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Henry Ford Health System Publication List – October 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 November, and then imported into EndNote for formatting. There are 138 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
Krouse RZ, Sorkness CA, Wildfire JJ, Calatroni A, Gruchalla R, Khurana Hershey GK, Kattan M, Liu AH, Makhija M, Teach SJ, West JB, Wood RA, **Zoratti EM**, and Gergen PJ. Minimally important differences and risk levels for the composite asthma severity index *J Allergy Clin Immunol* 2016;PMID: 27744028. Full Text

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College of Physicians and Surgeons, Columbia University, New York, NY.
National Jewish Health, Denver, CO, and Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, CO.
Ann and Robert H. Lurie Children's Hospital of Chicago, IL.
Children's National Health System, Washington, DC.
Boston University School of Medicine, Boston, MA.
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CASI is a quantitative measure of asthma severity that was introduced in the Journal of Allergy and Clinical Immunology in March 2012. This follow-up letter expands upon the initial report by comparing the CASI to an expert clinican assessment of asthma severity. Using expert assessment, we establish risk levels for CASI and calculate other useful parameters such as the minimal important difference (MID) and minimal important effect size.

Allergy
Liu AH, Babineau DC, Krouse RZ, **Zoratti EM**, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar CM, Gruchalla RS, Kattan M, Teach SJ, Makhija M, Pillai D, Lamm CI, Gern JE, Sigelman SM, Gergen PJ, Togias A, Visness CM, and Busse WW. Pathways through which asthma risk factors contribute to asthma severity in inner-city children *J Allergy Clin Immunol* 2016; 138(4):1042-1050. PMID: 27720018. Full Text

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Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington, DC.
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National Institute of Allergy and Infectious Diseases, Bethesda, Md.

BACKGROUND: Pathway analyses can be used to determine how host and environmental factors contribute to asthma severity. OBJECTIVE: To investigate pathways explaining asthma severity in inner-city children. METHODS: On the basis of medical evidence in the published literature, we developed a conceptual model to describe how 8 risk-factor domains (allergen sensitization, allergic inflammation, pulmonary physiology, stress, obesity, vitamin D, environmental tobacco smoke [ETS] exposure, and rhinitis severity) are linked to asthma severity. To estimate the relative magnitude and significance of hypothesized relationships among these domains and asthma severity, we applied a causal network analysis to test our model in an Inner-City Asthma Consortium study. Participants comprised 6- to 17-year-old children (n = 561) with asthma and rhinitis from 9 US inner cities who were evaluated every 2 months for 1 year. Asthma severity was measured by a longitudinal composite assessment of day and night symptoms, exacerbations, and controller usage. RESULTS: Our conceptual model explained 53.4% of the variance in asthma severity. An allergy pathway (linking allergen sensitization, allergic inflammation, pulmonary physiology, and rhinitis severity domains to asthma severity) and the ETS exposure pathway (linking ETS exposure and pulmonary physiology domains to asthma severity) exerted significant effects on asthma severity. Among the domains, pulmonary physiology and rhinitis severity had the largest significant standardized total effects on asthma severity (-0.51 and 0.48, respectively), followed by ETS exposure (0.30) and allergic inflammation (0.22). Although vitamin D had modest but significant indirect effects on asthma severity, its total effect was insignificant (0.01). CONCLUSIONS: The standardized effect sizes generated by a causal network analysis quantify the relative contributions of different domains and can be used to prioritize interventions to address asthma severity.

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National Institute of Allergy and Infectious Diseases, Bethesda, Md.
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BACKGROUND: Treatment levels required to control asthma vary greatly across a population with asthma. The factors that contribute to variability in treatment requirements of inner-city children have not been fully elucidated. OBJECTIVE: We sought to identify the clinical characteristics that distinguish difficult-to-control asthma from easy-to-control asthma. METHODS: Asthmatic children aged 6 to 17 years underwent baseline assessment and bimonthly guideline-based management visits over 1 year. Difficult-to-control and easy-to-control asthma were defined as daily therapy with 500 mug of fluticasone or greater with or without a long-acting beta-agonist versus 100 mug or less assigned on at least 4 visits. Forty-four baseline variables were used to compare the 2 groups by using univariate analyses and to identify the most relevant features of difficult-to-control asthma by using a variable selection algorithm. Nonlinear seasonal variation in longitudinal measures (symptoms, pulmonary physiology, and exacerbations) was examined by using generalized additive mixed-effects models. RESULTS: Among 619 recruited participants, 40.9% had difficult-to-control asthma, 37.5% had easy-to-control asthma, and 21.6% fell into neither group. At baseline, FEV1 bronchodilator responsiveness was the most important characteristic distinguishing difficult-to-control asthma from easy-to-control asthma. Markers of rhinitis severity and atopy were among the other major discriminating features. Over time, difficult-to-control asthma was characterized by high exacerbation rates,

particularly in spring and fall; greater daytime and nighttime symptoms, especially in fall and winter; and compromised pulmonary physiology despite ongoing high-dose controller therapy. CONCLUSIONS: Despite good adherence, difficult-to-control asthma showed little improvement in symptoms, exacerbations, or pulmonary physiology over the year. In addition to pulmonary physiology measures, rhinitis severity and atopy were associated with high-dose asthma controller therapy requirement.

Allergy
Yang IV, Pedersen BS, Liu AH, O'Connor GT, Pillai D, Kattan M, **Misiak RT**, Gruchalla R, Szefler SJ, Khurana Hershey GK, Kercsmar C, Richards A, Stevens AD, Kolakowski CA, Makhija M, Sorkness CA, Krouse RZ, Visness C, Davidson EJ, Hennessy CE, Martin RJ, Togias A, Busse WW, and Schwartz DA. The nasal methylome and childhood atopic asthma *J Allergy Clin Immunol* 2016;PMID: 27745942. Full Text

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BACKGROUND: Given the strong environmental influence on both epigenetic marks and allergic asthma in children, the epigenetic alterations in respiratory epithelia might provide insight into allergic asthma. OBJECTIVE: We sought to identify DNA methylation and gene expression changes associated with childhood allergic persistent asthma. METHODS: We compared genomic DNA methylation patterns and gene expression in African American children with persistent atopic asthma (n = 36) versus healthy control subjects (n = 36). Results were validated in an independent population of asthmatic children (n = 30) by using a shared healthy control population (n = 36) and in an independent population of white adult atopic asthmatic patients (n = 12) and control subjects (n = 12). RESULTS: We identified 186 genes with significant methylation changes, differentially methylated regions or differentially methylated probes, after adjustment for age, sex, race/ethnicity, batch effects, inflation, and multiple comparisons. Genes differentially methylated included those with established roles in asthma and atopy and genes related to extracellular matrix, immunity, cell adhesion, epigenetic regulation, and airflow obstruction. The methylation changes were substantial (median, 9.5%; range, 2.6% to 29.5%). Hypomethylated and hypermethylated genes were associated with increased and decreased gene expression, respectively (P < 2.8 x 10-6 for differentially methylated regions and P < 7.8 x 10-10 for differentially methylated probes). Quantitative analysis in 53 differentially expressed genes demonstrated that 32 (60%) have significant methylation-expression relationships within 5 kb of the gene. Ten loci selected based on the relevance to asthma, magnitude of methylation change, and methylation-expression relationships were validated in an independent cohort of children with atopic asthma. Sixty-seven of 186 genes also have significant asthma-associated methylation changes in nasal epithelia of adult white asthmatic patients. CONCLUSIONS: Epigenetic marks in respiratory epithelia are associated with allergic asthma and gene expression changes in inner-city children.

Allergy
Zoratti EM, Krouse RZ, Babineau DC, Pongracic JA, O'Connor GT, Wood RA, Khurana Hershey GK, Kercsmar CM, Gruchalla RS, Kattan M, Teach SJ, Sigelman SM, Gergen PJ, Togias A, Visness CM, Busse WW, and Liu AH. Asthma phenotypes in inner-city children *J Allergy Clin Immunol* 2016; 138(4):1016-1029. PMID: 27720016. Full Text

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BACKGROUND: Children with asthma in low-income urban areas have high morbidity. Phenotypic analysis in these children is lacking, but may identify characteristics to inform successful tailored management approaches. OBJECTIVE: We sought to identify distinct asthma phenotypes among inner-city children receiving guidelines-based management. METHODS: Nine inner-city asthma consortium centers enrolled 717 children aged 6 to 17 years. Data were collected at baseline and prospectively every 2 months for 1 year. Participants' asthma and rhinitis were optimally managed by study physicians on the basis of guidelines. Cluster analysis using 50 baseline and 12 longitudinal variables was performed in 616 participants completing 4 or more follow-up visits. RESULTS: Five clusters (designated A through E) were distinguished by indicators of asthma and rhinitis severity, pulmonary physiology, allergy (sensitization and total serum IgE), and allergic inflammation. In comparison to other clusters, cluster A was distinguished by lower allergy/inflammation, minimally symptomatic asthma and rhinitis, and normal pulmonary physiology. Cluster B had highly symptomatic asthma despite high step-level treatment, lower allergy and inflammation, and mildly altered pulmonary physiology. Cluster C had minimally symptomatic asthma and rhinitis, intermediate allergy and inflammation, and mildly impaired pulmonary physiology. Clusters D and E exhibited progressively higher asthma and rhinitis symptoms and allergy/inflammation. Cluster E had the most symptomatic asthma while receiving high step-level treatment and had the highest total serum IgE level (median, 733 kU/L), blood eosinophil count (median, 400 cells/mm3), and allergen sensitizations (15 of 22 tested). CONCLUSIONS: Allergy distinguishes asthma phenotypes in urban children. Severe asthma often coclusters with highly allergic children. However, a symptomatic phenotype with little allergy or allergic inflammation was identified.

