR amp (confirmed centrally), rGBM, normal end-organ function and no prior bevacizumab. Results: As of January 7, 2016, 48 EGFR amp, rGBM pts were treated in this cohort. The median age was 59 years (range, 35-80). Most pts had prior therapies: 40% had 1, 48% had 2, 10% had ≥ 3 prior therapies. Most common treatment emergent adverse events (TEAEs) (≥ 25% pts) were blurred vision (60%), headache, photophobia (29% each), dry eye, eye pain, fatigue (27% each). The most common serious AE (> 1 pt) was seizure (8%). Grade 3/4 TEAEs (> 1 pt) were keratitis (15%), corneal epithelial microcysts (8%), hemiparesis, hyperglycemia, muscular weakness, seizure (6% each), blurred vision, ulcerative keratitis (4% each). No dose-limiting toxicities were reported. Best RANO responses of 44 pts with complete data were: 2 partial responses, 18 stable disease, 24 progressive disease. The 6-month progression-free survival (PFS6) estimate was 30% [95% CI = 17, 44]. Conclusions: ABT-414 monotherapy, at 1.25 mg/kg RPTD, displayed frequent yet reversible ocular toxicities. An encouraging tumor stability/response and PFS6 were observed in this highly refractory EGFR amp, rGBM. A global randomized trial of ABT-414, alone or with TMZ, vs. TMZ or lomustine, is underway in EGFR amp, rGBM (NCT02343406).

Neurology

Venkat P, **Chopp M**, and **Chen J**. New insights into coupling and uncoupling of cerebral blood flow and metabolism in the brain *Croat Med J* 2016; 57(3):223-228. PMID: 27374823. Full Text

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The brain has high metabolic and energy needs and requires continuous cerebral blood flow (CBF), which is facilitated by a tight coupling between neuronal activity, CBF, and metabolism. Upon neuronal activation, there is an increase in energy demand, which is then met by a hemodynamic response that increases CBF. Such regional CBF increase in response to neuronal activation is observed using neuroimaging techniques such as functional magnetic resonance imaging and positron emission tomography. The mechanisms and mediators (eg, nitric oxide, astrocytes, and ion channels) that regulate CBF-metabolism coupling have been extensively studied. The neurovascular unit is a conceptual model encompassing the anatomical and metabolic interactions between the neurons, vascular components, and glial cells in the brain. It is compromised under disease states such as stroke, diabetes, hypertension, dementias, and with aging, all of which trigger a cascade of inflammatory responses that exacerbate brain damage. Hence, tight regulation and maintenance of neurovascular coupling is central for brain homeostasis. This review article also discusses the waste clearance pathways in the brain such as the glymphatic system. The glymphatic system is a functional waste clearance pathway that removes metabolic wastes and neurotoxins from the brain along paravascular channels. Disruption of the glymphatic system burdens the brain with accumulating waste and has been reported in aging as well as several neurological diseases.

Neurology

Venkat P, **Chopp M**, **Zacharek A**, **Ning R**, **Roberts C**, and **Chen J**. A multiple microinfarction based animal model for vascular dementia *J Cereb Blood Flow Metab* 2016; 36:217. PMID: Not assigned. Abstract

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Background and Purpose: Vascular Dementia (VaD) is a progressive disease caused by reduced blood flow to the brain and affects cognition and memory. VaD accounts for about 20% of all dementia patients and is prevalent among the older population. In this study, we investigated a multiple microinfarction (MMI) model using cholesterol crystals in male retired breeder rats as a potential VaD animal model and assessed the consequent progressive cognitive decline and white matter (WM) damage. Methods: Male young adult (young) rats, retired breeder (RB) rats, and aged (16-18m) rats were subjected to MMI model (500, 70-100 μm cholesterol crystals injected into the internal carotid artery, n=6/group). Neurological deficits and cognitive deficits were evaluated from 2 to 6 weeks after MMI. Additional sets of RB rats were prepared and sacrificed at the end of 2nd, 4th and 6th week after MMI to assess VaD progression and damage. Results: The MMI rat model induced cognitive decline that worsened with age starting at 2 weeks and persisting to 6 weeks after MMI. In RB rats, significant ($p<0.05$) loss of short term memory (novel object recognition test), over night memory (odor test), anxiety-like behavior (open field evaluation), and impaired spatial learning and memory (Morris water maze test) were observed starting at 2 weeks persisting up to 6 weeks after MMI. In young rats while cognitive loss was seen at 2 weeks, no significant damage in odor test or water maze were detected at 6 weeks. In aged rats, while the cognitive damage was more severe it was accompanied by higher mortality and tumor incidence (combined 40% in n=10/MMI group) making it unsuitable for establishing a reliable model. Neurological severity score indicated moderate functional deficits that declined over time with scores on a scale of 0-18 (minmax deficit) ranging from 2-4 in young, 4-6 in RB, 5-9 in aged rats. Hence, the RB MMI group was deemed most suitable for further analysis and establishing the VaD model. In RB rats, significant WM rarefaction and infarctions were observed in the corpus callosum (CC), striatum and cortex after MMI. While this WM damage was most severe at 3 weeks and decreased over time, it was still significant compared to control rats even at 6 weeks after MMI. MMI significantly decreased neurite branching and spine density in cortex and hippocampus measured by Golgi staining. Significant loss of Synaptophysin (synaptic protein) was observed in cortex and striatum and loss of myelin and axonal density was seen in CC and striatum. MMI also decreased oligodendrocyte progenitor cells and oligodendrocytes numbers in the CC and striatum. IBA1 (microglial marker) immunostaining showed MMI induced damaged processes and microglia in activated state in CC. Conclusion: The MMI model using cholesterol crystals in retired breeder rats is a suitable animal model for VaD. MMI induces significant WM damage mainly in the CC but also in striatum and cortex, loss of axonal density, demyelination, loss of synaptic plasticity, decreased neurite branching and spine density and activated microglia in CC. Further investigation of this model for VaD is warranted.

Neurology

Ye R, Shi M, Liu Q, and **Chen J**. Redox imbalance and stroke *Oxid Med Cell Longev* 2016; 2016:3065263. PMID: 27516831. Full Text

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Neurology

Zhang Y, **Chopp M**, **Zhang ZG**, **Katakowski M**, **Xin H**, **Qu C**, **Ali M**, **Mahmood A**, and **Xiong Y**. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury *Neurochem Int* 2016;PMID: 27539657. Article Request Form

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Multipotent human bone marrow derived mesenchymal stem cells (hMSCs) improve functional outcome after experimental traumatic brain injury (TBI). The present study was designed to investigate whether systemic

administration of cell-free exosomes generated from hMSCs cultured in 2-dimensional (2D) conventional conditions or in 3-dimensional (3D) collagen scaffolds promote functional recovery and neurovascular remodeling in rats after TBI. Wistar rats were subjected to TBI induced by controlled cortical impact; 24 h later tail vein injection of exosomes derived from hMSCs cultured under 2D or 3D conditions or an equal number of liposomes as a treatment control were performed. The modified Morris water maze, neurological severity score and footfault tests were employed to evaluate cognitive and sensorimotor functional recovery. Animals were sacrificed at 35 days after TBI. Histological and immunohistochemical analyses were performed for measurements of lesion volume, neurovascular remodeling (angiogenesis and neurogenesis), and neuroinflammation. Compared with liposome-treated control, exosome-treatments did not reduce lesion size but significantly improved spatial learning at 33-35 days measured by the Morris water maze test, and sensorimotor functional recovery, i.e., reduced neurological deficits and footfault frequency, observed at 14-35 days post injury ($p < 0.05$). Exosome treatments significantly increased the number of newborn endothelial cells in the lesion boundary zone and dentate gyrus, and significantly increased the number of newborn mature neurons in the dentate gyrus as well as reduced neuroinflammation. Exosomes derived from hMSCs cultured in 3D scaffolds provided better outcome in spatial learning than exosomes from hMSCs cultured in the 2D condition. In conclusion, hMSC-generated exosomes significantly improve functional recovery in rats after TBI, at least in part, by promoting endogenous angiogenesis and neurogenesis and reducing neuroinflammation. Thus, exosomes derived from hMSCs may be a novel cell-free therapy for TBI, and hMSC-scaffold generated exosomes may selectively enhance spatial learning.

Neurology

Zhang Z, and **Chopp M**. Neural stem cells and ischemic bra *J Stroke* 2016;PMID: 27488979. Full Text

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Stroke activates neural stem cells in the ventricular-subventricular zone (V/SVZ) of the lateral ventricle, which increases neuroblasts and oligodendrocyte progenitor cells (OPCs). Within the ischemic brain, neural stem cells, neuroblasts and OPCs appear to actively communicate with cerebral endothelial cells and other brain parenchymal cells to mediate ischemic brain repair; however, stroke-induced neurogenesis unlikely plays any significant roles in neuronal replacement. In this mini-review, we will discuss recent findings how intercellular communications between stroke-induced neurogenesis and oligodendrogenesis and brain parenchymal cells could potentially facilitate brain repair processes.

Neurosurgery

Broadbent B, Tseng J, Kast R, **Noh T**, Brusatori M, **Kalkanis SN**, and Auner GW. Shining light on neurosurgery diagnostics using Raman spectroscopy *J Neurooncol* 2016;PMID: 27522510. Full Text

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Surgical excision of brain tumors provides a means of cytoreduction and diagnosis while minimizing neurologic deficit and improving overall survival. Despite advances in functional and three-dimensional stereotactic navigation and intraoperative magnetic resonance imaging, delineating tissue in real time with physiological confirmation is challenging. Raman spectroscopy is a promising investigative and diagnostic tool for neurosurgery, which provides rapid, non-destructive molecular characterization in vivo or in vitro for biopsy, margin assessment, or laboratory uses. The Raman Effect occurs when light temporarily changes a bond's polarizability, causing change in the vibrational frequency, with a corresponding change in energy/wavelength of the scattered photon. The recorded inelastic scattering results in a "fingerprint" or Raman spectrum of the constituent under investigation. The amount, location, and intensity of peaks in the fingerprint vary based on the amount of vibrational bonds in a molecule and their ensemble interactions with each other. Distinct differences between various pathologic conditions are shown as different intensities of the same peak, or shifting of a peak based on the binding conformation. Raman spectroscopy has potential for integration into clinical practice, particularly in distinguishing normal and diseased tissue as an

adjunct to standard pathologic diagnosis. Further, development of fiber-optic Raman probes that fit through the instrument port of a standard endoscope now allows researchers and clinicians to utilize spectroscopic information for evaluation of in vivo tissue. This review highlights the need for such an instrument, summarizes neurosurgical Raman work performed to date, and discusses the future applications of neurosurgical Raman spectroscopy.

Neurosurgery
Cloughesy TF, Aghi MK, Chen C, Elder JB, Kesari S, **Kalkanis SN**, Kaptain G, Landolfi JC, **Mikkelsen T**, Portnow J, Robbins JM, Ostertag D, Das A, Chu A, and Vogelbaum MA. Encouraging survival with Toca 511 and Toca FC compared to external lomustine control *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

T.F. Cloughesy

Background: Recurrent glioblastoma (GBM) has an unmet need for effective therapies. Toca 511 (vocimagene amiretrorepvec), a retroviral replicating vector, encodes the transgene cytosine deaminase. Toca 511 selectively infects, persists and spreads in cancer cells. Subsequent oral administration of extended-release 5-fluorocytosine (Toca FC) produces 5-fluorouracil (5-FU) within infected cells. 5-FU kills cancer cells and myeloid derived suppressor cells, leading to robust antitumor immune responses in animal models. In 2 Phase 1 studies, Toca 511 was administered by surgical resection and injection into the cavity wall (NCT01470794) or intratumoral injection by biopsy needle (NCT01156584). To provide context to the results observed, patients were compared to an external lomustine treated control (Courtesy Denovo Biopharma; Wick 2010). Methods: Demographics, overall survival (OS) and safety profile of Toca 511/Toca FC treated subjects with GBM in 1 s t or 2 n d recurrence were compared to the lomustine control. Results: Toca 511/Toca FC treated patients were comparable to the lomustine control. Imbalances in KPS in favor of Toca 511/Toca FC treated patients were offset by younger age, higher number of subjects at 1strecurrence and lower steroid requirement in the lomustine control. Treatment with Toca 511/Toca FC, which was pooled from 2 Phase I studies, showed significant improvement in OS HR = 0.48, $p < 0.001$ with similar effect in the setting of surgical resection (OS HR 0.45, $p = 0.003$) and nonsurgical resection with a biopsy needle (OS HR 0.56, $p = 0.060$). Fewer related Grade ≥ 3 adverse events (AEs) were reported for Toca 511/Toca FC (2.5%) vs. lomustine (36.9%). There was a virtual absence of hematologic toxicity for Toca 511/Toca FC vs. lomustine (Grade ≥ 3 thrombocytopenia 23.8%). Discontinuations for AEs occurred in 0% for Toca 511/Toca FC vs. 4.8% for lomustine. Toca 511 is surgically delivered and treatment-emergent AEs regardless of attribution included incision site pain (20%), procedural pain (12.5%), and wound infection (5%) vs. 0%, 1.2%, 1.2% respectively for lomustine. Conclusions: Toca 511/Toca FC significantly improved survival and safety relative to lomustine. A Phase 2/3 trial has launched.

Neurosurgery
Jiang W, **Finniss S**, **Cazacu S**, **Xiang C**, **Brodie Z**, **Mikkelsen T**, **Poisson L**, Shackelford DB, and **Brodie C**. Repurposing phenformin for the targeting of glioma stem cells and the treatment of glioblastoma *Oncotarget* 2016;PMID: 27486821. Full Text

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Glioblastoma (GBM) is the most aggressive primary brain tumor with poor prognosis. Here, we studied the effects of phenformin, a mitochondrial complex I inhibitor and more potent chemical analog of the diabetes drug metformin on the inhibition of cell growth and induction of apoptosis of glioma stem cells (GSCs) using both in vitro and in vivo models. Phenformin inhibited the self-renewal of GSCs, decreased the expression of stemness and mesenchymal markers and increased the expression of miR-124, 137 and let-7. Silencing of let-7 abrogated phenformin effects on the self-renewal of GSCs via a pathway associated with inhibition of H19 and HMGA2 expression. Moreover, we demonstrate that phenformin inhibited tumor growth and prolonged the overall survival of mice orthotopically transplanted with GSCs. Combined treatments of phenformin and temozolomide exerted an increased antitumor effect on GSCs in vitro and in vivo. In addition, dichloroacetate, an inhibitor of the glycolysis enzyme pyruvate dehydrogenase kinase, that decreases lactic acidosis induced by biguanides, enhanced phenformin effects on the induction of cell death in GSCs and prolonged the survival of xenograft-bearing mice. Our results demonstrate for the first time that phenformin targets GSCs and can be efficiently combined with current therapies for GBM treatment and GSC eradication.

Neurosurgery

Mattour AH, **Walbert T**, **Lee I**, and **Wang D**. A revisit of the devastating outcome of leptomeningeal disease *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A.H. Mattour

Background: Leptomeningeal metastasis (LM) represents a devastating complication of malignancies by forming tumor deposits on the leptomeninges at about 5% to 8% of cancer patients (Pts). Standard therapies include radiotherapy (RT) to focal involved areas, systemic and/or intrathecal (IT) chemotherapies which have been recommended for palliation but with unclear benefit toward survival. This study is to review the pattern of the clinical practice and outcomes on Pts with LM who have received care at Henry Ford Hospital between 2004 and 2014 Methods: A retrospective study targeted all Pts of LM (icd-9 code 198.4) between 01/01/2004 and 01/01/2014. Pts with primary brain, orbital and spinal lesions as well as Pts with cord compressions were excluded from this study. LM Pts were included based on MRI images, cerebral spinal fluid (CSF) cytology and/or dural biopsy. Data from onset of primary tumor, therapeutic interventions, methods of LM diagnosis, duration (days) from initial cancer onset to LM diagnosis, then from LM diagnosis to death were collected and analyzed as shown Results: 328 Pts with LM (icd-9: 198.4) were identified, but 58 Pts fulfilled inclusions. Of 58 Pts, 22 (38%) had breast cancer (38%), 12 (21%) NSCLC. LM was diagnosed in 34 Pts (59%) based on MRI findings, 4 (6%) by CSF cytology and 19 (33%) by both. Majority (37 Pts, 64%) received therapy after LM diagnosis: 16 (27%) received IT chemotherapy, 15 (26%) received RT while 6 (10%) received both. Twenty-one of LM Pts (36%) received no treatment under various circumstances. Of 58 Pts, the median time from cancer onset to LM diagnosis was 686 days while median overall survival (OS) was 1038 days, and median OS from LM to death was 95 days. Survival difference was observed for Pts (37, 64%) received LM-directed treatment as 113 days but only 61 days for those received no therapies Conclusions: LM is a prognostic complication in malignancies. It poses a grave challenge due to limited therapeutics that only carry modest survival benefit. Data from these 58 Pts shown a benchmarks of survival from LM diagnosis was 4 months with treatment, and 2 months without. These are consistent with published data over last decades without improvement. Therefore, more clinical researches in LM diagnosis and therapies are needed.