Anesthesiology
Kim DD, and **Sibai N**. Prolongation of greater occipital neural blockade with 10% lidocaine neurolysis: a case series of a new technique *J Pain Res* 2016; 9:721-725. PMID: 27729811. Full Text

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INTRODUCTION: Greater occipital nerve blocks (GONB) have been used for headache but their benefit may be short. Ready et al performed intrathecal injections on rabbits and reported neurologic/histologic changes that required concentrations of at least 8%. Our study tests the hypothesis that the neurolytic effects of GONB with 10% lidocaine can prolong relief. METHODS: After an approval from Henry Ford Hospital Institutional Review Board, a chart review was performed for patients who had GONB with 10% lidocaine. Patients received 10% lidocaine after short response (<1 month / >50% relief) to GONB with 1 cc of a solution containing 9 mL 0.5 % bupivacaine and 40 mg methylprednisolone. They received a block with 10% lidocaine with volume given at <80% of the maximum dose of 4 mg/kg. Injections were performed under fluoroscopic guidance after injection of 0.1 cc of contrast (isovue or magnevist). All patients had intravenous access and were given fentanyl and midazolam. The visual analog scale (VAS) scores were recorded on follow-up, and the duration of response was noted. VAS changes with 10% lidocaine and comparison of duration with methylprednisolone were performed using paired t-test. RESULTS: Thirteen patients were reviewed; 12 were female and the mean age was 47. Ten were diagnosed with migraine, and three with occipital neuralgia; 12 had bilateral symptoms. Baseline VAS prior to 10% lidocaine averaged 86.92 mm. The mean volume injected per nerve was 1.096 mL. There was significant decrease in mean% VAS with 10% lidocaine at 60.4% (mean: -52.69 mm) (P=0.001). The mean duration of relief was significantly higher with 10% lidocaine at 148.05 days ([standard deviation]=98.87) versus methylprednisolone at 6.33 days (standard deviation=5.01) (P=0.001). No complications or side effects were reported. CONCLUSION: Ten percent lidocaine may be a useful neurolytic agent in prolonging the duration of GONB.

Anesthesiology

Konda P, Ai D, **Guerra CE**, Rodriguez-Restrepo A, Mehran RJ, Rice D, Hofstetter W, Heir J, Kwater P, Gottumukkala V, Hernandez M, and Cata JP. Identification of risk factors associated with postoperative acute kidney injury after esophagectomy for esophageal cancer *J Cardiothorac Vasc Anesth* 2016;PMID: 27720491. Full Text

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OBJECTIVE: To identify risks factors associated with acute kidney injury (AKI) after esophageal cancer surgery. DESIGN: This was a retrospective study. SETTING: Single academic center. PARTICIPANTS: Subjects with non-metastatic esophageal cancer. Patients were excluded if they were younger than 18 years and had missing data. MEASUREMENTS AND MAIN RESULTS: Primary outcome of the study was AKI according to AKI Network criteria. Demographic and perioperative variables were compared in patients with and without AKI. A multivariate Cox proportional model was used to assess the association between perioperative variables and AKI; $p<0.05$ was considered statistically significant. AKI was found in 107 (11.9%) of the 898 patients included in the study. The multivariate analysis also showed that BMI (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.03-1.11), number of comorbidities (OR 1.52, 95% CI 1.20-1.93, p = 0.001), and preoperative creatinine concentrations (OR 2.37, 95% CI 1.14-4.92, p = 0.02) were independent predictors for AKI. The use of dexamethasone was associated with a reduced risk for AKI. CONCLUSIONS: In support of previous reports in the literature, the authors found that AKI was not an uncommon complication after esophageal surgery. Obesity, cardiovascular comorbidities, and high preoperative concentrations were predictors of AKI. Dexamethasone administration during surgery appeared to have a protective effect. This finding opens an opportunity to further study in a randomized controlled trial the efficacy of dexamethasone in the prevention of AKI.

Cardiology

Al Rifai M, Patel J, Hung RK, Nasir K, **Keteyian SJ**, **Brawner CA**, **Ehrman JK**, **Sakr S**, Blumenthal RS, Blaha MJ, and **Al-Mallah MH**. Higher fitness is strongly protective in patients with family history of heart disease: The FIT project *Am J Med* 2016;PMID: 27751899. Full Text

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BACKGROUND: Cardiorespiratory fitness protects against mortality; however, little is known about the benefits of improved fitness in individuals with a family history of coronary heart disease. We studied the association between cardiorespiratory fitness and risk of incident coronary heart disease and all-cause mortality, hypothesizing an inverse relationship similar to individuals without a family history of coronary heart disease. METHODS: We included 57,999 patients (53+/-13 years; 49% females; 29% Black), from the Henry Ford Exercise Testing (FIT) Project. Cardiorespiratory fitness was expressed in metabolic equivalents of task based on exercise stress testing. Family history was determined as self-reported coronary heart disease in a first-degree relative at any age. We used Cox proportional hazards models adjusted for demographics and cardiovascular disease risk factors to examine the association between cardiorespiratory fitness and risk of incident coronary heart disease and mortality over median (interquartile range; IQR) follow up of 5.5 (5.6) and 10.4 (6.8) years. RESULTS: Overall, 51% reported a positive family history. Each 1 unit MET increase was associated with lower incident coronary heart disease and mortality risk regardless of family history status. The HR (95% CI) for family history negative and family history positive were as follows: 0.87 (0.84, 0.89) and 0.87 (0.85,0.89) for incident coronary heart disease, and 0.83 (0.82, 0.84) and 0.83

(0.82, 0.85) for mortality, respectively. There was no significant interaction between family history and categorical cardiorespiratory fitness, sex, or age (P>0.05 for all). CONCLUSION: Higher cardiorespiratory fitness is strongly protective in all patients regardless of family history status, supporting recommendations for regular exercise in those with a family history.

Cardiology
Bagur R, Teefy PJ, Kiaii B, Goela A, **Greenbaum A**, and Chu MW. Transcaval transcatheter aortic valve replacement with the ACURATE-neo aortic bioprosthesis: First north american experience *JACC Cardiovasc Interv* 2016; 9(20):e199-e201. PMID: 27692823. Full Text

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Cardiology
Cheruvu C, Precious B, Naoum C, Blanke P, Ahmadi A, 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, Min JK, and Leipsic J. Long term prognostic utility of coronary CT angiography in patients with no modifiable coronary artery disease risk factors: Results from the 5 year follow-up of the CONFIRM International Multicenter Registry *J Cardiovasc Comput Tomogr* 2016; 10(1):22-27. PMID: 26719237. Full Text

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BACKGROUND: Coronary computed tomography angiography (coronary CTA) can prognosticate outcomes in patients without modifiable risk factors over medium term follow-up. This ability was driven by major adverse cardiovascular events (MACE). OBJECTIVE: Determine if coronary CTA could discriminate risk of mortality with longer term follow-up. In addition we sought to determine the long-term relationship to MACE. METHODS: From 12 centers, 1884 patients undergoing coronary CTA without prior coronary artery disease (CAD) or any modifiable CAD risk factors were identified. The presence of CAD was classified as none (0% stenosis), mild (1% to 49% stenosis) and obstructive (>/=50% stenosis severity). The primary endpoint was all-cause mortality and the secondary endpoint was MACE. MACE was defined as the combination of death, nonfatal myocardial infarction, unstable angina, and late target vessel revascularization (>90 days). RESULTS: Mean age was 55.6 +/- 14.5 years. At mean 5.6 +/- 1.3 years follow-up, 145(7.7%) deaths occurred. All-cause mortality demonstrated a dose-response relationship to the severity and number of coronary vessels exhibiting CAD. Increased mortality was observed for >1 segment non-obstructive CAD (hazard ratio [HR]:1.73; 95% confidence interval [CI]: 1.07-2.79; p = 0.025), obstructive 1&2 vessel CAD (HR: 1.70; 95% CI: 1.08-2.71; p = 0.023) and 3-vessel or left main CAD (HR: 2.87; 95% CI: 1.57-5.23; p = 0.001). Both obstructive CAD (HR: 6.63; 95% CI: 3.91-11.26; p < 0.001) and non-obstructive CAD (HR: 2.20; 95% CI: 1.31-3.67; p = 0.003) predicted MACE with increased hazard associated with increasing CAD severity; 5.60% in no CAD, 13.24% in non-obstructive and 36.28% in obstructive CAD, p < 0.001 for trend. CONCLUSIONS: In individuals being assessed for CAD with no modifiable risk factors, all-cause mortality in the long term (>5 years) was predicted by the presence of more than 1 segment of non-obstructive plaque, obstructive 1- or 2-vessel CAD and 3 vessel/left main CAD. Any CAD, whether non-obstructive or obstructive, predicted MACE over the same time period.

Cardiology
Cremer PC, Wu Y, Ahmed HM, Pierson LM, Brennan DM, **Al-Mallah MH**, **Brawner CA**, **Ehrman JK**, **Keteyian SJ**, Blumenthal RS, Blaha MJ, and Cho L. Use of sex-specific clinical and exercise risk scores to identify patients at increased risk for all-cause mortality *JAMA Cardiol* 2016;PMID: 27784057. Full Text

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Importance: Risk assessment tools for exercise treadmill testing may have limited external validity. Cardiovascular mortality has decreased in recent decades, and women have been underrepresented in prior cohorts. Objectives: To determine whether exercise and clinical variables are associated with differential mortality outcomes in men and women and to assess whether sex-specific risk scores better estimate all-cause mortality. Design, Setting, and Participants: This retrospective cohort study included 59877 patients seen at the Cleveland Clinic Foundation (CCF cohort) from January 1, 2000, through December 31, 2010, and 49278 patients seen at the Henry Ford Hospital (FIT cohort) from January 1, 1991, through December 31, 2009. All patients were 18 years or older and underwent exercise treadmill testing. Data were analyzed from January 1, 2000, to October 27, 2011, in the CCF cohort and from January 1, 1991, to April 1, 2013, in the FIT cohort. Main Outcomes and Measurements: The CCF cohort was divided randomly into derivation and validation samples, and separate risk scores were developed for men and women. Net reclassification, C statistics, and integrated discrimination improvement were used to compare the sex-specific risk scores with other tools that have all-cause mortality as the outcome. Discrimination and calibration were also evaluated with these sex-specific risk scores in the FIT cohort. Results: The CCF cohort included 59877 patients (59.4% men; 40.5% women) with a median (interquartile range [IQR]) age of 54 (45-63) years and 2521 deaths (4.2%) during a median follow-up of 7 (IQR, 4.1-9.6) years. The FIT cohort included 49278 patients (52.5% men; 47.4% women) with a median (IQR) age of 54 (46-64) years and 6643 deaths (13.5%) during a median (IQR) follow-up of 10.2 (7-13.4) years. C statistics for the sex-specific risk scores in the CCF validation sample were higher (0.79 in women and 0.81 in men) than C statistics using other tools in women (0.70 for Duke Treadmill Score; 0.74 for Lauer nomogram) and men (0.72 for Duke Treadmill Score; 0.75 for Lauer nomogram). Net reclassification and integrated discrimination improvement were superior with the sex-specific risk scores, mostly owing to correct reclassification of events. The sex-specific risk scores in the FIT cohort demonstrated similar discrimination (C statistic, 0.78 for women and 0.79 for men), and calibration was reasonable. Conclusions and Relevance: Sex-specific risk scores better estimate mortality in patients undergoing exercise treadmill testing. In particular, these sex-specific risk scores help to identify patients at the highest residual risk in the present era.

Cardiology

Danek BA, Karatasakis A, Karmpaliotis D, **Alaswad K**, Yeh RW, Jaffer FA, Patel MP, Mahmud E, Lombardi WL, Wyman MR, Grantham JA, Doing A, Kandzari DE, Lembo NJ, Garcia S, Toma C, Moses JW, Kirtane AJ, Parikh MA, Ali ZA, Karacsonyi J, Rangan BV, Thompson CA, Banerjee S, and Brilakis ES. Development and validation of a scoring system for predicting periprocedural complications during percutaneous coronary interventions of chronic total occlusions: The prospective global registry for the study of chronic total occlusion intervention (progress cto) complications score *J Am Heart Assoc* 2016; 5(10)PMID: 27729332. Abstract

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BACKGROUND: High success rates are achievable for chronic total occlusion (CTO) percutaneous coronary intervention (PCI) using the hybrid approach, but periprocedural complications remain of concern. Although scores estimating success and efficiency in CTO PCI have been developed, there is currently no available score for estimation of the risk for periprocedural complications. We sought to develop a scoring tool for prediction of periprocedural complications during CTO PCI. METHODS AND RESULTS: We analyzed data from 1569 CTO PCIs in the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO) using a derivation and validation sampling ratio of 2:1. Variables independently associated with periprocedural complications in multivariable analysis in the derivation set were assigned points based on their respective odds ratios. Forty-four (2.8%) patients experienced complications. Three factors were independent predictors of complications and were included in the score: patient age >65 years, +3 points (odds ratio, OR=4.85, CI 1.82-16.77); lesion length >/=23 mm, +2 points (OR=3.22, CI 1.08-13.89); and use of the retrograde approach +1 point (OR=2.41, CI 1.04-6.05). The resulting score showed good calibration and discriminatory capacity in the derivation (Hosmer-Lemeshow chi2 6.271, P=0.281, receiver-operating characteristic [ROC] area=0.758) and validation (Hosmer-Lemeshow chi2 4.551, P=0.473, ROC area=0.793) sets. Score values of 0 to 2, 3 to 4, and >/=5 were defined as low, intermediate, and high risk of complications (derivation cohort 0.4%, 1.8%, 6.5%, P<0.001; validation cohort 0.0%, 2.5%, 6.8%, P<0.001). CONCLUSIONS: The PROGRESS CTO complication score is a useful tool for prediction of periprocedural complications in CTO PCI. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02061436.

Cardiology

Dinh W, Albrecht-Kupper B, Gheorghiade M, Voors AA, van der Laan M, and **Sabbah HN**. Partial adenosine a1 agonist in heart failure *Handb Exp Pharmacol* 2016;PMID: 27770217. Article request form

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Adenosine exerts a variety of physiological effects by binding to cell surface G-protein-coupled receptor subtypes, namely, A1, A2a, A2b, and A3. The central physiological role of adenosine is to preclude tissue injury and promote

repair in response to stress. In the heart, adenosine acts as a cytoprotective modulator, linking cardiac function to metabolic demand predominantly via activation of adenosine A1 receptors (A1Rs), which leads to inhibition of adenylate cyclase activity, modulation of protein kinase C, and opening of ATP-sensitive potassium channels. Activation of myocardial adenosine A1Rs has been shown to modulate a variety of pathologies associated with ischemic cardiac injury, including arrhythmogenesis, coronary and ventricular dysfunction, apoptosis, mitochondrial dysfunction, and ventricular remodeling. Partial A1R agonists are agents that are likely to elicit favorable pharmacological responses in heart failure (HF) without giving rise to the undesirable cardiac and extra-cardiac effects observed with full A1R agonism. Preclinical data have shown that partial adenosine A1R agonists protect and improve cardiac function at doses that do not result in undesirable effects on heart rate, atrioventricular conduction, and blood pressure, suggesting that these compounds may constitute a valuable new therapy for chronic HF. Neladenoson bialanate (BAY1067197) is the first oral partial and highly selective A1R agonist that has entered clinical development for the treatment of HF. This review provides an overview of adenosine A1R-mediated signaling in the heart, summarizes the results from preclinical and clinical studies of partial A1R agonists in HF, and discusses the potential benefits of these drugs in the clinical setting.

Cardiology
Greene SJ, **Sabbah HN**, Butler J, Voors AA, Albrecht-Kupper BE, Dungen HD, Dinh W, and Gheorghiade M. Partial adenosine A1 receptor agonism: a potential new therapeutic strategy for heart failure *Heart Fail Rev* 2016; 21(1):95-102. PMID: 26701329. Full Text

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Heart failure (HF) represents a global public health and economic problem associated with unacceptable rates of death, hospitalization, and healthcare expenditure. Despite available therapy, HF carries a prognosis comparable to many forms of cancer with a 5-year survival rate of ~50%. The current treatment paradigm for HF with reduced ejection fraction (EF) centers on blocking maladaptive neurohormonal activation and decreasing cardiac workload with therapies that concurrently lower blood pressure and heart rate. Continued development of hemodynamically active medications for stepwise addition to existing therapies carries the risk of limited tolerability and safety. Moreover, this treatment paradigm has thus far failed for HF with preserved EF. Accordingly, development of hemodynamically neutral HF therapies targeting primary cardiac pathologies must be considered. In this context, a partial adenosine A1 receptor (A1R) agonist holds promise as a potentially hemodynamically neutral therapy for HF that could simultaneous improve cardiomyocyte energetics, calcium homeostasis, cardiac structure and function, and long-term clinical outcomes when added to background therapies. In this review, we describe the physiology and pathophysiology of HF as it relates to adenosine agonism, examine the existing body of evidence and biologic rationale for modulation of adenosine A1R activity, and review the current state of drug development of a partial A1R agonist for the treatment of HF.

Cardiology
Kabbani LS, **Wasilenko S**, **Nypaver TJ**, **Weaver MR**, **Taylor AR**, **Abdul-Nour K**, **Borgi J**, and **Shepard AD**. Socioeconomic disparities affect survival after aortic dissection *J Vasc Surg* 2016; 64(5):1239-1245. PMID: 27374067. Full Text

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OBJECTIVE: The effect of socioeconomic status (SES) on the course of many disease states has been documented in the literature but has not been studied in aortic dissection. This study evaluated the effect of SES on 30-day and

long-term survival of patients after aortic dissection. METHODS: Hospital discharge records were used to identify patients with acute aortic dissection. Patient demographics, insurance status, comorbidities, and 30-day mortality were collected. Home addresses were used to estimate each patient's median household income, and the neighborhood deprivation index, a measure of SES, was determined. Long-term survival was assessed by review of the Social Security Death Index. Associations between demographics, insurance status, comorbidities, and poverty level were investigated to determine their effect on survival. RESULTS: There were 212 aortic dissections; of which, 118 were type A and 94 were type B. Median follow-up was 7.6 years. The neighborhood deprivation index (hazard ratio, 1.43; 95% confidence interval, 1.16-1.78; P = .001) was associated with reduced long-term survival and was also significantly associated with 30-day mortality (hazard ratio, 1.43; 95% confidence interval, 1.05-1.93; P = .02). The mean neighborhood deprivation index score was higher in patients with type B aortic dissections (0.45 +/- 0.93) than in those with type A aortic dissections (0.16 +/- 0.96; P = .029). CONCLUSIONS: Patients with a lower SES had reduced short-term and long-term survival after aortic dissection. Patients with type B dissection live in lower socioeconomic neighborhoods than patients with type A dissection.

Cardiology
Karatasakis A, Danek BA, Karmpaliotis D, **Alaswad K**, Jaffer FA, Yeh RW, Patel M, Bahadorani JN, Lombardi WL, Wyman RM, Grantham JA, Kandzari DE, Lembo NJ, Doing AH, Toma C, Moses JW, Kirtane AJ, Parikh MA, Ali ZA, Garcia S, Kalsaria P, Karacsonyi J, Alame AJ, Thompson CA, Banerjee S, and Brilakis ES. Comparison of various scores for predicting success of chronic total occlusion percutaneous coronary intervention *Int J Cardiol* 2016; 224:50-56. PMID: 27611917. Full Text

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BACKGROUND: Various scoring systems have been developed to predict the technical outcome and procedural efficiency of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). METHODS: We examined the predictive capacity of 3 CTO PCI scores (Clinical and Lesion-related [CL], Multicenter CTO registry in Japan [J-CTO] and Prospective Global Registry for the Study of Chronic Total Occlusion Intervention [PROGRESS CTO] scores) in 664 CTO PCIs performed between 2012 and 2016 at 13 US centers. RESULTS: Technical success was 88% and the retrograde approach was utilized in 41%. Mean CL, J-CTO and PROGRESS CTO scores were 3.9+/-1.9, 2.6+/-1.2 and 1.4+/-1.0, respectively. All scores were inversely associated with technical success (p<0.001 for all) and had moderate discriminatory capacity (area under the curve 0.691 for the CL score, 0.682 for the J-CTO score and 0.647 for the PROGRESS CTO score [p=non-significant for pairwise comparisons]). The difference in technical success between the minimum and maximum CL score strata was the highest (32%, vs. 15% for J-CTO and 18% for PROGRESS CTO scores). All scores tended to perform better in antegrade-only procedures and correlated significantly with procedure time and fluoroscopy dose; the CL score also correlated significantly with contrast utilization. CONCLUSIONS: CL, J-CTO and PROGRESS CTO scores perform moderately in predicting technical outcome of CTO PCI, with better performance for antegrade-only procedures. All scores correlate with procedure time and fluoroscopy dose, and the CL score also correlates with contrast utilization.