Neurosurgery

Munster PN, Mahlpal A, Nemunaitis JJ, Mlta MM, Paz-Ares LG, Massard C, **Mikkelsen T**, Cruz C, Rathkopf DE, Blumenschein GR, Hidalgo M, Smith DC, Eichhorst B, Cloughesy TF, Garrick B, Trowe T, Filvaroff E, Hege K, and Bendell JC. Phase I trial of a dual TOR kinase and DNA-PK inhibitor (CC- 115) in advanced solid and hematologic cancers *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

P.N. Munster

Background: CC-115 is a potent inhibitor of DNA-PK and TOR kinase (DNA-PKi/TORKi) with broad pre-clinical anti-tumor activity. Methods: Subjects with relapsed/refractory advanced solid and hematologic cancers enrolled in a first-in-human Phase 1a/b study of CC-115 given orally once or twice daily until disease progression in dose escalation and expansion cohorts. Results: 44 subjects evaluated across 10 dose escalation cohorts (0.5 - 40 mg) established 10 mg twice-daily (BID) as the recommended dose for cohort expansion in 62 additional subjects with glioblastoma multiforme (GBM: 14), head and neck squamous carcinoma (HNSCC: 18), chronic lymphocytic leukemia (CLL: 8), and ETSoverexpressing tumors (castration-resistant prostate cancer [CRPC: 12] and Ewing's sarcoma [ES: 10]). The most common (> 20%) expansion phase related adverse events were fatigue (37%), nausea (31%), decreased appetite (29%), and hyperglycemia (24%). Linear, dose proportional exposure was observed with a terminal half life of 4 to 8 hrs (mean steady state Cmax 75 ng/mL, AUC0-24 776 ngxhr/mL at 10mg BID). Gastric pHaltering drugs and food did not impact PK. Plasma accumulation was minimal, renal clearance was negligible and brain penetration was confirmed in resected GBM (tumor/plasma ratio 0.7). Inhibition of TORC1 (pS6, p4EBP1) and TORC2 (pAKT) biomarkers in blood cells was exposure-dependent and consistently achieved with 10 mg BID dosing. DNA-PK inhibition was demonstrated ex vivo in circulating CLL cells from one subject dosed with CC-115. Tumor responses during dose escalation included 1 complete response (endometrial; >3yr), 1 partial response (melanoma), and stable disease (SD) in 18 (41%) subjects. In the efficacy-evaluable expansion cohorts, SD was observed in CRPC (64%), HNSCC (53%), GBM (non-progression 21%), and ES (22%). One PR, and 3 PR with lymphocytosis (IWCLL), were seen in CLL. Conclusions: CC-115 was well tolerated with toxicities comparable with approved mTOR inhibitors. Evidence of TORC1/TORC2/DNA-PK pathway inhibition was observed as well as preliminary signals of broad anti-tumor activity. Phase 2 trials combining CC-115 with androgen deprivation in CRPC and radiation in GBM are planned.

Neurosurgery

Zhang Y, **Chopp M**, **Zhang ZG**, **Katakowski M**, **Xin H**, **Qu C**, **Ali M**, **Mahmood A**, and **Xiong Y**. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury *Neurochem Int* 2016;PMID: 27539657. Article Request Form

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Multipotent human bone marrow derived mesenchymal stem cells (hMSCs) improve functional outcome after experimental traumatic brain injury (TBI). The present study was designed to investigate whether systemic administration of cell-free exosomes generated from hMSCs cultured in 2-dimensional (2D) conventional conditions or in 3-dimensional (3D) collagen scaffolds promote functional recovery and neurovascular remodeling in rats after TBI. Wistar rats were subjected to TBI induced by controlled cortical impact; 24 h later tail vein injection of exosomes derived from hMSCs cultured under 2D or 3D conditions or an equal number of liposomes as a treatment control were performed. The modified Morris water maze, neurological severity score and footfault tests were employed to evaluate cognitive and sensorimotor functional recovery. Animals were sacrificed at 35 days after TBI. Histological and immunohistochemical analyses were performed for measurements of lesion volume, neurovascular remodeling (angiogenesis and neurogenesis), and neuroinflammation. Compared with liposome-treated control, exosome-treatments did not reduce lesion size but significantly improved spatial learning at 33-35 days measured by the Morris water maze test, and sensorimotor functional recovery, i.e., reduced neurological deficits and footfault frequency, observed at 14-35 days post injury ($p < 0.05$). Exosome treatments significantly increased the number of newborn endothelial cells in the lesion boundary zone and dentate gyrus, and significantly increased the number of newborn mature neurons in the dentate gyrus as well as reduced neuroinflammation. Exosomes derived from hMSCs cultured in 3D scaffolds provided better outcome in spatial learning than exosomes from hMSCs cultured in the 2D condition. In conclusion, hMSC-generated exosomes significantly improve functional recovery in rats after TBI, at least in part, by promoting endogenous angiogenesis and neurogenesis and reducing neuroinflammation. Thus, exosomes derived from hMSCs may be a novel cell-free therapy for TBI, and hMSC-scaffold generated exosomes may selectively enhance spatial learning.

Obstetrics, Gynecology and Women's Health Services

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Obstetrics, Gynecology and Women's Health Services

Ghanem AI, **Khan N**, **Mahan M**, **Buekers T**, and **Elshaikh MA**. Survival endpoints with or without lymphadenectomy in women with stage I endometrial carcinoma: A matched-pair analysis *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A.I. Ghanem

Background: The role of regional lymphadenectomy (LA) in women with stage I endometrial carcinoma (EC) is controversial. The objective of the study is to determine the prognostic impact of LA on survival endpoints of women with stage I EC solely of endometrioid histology using match-pair analysis. Survival endpoints included recurrencefree (RFS), disease-specific (DSS) and overall survival (OS). Methods: We identified 1257 patients with stage I EC who underwent hysterectomy between 1/1990 and 6/2015. Of those, 822 women underwent LA as part of their surgical staging while 435 did not (NLA). 435 women with NLA were matched to 435 women who had LA (1:1 match) based on 2009 FIGO stage, tumor grade and adjuvant management received (observation, vaginal brachytherapy or pelvic external beam radiation treatment). Univariate and multivariate modeling with Cox regression analysis was carried out for predictors of survival endpoints. Results: Median follow-up time for the study cohort was 48 months. The two groups were well balanced except for more peritoneal cytology performed and more lower uterine segment (LUS) involvement for LA group (p= 0.001 for both). 5-year survival endpoints between the two groups were similar. 5-year RFS for women in the LA group was 93.7% vs. 90% for NLA group (p= 0.081). Similarly, 5-year DSS was 97.7% vs. 98% (p= 0.536) and 5-year OS was 87.2% vs. 91.7% (p= 0.357). On multivariate analysis for the entire study cohort, older age, deep myometrial invasion and higher tumor grade were predictors of worse RFS (p= 0.031, p= 0.004 and p< 0.001), respectively. For DSS, higher tumor grade (p< 0.001), LUS involvement (p= 0.028) and FIGO stage IB (p= 0.022) were significant predictors of worse outcome. For OS, older age and LUS involvement were the only two independent predictors for shorter OS (p< 0.001). Conclusions: With this large study cohort, our study suggests that survival endpoints are not different between women with stage I endometrial carcinoma who underwent lymphadenectomy compared to those who did not. It appear that omitting lymphadenectomy for women with stage I disease is not associated with any worse survival outcome after matching for stage, grade and adjuvant management.

Obstetrics, Gynecology and Women's Health Services

Schiff L, **Tsafrir Z**, **Aoun J**, **Taylor A**, **Theoharis E**, and **Eisenstein D**. Quality of communication in robotic surgery and surgical outcomes *Jsls* 2016; 20(3)PMID: 27493469. Full Text

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Division of Minimally Invasive Gynecology, Women's Health Services, Henry Ford Hospital, West Bloomfield, Michigan, USA.
Division of Biostatistics, Public Health Sciences, Henry Ford Health System, Detroit, Michigan, USA.

BACKGROUND AND OBJECTIVES: Robotic surgery has introduced unique challenges to surgical workflow. The association between quality of communication in robotic-assisted laparoscopic surgery and surgical outcomes was evaluated. METHODS: After each gynecologic robotic surgery, the team members involved in the surgery completed a survey regarding the quality of communication. A composite quality-of-communication score was developed using principal component analysis. A higher composite quality-of-communication score signified poor communication. Objective parameters, such as operative time and estimated blood loss (EBL), were gathered from the patient's medical record and correlated with the composite quality-of-communication scores. RESULTS: Forty robotic cases from March through May 2013 were included. Thirty-two participants including surgeons, circulating nurses, and surgical technicians participated in the study. A higher composite quality-of-communication score was associated with greater EBL (P = .010) and longer operative time (P = .045), after adjustment for body mass index, prior major abdominal surgery, and uterine weight. Specifically, for every 1-SD increase in the perceived lack of communication, there was an additional 51 mL EBL and a 31-min increase in operative time. The most common reasons reported for poor communication in the operating room were noise level (28/36, 78%) and console-to-bedside communication problems (23/36, 64%). CONCLUSION: Our study demonstrates a significant association between poor intraoperative team communication and worse surgical outcomes in robotic gynecologic surgery. Employing strategies to decrease extraneous room noise, improve console-to-bedside communication and team training may have a positive impact on communication and related surgical outcomes.

Obstetrics, Gynecology and Women's Health Services

Tsafrir Z, **Aoun J**, **Hanna R**, Papalekas E, Schiff L, **Theoharis E**, and **Eisenstein D**. Robotic trachelectomy after supracervical hysterectomy for benign gynecologic disease *Jsls* 2016; 20(3)PMID: 27493470. Full Text

Division of Minimally Invasive Gynecology, Department of Obstetrics and Gynecology, Henry Ford Health System, Detroit, Michigan, USA.
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BACKGROUND AND OBJECTIVES: A renewed interest in the supra cervical approach to hysterectomy has created a cohort of patients with a retained cervix at risk of persistent symptoms requiring a subsequent trachelectomy. The objective of this study was to evaluate the efficacy of robotic trachelectomy after a previous supracervical hysterectomy. METHODS: This is a retrospective chart review of women who had robotic trachelectomy after supracervical hysterectomy for benign gynecologic disease from January 2009 through October 2014. RESULTS: Eleven patients underwent robotic trachelectomy for benign conditions during the observed period. Prior supracervical hysterectomy had been performed for pelvic pain (8/11, 73%), abnormal uterine bleeding (7/11, 64%), and dysmenorrhea (5/11, 45%). In 10 of 11 patients, the symptoms leading to robotic trachelectomy were the same as those leading to supracervical hysterectomy. The time from hysterectomy to recurrence of symptoms ranged from 0.5 to 26 months (median, 6), whereas the time interval from previous surgery to robotic trachelectomy ranged from 1 to 57 months (median, 26). Mean age and body mass index at robotic trachelectomy were 42 +/- 5.4 years and 32 +/- 6.1 kg/m(2). Mean length of surgery was 218 +/- 88 minutes (range, 100-405). There was 1 major postoperative complication involving bladder perforation and subsequent vesicovaginal fistula (VVF). Endometriosis was seen in 27% of pathologic specimens and cervicitis in another 27%; 45% showed normal tissue histology. In 6 (55%) cases, symptoms leading to trachelectomy resolved completely after surgery, and the other 5 (45%) patients reported a significant improvement. CONCLUSIONS: Although trachelectomy can be a challenging surgery, our experience suggests that the robotic approach may be a valuable means of achieving safe and reproducible outcomes.

Obstetrics, Gynecology and Women's Health Services
Winer IS, Patel D, Dalton V, Johnston C, Quint E, Zochowski M, **Munkarah AR**, Morris R, and Haefner H. The practice patterns and outlook of gynecology oncologists in the treatment of pediatric, adolescent and young adults with gynecologic malignancies: A survey study *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

I.S. Winer

Background: While rare, therapy for pediatric gynecologic malignancy impacts development, fertility and self-image. Limited data examining the divide between pediatric and adult providers exists. Methods: 33-question survey was disseminated to practicing gynecologic oncologists (GYO) and fellows within the United States. Responses were analyzed in aggregate for descriptive statistics. Results: Total response was 14.2%. 70% were 30-50 years-old and equally distributed among male and female providers. 80% were Caucasian. 74% were faculty, with 50% in practice > 6 years. 60% desire to care for these children with 14% against. Academicians were more likely to desire this($p < 0.004$). 43% felt they should be involved in care beginning at 6 years-old; > 65% were comfortable ≥ 11 years-old. Only 3.9% received formal fellowship training, while 50% felt this should be incorporated. Concerns regarding treatment in this population include comfort/knowledge of:surgery, chemotherapy/hormones, medication dosing, rare tumors, barriers allowing GYO involvement. 90% feel multidisciplinary teams (MDTs) should care for these patients, yet only 24% were confident their institution uses MDTs. In institutions that use MDTs, GYO providers are included. > 65% reported institutional GYO consultation is readily available. Finally, only 22% of institutions have clinics dedicated to the longitudinal care of pediatric/adolescent patients. Conclusions: Our survey demonstrates GYOs wish to be involved in pediatric care. Concerns regarding specialized treatment exist and few receive formal training. MDTs provide the ideal setting, but many institutions do not use these. Our results suggest an open dialogue between GYO and pediatric specialists is required to provide optimal, longitudinal care. Furthermore, formal training should be incorporated into fellowships.

Opthalmology and Eye Care Services
Baciu P, Nofar CM, **Spaulding J**, and **Gao H**. Branch retinal artery occlusion associated with paracentral acute middle maculopathy in a patient with livedo reticularis *Retin Cases Brief Rep* 2016;PMID: 27490977. Full Text

*Department of Ophthalmology, Henry Ford Hospital, Detroit, Michigan; and daggerSchool of Medicine, Wayne State University, Detroit, Michigan.

PURPOSE: To report the occurrence of a branch retinal artery occlusion with paracentral acute middle maculopathy in an otherwise healthy young man with a history of livedo reticularis (LR). METHODS: Retrospective case report. PATIENTS: A 21-year-old man with a history of LR being treated with pentoxifylline developed an acute branch retinal artery occlusion with initial best-corrected visual acuity at presentation of 20/80. RESULTS: A thorough

diagnostic work up was negative for potential causes of branch retinal artery occlusion or LR. The patient was continued on pentoxifylline and started on aspirin 81 mg daily. At five-month follow-up, vision had improved to 20/25. Optical coherence tomography testing showed a hyperreflective band in the inner nuclear layer and outer plexiform layers in the affected eye that ultimately thinned, consistent with paracentral acute middle maculopathy. CONCLUSION: To our knowledge, this is the first case of branch retinal artery occlusion occurring in a patient with a history of LR. This could potentially be an early manifestation of Sneddon syndrome, a rare entity characterized by LR and cerebrovascular disease, which has been previously associated with central retinal artery occlusions.