Cardiology
Keteyian SJ, **Kerrigan DJ**, **Ehrman JK**, and **Brawner CA**. Exercise training workloads upon exit from cardiac rehabilitation in men and women: The henry ford hospital experience *J Cardiopulm Rehabil Prev* 2016;PMID: 27755258. Full Text

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PURPOSE: To describe exercise training workloads, estimated as metabolic equivalents of task (METs) both upon exit from cardiac rehabilitation (CR) and as the change in MET level following CR, stratified by age, sex, initial MET level, number of sessions completed, and qualifying event at entry into CR. METHODS: A retrospective study involving 8319 (31% female) patients who completed >/=9 exercise training sessions in the early outpatient CR program at Henry Ford Hospital. Exercise training MET levels achieved during CR were estimated on the basis of the speed and grade recorded from a treadmill. Exercise training METs at the start of CR were defined as the average of the second and third sessions, whereas MET level upon exit from CR was determined from the average of the last 2 patient encounters. RESULTS: The overall mean MET level while training just prior to exit from CR was 3.9 +/- 1.4 (4.1 +/- 1.4 and 3.3 +/- 1.0 in men and women, respectively). The mean change in METs after CR was 1.3 +/- 1.1 (+45% +/- 37%) and 0.9 +/- 0.7 (+40% +/- 32%) in men and women, respectively. CONCLUSIONS: In a large and demographically diverse cohort of patients who participated in CR, increases in mean workload (ie, METs) during exercise training were observed that approximated 45% in men and 40% in women. These data could be considered when establishing benchmarks for program-related performance outcome measures.

Cardiology
Likosky DS, Paugh TA, **Harrington SD**, Wu X, Rogers MA, Dickinson TA, DeLucia A, 3rd, Benedetti BR, Prager RL, Zhang M, and **Paone G**. Prediction of transfusions after isolated coronary artery bypass grafting surgical procedures *Ann Thorac Surg* 2016;PMID: 27726856. Full Text

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BACKGROUND: Although blood transfusions are common and have been associated with adverse sequelae after cardiac surgical procedures, few contemporaneous models exist to support clinical decision making. This study developed a preoperative clinical decision support tool to predict perioperative red blood cell transfusions in the setting of isolated coronary artery bypass grafting. METHODS: We performed a multicenter, observational study of 20,377 patients undergoing isolated coronary artery bypass grafting among patients at 39 hospitals participating in the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative's PERFusion measures and outcomes (PERForm) registry between 2011 and 2015. Candidates' preoperative risk factors were identified based on previous work and clinical input. The study population was randomly divided into a 70% development sample and a 30% validation sample. A generalized linear mixed-effect model was developed to predict perioperative red blood cell transfusion. The model's performance was assessed for calibration and discrimination. Sensitivity analysis was performed to assess the robustness of the model in different clinical subgroups. RESULTS: Transfusions occurred in 36.8% of patients. The final regression model included 16 preoperative variables. The correlation between the observed and expected transfusions was 1.0. The risk prediction model discriminated well (receiver operator characteristic [ROC]development, 0.81; ROCvalidation, 0.82) and had satisfactory calibration (correlation between observed and expected rates was r = 0.999). The model performance was confirmed across medical centers and clinical subgroups. CONCLUSIONS: Our risk prediction model uses 16 readily obtainable preoperative variables. This model, which provides a patient-specific estimate of the need for transfusion, offers clinicians a guide for decision making and evaluating the effectiveness of blood management strategies.

Cardiology
Martinez-Parachini JR, Karatasakis A, Karmpaliotis D, **Alaswad K**, Jaffer FA, Yeh RW, Patel M, Bahadorani J, Doing A, Nguyen-Trong PK, Danek BA, Karacsonyi J, Alame A, Rangan BV, Thompson CA, Banerjee S, and Brilakis ES. Impact of diabetes mellitus on acute outcomes of percutaneous coronary intervention in chronic total occlusions: insights from a US multicentre registry *Diabet Med* 2016;PMID: 27743404. Full Text

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AIM: To examine the impact of diabetes mellitus on procedural outcomes of patients who underwent percutaneous coronary intervention for chronic total occlusion. METHODS: We assessed the impact of diabetes mellitus on the outcomes of percutaneous coronary intervention for chronic total occlusion among 1308 people who underwent such procedures at 11 US centres between 2012 and 2015. RESULTS: The participants' mean +/- sd age was 66+/-10 years, 84% of the participants were men and 44.6% had diabetes. As compared with participants without diabetes, participants with diabetes were more likely to have undergone coronary artery bypass graft surgery (38 vs 31%; P=0.006), and to have had previous heart failure (35 vs 22%; P=0.0001) and peripheral arterial disease (19 vs 13%; P=0.002). They also had a higher BMI (31+/-6 kg/m2 vs 29+/-6 kg/m2 ; P=0.001), similar Japanese chronic total occlusion scores (2.6 +/- 1.2 vs 2.5 +/- 1.2; P=0.82) and similar final successful crossing technique: antegrade wire escalation (46 vs 47%; P=0.66), retrograde (30 vs 28%; P=0.66) and antegrade dissection re-entry (24 vs 25%; P=0.66). Technical (91 vs 90%; P=0.80) and procedural (89 vs 89%; P=0.93) success was similar in the two groups, as was the incidence of major adverse cardiac events (2.2 vs 2.5%; P=0.61). CONCLUSIONS: In a contemporary cohort of people undergoing percutaneous coronary intervention for chronic total occlusion, nearly one in two (45%) had diabetes mellitus. Procedural success and complication rates were similar in people with and without diabetes.

Cardiology
Sabbah HN. Targeting mitochondrial dysfunction in the treatment of heart failure *Expert Rev Cardiovasc Ther* 2016;PMID: 27758146. Article request form

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Introduction Heart failure (HF) has reached epidemic proportions worldwide. Despite the availability of drugs that reduce mortality and afford good symptom relief, HF continues to exact a considerable clinical and economic burden. Current HF therapies elicit benefit by reducing cardiac workload by lowering heart rate and loading conditions, thereby reducing myocardial energy demands. Areas covered Recent recognition that the failing heart is "energy deprived" and its primary energy source, the mitochondria, is dysfunctional, has focused attention on mitochondria as a worthy therapeutic target. In HF, mitochondrial dysfunction leads to reduced ATP synthesis and excessive formation of damaging reactive oxygen species (ROS), a combination the failing heart can ill afford. Expert Commentary Correcting mitochondrial dysfunction can help forge a new therapeutic approach based on readily available energy that can meet increasing cardiac demands. This paradigm shift, once implemented successfully, is likely to elicit better overall cardiac function, better quality of life and improved survival for patients with HF.

Center for Health Policy and Health Services Research
Brady JE, Liffmann DK, Yartel A, Kil N, Federman AD, Kannry J, Jordan C, Massoud OI, **Nerenz DR**, **Brown KA**, Smith BD, Vellozzi C, and Rein DB. Uptake of hepatitis c screening, characteristics of patients tested, and intervention costs in the BEST-C study *Hepatology* 2016;PMID: 27770543. Full Text

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BACKGROUND: From December 2012-March 2014, three randomized trials, each implementing a unique intervention in primary care settings (mail recruitment [repeated-mailing], an electronic health record best practice

alert [BPA], and patient-solicitation [patient-solicitation]), evaluated HCV antibody testing, diagnosis, and costs for each of the interventions compared to standard-of-care testing. Multilevel multivariable models were used to estimate the adjusted risk ratio (aRR) for receiving an HCV antibody test, and costs were estimated using activity-based costing. RATIONALE: To estimate the effects of interventions conducted as part of the Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C study on hepatitis C virus (HCV) testing and costs among persons of the 1945-1965 birth-cohort (BC). MAIN RESULTS: Intervention resulted in substantially higher HCV testing rates compared to standard-of-care (26.9% vs. 1.4% for repeated-mailing, 30.9% vs. 3.6% for BPA, and 63.5% vs. 2.0% for patient-solicitation), and significantly higher aRR for testing after controlling for sex, birth year, race, insurance type, and median household income (19.2 [95% Confidence Interval (CI) 9.7-38.2] for repeated-mailing, 13.2 [95% CI 3.6-48.6] for BPA, and 32.9 [95% CI 19.3-56.1] for patient-solicitation). The BPA intervention had the lowest incremental cost per completed test ($24 with fixed startup costs, $3 without) and also the lowest incremental cost per new case identified after omitting fixed startup costs ($1,691). CONCLUSION: HCV testing interventions resulted in an increase in BC testing compared to standard-of-care but also increased costs. The effect size and incremental costs of BPA intervention (excluding startup costs) support more widespread adoption compared to the other interventions. This article is protected by copyright. All rights reserved.