Opthalmology and Eye Care Services

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Opthalmology and Eye Care Services

Farley ND, **Sassalos TM**, and Ober MD. Basal cell nevus syndrome presenting as epiretinal membrane and myelinated nerve fiber layer *Retin Cases Brief Rep* 2016;PMID: 27533646. Full Text

*Department of Ophthalmology, Henry Ford Hospital, Detroit, Michigan; and daggerRetina Consultants of Michigan, Southfield, Michigan.

PURPOSE: To report a case of epiretinal membrane and myelinated nerve fiber layer, which preceded the diagnosis of basal cell nevus syndrome, in a young girl. METHODS: Observational case report. RESULTS: A 12-year-old girl was referred for an asymptomatic epiretinal membrane. Examination revealed epiretinal membrane in the right eye without posterior vitreous separation or vitreous abnormality and bilateral myelinated nerve fiber layer. Subsequent workup yielded pathologic diagnosis of multiple skin basal cell carcinoma and odontogenic keratocysts in the jaw. Genetic testing revealed a frameshift mutation in the PTCH1 gene. CONCLUSION: Basal cell nevus syndrome is a rare autosomal dominant disease that affects multiple organ systems, including the eyes. Recognition of common ocular findings in children with basal cell nevus syndrome can lead to systemic diagnosis. Early diagnosis is critical to initiate early screening for known neoplastic associations and lifelong minimization of sun exposure to reduce the incidence and severity of basal cell carcinoma.

Opthalmology and Eye Care Services

Vemuri S, **Christianson MD**, and Demirci H. Correcting myogenic ptosis accompanying extraocular muscle weakness: The "Bobby Pin" procedure *Orbit* 2016; 35(5):267-270. PMID: 27541941. Article Request Form

a Department of Ophthalmology , Henry Ford Hospital , Detroit , Michigan , USA.
b Department of Ophthalmology and Visual Sciences, W. K. Kellogg Eye Center , University of Michigan , Ann Arbor , Michigan , USA.

This article evaluates the "Bobby Pin" procedure in the correction of myogenic ptosis accompanying extraocular muscle weakness. We retrospectively reviewed 26 eyelids of 13 patients who underwent "Bobby Pin" procedure for

myogenic ptosis accompanying extraocular muscle weakness. We evaluated the patients' clinical features such as age, etiology of ptosis, symptoms, standard ptosis measurements, associated systemic diseases, additional ophthalmic conditions, complications, and recurrence. Etiology of myogenic ptosis and extraocular muscle weakness was oculopharyngeal dystrophy in 4 (31%) patients, chronic progressive external ophthalmoplegia in 4 (31%) patients, myotonic dystrophy in 2 (23%) patients, and idiopathic in 3 (15%) patients. The mean levator function was approximately 5 mm pre- and post-operatively (range 1 to 12 mm). The mean margin-to-reflex distance 1 increased from -1.1 mm (below the light reflex) pre-operatively to +0.4 mm (above the light reflex) post-operatively. After a mean follow-up of 40 months, only 1 (8%) patient experienced ptosis recurrence. Upper eyelids were symmetric in both contour and height in all patients. Mild superficial keratopathy involving less than 10% of cornea was observed in 4 (31%) patients. The "Bobby Pin" procedure is an effective and long-lasting treatment option for correcting acquired ptosis accompanying extraocular muscle weakness. The procedure is safe, simple, easily learned, time- and cost-effective, and does not require any expensive equipment.

Opthalmology and Eye Care Services

Wang SY, Ghodasra DH, **Amin SR**, Mian SI, and Jayasundera KT. Fungal endophthalmitis associated with DSAEK and thermal sclerostomy *Ophthalmic Surg Lasers Imaging Retina* 2016; 47(7):691-693. PMID: 27434905. Article Request Form

An 85-year-old man with remote thermal sclerostomy and Descemet's stripping automated endothelial keratoplasty (DSAEK) in the right eye presented urgently for pain and blurred vision in that eye. Examination revealed bleb purulence and vitreous cellular aggregates concerning for endophthalmitis. Microscopy of a vitreous sample revealed yeast and pseudohyphae. He developed corneal infiltrates consistent with fungal infection. Therapy included topical, intravitreal, and systemic antifungals voriconazole and amphotericin. Fungal pathogens have very rarely been reported to cause bleb-associated endophthalmitis and should be considered in addition to bacterial pathogens. Vitreous aspiration should be performed in all cases of bleb-related endophthalmitis and include fungal studies. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:691-693.].

Otolaryngology – Head and Neck Surgery

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Pathology

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

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Pathology

Calio A, Eble JN, Hes O, Martignoni G, Harari SE, **Williamson SR**, Brunelli M, Osunkoya AO, Wang L, Comperat E, Lopez-Beltran A, Wang M, Zhang S, Curless KL, Post KM, Chang HY, Luchini C, Baldrige LA, MacLennan GT, Montironi R, Grignon DJ, and Cheng L. Distinct clinicopathological features in metanephric adenoma harboring BRAF mutation *Oncotarget* 2016;PMID: 27517493. Full Text

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BRAF mutation recently has been reported in metanephric adenoma. We sought to determine the clinical and morphologic features of BRAF-mutated metanephric adenoma and to correlate BRAF mutation with BRAF V600E immunohistochemical staining results. A series of 48 metanephric adenomas and 15 epithelial-predominant nephroblastomas were analyzed for the occurrence of BRAF mutation (BRAF V600E/V600E complex, BRAF V600D, BRAF V600K and BRAF V600R) using the BRAF RGQ PCR kit (Qiagen). Immunohistochemistry was performed using monoclonal mouse antibodies against p16INK4 and VE1 (Spring Bioscience), recognizing the BRAF V600E mutant protein. Forty-one of 48 cases (85%) showed BRAF V600E mutation; none of the other BRAF variants was detected. Of 41 BRAF-mutated metanephric adenomas, 33 showed positive VE1 immunostaining (sensitivity 80%, specificity 100%); in all cases we detected p16INK4 expression regardless of BRAF mutation status. All epithelial-predominant nephroblastomas were BRAF-wild-type and none expressed VE1. The following features were associated with BRAF V600E mutation: older patients (p=0.01), female predominance (p=0.005) and the presence of a predominantly acinar architecture (p=0.003). In summary, BRAF-mutated metanephric adenomas were associated with older age, female predominance, and the presence of a predominant acinar component. A subset (20%) of BRAF-mutated metanephric adenomas was not detected by VE1 immunostaining.

Pathology

Fisher KW, Zhang S, Wang M, Montironi R, Wang L, Baldrige LA, Wang JY, MacLennan GT, **Williamson SR**, Lopez-Beltran A, and Cheng L. TMPRSS2-ERG gene fusion is rare compared to PTEN deletions in stage T1a prostate cancer *Mol Carcinog* 2016;PMID: 27500376. Full Text

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T1a prostate cancers (cancer found incidentally in transurethral resection, <5% of the tissue) are indolent tumors of the transition zone. The overexpression of ERG and the inactivation of PTEN have been shown to be important drivers of carcinogenesis in large series of prostate cancer, but the genetics of transition zone tumors have not been well characterized. We evaluated the status of ERG and PTEN in formalin-fixed paraffin-embedded tissue using immunohistochemical and FISH analysis in 54 T1a transition zone tumors. The protein expression of ERG was determined using a rabbit monoclonal antibody and nuclear staining was scored as positive or negative. The genomic status of ERG was determined using 3 colored FISH using an ERG-TMPRSS2 tri-color probe set. The protein expression of PTEN was determined using a rabbit monoclonal antibody and cytoplasmic and nuclear staining was scored as positive or negative. The genomic status of PTEN was determined using dual color FISH with a PTEN probe and a CEP10 probe. We found ERG rearrangement in 2 of 54 tumors (4%), one with protein overexpression by immunohistochemistry. PTEN inactivation was seen in 13 of 54 tumors (24%). Nine of the 13 PTEN alleles were inactivated by hemizygous deletion. No homozygous PTEN deletion was observed. PTEN deletion and ERG rearrangement were mutually exclusive. ERG rearrangement was rare compared to peripheral zone tumors and to PTEN inactivation in T1a transition zone tumors.

Pathology

Joseph L, **Cankovic M**, Caughron S, Chandra P, Emmadi R, Hagenkord J, Hallam S, Jewell KE, Klein RD, Pratt VM, Rothberg PG, Temple-Smolkin RL, and Lyon E. The spectrum of clinical utilities in molecular pathology testing procedures for inherited conditions and cancer: A report of the association for molecular pathology *J Mol Diagn* 2016; 18(5):605-619. PMID: 27542512. Full Text

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Association for Molecular Pathology's Framework for the Evidence Needed to Demonstrate Clinical Utility Task Force, Bethesda, Maryland; Good Start Genetics, Inc., Cambridge, Massachusetts.
Association for Molecular Pathology's Framework for the Evidence Needed to Demonstrate Clinical Utility Task Force, Bethesda, Maryland; Tara Center, LLC, Stevens Point, Wisconsin.
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Clinical utility describes the benefits of each laboratory test for that patient. Many stakeholders have adopted narrow definitions for the clinical utility of molecular testing as applied to targeted pharmacotherapy in oncology, regardless of the population tested or the purpose of the testing. This definition does not address all of the important applications of molecular diagnostic testing. Definitions consistent with a patient-centered approach emphasize and recognize that a clinical test result's utility depends on the context in which it is used and are particularly relevant to molecular diagnostic testing because of the nature of the information they provide. Debates surrounding levels and types of evidence needed to properly evaluate the clinical value of molecular diagnostics are increasingly important because the growing body of knowledge, stemming from the increase of genomic medicine, provides many new opportunities for molecular testing to improve health care. We address the challenges in defining the clinical utility of molecular diagnostics for inherited diseases or cancer and provide assessment recommendations. Starting with a modified analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications model for addressing clinical utility of molecular diagnostics with a variety of testing purposes, we recommend promotion of patient-centered definitions of clinical utility that appropriately recognize the valuable contribution of molecular diagnostic testing to improve patient care.

Pathology

Krasnick BA, **Nathanson SD**, Arbabi CN, **Chitale DA**, and **Peterson EL**. The predictive value of increased sentinel lymph node volume in breast cancer *Surg Oncol* 2016; 25(3):321-325. PMID: 27566039. Full Text

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BACKGROUND: Breast cancer sentinel lymph nodes (SLNs) with metastases (mets) are often palpably enlarged. We hypothesized that the volume of the SLN and the size of mets are directly related. SLNs harboring mets are often firm, with increased intra-nodal pressure (INP), and we hypothesized that SLN volume, as well as INP, would correlate directly with SLN metastasis size. METHODS: The SLN volume, INP and met size were measured in 296 SLNs and compared using linear regression analysis. The SLNs were subsequently grouped based upon pN stage. SLN INP and volume were compared between these resultant groups. RESULTS: Increased SLN volume significantly predicted increased SLN met size on univariate and multivariate analysis ($p = 0.001$ and $p = 0.011$, respectively). SLN met size predicted increased SLN INP on both univariate and multivariate analysis (both $p = 0.001$). SLN volume only significantly correlated with increased SLN INP on univariate analysis ($p = 0.001$). On subgroup analysis of nodal disease, pN1/2/3 nodes (SLN met sizes >2 mm) were significantly larger ($p = 0.039$ and $p = 0.003$, respectively) than pN0 and pN1(mi) nodes, and had significantly increased INP (all $p = 0.001$) as compared to pN0, pN0(i+), and pN1(mi) nodes. CONCLUSIONS: SLN volume and INP increased with increasing SLN met size. The threshold met size for this increase was >2 mm (pN1 disease).

Pediatrics

Connolly MD, **Zervos MJ**, **Barone CJ, 2nd**, **Johnson CC**, and **Joseph CL**. The mental health of transgender youth: Advances in understanding *J Adolesc Health* 2016;PMID: 27544457. Full Text

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This review provides an update on the growing body of research related to the mental health of transgender youth that has emerged since the 2011 publication of the Institute of Medicine report on the health of lesbian, gay, bisexual, and transgender people. The databases PubMed and Ovid Medline were searched for studies that were published from January 2011 to March 2016 in English. The following search terms were used: transgender, gender nonconforming, gender minority, gender queer, and gender dysphoria. Age limits included the terms youth, child, children, teenager*, and adolescen*. The combined search produced 654 articles of potential relevance. The resulting abstracts went through a tiered elimination system, and the remaining 15 articles, which presented quantitative data related to the prevalence of transgender youth and their mental health, were included in the present review. In addition to providing new estimates of the number of young people who identify as transgender (.17%-1.3%), studies since 2011 have shown that transgender youth have higher rates of depression, suicidality and self-harm, and eating

disorders when compared with their peers. Gender-affirming medical therapy and supported social transition in childhood have been shown to correlate with improved psychological functioning for gender-variant children and adolescents. Recent research has demonstrated increased rates of psychiatric morbidity among transgender youth compared to their peers. Future work is needed to understand those youth who identify as gender nonbinary, improve methods to capture and understand diverse gender identities and related health disparities, and delineate the social determinants of such disparities.

Pharmacy

Athans V, Kenney RM, **Wong J**, and **Davis SL**. Outpatient use of ceftaroline fosamil versus vancomycin for osteoarticular infection: a matched cohort study *J Antimicrob Chemother* 2016;PMID: 27530754. Full Text

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OBJECTIVES: There are few convenient intravenous options for long-term outpatient treatment of osteoarticular infection (OAI) and limited effectiveness and safety data exist for this off-label use of ceftaroline. The objective of this study was to describe the long-term effectiveness and safety of ceftaroline for the treatment of OAI. METHODS: This was a matched retrospective cohort study of patients receiving ceftaroline- or vancomycin-based therapy for OAI in the outpatient setting. Patients were matched according to infection subtype, anatomical site and microbiology. The primary endpoint was 180 day infection-related readmission (IRR). Secondary endpoints included all-cause readmission, time-to-IRR and adverse event incidence. RESULTS: The final matched cohort consisted of 50 ceftaroline-treated patients and 50 vancomycin-treated patients. The IRR incidence was 22% for ceftaroline patients and 30% for vancomycin patients; OR = 0.66 (95% CI = 0.27-1.62; P = 0.362). There was no significant difference between groups in all-cause readmission or time-to-IRR. Attributable adverse event incidences were 24% and 18% for ceftaroline and vancomycin, respectively. Rash (10%) and nausea (6%) were the most common ceftaroline adverse events, while acute kidney injury (6%) and rash (4%) were the most common vancomycin adverse events. CONCLUSIONS: Attributable readmission and adverse events were common among patients treated with outpatient intravenous antimicrobials for OAI. This study found no appreciable difference in effectiveness or tolerability between ceftaroline- or vancomycin-treated patients. Although further research will be important to delineate the role of ceftaroline in the management of OAI, data derived from this study may aid clinicians in determining therapy when limited options exist.

Psychiatry

Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Public Health Sciences

Cajigal S, **Wells KE**, **Peterson EL**, **Ahmedani BK**, Yang JJ, Kumar R, Burchard EG, and **Williams LK**. Predictive properties of the asthma control test and its component questions for severe asthma exacerbations *J Allergy Clin Immunol Pract* 2016;PMID: 27544712. Full Text

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BACKGROUND: Current US guidelines recommend the Asthma Control Test (ACT) for assessing disease control and selecting treatment. OBJECTIVE: The goal of this study was to prospectively assess the ACT and its component questions for their utility in predicting the risk of severe asthma exacerbations. METHODS: Individuals were participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity, and those included in the current analysis had the following characteristics: age 18 years or more, physician-diagnosed asthma, and longitudinal care received at a large health system in southeastern Michigan. Study participants underwent a baseline evaluation, which included answering the ACT. A severe asthma exacerbation was defined as one requiring oral steroids, an emergency department visit, or inpatient admission. Receiver-operator characteristic curves were used to measure and compare the predictive utility of the ACT and its component questions for severe asthma exacerbations. RESULTS: Of 1180 participants, 354 (30.0%) experienced a severe asthma exacerbation within 6 months of their baseline evaluation. When compared with the individual questions that composed the ACT, the composite score was significantly better at predicting severe exacerbations with 1 exception; the composite ACT score and the question assessing rescue medication use were not significantly different (P = .580). Pharmacy-based records of metered-dose inhaler short-acting beta-agonist use and asthma severity were also not significantly different from the composite ACT score. CONCLUSIONS: Our study demonstrates that although the ACT is modestly predictive for exacerbations, the composite score may not be superior to assessing rescue medication use alone for predicting the risk of severe asthma exacerbations.