Center for Health Policy and Health Services Research
Kabbani LS, **Wasilenko S**, **Nypaver TJ**, **Weaver MR**, **Taylor AR**, **Abdul-Nour K**, **Borgi J**, and **Shepard AD**. Socioeconomic disparities affect survival after aortic dissection *J Vasc Surg* 2016; 64(5):1239-1245. PMID: 27374067. Full Text

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

Center for Health Policy and Health Services Research
Karvelas DA, Rundell SD, Friedly JL, Gellhorn AC, Gold LS, Comstock BA, Heagerty PJ, Bresnahan BW, **Nerenz DR**, and Jarvik JG. Subsequent healthcare utilization associated with early physical therapy for new episodes of low back pain in older adults *Spine J* 2016;PMID: 27765707. Full Text

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BACKGROUND: The association between early physical therapy (PT) and subsequent healthcare utilization following a new visit for low back pain is not clear, particularly in the setting of acute low back pain. PURPOSE: To estimate the association between initiating early physical therapy following a new visit for an episode of low back pain and subsequent back-pain-specific health care utilization in older adults. STUDY DESIGN/SETTING: Prospective cohort study. Data were collected at 3 integrated health care systems in the United States through the Back Pain Outcomes using Longitudinal Data (BOLD) registry. PATIENT SAMPLE: 4,723 adults, aged 65 and older, presenting to a primary care setting with a new episode of low back pain. OUTCOME MEASURES: Primary outcome was total back-pain-specific relative value units (RVUs), from days 29-365. Secondary outcomes included overall RVUs for all healthcare and use of specific health care services including: imaging (x-ray and MRI or CT), Emergency Department visits, physician visits, physical therapy, spinal injections, spinal surgeries and opioid use. METHODS: We compared patients that had early PT (initiated within 28 days of the index visit) to those not initiating early PT using appropriate, generalized linear models to adjust for potential confounding variables. BOLD was funded by an Agency for Healthcare Research and Quality grant, R01 HS019222-01. The authors report no potential conflict of interest related to this study. RESULTS: Adjusted analysis found no statistically significant difference in total spine RVUs between the two groups (ratio of means 1.19, 95% CI of 0.72 to 1.96, p=0.49). For secondary outcomes, only the difference between total spine imaging RVUs and total PT RVUs was statistically significant. The early PT group had greater PT RVUs, the ratio of means was 2.56 (95% CI of 2.17-3.03, p<0.001.) The early PT group had greater imaging RVUs, the ratio of means was 1.37 (95% CI of 1.09-1.71, p=0.01.) CONCLUSIONS: We found that, in a group of older adults presenting for a new episode of low back pain, the use of early PT is not associated with any statistically significant difference in subsequent back-pain-specific healthcare utilization compared to patients not receiving early PT.

Center for Health Policy and Health Services Research
Kessler MD, Yerges-Armstrong L, Taub MA, Shetty AC, Maloney K, Jeng LJ, Ruczinski I, **Levin AM**, **Williams LK**, Beaty TH, Mathias RA, Barnes KC, and O'Connor TD. Challenges and disparities in the application of personalized genomic medicine to populations with African ancestry *Nat Commun* 2016; 7:12521. PMID: 27725664. Full Text

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To characterize the extent and impact of ancestry-related biases in precision genomic medicine, we use 642 whole-genome sequences from the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) project to evaluate typical filters and databases. We find significant correlations between estimated African ancestry proportions and the number of variants per individual in all variant classification sets but one. The source of these correlations is highlighted in more detail by looking at the interaction between filtering criteria and the ClinVar and Human Gene Mutation databases. ClinVar's correlation, representing African ancestry-related bias, has changed over time amidst monthly updates, with the most extreme switch happening between March and April of 2014 (r=0.733 to r=-0.683). We identify 68 SNPs as the major drivers of this change in correlation. As long as ancestry-related bias when using these clinical databases is minimally recognized, the genetics community will face challenges with implementation, interpretation and cost-effectiveness when treating minority populations.

Center for Health Policy and Health Services Research
Mathias RA, Taub MA, Gignoux CR, Fu W, Musharoff S, O'Connor TD, Vergara C, Torgerson DG, Pino-Yanes M, Shringarpure SS, Huang L, Rafaels N, Boorgula MP, Johnston HR, Ortega VE, **Levin AM**, Song W, Torres R, **Padhukasahasram B**, Eng C, Mejia-Mejia DA, Ferguson T, Qin ZS, Scott AF, Yazdanbakhsh M, Wilson JG, Marrugo J, Lange LA, Kumar R, Avila PC, **Williams LK**, Watson H, Ware LB, Olopade C, Olopade O, Oliveira R, Ober C, Nicolae DL, Meyers D, Mayorga A, Knight-Madden J, Hartert T, Hansel NN, Foreman MG, Ford JG, Faruque MU,

Dunston GM, Caraballo L, Burchard EG, Bleecker E, Araujo MI, Herrera-Paz EF, Gietzen K, Grus WE, Bamshad M, Bustamante CD, Kenny EE, Hernandez RD, Beaty TH, Ruczinski I, Akey J, and Barnes KC. A continuum of admixture in the Western Hemisphere revealed by the African Diaspora genome *Nat Commun* 2016; 7:12522. PMID: 27725671. [Full Text]

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The African Diaspora in the Western Hemisphere represents one of the largest forced migrations in history and had a profound impact on genetic diversity in modern populations. To date, the fine-scale population structure of

descendants of the African Diaspora remains largely uncharacterized. Here we present genetic variation from deeply sequenced genomes of 642 individuals from North and South American, Caribbean and West African populations, substantially increasing the lexicon of human genomic variation and suggesting much variation remains to be discovered in African-admixed populations in the Americas. We summarize genetic variation in these populations, quantifying the postcolonial sex-biased European gene flow across multiple regions. Moreover, we refine estimates on the burden of deleterious variants carried across populations and how this varies with African ancestry. Our data are an important resource for empowering disease mapping studies in African-admixed individuals and will facilitate gene discovery for diseases disproportionately affecting individuals of African ancestry.

Center for Health Policy and Health Services Research
Owen-Smith A, Stewart C, Green C, **Ahmedani BK**, Waitzfelder BE, Rossom R, Copeland LA, and Simon GE. Adherence to common cardiovascular medications in patients with schizophrenia vs. patients without psychiatric illness *Gen Hosp Psychiatry* 2016; 38:9-14. PMID: 26423559. Full Text

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OBJECTIVE: The purpose of the study was to examine whether individuals with diagnoses of schizophrenia were differentially adherent to their statin or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) medications compared to individuals without psychiatric illness. METHOD: Using electronic medical record data across 13 Mental Health Research Network sites, individuals with diagnoses of schizophrenia or schizoaffective disorder receiving two or more medication dispensings of a statin or an ACEI/ARB in 2011 (N=710) were identified and matched on age, sex and Medicare status to controls with no documented mental illness and two or more medication dispensings of a statin in 2011 (N=710). Medication adherence, and sociodemographic and clinical characteristics of the study population were assessed. RESULTS: Multivariable models indicated that having a schizophrenia diagnosis was associated with increased odds of statin medication adherence; the odds ratio suggested a small effect. After adjustment for medication regimen, schizophrenia no longer showed an association with statin adherence. Having a schizophrenia diagnosis was not associated with ACEI/ARB medication adherence. CONCLUSIONS: Compared to patients without any psychiatric illness, individuals with schizophrenia were marginally more likely to be adherent to their statin medications. Given that patterns of adherence to cardioprotective medications may be different from patterns of adherence to antipsychotic medications, improving adherence to the former may require unique intervention strategies.

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

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BACKGROUND: The results of observational studies evaluating and comparing the cardiovascular safety of glitazones, metformin and sufonylureas are inconsistent.To conduct and evaluate heterogeneity in a meta-analysis of observational studies on the risk of acute myocardial infarction (AMI) or stroke in patients with type 2 diabetes using non-insulin blood glucose-lowering drugs (NIBGLD). METHODS: We systematically identified and reviewed studies evaluating NIBGLD in patients with type 2 diabetes indexed in Medline, Embase, or the Cochrane Library that met prespecified criteria. The quality of included studies was assessed with the RTI item bank. Results were combined using fixed- and random-effects models, and the Higgins I(2) statistic was used to evaluate heterogeneity. Sensitivity analyses by study quality were conducted. RESULTS: The summary relative risk (sRR) (95% CI) of AMI for

rosiglitazone versus pioglitazone was 1.13 (1.04-1.24) [I(2) = 55%]. In the sensitivity analysis, heterogeneity was reduced [I(2) = 16%]. The sRR (95% CI) of stroke for rosiglitazone versus pioglitazone was 1.18 (1.02-1.36) [I(2) = 42%]. There was strong evidence of heterogeneity related to study quality in the comparisons of rosiglitazone versus metformin and rosiglitazone versus sulfonylureas (I (2) >/= 70%). The sRR (95% CI) of AMI for sulfonylurea versus metformin was 1.24 (1.14-1.34) [I(2) = 41%] and for pioglitazone versus metformin was 1.02 (0.75-1.38) [I(2) = 17%]. Sensitivity analyses decreased heterogeneity in most comparisons. CONCLUSION/INTERPRETATION: Sulfonylureas increased the risk of AMI by 24% compared with metformin; an imprecise point estimate indicated no difference in risk of AMI when comparing pioglitazone with metformin. The presence of heterogeneity precluded any conclusions on the other comparisons. The quality assessment was valuable in identifying methodological problems in the individual studies and for analysing potential sources of heterogeneity.

Center for Health Policy and Health Services Research
Rossom RC, Simon GE, Beck A, **Ahmedani BK**, Steinfeld B, Trangle M, and Solberg L. Facilitating action for suicide prevention by learning health care systems *Psychiatr Serv* 2016; 67(8):830-832. PMID: 27032667. Full Text

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The Mental Health Research Network (MHRN), funded by the National Institute of Mental Health to serve as a national laboratory to improve mental health care, includes researchers embedded in 13 health systems in 15 states. This column describes practice changes and effectiveness and exploratory research undertaken by MHRN partners when they found a sustained elevated risk of suicide attempts among patients who reported suicidal ideation on the nine-item Patient Health Questionnaire. Challenges described include finding common ground between what health care systems and funding agencies find compelling, choosing study designs that balance research and clinical tensions, and implementing studies in ways that minimize disruption to health systems. The authors conclude that the greatest benefit to working collaboratively with care system partners is the opportunity to improve care and to simultaneously measure the impact of change.