Public Health Sciences

Connolly MD, **Zervos MJ**, **Barone CJ, 2nd**, **Johnson CC**, and **Joseph CL**. The mental health of transgender youth: Advances in understanding *J Adolesc Health* 2016;PMID: 27544457. Full Text

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Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan.

This review provides an update on the growing body of research related to the mental health of transgender youth that has emerged since the 2011 publication of the Institute of Medicine report on the health of lesbian, gay, bisexual, and transgender people. The databases PubMed and Ovid Medline were searched for studies that were published from January 2011 to March 2016 in English. The following search terms were used: transgender, gender nonconforming, gender minority, gender queer, and gender dysphoria. Age limits included the terms youth, child, children, teenager*, and adolescen*. The combined search produced 654 articles of potential relevance. The resulting abstracts went through a tiered elimination system, and the remaining 15 articles, which presented quantitative data related to the prevalence of transgender youth and their mental health, were included in the present review. In addition to providing new estimates of the number of young people who identify as transgender (.17%-1.3%), studies since 2011 have shown that transgender youth have higher rates of depression, suicidality and self-harm, and eating disorders when compared with their peers. Gender-affirming medical therapy and supported social transition in childhood have been shown to correlate with improved psychological functioning for gender-variant children and adolescents. Recent research has demonstrated increased rates of psychiatric morbidity among transgender youth compared to their peers. Future work is needed to understand those youth who identify as gender nonbinary, improve methods to capture and understand diverse gender identities and related health disparities, and delineate the social determinants of such disparities.

Public Health Sciences

Ghanem AI, **Khan N**, **Mahan M**, **Buekers T**, and **Elshaikh MA**. Survival endpoints with or without lymphadenectomy in women with stage I endometrial carcinoma: A matched-pair analysis *J Clin Oncol* 2016; 34PMID: Not assigned.

Abstract

A.I. Ghanem

Background: The role of regional lymphadenectomy (LA) in women with stage I endometrial carcinoma (EC) is controversial. The objective of the study is to determine the prognostic impact of LA on survival endpoints of women with stage I EC solely of endometrioid histology using match-pair analysis. Survival endpoints included recurrencefree (RFS), disease-specific (DSS) and overall survival (OS). Methods: We identified 1257 patients with stage I EC who underwent hysterectomy between 1/1990 and 6/2015. Of those, 822 women underwent LA as part of their surgical staging while 435 did not (NLA). 435 women with NLA were matched to 435 women who had LA (1:1 match) based on 2009 FIGO stage, tumor grade and adjuvant management received (observation, vaginal brachytherapy or pelvic external beam radiation treatment). Univariate and multivariate modeling with Cox regression analysis was carried out for predictors of survival endpoints. Results: Median follow-up time for the study cohort was 48 months. The two groups were well balanced except for more peritoneal cytology performed and more lower uterine segment (LUS) involvement for LA group (p= 0.001 for both). 5-year survival endpoints between the two groups were similar. 5-year RFS for women in the LA group was 93.7% vs. 90% for NLA group (p= 0.081). Similarly, 5-year DSS was 97.7% vs. 98% (p= 0.536) and 5-year OS was 87.2% vs. 91.7% (p= 0.357). On multivariate analysis for the entire study cohort, older age, deep myometrial invasion and higher tumor grade were predictors of worse RFS (p= 0.031, p= 0.004 and p< 0.001), respectively. For DSS, higher tumor grade (p< 0.001), LUS involvement (p= 0.028) and FIGO stage IB (p= 0.022) were significant predictors of worse outcome. For OS, older age and LUS involvement were the only two independent predictors for shorter OS (p< 0.001). Conclusions: With this large study cohort, our study suggests that survival endpoints are not different between women with stage I endometrial carcinoma who underwent lymphadenectomy compared to those who did not. It appear that omitting lymphadenectomy for women with stage I disease is not associated with any worse survival outcome after matching for stage, grade and adjuvant management.

Public Health Sciences

Gu X, **Xu J**, **Zhu L**, Bryson T, **Yang XP**, **Peterson E**, and **Harding P**. Prostaglandin e2 reduces cardiac contractility via ep3 receptor *Circ Heart Fail* 2016; 9(8)PMID: 27502370. Full Text

From the Hypertension and Vascular Research Division, Department of Internal Medicine (X.G., J.X., L.Z., T.B., X.-P.Y., P.H.) and Department of Physiology (T.B., P.H.), Wayne State University School of Medicine, Detroit, MI; Department of Public Health Sciences (E.P.), Henry Ford Hospital, Detroit, MI; and Department of Cardiology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China (X.G.).
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BACKGROUND: Prostaglandin E2 (PGE2) EP receptors EP3 and EP4 signal via decreased and increased cAMP production, respectively. Previously, we reported that cardiomyocyte-specific EP4 knockout mice develop dilated cardiomyopathy with reduced ejection fraction. Thus, we hypothesized that PGE2 increases contractility via EP4 but decreases contractility via EP3. METHODS AND RESULTS: The effects of PGE2 and the EP1/EP3 agonist sulprostone on contractility were examined in the mouse Langendorff preparation and in adult mouse cardiomyocytes. Isolated hearts of adult male C57Bl/6 mice were perfused with PGE2 (10(-6) M) or sulprostone (10(-6) M) and compared with vehicle. Both PGE2 and sulprostone decreased +dp/dt (P<0.01) and left ventricular developed pressure (P<0.001) with reversal by an EP3 antagonist. In contrast, the EP4 agonist had the opposite effect. Adult mouse cardiomyocytes contractility was also reduced after treatment with either PGE2 or sulprostone for 10 minutes. We then examined the acute effects of PGE2, sulprostone, and the EP4 agonist on expression of phosphorylated phospholamban and sarcoendoplasmic reticulum Ca(2+)-ATPase 2a in adult mouse cardiomyocytes using Western blot. Treatment with either PGE2 or sulprostone decreased expression of phosphorylated phospholamban corrected to total phospholamban, whereas treatment with the EP4 agonist had the opposite effect. Sarcoendoplasmic reticulum Ca(2+)-ATPase 2a expression was unaffected. Finally, we examined the effect of these compounds in vivo using pressure-volume loops. Both PGE2 and sulprostone decreased +dp/dt, whereas the EP4 agonist increased +dp/dt. CONCLUSIONS: Contractility is reduced via the EP3 receptor but increased via EP4. These effects may be mediated through changes in phospholamban phosphorylation and has relevance to detrimental effects of inflammation.

Public Health Sciences

Jiang W, **Finniss S**, **Cazacu S**, **Xiang C**, **Brodie Z**, **Mikkelsen T**, **Poisson L**, Shackelford DB, and **Brodie C**. Repurposing phenformin for the targeting of glioma stem cells and the treatment of glioblastoma *Oncotarget* 2016;PMID: 27486821. Full Text

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Glioblastoma (GBM) is the most aggressive primary brain tumor with poor prognosis. Here, we studied the effects of phenformin, a mitochondrial complex I inhibitor and more potent chemical analog of the diabetes drug metformin on the inhibition of cell growth and induction of apoptosis of glioma stem cells (GSCs) using both in vitro and in vivo models. Phenformin inhibited the self-renewal of GSCs, decreased the expression of stemness and mesenchymal markers and increased the expression of miR-124, 137 and let-7. Silencing of let-7 abrogated phenformin effects on the self-renewal of GSCs via a pathway associated with inhibition of H19 and HMGA2 expression. Moreover, we demonstrate that phenformin inhibited tumor growth and prolonged the overall survival of mice orthotopically transplanted with GSCs. Combined treatments of phenformin and temozolomide exerted an increased antitumor effect on GSCs in vitro and in vivo. In addition, dichloroacetate, an inhibitor of the glycolysis enzyme pyruvate dehydrogenase kinase, that decreases lactic acidosis induced by biguanides, enhanced phenformin effects on the induction of cell death in GSCs and prolonged the survival of xenograft-bearing mice. Our results demonstrate for the first time that phenformin targets GSCs and can be efficiently combined with current therapies for GBM treatment and GSC eradication.

Public Health Sciences

Krasnick BA, **Nathanson SD**, Arbabi CN, **Chitale DA**, and **Peterson EL**. The predictive value of increased sentinel lymph node volume in breast cancer *Surg Oncol* 2016; 25(3):321-325. PMID: 27566039. Full Text

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BACKGROUND: Breast cancer sentinel lymph nodes (SLNs) with metastases (mets) are often palpably enlarged. We hypothesized that the volume of the SLN and the size of mets are directly related. SLNs harboring mets are often firm, with increased intra-nodal pressure (INP), and we hypothesized that SLN volume, as well as INP, would correlate directly with SLN metastasis size. METHODS: The SLN volume, INP and met size were measured in 296 SLNs and compared using linear regression analysis. The SLNs were subsequently grouped based upon pN stage. SLN INP and volume were compared between these resultant groups. RESULTS: Increased SLN volume significantly predicted increased SLN met size on univariate and multivariate analysis ($p = 0.001$ and $p = 0.011$, respectively). SLN met size predicted increased SLN INP on both univariate and multivariate analysis (both $p = 0.001$). SLN volume only significantly correlated with increased SLN INP on univariate analysis ($p = 0.001$). On subgroup analysis of nodal disease, pN1/2/3 nodes (SLN met sizes >2 mm) were significantly larger ($p = 0.039$ and $p = 0.003$, respectively) than pN0 and pN1(mi) nodes, and had significantly increased INP (all $p = 0.001$) as compared to pN0, pN0(i+), and pN1(mi) nodes. CONCLUSIONS: SLN volume and INP increased with increasing SLN met size. The threshold met size for this increase was >2 mm (pN1 disease).

Public Health Sciences

Levin AM, **Sitarik AR**, **Havstad SL**, Fujimura KE, **Wegienka G**, **Cassidy-Bushrow AE**, **Kim H**, **Zoratti EM**, Lukacs NW, Boushey HA, Ownby DR, Lynch SV, and **Johnson CC**. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity *Sci Rep* 2016; 6:31775. PMID: 27558272. Full Text

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The joint impact of pregnancy, environmental, and sociocultural exposures on early life gut microbiome is not yet well-characterized, especially in racially and socioeconomically diverse populations. Gut microbiota of 298 children from a Detroit-based birth cohort were profiled using 16S rRNA sequencing: 130 neonates (median age = 1.2 months) and 168 infants (median age = 6.6 months). Multiple factors were associated with neonatal gut microbiome composition in both single- and multi-factor models, with independent contributions of maternal race-ethnicity, breastfeeding, mode of delivery, marital status, exposure to environmental tobacco smoke, and indoor pets. These findings were consistent in the infants, and networks demonstrating the shared impact of factors on gut microbial composition also showed notable topological similarity between neonates and infants. Further, latent groups defined by these factors explained additional variation, highlighting the importance of combinatorial effects. Our findings also have implications for studies investigating the impact of the early life gut microbiota on disease.

Public Health Sciences

Michaels AT, **Radjef R**, **She RC**, **Liu B**, **Peterson E**, Pinto Y, **Williams K**, **Sabbah H**, and **Lanfear D**. Improving risk prediction in heart failure: MAGGIC plus natriuretic peptides *J Card Fail* 2016; 22(8):S99-S99. PMID: Not assigned. Abstract

Background: Risk stratification of patients with heart failure (HF) remains challenging but is a critical need. The MAGGIC score is a clinical risk model derived from meta-analysis of nearly 40k patients. Natriuretic peptides (NP) have consistently shown powerful risk prediction in HF patients, but the incremental value in addition to MAGGIC score is not known. Methods: In this single center study 4264 patients were analyzed from two cohorts; a prospective ambulatory registry of HF patients (n = 1314) who had baseline NTproBNP levels measured, and a retrospective cohort collected utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015; n = 2503) with clinical BNP levels measured at or near discharge. The hospital discharge cohort were all assigned NYHA class IV. The primary end-point was all cause mortality. Performance of the MAGGIC score and NP levels was assessed within each cohort utilizing Cox regression and receiver operating curves (ROC) analysis (MAGGIC alone vs. MAGGIC+NP) with the net reclassification improvement (NRI) also calculated. Results: The overall cohort had an average age of 71.2 years, was 47.8% females, and 41% self-identified African Americans. Median follow up was 1.52 years during which there were 1139 deaths (27%). The MAGGIC score was a strong predictor of outcome in both cohorts (P < .001). In ROC analysis of the ambulatory registry, NP significantly improved area under the curve (AUC) compared to MAGGIC alone from 0.74 to 0.79 (P = .002) and had a NRI of 0.354 (Figure). In contrast, within the hospital discharge cohort NP levels did not significantly add to MAGGIC score (AUC 0.681 vs. 0.676, NRI = 0.033, P = .284) (Figure). Conclusion: In our study, NP levels in the ambulatory setting significantly improved risk stratification provided by the MAGGIC score, but discharge NP levels did not improve MAGGIC prediction of post-hospital survival. Overall risk stratification and particularly NP utility is much better in the ambulatory setting.

Public Health Sciences

Michaels AT, **Radjef R**, **She RC**, **Peterson E**, **Liu B**, and **Lanfear DE**. Predicting mortality at discharge following hospitalization for acute heart failure *J Card Fail* 2016; 22(8):S21-S22. PMID: Not assigned. Abstract

Background : Risk stratification for heart failure (HF) patients remains a critical need, particularly among those hospitalized where many clinical decisions are being made at discharge. Recently a robust risk model, the MAGGIC score, was derived from data on nearly 40k patients. This provides 1 year mortality estimates and is available as an online clinical tool. Whether it is useful to risk-stratify patients being discharged from the hospital is unknown. Methods : This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. For the hospital discharge subjects, when tabulating MAGGIC all patients were assigned NYHA class IV. The primary endpoint was all-cause mortality. Vital status was assessed utilizing system administrative data and the social security death master file. Performance of the MAGGIC score was evaluated within cohorts and compared across the two groups using Cox models stratified by cohort and then with an interaction term (MAGGIC*Cohort). Calibration was assessed by comparing observed vs. MAGGIC-predicted 1 year mortality. Results : Overall the study patients had an average age of 71.2 years, 47.8% were female and 41% were self-identified African Americans, and there were 1139 deaths (27%) over a median

follow up of 1.52 years. The hospital discharge cohort was overall much higher risk than the ambulatory cohort (figure). The MAGGIC score was a strong predictor of outcomes in both groups (both P < .001). With a HR (per MAGGIC point) of 1.13 in the ambulatory registry and 1.10 in the hospital discharge patients. In ROC analysis MAGGIC showed an area under the curve (AUC) of 0.74, but an AUC in the hospital discharge cohort of 0.67. When modeled using an interaction term, MAGGIC did appear to be more predictive in the ambulatory group with an interaction coefficient of 0.03 (P = .004). Although calibration appeared suboptimal in both cohorts (Figure), with MAGGIC underestimating the true risk, this appeared similar in both cohorts. Discussion : The MAGGIC score is able to provide important prognostic information on patients being discharged from the hospital for HF, though the performance was somewhat inferior than in a comparable ambulatory cohort. MAGGIC underestimated risk in both ambulatory and hospital cohorts, suggesting calibration may need to be reassessed in more real-world patient data sets.

Public Health Sciences

Radjef R, **Michaels A**, **Peterson E**, **She R**, **Liu B**, **Williams K**, **Sabbah H**, and **Lanfear D**. Performance of MAGGIC score in african americans compared to whites *J Card Fail* 2016; 22(8):S101-S101. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Public Health Sciences

Sabbah HN, **Gupta RC**, **Sing-Gupta V**, **Zhang KF**, and **Xu J**. Long-Term Therapy with Elamipretide Normalizes ATP Synthase Activity in Left Ventricular *J Card Fail* 2016; 22(8):S23-S23. PMID: Not assigned. Abstract

Background: Risk stratification is critical in Heart Failure (HF) care. The MAGGIC score is a validated tool derived from a large multi-study cohort of nearly 40,000 but very few of the patients self-identified as Black or of African Ancestry (less than 400). There is little data assessing MAGGIC score utility in African Americans (AA). Methods: This single center study analyzed a total of 4264 patients from 2 cohorts; one utilizing administrative data from hospital discharges for HF (January 1 st , 2014 through July 30 th , 2015, n = 2503) and a prospective registry of ambulatory HF patients (n = 1761), both based in southeast Michigan. Baseline characteristics were collected to tabulate MAGGIC score and test its risk stratification in self-identified African Americans (AA) and whites. The primary endpoint was time to all-cause mortality. Death was detected using system records and the social security death master file. Cox models with MAGGIC score as the only variable stratified by race, and a combined model including MAGGIC, race, and MAGGIC*race were tested. P < .05 was considered significant. Results: Overall, 1748 patients (41%) were AA, and a total of 1151 (27%) patients died during follow up. MAGGIC score was strongly and similarly predictive of survival in both race groups. Among AA, each MAGGIC point carried HR of 1.12 (95%CI 1.10, 1.14; P < .001) while in whites the HR was 1.13 (95%CI 1.12, 1.14; P < .001). Formal test of interaction of MAGGIC by race was not significant (P = .153). However, there was a difference in survival by race, with African Americans showing a survival advantage (HR = 0.72, P = .001) which appears to be isolated to the highest risk subgroup (Figure). Conclusion: These data support the utility of the MAGGIC score for risk stratification in African Americans who suffer from HF. However, there may still be residual differences in outcomes between AA and whites despite overall risk adjustment, particularly in highest risk subgroup.

Public Health Sciences
Salafia CM, Thomas DM, Roberts DJ, **Straughen JK**, Catalano PM, and Perez-Avilan G. First trimester detection of placental disease: Challenges and opportunities *Am J Perinatol* 2016;PMID: 27490774. Article Request Form

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It is generally agreed that placental pathology accounts for the majority of perinatal morbidity and mortality. If a placental prodrome could be diagnosed in vivo, risk for maternal or fetal complications could be estimated and acted upon before clinical symptoms are apparent. This is especially relevant in early diagnoses of gestational diabetes mellitus, which can be controlled through carefully monitored diet and activity changes. To meet this important need, there have been increased efforts to identify early gestation biomarkers of placental dysfunction using innovative imaging technologies. Here we outline innovative quantitative markers of placental shape and their relationship to placental function, clinical implications of these quantifiers, and the most recent mathematical models that utilize placental images to delineate at risk from normal pregnancies. We propose that novel contexts of readily available placental measures and routine collection of in vivo placental images in all pregnancies may be all that are needed to advance the identification of early risk determination of complicated pregnancies from placental images.

Public Health Sciences
Schiff L, **Tsafrir Z**, **Aoun J**, **Taylor A**, **Theoharis E**, and **Eisenstein D**. Quality of communication in robotic surgery and surgical outcomes *Jsls* 2016; 20(3)PMID: 27493469. Full Text

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BACKGROUND AND OBJECTIVES: Robotic surgery has introduced unique challenges to surgical workflow. The association between quality of communication in robotic-assisted laparoscopic surgery and surgical outcomes was evaluated. METHODS: After each gynecologic robotic surgery, the team members involved in the surgery completed a survey regarding the quality of communication. A composite quality-of-communication score was developed using principal component analysis. A higher composite quality-of-communication score signified poor communication. Objective parameters, such as operative time and estimated blood loss (EBL), were gathered from the patient's medical record and correlated with the composite quality-of-communication scores. RESULTS: Forty robotic cases from March through May 2013 were included. Thirty-two participants including surgeons, circulating nurses, and surgical technicians participated in the study. A higher composite quality-of-communication score was associated with greater EBL (P = .010) and longer operative time (P = .045), after adjustment for body mass index, prior major abdominal surgery, and uterine weight. Specifically, for every 1-SD increase in the perceived lack of communication, there was an additional 51 mL EBL and a 31-min increase in operative time. The most common reasons reported for poor communication in the operating room were noise level (28/36, 78%) and console-to-bedside communication problems (23/36, 64%). CONCLUSION: Our study demonstrates a significant association between poor intraoperative team communication and worse surgical outcomes in robotic gynecologic surgery. Employing strategies to decrease extraneous room noise, improve console-to-bedside communication and team training may have a positive impact on communication and related surgical outcomes.

Public Health Sciences
Wegienka G, **Havstad S**, **Kim H**, **Zoratti E**, Ownby D, **Woodcroft KJ**, and **Johnson CC**. Subgroup differences in the associations between dog exposure during the first year of life and early life allergic outcomes *Clin Exp Allergy* 2016;PMID: 27562398. Full Text

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BACKGROUND: The effect of dog exposure on the risk of children developing allergic disease remains controversial. Many analyses have not considered that associations may vary within population subgroups. OBJECTIVE: Examine whether associations between living with a dog in the first year of life and allergic outcomes vary within subgroups selected a priori (race, gender and delivery mode). METHODS: Black (n=496) and White (n=196) children enrolled in the WHEALS birth cohort study had a clinical examination at age 2 years to assess eczema and allergen-specific IgE (sIgE) and perform skin prick testing (SPT). Whether the child lived with an indoor dog in the first year of life was assessed through interview, as was doctor diagnosis of asthma at ages 3-6 years. RESULTS: Living with a dog was associated with decreased odds of having >/=1 positive SPT (OR=0.56, 95%CI 0.34, 0.91) and having eczema (OR=0.34, 95%CI 0.20, 0.60). The association with SPT was stronger in those children born via cesarian-section versus vaginally (OR=0.29, 95%CI 0.12, 0.74 versus OR=0.76, 95%CI 0.43, 1.37, respectively, interaction p=0.087) and in those who were firstborn versus not (OR=0.27, 95%CI 0.11, 0.67 versus OR=0.82, 95%CI 0.45, 1.47, respectively, interaction p=0.044). The association with eczema was stronger in children born vaginally compared with those born via cesarian-section (OR=0.17, 95%CI 0.06, 0.43 versus OR=0.65, 95%CI 0.31, 1.35, respectively, interaction p=0.025) and was stronger in Black versus White children (OR=0.30, 95%CI 0.15, 0.61 versus OR=0.78, 95%CI 0.29, 2.11, respectively, interaction p=0.12). Dog keeping was not significantly inversely associated with having >/=1 elevated sIgE and only approached statistical significance with asthma.

Public Health Sciences

Zhou K, Yee SW, Seiser EL, van Leeuwen N, Tavendale R, Bennett AJ, Groves CJ, Coleman RL, van der Heijden AA, Beulens JW, de Keyser CE, Zaharenko L, Rotroff DM, Out M, Jablonski KA, Chen L, Javorsky M, Zidzik J, **Levin AM**, **Williams LK**, Dujic T, Semiz S, Kubo M, Chien HC, Maeda S, Witte JS, Wu L, Tkac I, Kooy A, van Schaik RH, Stehouwer CD, Logie L, Sutherland C, Klovins J, Pirags V, Hofman A, Stricker BH, Motsinger-Reif AA, Wagner MJ, Innocenti F, Hart LM, Holman RR, McCarthy MI, Hedderson MM, Palmer CN, Florez JC, Giacomini KM, and Pearson ER. Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin *Nat Genet* 2016;PMID: 27500523. Full Text

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Metformin is the first-line antidiabetic drug with over 100 million users worldwide, yet its mechanism of action remains unclear. Here the Metformin Genetics (MetGen) Consortium reports a three-stage genome-wide association study (GWAS), consisting of 13,123 participants of different ancestries. The C allele of rs8192675 in the intron of SLC2A2, which encodes the facilitated glucose transporter GLUT2, was associated with a 0.17% (P = 6.6 x 10-14) greater metformin-induced reduction in hemoglobin A1c (HbA1c) in 10,577 participants of European ancestry. rs8192675 was the top cis expression quantitative trait locus (cis-eQTL) for SLC2A2 in 1,226 human liver samples, suggesting a key role for hepatic GLUT2 in regulation of metformin action. Among obese individuals, C-allele homozygotes at rs8192675 had a 0.33% (3.6 mmol/mol) greater absolute HbA1c reduction than T-allele homozygotes. This was about half the effect seen with the addition of a DPP-4 inhibitor, and equated to a dose difference of 550 mg of metformin, suggesting rs8192675 as a potential biomarker for stratified medicine.

Radiation Oncology

Cerrato BD, **Carretero OA**, **Janic B**, Grecco HE, and Gironacci MM. Heteromerization between the bradykinin b2 receptor and the angiotensin-(1-7) mas receptor: Functional consequences *Hypertension* 2016;PMID: 27550920.
Full Text

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Bradykinin B2 receptor (B2R) and angiotensin-(1-7) Mas receptor (MasR)-mediated effects are physiologically interconnected. The molecular basis for such cross talk is unknown. It is hypothesized that the cross talk occurs at the receptor level. We investigated B2R-MasR heteromerization and the functional consequences of such interaction. B2R fused to the cyan fluorescent protein and MasR fused to the yellow fluorescent protein were transiently coexpressed in human embryonic kidney293T cells. Fluorescence resonance energy transfer analysis showed that B2R and MasR formed a constitutive heteromer, which was not modified by their agonists. B2R or MasR antagonists decreased fluorescence resonance energy transfer efficiency, suggesting that the antagonist promoted heteromer dissociation. B2R-MasR heteromerization induced an 8-fold increase in the MasR ligand-binding affinity. On agonist stimulation, the heteromer was internalized into early endosomes with a slower sequestration rate from the plasma membrane, compared with single receptors. B2R-MasR heteromerization induced a greater increase in arachidonic acid release and extracellular signal-regulated kinase phosphorylation after angiotensin-(1-7) stimulation, and this effect was blocked by the B2R antagonist. Concerning serine/threonine kinase Akt activity, a significant bradykinin-promoted activation was detected in B2R-MasR but not in B2R-expressing cells. Angiotensin-(1-7) and bradykinin elicited antiproliferative effects only in cells expressing B2R-MasR heteromers, but not in cells expressing each

receptor alone. Proximity ligation assay confirmed B2R-MasR interaction in human glomerular endothelial cells supporting the interaction between both receptors in vivo. Our findings provide an explanation for the cross talk between bradykinin B2R and angiotensin-(1-7) MasR-mediated effects. B2R-MasR heteromerization induces functional changes in the receptor that may lead to long-lasting protective properties.

Radiation Oncology
Ghanem AI, **Khan N**, **Mahan M**, **Buekers T**, and **Elshaikh MA**. Survival endpoints with or without lymphadenectomy in women with stage I endometrial carcinoma: A matched-pair analysis *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

A.I. Ghanem

Background: The role of regional lymphadenectomy (LA) in women with stage I endometrial carcinoma (EC) is controversial. The objective of the study is to determine the prognostic impact of LA on survival endpoints of women with stage I EC solely of endometrioid histology using match-pair analysis. Survival endpoints included recurrencefree (RFS), disease-specific (DSS) and overall survival (OS). Methods: We identified 1257 patients with stage I EC who underwent hysterectomy between 1/1990 and 6/2015. Of those, 822 women underwent LA as part of their surgical staging while 435 did not (NLA). 435 women with NLA were matched to 435 women who had LA (1:1 match) based on 2009 FIGO stage, tumor grade and adjuvant management received (observation, vaginal brachytherapy or pelvic external beam radiation treatment). Univariate and multivariate modeling with Cox regression analysis was carried out for predictors of survival endpoints. Results: Median follow-up time for the study cohort was 48 months. The two groups were well balanced except for more peritoneal cytology performed and more lower uterine segment (LUS) involvement for LA group (p= 0.001 for both). 5-year survival endpoints between the two groups were similar. 5-year RFS for women in the LA group was 93.7% vs. 90% for NLA group (p= 0.081). Similarly, 5-year DSS was 97.7% vs. 98% (p= 0.536) and 5-year OS was 87.2% vs. 91.7% (p= 0.357). On multivariate analysis for the entire study cohort, older age, deep myometrial invasion and higher tumor grade were predictors of worse RFS (p= 0.031, p= 0.004 and p< 0.001), respectively. For DSS, higher tumor grade (p< 0.001), LUS involvement (p= 0.028) and FIGO stage IB (p= 0.022) were significant predictors of worse outcome. For OS, older age and LUS involvement were the only two independent predictors for shorter OS (p< 0.001). Conclusions: With this large study cohort, our study suggests that survival endpoints are not different between women with stage I endometrial carcinoma who underwent lymphadenectomy compared to those who did not. It appear that omitting lymphadenectomy for women with stage I disease is not associated with any worse survival outcome after matching for stage, grade and adjuvant management.

Radiation Oncology
Gladstone DJ, Kry SF, Xiao Y, and **Chetty IJ**. Dose specification for NRG radiation therapy trials *Int J Radiat Oncol Biol Phys* 2016; 95(5):1344-1345. PMID: 27479721. Full Text

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Radiation Oncology
Stinchcombe T, Zhang YJ, Vokes EE, Schiller JH, Bradley JD, Curran WJ, **Movsas B**, Schild SE, Clamon GH, Govindan R, Blumenschein GR, Socinski MA, Ready N, Akerley WL, Cohen HJ, Pang H, and Wang XF. A pooled analysis of concurrent chemoradiotherapy (CCRT) for patients with stage III non-small cell lung cancer (NSCLC) who participated in U.S. cooperative group trials: Comparing the outcomes of elderly to younger patients (pts) *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

T. Stinchcombe

Background: CCRT is the standard treatment (TRT) for stage 3 NSCLC. Elderly pts are common and may have increased toxicity and poorer results from CCRT. Methods: We collected individual patient data (IPD) of pts who participated in cooperative group phase 2/3 trials of CCRT for stage 3A/3B pts from 1990-2012. We compared the overall survival (OS), progression-free survival (PFS), and adverse events (AE's) for pts age >70 years (yrs) (elderly) vs. <70 yrs (younger). Unadjusted and adjusted Hazard Ratios (HRs) for survival time and their confidence intervals

(CIs) were estimated by single-predictor and multivariable Cox models. Unadjusted and adjusted Odds Ratios (ORs) for AE's and their CIs were obtained from single-predictor and multivariable logistic regression models. Results: IPD from 15 trials were analyzed; 2243 pts were younger and 702 were elderly. Median OS and PFS for elderly and younger pts are in the table. In the unadjusted and multivariable models elderly pts had worse OS (HR=1.19; 95%CI=1.08-1.31, and 1.18; 95% CI=1.06-1.32, respectively). In the unadjusted & multivariable models, elderly and younger pts had a similar PFS (HR=1.05; 95% CI=0.96-1.15 and 1.06, 95% CI=0.95-1.17, respectively). The rates of AE's and TRT related deaths are presented in the table. Elderly pts had a higher rate of AE's in the unadjusted & multivariable models (OR=1.27; 95% CI=0.99-1.63 and 1.33; 95% CI=1.04-1.72, respectively). A lower percentage of elderly pts completed TRT (50.9% and 61.2%, respectively; P < 0.0001) and higher percentage stopped due to AE's (20.5% and 14.1%; P<0.0001). Conclusions: Elderly pts enrolled in cooperative group CCRT trials had worse OS, but similar PFS. The rates of severe AE's was higher and a lower percentage of elderly pts completed TRT. (Table Presented).