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

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PURPOSE: Recent results suggests the risk of a new onset of depression increases with longer duration of opioid analgesic use. It is unclear whether new-onset depression related to opioid analgesic use is a function of the dose prescribed or the duration of use or both. METHODS: Using a retrospective cohort design, we collected patient data from 2000 to 2012 from the Veterans Health Administration (VHA), and from 2003 to 2012 from both Baylor Scott &

White Health (BSWH) and the Henry Ford Health System (HFHS). Patients (70,997 VHA patients, 13,777 BSWH patients, and 22,981 HFHS patients) were new opioid users, aged 18 to 80 years, without a diagnosis of depression at baseline. Opioid analgesic use duration was defined as 1 to 30, 31 to 90, and more than 90 days, and morphine equivalent dose (MED) was defined as 1 to 50 mg/d, 51 to 100 mg/d, and greater than 100 mg/d of analgesic. Pain and other potential confounders were controlled for by inverse probability of treatment-weighted propensity scores. RESULTS: New-onset depression after opioid analgesic use occurred in 12% of the VHA sample, 9% of the BSWH sample, and 11% of the HFHS sample. Compared with 1- to 30-day users, new-onset depression increased in those with longer opioid analgesic use. Risk of new-onset depression with 31 to 90 days of opioid analgesic use ranged from hazard ratio [HR] = 1.18 (95% CI, 1.10-1.25) in VHA to HR = 1.33 (95% CI, 1.16-1.52) in HFHS; in opioid analgesic use of more than 90 days, it ranged from HR = 1.35 (95% CI, 1.26-1.44) in VHA to HR = 2.05 (95% CI, 1.75-2.40) in HFHS. Dose was not significantly associated with a new onset of depression. CONCLUSIONS: Opioid-related new onset of depression is associated with longer duration of use but not dose. Patients and practitioners should be aware that opioid analgesic use of longer than 30 days imposes risk of new-onset depression. Opioid analgesic use, not just pain, should be considered a potential source when patients report depressed mood.

Center for Health Policy and Health Services Research
Xu F, Moorman AC, Tong X, **Gordon SC**, **Rupp LB**, **Lu M**, Teshale EH, Spradling PR, Boscarino JA, Trinacty CM, Schmidt MA, and Holmberg SD. All-cause mortality and progression risks to hepatic decompensation and hepatocellular carcinoma in patients infected with hepatitis c virus *Clin Infect Dis* 2016; 62(3):289-297. PMID: 26417034. Full Text

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BACKGROUND: A key question in care of patients with chronic hepatitis C virus (HCV) infection is beginning treatment immediately vs delaying treatment. Risks of mortality and disease progression in "real world" settings are important to assess the implications of delaying HCV treatment. METHODS: This was a cohort study of HCV patients identified from 4 integrated health systems in the United States who had liver biopsies during 2001-2012. The probabilities of death and progression to hepatocellular carcinoma, hepatic decompensation (hepatic encephalopathy, esophageal varices, ascites, or portal hypertension) or liver transplant were estimated over 1, 2, or 5 years by fibrosis stage (Metavir F0-F4) determined by biopsy at beginning of observation. RESULTS: Among 2799 HCV-monoinfected patients who had a qualifying liver biopsy, the mean age at the time of biopsy was 50.7 years. The majority were male (58.9%) and non-Hispanic white (66.9%). Over a mean observation of 5.0 years, 261 (9.3%) patients died and 34 (1.2%) received liver transplants. At 5 years after biopsy, the estimated risk of progression to hepatic decompensation or hepatocellular carcinoma was 37.2% in stage F4, 19.6% in F3, 4.7% in F2, and 2.3% in F0-F1 patients. Baseline biopsy stage F3 or F4 and platelet count below normal were the strongest predictors of progression to hepatic decompensation or hepatocellular carcinoma. CONCLUSIONS: The risks of death and progression to liver failure varied greatly by fibrosis stage. Clinicians and policy makers could use these progression risk data in prioritization and in determining the timing of treatment for patients in early stages of liver disease.

Dermatology
Agrawal S, **Porto DA**, and **Lim HW**. Paradoxically dark spontaneous repigmentation: a rare complication of generalized vitiligo *J Eur Acad Dermatol Venereol* 2016;PMID: 27785821. Full Text

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Vitiligo is an acquired disease characterized by progressive depigmentation of the skin, mucosa, or hair due to destruction of melanocytes.1,2 Vitiligo can be divided into two broad subtypes: generalized vitiligo with bilateral and symmetric skin involvement, and segmental vitiligo with unilateral skin involvement.3 Current evidence indicates that generalized vitiligo is at least in part an autoimmune process.3,4 As such, suppression of this autoimmunity can result in repigmentation. This article is protected by copyright. All rights reserved.

Dermatology

Garzon MC, Epstein LG, Heyer GL, Frommelt PC, Orbach DB, Baylis AL, Blei F, Burrows PE, Chamlin SL, Chun RH, Hess CP, Joachim S, **Johnson K**, Kim W, Liang MG, Maheshwari M, McCoy GN, Metry DW, Monrad PA, Pope E, Powell J, Shwayder TA, Siegel DH, Tollefson MM, Vadivelu S, Lew SM, Frieden IJ, and Drolet BA. PHACE syndrome: Consensus-derived diagnosis and care recommendations *J Pediatr* 2016; 178:24-33.e22. PMID: 27659028. Full Text

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Dermatology

Gaulding JV, Yang S, and **Lim HW**. An african american man with diffuse erythematous papules *JAMA Dermatol* 2016;PMID: 27760240. Full Text

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Dermatology

Giordano CN, Yew YW, Spivak G, and **Lim HW**. Understanding photodermatoses associated with defective DNA repair: Syndromes with cancer predisposition *J Am Acad Dermatol* 2016; 75(5):855-870. PMID: 27745641. Full Text

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Hereditary photodermatoses are a spectrum of rare photosensitive disorders that are often caused by genetic deficiency or malfunction of various components of the DNA repair pathway. This results clinically in extreme photosensitivity, with many syndromes exhibiting an increased risk of cutaneous malignancies. This review will focus specifically on the syndromes with malignant potential, including xeroderma pigmentosum, Bloom syndrome, and Rothmund-Thomson syndrome. The typical phenotypic findings of each disorder will be examined and contrasted, including noncutaneous identifiers to aid in diagnosis. The management of these patients will also be discussed. At this time, the mainstay of therapy remains strict photoprotection; however, genetic therapies are under investigation.

Dermatology
Jin Y, Andersen G, Yorgov D, Ferrara TM, Ben S, Brownson KM, Holland PJ, Birlea SA, Siebert J, Hartmann A, Lienert A, van Geel N, Lambert J, Luiten RM, Wolkerstorfer A, Wietze van der Veen JP, Bennett DC, Taieb A, Ezzedine K, Kemp EH, Gawkrodger DJ, Weetman AP, Koks S, Prans E, Kingo K, Karelson M, Wallace MR, McCormack WT, Overbeck A, Moretti S, Colucci R, Picardo M, Silverberg NB, Olsson M, Valle Y, Korobko I, Bohm M, **Lim HW**, **Hamzavi I**, **Zhou L**, **Mi QS**, Fain PR, Santorico SA, and Spritz RA. Genome-wide association studies of autoimmune vitiligo identify 23 new risk loci and highlight key pathways and regulatory variants *Nat Genet* 2016; 48(11):1418-1424. PMID: 27723757. Full Text

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Vitiligo is an autoimmune disease in which depigmented skin results from the destruction of melanocytes, with epidemiological association with other autoimmune diseases. In previous linkage and genome-wide association studies (GWAS1 and GWAS2), we identified 27 vitiligo susceptibility loci in patients of European ancestry. We carried out a third GWAS (GWAS3) in European-ancestry subjects, with augmented GWAS1 and GWAS2 controls, genome-wide imputation, and meta-analysis of all three GWAS, followed by an independent replication. The combined analyses, with 4,680 cases and 39,586 controls, identified 23 new significantly associated loci and 7 suggestive loci. Most encode immune and apoptotic regulators, with some also associated with other autoimmune diseases, as well as several melanocyte regulators. Bioinformatic analyses indicate a predominance of causal regulatory variation, some of which corresponds to expression quantitative trait loci (eQTLs) at these loci. Together, the identified genes provide a framework for the genetic architecture and pathobiology of vitiligo, highlight relationships with other autoimmune diseases and melanoma, and offer potential targets for treatment.

Dermatology
Kannan S, **Mehta D**, and **Ozog D**. Scalp closures with pulley sutures reduce time and cost compared to traditional layered technique-a prospective, randomized, observer-blinded study *Dermatol Surg* 2016; 42(11):1248-1255. PMID: 27598452. Full Text

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BACKGROUND: Reconstruction of postsurgical scalp defects can be difficult and time-consuming using a conventional bilayered technique. A specialized closure using a pulley suture can assist in closing wounds under high tension and can decrease time and cost for the surgeon. OBJECTIVE: To determine if closing scalp defects with a single-layered closure using pulley sutures would result in decreased time but equivalent scar cosmesis compared to bilayered closures. MATERIALS AND METHODS: A total of 21 patients with postsurgical scalp defects were randomized to a bilayered or a pulley group, and time was measured for each closure. Scar appearance was assessed using the Patient and Observer Scar Assessment Scale at 2 weeks, 2 months, and 6 months postsurgery. Before and after photographs were also assessed by a blinded dermatologist using the visual analog scale. RESULTS: Compared to a bilayered closure, the pulley technique resulted in significantly reduced closure time (p < .001). Even though patient overall scores at 2 weeks and observer total score at 6 months were superior in the pulley group, the visual analog scale scores were similar between the 2 groups. CONCLUSION: Scalp reconstructions using a single layer of pulley sutures result in time and cost reduction and similar scar appearance compared to bilayered closures.