Radiology
Aljundi L, Miller N, **Taylor A**, **Hung J**, and **Hwang C**. Time to castration-resistance and docetaxel outcomes in metastatic prostate cancer *J Clin Oncol* 2016; 34PMID: Not assigned. Abstract

L. Aljundi

Background: Castration resistant prostate cancer (CRPC) continues to present a challenge for oncologists. There is renewed interest in the use of docetaxel in advanced prostate cancer; however, a significant portion of patients do not respond and eventually all patients develop resistance. Androgen receptor (AR) variants have been hypothesized to be a common resistance mechanism to both androgen deprivation therapy (ADT) and docetaxel. We thus proposed that initial response to ADT might predict future response to docetaxel. Methods: A set of Cox regressions was computed to investigate the time to progression while on ADT and other factors on time to progression and overall survival while on docetaxel. Hazard ratios and pvalues for each factor were calculated. Patients were stratified according to their time to progression while on ADT into three groups by tertiles. Rapid progressors were patients who progressed within less than a year while on ADT, intermediate progressors progressed within 1 and 2.6 years and slow progressors progressed after more than 2.6 years. Survival for each of these three categories was plotted using the Kaplan-Meier method and differences were assessed with the log-rank test. Results: Time to prostate specific antigen (PSA) progression while on ADT predicted future docetaxel response (HR = 0.8, p = 0.03) in univariate analysis. A difference in time to PSA progression was noted between rapid and fast progressors on ADT (p = 0.009, log-rank test). Overall survival for rapidly progressing patients was significantly inferior to intermediate and slow progressors (p = < 0.001, logrank). However, multivariate analysis did not meet criteria for statistical significance between time to progression while on ADT and time to progression while on docetaxel (p = 0.062). Conclusions: Although time to CRPC was correlated with docetaxel outcomes, the relationship was not statistically significant on multivariate analysis. Further research is required to identify molecular characteristics in patients with CRPC that will predict response and outcomes with more precision.

Radiology
Rheinboldt M, **Delproposto Z**, **Blase J**, and **Hakim B**. Acute presentation of lhermitte-duclos disease in adult patient in association with cowden syndrome *Appl Radiol* 2016; 45(8):28-31. PMID: Not assigned.
Article Request Form

Radiology
Zhang Y, **Chopp M**, **Zhang ZG**, **Katakowski M**, **Xin H**, **Qu C**, **Ali M**, **Mahmood A**, and **Xiong Y**. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury *Neurochem Int* 2016;PMID: 27539657. Article Request Form

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Multipotent human bone marrow derived mesenchymal stem cells (hMSCs) improve functional outcome after experimental traumatic brain injury (TBI). The present study was designed to investigate whether systemic

administration of cell-free exosomes generated from hMSCs cultured in 2-dimensional (2D) conventional conditions or in 3-dimensional (3D) collagen scaffolds promote functional recovery and neurovascular remodeling in rats after TBI. Wistar rats were subjected to TBI induced by controlled cortical impact; 24 h later tail vein injection of exosomes derived from hMSCs cultured under 2D or 3D conditions or an equal number of liposomes as a treatment control were performed. The modified Morris water maze, neurological severity score and footfault tests were employed to evaluate cognitive and sensorimotor functional recovery. Animals were sacrificed at 35 days after TBI. Histological and immunohistochemical analyses were performed for measurements of lesion volume, neurovascular remodeling (angiogenesis and neurogenesis), and neuroinflammation. Compared with liposome-treated control, exosome-treatments did not reduce lesion size but significantly improved spatial learning at 33-35 days measured by the Morris water maze test, and sensorimotor functional recovery, i.e., reduced neurological deficits and footfault frequency, observed at 14-35 days post injury ($p < 0.05$). Exosome treatments significantly increased the number of newborn endothelial cells in the lesion boundary zone and dentate gyrus, and significantly increased the number of newborn mature neurons in the dentate gyrus as well as reduced neuroinflammation. Exosomes derived from hMSCs cultured in 3D scaffolds provided better outcome in spatial learning than exosomes from hMSCs cultured in the 2D condition. In conclusion, hMSC-generated exosomes significantly improve functional recovery in rats after TBI, at least in part, by promoting endogenous angiogenesis and neurogenesis and reducing neuroinflammation. Thus, exosomes derived from hMSCs may be a novel cell-free therapy for TBI, and hMSC-scaffold generated exosomes may selectively enhance spatial learning.

Sleep Medicine
Roehrs TA, and **Roth T**. Hyperarousal in insomnia and hypnotic dose escalation *Sleep Med* 2016; 23:16-20. PMID: Not assigned. Full Text

T.A. Roehrs, Sleep Disorders & Research Center, Henry Ford Hospital, Detroit, United States

Background Given concerns about the abuse liability of hypnotics, this study assessed hyperarousal in people with insomnia and its relation to hypnotic self-administration over 12 months of nightly hypnotic use. Methods Ninety-five subjects with insomnia (age 32–64 years) underwent screening nocturnal polysomnogram (NPSG) and Multiple Sleep Latency Test (MSLT) the following day and, then, were randomized to receive zolpidem 10 mg or placebo nightly for 12 months. NPSGs and MSLTs were conducted and urine was collected (0700–1500 h) and analyzed for norepinephrine (NE) levels during months one and eight on study medication. A subset (n = 54) underwent hypnotic self-administration assessments in months one, four, and 12. Results Mean daily sleep latency on screening MSLT was distributed across the full range of MSLT latencies (2–20 min). The highest screening MSLT latencies were detected in subjects with higher NE levels, compared to those with the lowest MSLT latencies. In the subset undergoing self-administration assessment, those with the highest MSLT latencies chose more capsules (placebo and zolpidem) and increased the number of capsules chosen in months four relative to month one, compared to those with the lowest MSLT latencies. Conclusions These data show that some insomniacs are hyperaroused with high MSLT/NE levels and, compared to low MSLT/NE insomniacs, they increase the number of capsules (zolpidem and placebo) self-administered on months four and 12 relative to Month one.

Sleep Medicine
Ruwe F, Ijzerman-Boon P, **Roth T**, Zammit G, and Ivgy-May N. A phase 2 randomized dose-finding study with esmirtazapine in patients with primary insomnia *J Clin Psychopharmacol* 2016;PMID: 27482970. Full Text

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ABSTRACT: The antidepressant mirtazapine is an alternative to classical hypnotics, and this study investigated the efficacy and safety of esmirtazapine (Org 50081, the maleic acid salt of S-mirtazapine) in patients given a diagnosis of primary insomnia after acute (2-day) treatment. Patients aged 18 to 65 years with primary insomnia were randomized to receive placebo or 1.5-, 3.0-, or 4.5-mg esmirtazapine in a balanced 4-way crossover study; 2 sleep laboratory nights with polysomnography were separated by 5-day, single-blind placebo washout periods. Polysomnography-determined total sleep time (primary end point) and patient-reported total sleep time improved by at least 25 minutes with all 3 doses of esmirtazapine ($P \leq 0.001$ vs placebo). Polysomnography-measured wake time after sleep onset ($P \leq 0.0001$) and latency to persistent sleep also improved vs placebo ($P \leq 0.01$, 3.0 and 4.5 mg). Patient-reported sleep quality improved with 3.0- and 4.5-mg esmirtazapine ($P \leq 0.01$ and $P \leq 0.05$, respectively, vs placebo). Morning alertness and contentment were not altered after esmirtazapine, and calmness increased with 4.5-mg esmirtazapine vs placebo. Evening questionnaires showed no difference in duration of daytime naps but reduced energy and ability to work/function after esmirtazapine treatment periods vs placebo ($P < 0.05$), although this effect was limited to the first night of each 2-night period. There were few adverse events, no serious adverse events, or

clinically relevant treatment differences in vital signs, laboratory values, or electrocardiogram. Esmirtazapine doses of 1.5 to 4.5 mg/day significantly improved quantity and quality of sleep and were generally well tolerated, with no evidence of safety concerns or consistent pattern of residual effects.

Surgery
Baker-Genaw K, **Kokas MS**, **Ahsan SF**, **Darnley-Fisch D**, **Drake S**, **Goyal N**, **Inamdar K**, **Moutzouros V**, **Prabhakar D**, **Rolland L**, **Sangha R**, **Shreve M**, and **Woodward A**. Mapping direct observations from objective structured clinical examinations to the milestones across specialties *J Grad Med Educ* 2016; 8(3):429-434. PMID: 27413450. Full Text

BACKGROUND: Little is known about residents' performance on the milestones at the institutional level. Our institution formed a work group to explore this using an institutional-level curriculum and residents' evaluation of the milestones. OBJECTIVE: We assessed whether beginner-level milestones for interpersonal and communication skills (ICS) related to observable behaviors in ICS-focused objective structured clinical examinations (OSCEs) for postgraduate year (PGY) 1 residents across specialties. METHODS: The work group compared ICS subcompetencies across 12 programs to identify common beginner-level physician-patient communication milestones. The selected ICS milestone sets were compared for common language with the ICS-OSCE assessment tool-the Kalamazoo Essential Elements of Communication Checklist-Adapted (KEECC-A). To assess whether OSCE scores related to ICS milestone scores, all PGY-1 residents from programs that were part of Next Accreditation System Phase 1 were identified; their OSCE scores from July 2013 to June 2014 and ICS subcompetency scores from December 2014 were compared. RESULTS: The milestones for 10 specialties and the transitional year had at least 1 ICS subcompetency that related to physician-patient communication. The language of the ICS beginner-level milestones appears similar to behaviors outlined in the KEECC-A. All 60 residents with complete data received at least a beginner-level ICS subcompetency score and at least a satisfactory score on all 3 OSCEs. CONCLUSIONS: The ICS-OSCE scores for PGY-1 residents appear to relate to beginner-level milestones for physician-patient communication across multiple specialties.

Surgery
Deeb D, **Gao X**, **Liu Y**, **Zhang Y**, **Shaw J**, **Valeriote FA**, and **Gautam SC**. The inhibition of cell proliferation and induction of apoptosis in pancreatic ductal adenocarcinoma cells by verrucarin A, a macrocyclic trichothecene, is associated with the inhibition of Akt/NF-small ka, CyrillicB/mTOR prosurvival signaling *Int J Oncol* 2016; 49(3):1139-1147. PMID: 27573873. Article Request Form

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Pancreatic ductal adenocarcinoma (PDA) remains one of the most difficult to treat of all malignancies. Multimodality regimens provide only short-term symptomatic improvement with minor impact on survival, underscoring the urgent need for novel therapeutics and treatment strategies for PDA. Trichothecenes are powerful mycotoxins that inhibit protein synthesis and induce ribotoxic stress response in mammalian cells. Verrucarin A (VC-A) is a Type D macrocyclic mycotoxin which inhibited cell proliferation and induced apoptosis in breast cancer cells. However, the antitumor activity of VC-A for PDA cells has not been investigated. Here we show potent antitumor activity and the mechanism of action of VC-A in PDA cell lines. VC-A strongly inhibited the proliferation and arrested cells in the S phase of the cell cycle. The blocking of cell cycle progression by VC-A was associated with the inhibition of cell cycle regulatory proteins cyclin D1, cyclin E, cyclin-dependent kinases (cdks) cdk2, cdk4 and cdk inhibitor WAF1/21. VC-A induced apoptosis in PDA cells as indicated by the increased Annexin V FITC-binding, cleavage of poly(ADP-ribose) polymerase1 (PARP-1) and procaspases-3, -8 and -9. VC-A also induced mitochondrial depolarization and release of cytochrome c and it inhibited Bcl-2 family proteins that regulate apoptosis (Bcl-2, Bcl-xL, Bax and Bad). In addition, VC-A reduced the levels of inhibitors of apoptosis survivin and c-IAP-2. Finally, VC-A downregulated the expression of prosurvival phospho-Akt (p-Akt), nuclear factor kappaB (NF-kappaB) (p65) and mammalian target of rapamycin (p-mTOR) signaling proteins and their downstream mediators. Together, these results demonstrated strong antiproliferative and apoptosis-inducing activity of verrucarin A for PDA cells through cell cycle arrest and inhibition of the prosurvival (antiapoptotic) AKT/NF-kappaB/mTOR signaling.

Surgery
Gunn T, **Paone G**, Emery RW, and Ferraris VA. The case for a conservative approach to blood transfusion management in cardiac surgery *Innovations (Phila)* 2016; 11(3):157-164. PMID: 27532302. Full Text

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Limiting blood transfusion in cardiac operations is a well-meaning goal of perioperative care. Potential benefits include decreasing morbidity and limiting procedural costs. It is difficult to identify transfusion as the cause of adverse outcomes. The need for transfusion may identify a sicker patient population at greater risk for a worse outcome that may or may not be related to the transfusion. We reviewed the indications for and adverse effects of blood transfusion in patients undergoing cardiac procedures to provide a balanced approach to management of blood resources in this population. We reviewed current literature, including systematic reviews and practice guidelines, to synthesize a practice management plan in patients having cardiac operations. Several prospective randomized studies and large population cohort studies compared a postoperative restrictive transfusion policy to a more liberal policy and found very little difference in outcomes but decreased costs with a restrictive policy. Evidence-based practice guidelines and implementation standards provide robust intervention plans that can limit harmful effects of transfusion and provide safe and effective procedure outcomes. A restrictive transfusion policy seems to be safe and effective but does not necessarily provide better outcome in most patient cohorts. The implications of these findings suggest that many discretionary transfusions could be avoided. A subset of high-risk patients could undoubtedly benefit from a more liberal transfusion policy, but the definition of high risk is ill defined.

Surgery
Hammoud Z. The 5 most important recent publications regarding robotic esophageal surgery *Semin Thorac Cardiovasc Surg* 2016; 28(1):147-150. PMID: 27568152. Full Text

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

Surgery
Jesse M, **Abouljoud M**, **Eshelman A**, DeReyck C, and Lerut J. American and european transplant surgeons: Research, teaching, and burnout *Am J Transplant* 2016; 16:790. PMID: Not assigned. Abstract

M. Jesse, Transplant Institute, Henry Ford Health System, Detroit, United States

Purpose: Examine whether location or research/teaching demands impacts burnout (emotional exhaustion, depersonalization, personal accomplishment). Method: Cross-sectional survey of American (US) and European (EU) organ transplant surgeons. Results: 218 US and 112 EU transplant surgeons, predominantly male (n282, 86.5%). EU transplant surgeons were younger, worked fewer hours per week, and were more likely to have designated time for research or teaching than US surgeons. Next, examined research or teaching demands by location (US vs EU) on burnout. No significant interactions or main effects for location. There were also no significant differences on personal accomplishment. There were three significant main effects for research or teaching demands. On emotional exhaustion, surgeons with research demands but not designated research time reported significantly greater emotional exhaustion (M 24.43, SD 11.75) than surgeons with designated research time (M 16.64, SD 11.29), p<.01. On depersonalization, surgeons with research demands without designated time reported higher depersonalization (M 7.52, SD 5.61) than surgeons with designated research time (M 5.31, SD 4.87), p=.01. On emotional exhaustion, surgeons with teaching expectations without designated time reported significantly greater depersonalization (M 23.88, SD 11.95), than surgeons with designated teaching time (M 19.18, SD 11.75), p=.01. Conclusions: EU and US surgeons reported similar levels of burnout, but US transplant surgeons were older, reported working more hours, and were less likely to have designated time for either teaching or research despite expectations for both. As much of the burnout literature focuses on specialties within individual countries, international comparisons are needed to examine environmental demands and professional culture in relation to the development of burnout. (Table Presented).

Surgery
Jesse M, **Goldstein E**, **Macaulay T**, **Rebhan N**, **Ho CX**, **Bebanic M**, **Shkokani L**, **Abouljoud M**, **Eshelman A**, and **Yoshida A**. Racial disparities in cognitive and social requirements prior to listing for liver transplant *Am J Transplant* 2016; 16:517. PMID: Not assigned. Abstract

M. Jesse, Transplant Institute, Henry Ford Health System, Detroit, United States

Guidelines for liver transplant candidates outline increased engagement of social supports in the context of patient cognitive impairments. However, there is little direction when limitations in both. The purpose of this study was to examine differences and disparities in cognitive and support concerns identified in liver transplant candidates. Methods: Retrospective clinical chart review of patients referred for liver transplantation from January 2004 through December 2012. Doctoral level psychologists made cognitive recommendations from cognitive screeners and patient interviews. Cognitive accommodations are specific to patient needs, but frequently require additional social support involvement. Social support requirements included at least two adults willing/able to help, drive, and take time off work/other responsibilities post-transplant. Results: 1,753 patient referrals reviewed, 21.3% African American. African Americans were more likely to present with cognitive concerns (8% greater) and support related issues (5.6% greater) and twice as likely to have overlapping cognitive/social concerns as Caucasian patients. Conclusions: This study identified significant disparities between Caucasian and African American patients in cognitive functioning and support related issues. African Americans may be more likely to present further decompensated, which contributes to cognitive impairments. Efforts towards facilitating support networks of liver transplant candidates (e.g., engagement of community groups) are needed as this may address some disparities in access to liver transplantation. (Table Presented).