Dermatology
Liu Q, **Wu D**, **Han L**, **Deng J**, **Zhou L**, He R, Lu C, and **Mi QS**. Roles of MicroRNAs in psoriasis: immunological functions and potential biomarkers *Exp Dermatol* 2016;PMID: 27783430. Full Text

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MicroRNAs (miRNAs) are small non-coding RNA molecules, which function in RNA silencing and post-transcriptional regulation of gene expression. Psoriasis is an inflammatory skin disease characterized by the dysfunction of keratinocytes, with the immune dysregulation. We reviewed the recent studies on the roles of miRNAs in psoriasis, and showed that miRNAs play key roles in psoriasis, including the regulation of hyperproliferation, cytokine and chemokine production in keratinocyte, as well as mediating immune dysfunction in psoriasis. Furthermore, miRNAs, particularly, circulating miRNAs may serve as novel biomarkers for diagnosis, monitoring therapy response, and reflecting the disease severity. Thus, targeting specific miRNAs may be used to develop new therapeutic methods for psoriasis. This article is protected by copyright. All rights reserved.

Dermatology
Stein Gold L, Villumsen J, and Rosen M. Calcipotriol plus betamethasone dipropionate aerosol foam is effective, independent of body mass index and the extent and severity of psoriasis *Dermatol Ther (Heidelb)* 2016;PMID: 27714595. Article request form

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INTRODUCTION: Good treatment adherence is important in the effective management of psoriasis and is related to both the frequency of applications and the amount of product used versus the recommended dose. The efficacy and safety of fixed combination calcipotriol 50 microg/g (Cal) and betamethasone 0.5 mg/g as dipropionate (BD) in the treatment of psoriasis is well established; an aerosol foam formulation has been developed to enhance adherence. This subanalysis from the Phase III PSO-FAST study evaluates the amount of Cal/BD foam used during treatment and the association between the extent and severity of baseline disease. METHODS: Patients (>/=18 years) with mild-to-severe body psoriasis were randomized 3:1 to once-daily Cal/BD foam or vehicle. The amount of Cal/BD foam and vehicle used over the 4-week study period was evaluated according to three baseline disease assessments: extent of body surface area (BSA) affected by psoriasis, physician's global assessment of disease severity (PGA) and modified psoriasis area and severity index (mPASI). Treatment success and mPASI75 rates were

assessed according to body mass index (BMI) and body weight. RESULTS: 323 patients were randomized to Cal/BD foam and 103 to vehicle. At week 4, the mean total amount of Cal/BD foam used was 120.8 g (n = 293), which was similar to the amount of vehicle used (128.9 g; n = 98). The total amount of Cal/BD foam used at week 4 was greater with increasing BSA and increasing severity of baseline PGA and mPASI. Throughout the study, 93.1% of patients in the Cal/BD foam group and 99.0% of patients in the vehicle group missed </=10% of treatment applications. Treatment success and mPASI75 rates were generally similar when stratified according to BMI and body weight. CONCLUSIONS: This subanalysis demonstrates that Cal/BD aerosol foam is used appropriately and is effective for the treatment of psoriasis, independent of BMI and the extent or severity of disease. CLINICAL TRIALS NUMBER: NCT01866163. FUNDING: LEO Pharma A/S.

Dermatology
Vyas NS, **Kannan S**, **M NJ**, Hu RH, Choate KA, and **Shwayder TA**. Congenital ichthyosiform erythroderma superimposed with chronic dermatophytosis: A report of three siblings *Pediatr Dermatol* 2016; 33(1):e6-9. PMID: 26645853. Full Text

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Congenital ichthyosiform erythroderma is an autosomal recessive ichthyosis characterized by severe scaling and erythroderma. We report a family of three siblings who were all born with a collodion membrane and presented with diffuse scaling and pruritus. All three children subsequently developed chronic cutaneous dermatophyte infections requiring oral antifungals. One child developed superinfection with methicillin-resistant Staphylococcus aureus requiring antibiotics.

Dermatology
Wang SQ, Virmani P, and **Lim HW**. Consumer acceptability and compliance: the next frontier in sunscreen innovation *Photodermatol Photoimmunol Photomed* 2016; 32(1):55-56. PMID: 26409211. Full Text

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Dermatology
Yew YW, **Giordano CN**, Spivak G, and **Lim HW**. Understanding photodermatoses associated with defective DNA repair: Photosensitive syndromes without associated cancer predisposition *J Am Acad Dermatol* 2016; 75(5):873-882. PMID: 27745642. Full Text

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Photodermatoses associated with defective DNA repair are a group of photosensitive hereditary skin disorders. In this review, we focus on diseases and syndromes with defective nucleotide excision repair that are not accompanied by an increased risk of cutaneous malignancies despite having photosensitivity. Specifically, the gene mutations and transcription defects, epidemiology, and clinical features of Cockayne syndrome, cerebro-oculo-facial-skeletal syndrome, ultraviolet-sensitive syndrome, and trichothiodystrophy will be discussed. These conditions may also have other extracutaneous involvement affecting the neurologic system and growth and development. Rigorous photoprotection remains an important component of the management of these inherited DNA repair-deficiency photodermatoses.

Dermatology
Zhang X, **Liu Q**, **Wang J**, **Li G**, **Weiland M**, Yu FS, **Mi QS**, Gu J, and **Zhou L**. TIM-4 is differentially expressed in the distinct subsets of dendritic cells in skin and skin-draining lymph nodes and controls skin Langerhans cell homeostasis *Oncotarget* 2016; 7(25):37498-37512. PMID: 27224924. Full Text

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T cell immunoglobulin and mucin-4 (TIM-4), mainly expressed on dendritic cells (DC) and macrophages, plays an essential role in regulating immune responses. Langerhans cells (LC), which are the sole DC subpopulation residing at the epidermis, are potent mediators of immune surveillance and tolerance. However, the significance of TIM-4 on epidermal LCs, along with other cutaneous DCs, remains totally unexplored. For the first time, we discovered that epidermal LCs expressed TIM-4 and displayed an increased level of TIM-4 expression upon migration. We also found that dermal CD207+ DCs and lymph node (LN) resident CD207-CD4+ DCs highly expressed TIM-4, while dermal CD207- DCs and LN CD207-CD4- DCs had limited TIM-4 expressions. Using TIM-4-deficient mice, we further demonstrated that loss of TIM-4 significantly upregulated the frequencies of epidermal LCs and LN resident CD207-CD4+ DCs. In spite of this, the epidermal LCs of TIM-4-deficient mice displayed normal phagocytic and migratory abilities, comparable maturation status upon the stimulation as well as normal repopulation under the inflamed state. Moreover, lack of TIM-4 did not affect dinitrofluorobenzene-induced contact hypersensitivity response. In conclusion, our results indicated that TIM-4 was differentially expressed in the distinct subsets of DCs in skin and skin-draining LNs, and specifically regulated epidermal LC and LN CD207-CD4+ DC homeostasis.

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

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

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

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BACKGROUND: Clinical heterogeneity can be defined as differences in participant characteristics, types or timing of outcome measurements and intervention characteristics. Clinical heterogeneity in systematic reviews has the possibility to significantly affect statistical heterogeneity leading to inaccurate conclusions and misled decision making. The aim of this study is to identify to what extent investigators are assessing clinical heterogeneity in both Cochrane and non-Cochrane systematic reviews. METHODS: The most recent 100 systematic reviews from the top

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

Emergency Medicine

Jaehne AK, and **Rivers EP**. Early liberal fluid therapy for sepsis patients is not harmful: Hydrophobia is unwarranted but drink responsibly *Crit Care Med* 2016;PMID: 27749314. Full Text

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Emergency Medicine

O'Brien PD, Hur J, **Robell NJ**, Hayes JM, Sakowski SA, and Feldman EL. Gender-specific differences in diabetic neuropathy in BTBR ob/ob mice *J Diabetes Complications* 2016; 30(1):30-37. PMID: 26525588. Full Text

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AIMS: To identify a female mouse model of diabetic peripheral neuropathy (DPN), we characterized DPN in female BTBR ob/ob mice and compared their phenotype to non-diabetic and gender-matched controls. We also identified dysregulated genes and pathways in sciatic nerve (SCN) and dorsal root ganglia (DRG) of female BTBR ob/ob mice to determine potential DPN mechanisms. METHODS: Terminal neuropathy phenotyping consisted of examining latency to heat stimuli, sciatic motor and sural sensory nerve conduction velocities (NCV), and intraepidermal nerve fiber (IENF) density. For gene expression profiling, DRG and SCN were dissected, RNA was isolated and processed using microarray technology and differentially expressed genes were identified. RESULTS: Similar motor and sensory NCV deficits were observed in male and female BTBR ob/ob mice at study termination; however, IENF density was greater in female ob/ob mice than their male counterparts. Male and female ob/ob mice exhibited similar weight gain, hyperglycemia, and hyperinsulinemia compared to non-diabetic controls, although triglycerides were elevated more so in males than in females. Transcriptional profiling of nerve tissue from female mice identified dysregulation of pathways related to inflammation. CONCLUSIONS: Similar to males, female BTBR ob/ob mice display robust DPN, and pathways related to inflammation are dysregulated in peripheral nerve.

Emergency Medicine

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

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

Endocrinology
Gomez-Sanchez CE, Qi X, Gomez-Sanchez EP, Sasano H, Bohlen MO, and **Wisgerhof M**. Disordered zonal and cellular CYP11B2 enzyme expression in familial hyperaldosteronism type 3 *Mol Cell Endocrinol* 2016;PMID: 27793677. Article request form

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Three forms of familial primary aldosteronism have been recognized. Familial Hyperaldosteronism type 1 (FH1) or dexamethasone suppressible hyperaldosteronism, FH2, the most common form of as yet unknown cause(s), and FH3. FH3 is due to activating mutations of the potassium channel gene KCNJ5 that increase constitutive and angiotensin II-induced aldosterone synthesis. In this study we examined the cellular distribution of CYP11B2, CYP11B1, CYP17A1 and KCNJ5 in adrenals from two FH3 siblings using immunohistochemistry and immunofluorescence and obtained unexpected results. The adrenals were markedly enlarged with loss of zonation. CYP11B2 was expressed sporadically throughout the adrenal cortex. CYP11B2 was most often expressed by itself, relatively frequently with CYP17A1, and less frequently with CYP11B1. KCNJ5 was co-expressed with CYP11B2 and in some cells with CYP11B1. This aberrant co-expression of enzymes likely explains the abnormally high secretion rate of the hybrid steroid, 18-oxocortisol.