Surgery

Jesse M, **Goldstein E**, **Rebhan N**, **Ho CX**, **Macaulay T**, **Bebanic M**, **Shkokani L**, **Moonka D**, **Abouljoud M**, and **Yoshida A**. Racial disparities in the evaluation for liver transplantation *Am J Transplant* 2016; 16:520-521. PMID: Not assigned. Abstract

M. Jesse, Transplant Institute, Henry Ford Health System, Detroit, United States

The majority of research on disparities in liver transplantation is on patients listed for transplant in the OPTN/UNOS database, not patients in the evaluation process for listing. This study reports the outcomes of liver transplant evaluations of Caucasian and African American patients at a single center. Method: Retrospective clinical chart review of patients referred for liver transplantation from January 2004 through December 2012. Results: 1,855 patient referrals, 78.8% (n=1,461) Caucasian and 21.2% (n=394) African American. Most frequent reasons for not listed were medical, patient failure to complete work-up, and patient expired during evaluation (Table 1). African Americans were more likely to not be listed and not be listed due to psychosocial contraindications. Of those not listed for psychosocial contraindications, frequencies of potential barriers (Table 2) indicate higher rates of chemical dependency issues and impaired cognitive functioning in African Americans with mental health and support concerns approaching significance. There were not differences between medical or insurance exclusions. Conclusions: African Americans are significantly less likely to be listed for liver transplant than Caucasian patients. This is not due to medical issues or insurance, but rather psychosocial barriers. Identifying why African Americans are less likely to complete work-up and psychosocial contraindications will be important in addressing this disparity. (Table Presented).

Surgery

Kabbani L, **Munie S**, **Lin J**, **Velez M**, **Isseh I**, **Brooks S**, **Leix S**, and **Shepard A**. Flow patterns in the carotid arteries of patients with left ventricular assist devices *Ann Vasc Surg* 2016;PMID: 27531092. Full Text

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OBJECTIVE: To evaluate and define the expected flow pattern changes of carotid artery duplex ultrasound after LVAD placement. METHODS: Retrospective review of Henry Ford Hospital database of patients who had undergone LVAD placement between March 2008 and July 2012 was performed. All patients who had carotid artery duplex scanning before and after LVAD placement within two years of each other and showed less than 50% stenosis were included in this study. Type of waveform, carotid peak systolic velocity and end-diastolic velocities were analyzed, and the values were compared before and after LVAD placement. RESULTS: A total of 13 patients with LVAD had at least two carotid duplex studies before and after LVAD placement within two years of each other. Of those, 92% (n=12) were men, and 61% (n=8) were Caucasian. Mean age was 61 years old. The Heartware ventricular assist device (HVAD) was implanted in 4 patients and the HeartMate II left ventricular assist device was implanted in 9 patients. Post-LVAD Doppler imaging demonstrated parvus tardus waveform. Analysis of flow velocities revealed that

peak systolic velocity was diminished after LVAD placement in both the internal and common carotid arteries (p=0.006 and p<0.0001 respectively). End-diastolic velocity, however, was noted to be increased post LVAD (p<0.0001). Interestingly, mean flow velocities in both the common and internal carotid arteries remained stable after LVAD placement. CONCLUSION: This study reveals changes in waveform morphology and peak systolic and diastolic velocities in the common and internal carotid arteries on carotid duplex after LVAD placement. Additionally, it shows that despite changes in post LVAD pulse pressure in the carotid arteries, the mean flow velocity remained unchanged.

Surgery

Krasnick BA, **Nathanson SD**, Arbabi CN, **Chitale DA**, and **Peterson EL**. The predictive value of increased sentinel lymph node volume in breast cancer *Surg Oncol* 2016; 25(3):321-325. PMID: 27566039. Full Text

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BACKGROUND: Breast cancer sentinel lymph nodes (SLNs) with metastases (mets) are often palpably enlarged. We hypothesized that the volume of the SLN and the size of mets are directly related. SLNs harboring mets are often firm, with increased intra-nodal pressure (INP), and we hypothesized that SLN volume, as well as INP, would correlate directly with SLN metastasis size. METHODS: The SLN volume, INP and met size were measured in 296 SLNs and compared using linear regression analysis. The SLNs were subsequently grouped based upon pN stage. SLN INP and volume were compared between these resultant groups. RESULTS: Increased SLN volume significantly predicted increased SLN met size on univariate and multivariate analysis (p = 0.001 and p = 0.011, respectively). SLN met size predicted increased SLN INP on both univariate and multivariate analysis (both p = 0.001). SLN volume only significantly correlated with increased SLN INP on univariate analysis (p = 0.001). On subgroup analysis of nodal disease, pN1/2/3 nodes (SLN met sizes >2 mm) were significantly larger (p = 0.039 and p = 0.003, respectively) than pN0 and pN1(mi) nodes, and had significantly increased INP (all p = 0.001) as compared to pN0, pN0(i+), and pN1(mi) nodes. CONCLUSIONS: SLN volume and INP increased with increasing SLN met size. The threshold met size for this increase was >2 mm (pN1 disease).

Surgery

Krittanawong C, Namath A, **Lanfear DE**, and Tang WH. Practical pharmacogenomic approaches to heart failure therapeutics *Curr Treat Options Cardiovasc Med* 2016; 18(10):60. PMID: 27566707. Full Text

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OPINION STATEMENT: The major challenge in applying pharmacogenomics to everyday clinical practice in heart failure (HF) is based on (1) a lack of robust clinical evidence for the differential utilization of neurohormonal antagonists in the management of HF in different subgroups, (2) inconsistent results regarding appropriate subgroups that may potentially benefit from an alternative strategy based on pharmacogenomic analyses, and (3) a lack of clinical trials that focused on testing gene-guided treatment in HF. To date, all pharmacogenomic analyses in HF have been conducted as post hoc retrospective analyses of clinical trial data or of observational patient series studies. This is in direct contrast with the guideline-directed HF therapies that have demonstrated their safety and efficacy in the absence of pharmacogenomic guidance. Therefore, the future of clinical applications of pharmacogenomic testing will largely depend on our ability to incorporate gene-drug interactions into the prescribing process, requiring that preemptive and cost-effective testing be paired with decision-support tools in a value-based care approach.

Surgery
Lin JC, and **Myers E**. Three-dimensional printing for preoperative planning of renal artery aneurysm surgery *J Vasc Surg* 2016; 64(3):810. PMID: 27565599. Full Text

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Surgery
Nagai S, **Yoshida A**, **Rizzari M**, **Collins K**, **Kim D**, and **Abouljoud M**. Center and surgeons' experience improves outcome in adult-to-adult living donor liver transplantation: Validation of the report of the A2ALL consortium *Am J Transplant* 2016; 16:475. PMID: Not assigned. Abstract

S. Nagai, Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, United States

Background: Adult-to-adult living donor liver transplantation cohort study (A2ALL) has reported improved outcomes in centers with greater experience (>20 cases). The aim of this study was to validate and investigate the influence of center's and surgeons' experience by reviewing living donor liver transplantation (LDLT) outcomes in non-A2ALL single center. Methods: LDLT from December 2000 to March 2015 was reviewed (n=90). Risk factor analysis for graft survival and postoperative biliary complications (leak [BL] and anastomotic stricture [BAS]) were conducted. Surgeons' and center's experience were included in potential factors. Surgeons A, B and C performed 75 (between center's case #1-89, 2000-2015), 8 (between case#15-25, 2005-2006), and 7 LDLTs (between case #73-90, 2011-2015), respectively. Results: Graft survival in the center's first 20 cases was significantly worse (P=0.01, hazard ratio [HR]=3.57). Surgeon A's first 20 cases (early experience) was considered to be a risk factor of worse graft survival (P=0.01, HR=4.02 [Ref. Surgeon A's late experience]), but not surgeons B's and C's early experience (P=0.16 and 0.99, respectively). (Table Presented) BL and BAS rates were 24% (22/90) and 19% (17/90). Surgeons A's and C's early experience remained independent risk factors for BL (P=0.01 and 0.02, odds ratio [OR]=3.96 and 7.67, respectively), along with recipient age (P=0.01, OR=1.06 per year) on multivariate analysis. Surgeon B's early experience increased a risk of BL, but not significant (P=0.27, OR=2.88). Type of biliary reconstruction (duct-to-duct vs. Roux-en-Y) or the number of ducts reconstructed was not a risk factor for BL. Center's or each surgeon's experience was not associated with BAS and no significant risk factors were identified. Conclusion: Once center experience reached 20 LDLTs, early experience of new surgeons no longer affected graft survival. However, regardless of center's experience, BL was consistently associated with surgeons' early experience. Surgeon's technical experience may play an important role in complex biliary reconstructions.

Surgery
Nagai S, **Yoshida A**, **Rizzari M**, **Collins K**, **Kim D**, and **Abouljoud M**. Updated experience of living donor right hepatectomy using mini-incision technique *Am J Transplant* 2016; 16:475. PMID: Not assigned. Abstract

S. Nagai, Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, United States

Aim: We previously reported 28 consecutive cases of minimally invasive living donor right hepatectomy (10cm mini-incision right hepatectomy with or without laparoscopic assistance). Currently, we routinely use the upper midline incision without laparoscopic assistance. The aim of this study was to investigate the surgical feasibility and safety of this approach based on our updated experience. Methods: Between December 2000 and March 2015, living donor right hepatectomy was performed in 91 patients. The first 33 cases were performed through standard subcostal incision with midline extension (Group 1). Hybrid technique (handassisted laparoscopic liver mobilization and mini-laparotomy for hilar and parenchymal dissection) was introduced in 2008 and used in 19 patients until 2011 (Group 2). Upper midline incision (10 cm) right hepatectomy without laparoscopic assistance was introduced in 2010 and was applied to the rest of 39 cases (Group 3). All procedures were performed by the same surgeon. Surgical factors, donor characteristics, and postoperative course in the mini-incision group (Group 3) were investigated in comparison with those in the standard incision group (Group 1). Surgical complications were evaluated according to the Clavien-Dindo classification. Results: Operative time was significantly shorter in Group 3 than in Group 1 (337min vs. 365min, P=0.02). Estimated blood loss was comparable (338ml vs. 318ml, P=0.53). Length of hospital stay was significantly shorter in the Group 3 (6.2 days vs. 7.9 days, P<0.001). Postoperative complication rate was lower in Group 3 (6/32 [18%] vs. 3/39 [8%], P=0.26). Of these 3 patients in Group 3, one patient was categorized as grade 3b (exploratory laparotomy for postoperative bleeding), and two patients had grade 2 complication (biloma and postoperative transfusion). There was no patient in our entire cohort who had grade 4 (life-threatening) or 5 (death) complication . With regard to donor body habitus in Group 3, the maximum body mass index, and estimated graft weight were 35 and 1549mL, respectively. No conversion was observed from the mini midline incision technique to the standard

subcostal incision technique. Conclusion: Our increased experience with the mini-laparotomy technique validates the safety and feasibility of this approach. This unique procedure could be safely applied in experienced hands to living liver donor without laparoscopic assistance and within a broad weight range.

Surgery

Prashar R, **Goggins M**, **Yessayan L**, **Patel A**, and **Goggins M**. Focal C4d staining in biopsies of kidney transplant recipients is not associated with antibody mediated rejection and does not correlate with graft survival *Am J Transplant* 2016; 16:702. PMID: Not assigned. Abstract

R. Prashar, Transplant Institute, Henry Ford Hospital, Detroit, United States

Introduction: While diffuse C4d positivity in kidney transplant peritubular capillaries(PTC) strongly co-relates with the presence of antibody mediated rejection(AMR),data on the significance of focal C4d deposits are lacking. The effect of DGF, anti-HLA DSA and high PRA on C4d staining remains uncertain. We present our center's experience of C4d staining in kidney transplant biopsies Methods: All consecutive biopsies in kidney transplant recipients done at our institution between December 2011 and March 2013 were retrospectively reviewed. C4d was assessed by immunohistochemistry and histopathological examination. Biopsies were classified as PTC C4d negative(<10%),focal(10%-50%)or diffuse(>50%).AMR and Cell Mediated Rejection(CMR) were diagnosed using Banff criteria Results: Patient characteristics Follow up was a mean of 646 +/- 273 days. Out of 100 biopsies,58% were C4d negative,33% focal C4d,9% were diffuse C4d positive. While 6/9 patients with diffuse C4d had AMR, no patients with negative or focal C4d had AMR.CMR was diagnosed in 5/9 patients with diffuse C4d and the incidence of CMR was 24% and 29% in focal or no C4d biopsies.(statistically insignificant).While graft loss was 55% in diffuse C4d biopsies, there was no statistically significant difference between incidence of graft loss in focal positive(25%) and C4d negative(31%) biopsies. There was no statistically significant difference between C4d positivity in patients with or without DGF. We found no statistically significant difference in C4d positivity in patients with low(<30%) vs high cPRA(>30%). Summary of DSA : Conclusion: Our data suggest no implication of focal C4d in PTC in kidney transplant biopsies in diagnosis of AMR, CMR or incidence of graft loss. Additionally, high cPRA and DGF appear to have no association with C4d positivity in kidney transplant biopsies. (Table Presented).

Surgery

Putchakayala K, **Kane W**, **Takahashi K**, **Rizzari M**, **Yoshida A**, and **Abouljoud M**. Left renal vein ligation for management of portal hypoperfusion in liver transplantation *Am J Transplant* 2016; 16:672. PMID: Not assigned. Abstract

K. Putchakayala, Henry Ford Transplant Institute, Henry Ford Hospital, Detroit, United States

Intro: In orthotopic liver transplant (OLT), low portal venous flow (PVF) is an independent risk factor for 1-year mortality. Ligation of existing portosystemic shunts is recommended. We describe our institutional experience with left renal vein (LRV) ligation to augment low PVF via spontaneous splenorenal shunts. Methods: We routinely measure intraoperative PVF following reperfusion. PVF<800mL/min leads to evaluation for intervention. If the portal vein anastomosis is normal, and ligation of spontaneous portosystemic shunts is unsuccessful, we evaluate for spontaneous LRV collaterals. If present, we proceed with temporary LRV occlusion. Augmentation results in ligation, otherwise alternative methods are pursued. We reviewed all deceased-donor OLTs performed at Henry Ford Hospital from 3/1/2009 to 9/1/2015. Results: Eight cases describing LRV ligation were identified. PVF increased from 550 to 1380 mL/min. Two patients required post-transplant hemodialysis (HD). Patient #6 underwent reoperation for removal of the tie used to ligate the LRV due to worsening renal function, however HD was required due to lack of improvement. Patient #2 did not have improvement in PVF with ligation, so the portal vein was arterialized with donor gastroduodenal artery and improved to 1200mL/min. Table 1 and 2 summarize the patients reviewed Conclusion: Selective LRV ligation in patients with low PVF during OLT is a viable option for augmentation if ligation of spontaneous portosystemic shunts is not beneficial. (Table Presented).

Surgery

Rao B, **Yoshida A**, **Ibrahim M**, and **Jafri SM**. The use of perioperative lactate values as markers for adverse outcomes in liver transplantation *Am J Transplant* 2016; 16:672. PMID: Not assigned. Abstract

B. Rao, Internal Medicine, Henry Ford Hospital, Detroit, United States

Introduction: We examined the utility of perioperative lactate values for the prediction of multiple post-transplant outcomes including length of hospital stay (LOS), acute cellular rejection (ACR), and mortality in a single center liver transplant population. Methods: Retrospective chart review of all patients undergoing primary orthotopic liver

transplant at a large urban tertiary care center from 2008-2010. Data was obtained on recipient demographics, donor age, donor gender, surgical time points, cold ischemia time (CIT), preoperative lactate, peak intraoperative lactate, and peak postoperative lactate (maximum lactate value within 48 hours post-surgery). We examined outcomes of postoperative LOS, history of moderate or severe ACR, and mortality. Analysis was performed using multivariate linear and logistic regression models. Results: 273 patients were included for analysis. Mean recipient age was 52 (range 17-72) with 66% males. Mean donor age was 43 (range 7-83) with 40% males. Mean CIT was 312 minutes (range 12-699). Mean MELD was 22 (range 6-53). For every one unit increase in peak intraoperative lactate there was a 1.64 day increase in LOS ($p < 0.001$). For every one unit increase in peak intraoperative lactate the odds of death was significantly increased at one month (OR = 1.37, $p = 0.001$) and one year (OR = 1.14; $p = 0.021$). For every one unit increase in peak postoperative lactate there was a 1.76 day increase in LOS ($p < 0.001$). The odds of death was significantly increased for every one unit increase in peak postoperative lactate at one month (OR = 1.28; $p = 0.004$) and one year (OR = 1.13; $p = 0.003$). Preoperative lactate was not associated with any significant adverse outcomes. None of the perioperative lactate values were associated with developing an episode of moderate or severe ACR after transplant. Conclusion: Our results create a better understanding and interpretation of perioperative lactate values in liver transplantation. Findings clearly show an association between perioperative lactate values and mortality up to one year after transplant.

Surgery

Rebhan N, **Bebanic M**, **Yoshida A**, **Macaulay T**, **Goldstein E**, **Ho CX**, **Eshelman A**, **Abouljoud M**, **Jesse M**, and **Rizzari M**. Psychiatric characteristics of acute liver failure patients: Acetaminophen overdose versus other etiologies *Am J Transplant* 2016; 16:524. PMID: Not assigned. Abstract

N. Rebhan, Transplant Institute, Henry Ford Health System, Detroit, United States

Scant research exists on the psychiatric history of patients with acute liver failure (ALF) presenting for liver transplantation. This study compared psychiatric profiles of patients in ALF due to acetaminophen (APAP) overdose versus other etiologies. Methods: Retrospective clinical chart review of patients referred for liver transplantation at a single center from January 2004 through December 2012. Results: 105 patients presented in ALF, mean age 42.4 years (SD 15.3, range 17 to 71), predominantly female (n 76, 72.4%), and mostly Caucasian (n 72, 68.6%) or African American (n 22, 21.0%). Caucasian patients were significantly more likely to have substance abuse histories compared to African American patients (51.4% vs. 25.0%; p=.03). Similarly, family psychiatric histories were more common in Caucasian than in African American patients (39.7% vs. 12.5%; p=.04). There were no other significant differences in psychiatric characteristics between races. Psychiatric characteristics of patients who presented with overdose versus other etiologies outlined in Table 1. Conclusions: There is a significant presence of psychiatric diagnoses, substance abuse histories, and psychiatric treatment histories in patients presenting in ALF due to overdose compared to other etiologies. There was no significant difference in support-related concerns for transplant, indicating that a supportive network may not necessarily be protective. This emphasizes the importance of thorough assessments and close monitoring when prescribing APAP-containing medications, especially in patients with known psychiatric histories. (Table Presented).

Surgery

Rodriguez J, **Patel A**, and **Goggins M**. Age gap analysis between live donor and recipients in kidney transplantation: Opportunities to improve voluntary exchange programs and kidney paired donation *Am J Transplant* 2016; 16:450. PMID: Not assigned. Abstract

J. Rodriguez, Internal Medicine, Henry Ford Hospital, Detroit, United States

Graft survival(GS) perception is that, with a smaller age gap between the donor(D) and recipient(R), better the outcome. It is unclear if there is an age-gap limit at which the benefit in GS disappears. We chose to analyze graft failure(GF)rates among R of living donors(LD) with an incremental D minus R age gap. We compared such groups to standard criteria deceased donors(SCD)transplants. Methods: Using the UNOS database from 1995 to 2013, we evaluated GF involving LD with R ages 18-79 from 1995 onward. We compared GF among R from LD with an age-gap, D minus R, of <10, 10-14, 15-19, 20-24, 25-30 and 30+. These age-gap groups were compared to SCD R. D and R demographic and transplant data were used to allow Cox regression analysis. Endpoints were plotted using Kaplan-Meir analysis. Results: When D are older than R, Cox regression analysis(n=13,930)showed no statistical difference in GF comparing a D-R age-gap less than 10 vs age-gap 10-14(p 0.636).There was a significant increase in GF in age-gap 15-19 (n=3,127)compared to 10-14 (P<0.001, HR 1.55).There was no GF difference comparing remaining age-gap groups.Kaplan-Meier curve confirmed findings.Fig1 Comparing LD R of same age-gap groups with R of SCD(n=29,058) a statistical significance decreased in GF was found between age-gap<15 (p<0.001, HR 0.67). There was no statistical difference between the wider age-gap groups and SCD R. When R are older than D, Cox regression analysis(n=41,881) showed that age-gap of <10 had statistically significant improved GF compared to age gap>10(p<0.001, HR 1.18)however, it was not significant when compared to age gap >15 (p=0.1). Conclusions:

There appears to be a statistical significant benefit on GF within LD R if the age-gap is <15 compared to age gap>15. Within age gap groups of >15, there was no difference in GF. LD R had decreased GF when compared to SCD R, if age gap was <15, but not if gap was>15.For R older than D,there is no GF benefit with an age gap of >15 compared to <15. (Figure Presented).

Surgery
Takahashi K, **Patel AK**, **Putchakayala KG**, **Denny JE**, **Kim DY**, and **Malinzak LE**. Arterioenteric fistula 12 years after kidney transplant *Kidney Int* 2016; 90(3):710. PMID: 27521122. Full Text

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Surgery
Takahashi K, **Putchakayala K**, **Malinzak L**, **Denny J**, **Abouljoud M**, and **Kim D**. Is ketorolac really safe for donor nephrectomy? *Am J Transplant* 2016; 16:485. PMID: Not assigned. Abstract

K. Takahashi, Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, United States

Background. Ketorolac is a nonsteroidal anti-inflammatory drug used for postoperative pain management. The purpose of this study is to assess the impact of ketorolac after donor nephrectomy.Material and Methods. We retrospectively reviewed all laparoscopic or robotic donor nephrectomy from April 2008 to January 2015, and enrolled 211 patients. 126 patients received ketorolac intraoperatively and/or postoperatively within 24 hours after nephrectomy, and 85 patients without ketorolac. The pain scores immediately and 24 hours after nephrectomy, length of hospital stay, and reduction of glomerular filtration rate (GFR)at 1 day, 14 days, and 6 monthsafter nephrectomy were compared between the patients with and without ketorolac. Results. Length of hospital stay was significantly shorter in the ketorolac group compared with non-ketorolac group (2.9 vs 3.3 days). Despite no difference in the pain scores immediately after surgery, pain scores at 24 hours were significantly lower in the ketorolac group (3.0 vs 4.5). Although reduction of GFR on day 1 was significantly larger in the ketorolac group, there were no differences on day 14 and 6 months. When patients were classified with the usage doses, reduction of GFR at 6 months after nephrectomy was larger in the total dose ≥ 75mg group, compared with the non-ketorolac group and total dose < 75mg group (non-ketorolac 33% vs total dose < 75mg 36% vs total dose ≥ 75mg 41%, P= 0.07). (Figure Presented) Conclusion. Ketorolac showed significant impact in shortening hospital stay and pain control after nephrectomy. However, using dose higher than 75mg might impair renal function in the long term.

Surgery
Takahashi K, **Putchakayala K**, **Rizzari M**, **Collins K**, **Nagai S**, **Yoshida A**, **Abouljoud M**, and **Schnickel G**. Multifactorial prediction of biliary stricture after liver transplantation: The impact of platelet counts *Am J Transplant* 2016; 16:667-668. PMID: Not assigned. Abstract

K. Takahashi, Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, United States

Background: Biliary stricture is a common cause of morbidity after liver transplantation (LT). This study aimed to determine the risk factors for posttransplantation biliary anastomotic strictures (BAS), focusing on perioperative platelet counts. Methods: We retrospectively reviewed all ABO-identical or compatible cadaveric LT and enrolled 771 consecutive recipients who underwent LT with duct-to-duct biliary reconstruction from January 2000 to June 2012. Recipients who received donation from after cardiac death donors were excluded. Results: BAS was reported in 142 cases (18.4%). The mean time for stricture development was 176.3 days. Postoperative platelet counts after LT were highly correlated with preoperative platelet counts. Preoperative and postoperative platelet counts within 5 days after LT were significantly lower in the patients with BAS than those without BAS. Using the cutoff values acquired by receiver operating curve analysis, univariate analysis revealed that recipient age, recipient male gender, the Model for End-Stage Liver Disease (MELD) score >30, preoperative INR, and preoperative platelet count <76.500/ml were risk factors for stricture development. No associations were observed in terms of donor and surgical factors. Multivariate analysis indicated that recipient age (odds ratio (OR) =1.03), recipient male gender (OR =1.65), the MELD score >30 (OR =2.00), and preoperative platelet count <76.500/ml (OR =1.60) were independent risk factors. Conclusion: We demonstrated for the first time that low platelet count was associated with progression of BAS after LT. Increasing preoperative platelet count and maintaining platelet counts higher by platelet therapy such as thrombopoietin-receptor agonist administration could potentially reduce post-transplantation BAS. (Figure Presented).

Surgery

Tinney F, **Yessayan L**, **Abouljoud M**, and **Patel A**. Characterization of vascular lesions in living donor renal transplant implant biopsies *Am J Transplant* 2016; 16:646. PMID: Not assigned. Abstract

F. Tinney, Wayne State University, School of Medicine, Detroit, United States

INTRODUCTION: Nephrosclerosis is often associated with pathological injury to kidneys resulting from chronic high blood pressure and/or aging, and may predict the progression of decline in renal function. We sought to evaluate pathological features of implant biopsies, such as arteriolosclerosis (AS), arteriolar hyalinosis (AH), microthrombi, and glomerulosclerosis (GS), and to correlate this pathology with renal function in living transplant donors. METHODS: A retrospective review of 100 living donor renal transplants was conducted, from June 2012 to June 2015. All recipient biopsies were obtained intra-operatively, and evaluated for pathological abnormalities. The impact of the presence of arterial abnormalities on donor serum creatinine at five different time points was evaluated (pre-operative, and at 2, 26, 52, and 104 weeks post-donation). Arterial changes were defined as the presence of at least one of the following: AS, AH or microthrombi. RESULTS: Donors' (N=100) mean age was 43 years (range 20-67), 66 were female and 80 were white. Of the recipient biopsies done intra-operatively, 55/100 reported abnormal pathology (31% GS, 17% AS, and 13% AH). Donors with age greater than 50 years were more likely to have arterial changes (OR 3.35; 95% CI [1.31-8.59]). In a multivariate model adjusting for race, gender, body mass index (BMI), and baseline kidney function, arterial hyalinosis was associated with age (OR 1.10; 95% CI [1.03-1.17]). However, age was not associated with neither AS, microthrombi or GS. Arterial changes were not significantly associated with race, BMI, or pre/post-operative serum creatinine values. CONCLUSIONS: These results suggest that despite all donors meeting preoperative criteria, older donors demonstrated more pathological arterial changes, especially AH. Of additional concern, the shear number of healthy donors who displayed pathological changes at the time of transplant suggests that the evaluation of donor candidates may not be entirely adequate. Further research into the longterm outcomes of donor populations, as well as the recovery of renal function in recipients, is underway. (Table Presented).

Surgery

Vincenti F, Medina Pestana J, **Abouljoud M**, Bresnahan B, Duro Garcia V, Mulloy L, Rice K, Rostaing L, Zayas C, Calderon K, Meier-Kriesche U, Polinsky M, Zhao H, and Larsen C. Outcomes in black vs non-black patients administered belatacept (bela) or cyclosporine (CSA) in benefit *Am J Transplant* 2016; 16:743. PMID: Not assigned. Abstract

F. Vincenti, UCSF, San Francisco, United States

Studies consistently show worse outcomes for black vs non-black kidney transplant recipients. At 7 yrs post-transplant in BENEFIT, bela was associated with superior graft survival and renal function vs CsA. We examined outcomes by race in BENEFIT. Recipients of living or SCD kidneys were randomized to bela more intense (MI), bela less intense (LI), or CsA. All randomized, transplanted pts were analyzed to 7 yrs. Time to death or graft loss was compared between regimens with Cox regression. Race and treatment effect were assessed. The interaction of treatment and race was also considered. GFR was estimated from months 1-84 using a repeated measures model. Of 666 randomized pts, 55 were black. SAE rates in black vs non-black pts were similar. In both subgroups, estimated mean GFR increased over 7 yrs for bela but declined for CsA. In black pts, GFR slopes diverged over time between bela LI and CsA (P<.0001), but not bela MI and CsA (P=.11). In non-black pts, the interaction of the treatment vs time effect deriving from the model favored each bela regimen vs CsA (P<.0001). In this post-hoc analysis, outcomes were similar in bela-treated black and non-black pts. While estimated mean GFR was higher in black pts treated with bela vs CsA, the number of black pts was small. (Figure Presented).

Surgery

Yip J, **Bruno DA**, **Burmeister C**, **Kazimi M**, **Yoshida A**, **Abouljoud MS**, and **Schnickel GT**. Deep vein thrombosis and pulmonary embolism in liver transplant patients: Risks and prevention *Transplant Direct* 2016; 2(4):e68. PMID: 27500259. Full Text

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) are surgical complications estimated to occur in 5% to 10% of patients. There are limited data regarding DVT/PE in the early postoperative period in liver transplant patients. The aim of this study is to determine risk factors that influence the incidence of DVT/PE and the effectiveness of prophylaxis. METHODS: We reviewed the records of 999 patients who underwent initial liver transplant between January 2000 and June 2012 at Henry Ford Hospital. In 2011, a standardized prophylactic regimen using subcutaneous (SQ) heparin was initiated. All patients that developed either upper/lower extremity DVT or PE within the first 30 days of transplant formed the cohort of this study. RESULTS: On multivariate analysis, only peripherally inserted central catheter (PICC) placement and SQ heparin were associated with DVT/PE. In patients receiving heparin, 3 (1.0%) had DVT/PE versus 25 (3.5%) who did not receive heparin (P = 0.03). Sixteen (6.9%) patients that

had a PICC developed DVT/PE compared with 12 (1.6%) patients without a PICC (P < 0.001). In the heparin group, DVT/PE with PICC was reduced to 3 (3.0%) versus 13 (9.9%) in those with a PICC and did not receive heparin (P = 0.03). Mean time from transplant to DVT/PE diagnosis was 12.3 days. Length of hospitalization was significantly longer in patients who developed DVT/PE (18.5 vs 10.0 days, P < 0.001). CONCLUSIONS: In this study, we demonstrated that PICC placement significantly increases the likelihood of DVT/PE in liver transplant recipients. Prophylactic SQ heparin effectively reduced DVT/PE events in this patient population.

Urology

Zhang Z, Shiratsuchi H, **Palanisamy N**, Nagrath S, and Ramnath N. Expanded ctcs from a patient with alk positive lung cancer present eml4-alk rearrangement along with resistance mutation and enable drug sensitivity testing: A case study *J Thorac Oncol* 2016;PMID: 27507192. Article Request Form

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The emergence of liquid biopsy using circulating tumor cells (CTCs) as a resource to identify genomic alterations in cancer presents new opportunities for diagnosis, therapy and surveillance. The presented study identified EML4-ALK gene rearrangement in expanded CTCs from one ALK positive lung adenocarcinoma patient. At the time of radiographic progression, CTCs obtained from the patient revealed a drug resistance mutation, L1196M on the ALK gene. CTCs were expanded ex-vivo and drug sensitivity testing was performed using 2 ALK inhibitors, crizotinib and ceritinib. The half maximal inhibitory concentration (IC50) of ceritinib was 1664 nM compared with crizotinib, 2268 nM showing that ceritinib was a more potent ALK inhibitor. We demonstrate that it is feasible to detect serial genetic alterations in expanded CTCs and perform in vitro drug screening. These findings support the clinical utility of CTCs not only for diagnosis, but also a potential tool for drug sensitivity testing in distinct subsets of lung cancer and for personalized precision medicine.