Endocrinology
Kruger DF. A toast to our history *Clin Diabetes* 2016; 34(4):171-172. PMID: 27766007. <u>Article request form</u>

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Gastroenterology
Brady JE, Liffmann DK, Yartel A, Kil N, Federman AD, Kannry J, Jordan C, Massoud OI, **Nerenz DR**, **Brown KA**, Smith BD, Vellozzi C, and Rein DB. Uptake of hepatitis c screening, characteristics of patients tested, and intervention costs in the BEST-C study *Hepatology* 2016;PMID: 27770543. <u>Full Text</u>

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BACKGROUND: From December 2012-March 2014, three randomized trials, each implementing a unique intervention in primary care settings (mail recruitment [repeated-mailing], an electronic health record best practice alert [BPA], and patient-solicitation [patient-solicitation]), evaluated HCV antibody testing, diagnosis, and costs for each of the interventions compared to standard-of-care testing. Multilevel multivariable models were used to estimate the adjusted risk ratio (aRR) for receiving an HCV antibody test, and costs were estimated using activity-based costing. RATIONALE: To estimate the effects of interventions conducted as part of the Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C study on hepatitis C virus (HCV) testing and costs among persons of the 1945-1965 birth-cohort (BC). MAIN RESULTS: Intervention resulted in substantially higher HCV testing rates compared to standard-of-care (26.9% vs. 1.4% for repeated-mailing, 30.9% vs. 3.6% for BPA, and 63.5% vs. 2.0% for patient-solicitation), and significantly higher aRR for testing after controlling for sex, birth year, race, insurance type, and median household income (19.2 [95% Confidence Interval (CI) 9.7-38.2] for repeated-mailing, 13.2 [95% CI 3.6-48.6] for BPA, and 32.9 [95% CI 19.3-56.1] for patient-solicitation). The BPA intervention had the lowest incremental cost per completed test ($24 with fixed startup costs, $3 without) and also the lowest incremental cost per new case identified after omitting fixed startup costs ($1,691). CONCLUSION: HCV testing interventions resulted in an increase in BC testing compared to standard-of-care but also increased costs. The effect size and incremental costs of BPA intervention (excluding startup costs) support more widespread adoption compared to the other interventions. This article is protected by copyright. All rights reserved.

Gastroenterology
Xu F, Moorman AC, Tong X, **Gordon SC**, **Rupp LB**, **Lu M**, Teshale EH, Spradling PR, Boscarino JA, Trinacty CM, Schmidt MA, and Holmberg SD. All-cause mortality and progression risks to hepatic decompensation and hepatocellular carcinoma in patients infected with hepatitis c virus *Clin Infect Dis* 2016; 62(3):289-297. PMID: 26417034. <u>Full Text</u>

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BACKGROUND: A key question in care of patients with chronic hepatitis C virus (HCV) infection is beginning treatment immediately vs delaying treatment. Risks of mortality and disease progression in "real world" settings are important to assess the implications of delaying HCV treatment. METHODS: This was a cohort study of HCV patients identified from 4 integrated health systems in the United States who had liver biopsies during 2001-2012. The probabilities of death and progression to hepatocellular carcinoma, hepatic decompensation (hepatic encephalopathy, esophageal varices, ascites, or portal hypertension) or liver transplant were estimated over 1, 2, or 5 years by fibrosis stage (Metavir F0-F4) determined by biopsy at beginning of observation. RESULTS: Among 2799 HCV-monoinfected patients who had a qualifying liver biopsy, the mean age at the time of biopsy was 50.7 years. The majority were male (58.9%) and non-Hispanic white (66.9%). Over a mean observation of 5.0 years, 261 (9.3%) patients died and 34 (1.2%) received liver transplants. At 5 years after biopsy, the estimated risk of progression to hepatic decompensation or hepatocellular carcinoma was 37.2% in stage F4, 19.6% in F3, 4.7% in F2, and 2.3% in F0-F1 patients. Baseline biopsy stage F3 or F4 and platelet count below normal were the strongest predictors of progression to hepatic decompensation or hepatocellular carcinoma. CONCLUSIONS: The risks of death and progression to liver failure varied greatly by fibrosis stage. Clinicians and policy makers could use these progression risk data in prioritization and in determining the timing of treatment for patients in early stages of liver disease.

Hematology, Oncology and the Josephine Ford Cancer Institute
Alkhatib Y, **Abdel Rahman Z**, and **Kuriakose P**. Clinical impact of metformin in diabetic diffuse large B-cell lymphoma patients: a case-control study *Leuk Lymphoma* 2016:1-5. PMID: 27701994. Article request form

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Molecular studies have shown metformin to have a promising effect in lymphoma; however, there is lack of studies translating this effect into clinical settings. This was a case-control study to assess the clinical effect of metformin in diabetic diffuse large B-cell lymphoma (DLBCL) patients. Case subjects were diabetic on metformin with a new diagnosis of DLBCL. A total of 24 case subjects were identified, and for each case a control was matched. Outcomes of this study were to assess overall response rate, complete remission rate, progression free survival, and overall survival between the two groups. There was a significant increase in overall response rate, complete remission rate, and improved progression free survival in the metformin group compared to the control group, however, no significant overall survival difference was observed. Metformin use might be associated with an improved response rates and progression-free survival in diabetic DLBCL patients.

Hematology, Oncology and the Josephine Ford Cancer Institute
Edhayan G, Ohara RA, Stinson WA, Amin MA, Isozaki T, Ha CM, Haines GK, 3rd, Morgan R, Campbell PL, **Arbab AS**, Friday SC, Fox DA, and Ruth JH. Inflammatory properties of inhibitor of DNA binding 1 secreted by synovial fibroblasts in rheumatoid arthritis *Arthritis Res Ther* 2016; 18:87. PMID: 27071670. Full Text

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BACKGROUND: Inhibitor of DNA binding 1 (Id1) is a nuclear protein containing a basic helix-loop-helix (bHLH) domain that regulates cell growth by selective binding and prevention of gene transcription. Sources of Id1 production in rheumatoid arthritis synovial tissue (RA ST) and its range of functional effects in RA remain to be clarified. METHODS: We analyzed Id1 produced from synovial fibroblasts and endothelial cells (ECs) with histology and real-time polymerase chain reaction (RT-PCR). Fibroblast supernatants subjected to differential centrifugation to isolate and purify exosomes were measured for Id1 by enzyme-linked immunosorbent assay (ELISA). Western blotting of Id1-stimulated ECs was performed to determine the kinetics of intracellular protein phosphorylation. EC intracellular signaling pathways induced by Id1 were subsequently targeted with silencing RNA (siRNA) for angiogenesis

inhibition. RESULTS: By PCR and histologic analysis, we found that the primary source of Id1 in STs is from activated fibroblasts that correlate with inflammatory scores in human RA ST and in joints from K/BxN serum-induced mice. Normal (NL) and RA synovial fibroblasts increase Id1 production with stimulation by transforming growth factor beta (TGF-beta). Most of the Id1 released by RA synovial fibroblasts is contained within exosomes. Endothelial progenitor cells (EPCs) and human dermal microvascular ECs (HMVECs) activate the Jnk signaling pathway in response to Id1, and Jnk siRNA reverses Id1-induced HMVEC vessel formation in Matrigel plugs in vivo. CONCLUSIONS: Id1 is a pleotropic molecule affecting angiogenesis, vasculogenesis, and fibrosis. Our data shows that Id1 is not only an important nuclear protein, but also can be released from fibroblasts via exosomes. The ability of extracellular Id1 to activate signaling pathways expands the role of Id1 in the orchestration of tissue inflammation.

Hematology, Oncology and the Josephine Ford Cancer Institute
Henry NL, Braun TM, **Ali HY**, Munir K, Silver SM, Gorski DH, Breslin TM, and Griggs JJ. Associations between use of the 21-gene recurrence score assay and chemotherapy regimen selection in a statewide registry *Cancer* 2016;PMID: 27787892. Full Text

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BACKGROUND: The 21-gene recurrence score (RS) assay predicts response to adjuvant chemotherapy in patients with early-stage, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative invasive breast cancer, but to the authors' knowledge, the role of the assay in guiding the selection of chemotherapy regimen has not been established. The current study was conducted to examine patterns of use of the RS assay for selecting chemotherapy regimens across a statewide registry from 2006 through 2013. METHODS: Demographic, pathologic, and treatment data were abstracted from medical records for 16,666 women with breast cancer who were treated at 25 hospital systems across Michigan that were participating in the Michigan Breast Oncology Quality Initiative. Treatment patterns were examined based on the RS assay test result. RESULTS: Approximately 25% of patients with lymph node-negative disease who underwent testing with the RS assay and who were treated with chemotherapy received an anthracycline-based regimen, compared with 49% of patients with lymph node-negative disease who were treated with chemotherapy and who had not undergone testing with the RS assay. Of those patients with lymph node-positive disease who underwent testing with the RS assay and who received chemotherapy, 31% received an anthracycline-based regimen. In comparison, 71% of patients with lymph node-positive, chemotherapy-treated disease who did not undergo testing received an anthracycline. From 2006 through 2013, there was a statistically significant decrease in the use of anthracycline-containing regimens in both patients with lymph node-negative and lymph node-positive disease. CONCLUSIONS: Use of anthracycline-containing chemotherapy regimens in eligible patients appears to vary with use of the RS assay, despite the lack of evidence supporting use of the assay to guide regimen selection. Results of ongoing prospective trials should help to define the role of the RS assay in this setting.

Hematology, Oncology and the Josephine Ford Cancer Institute
Sak M, Duric N, Littrup P, Bey-Knight L, **Ali H**, **Vallieres P**, Sherman ME, and Gierach GL. Using speed of sound imaging to characterize breast density *Ultrasound Med Biol* 2016;PMID: 27692872. Full Text

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A population of 165 women with negative mammographic screens also received an ultrasound tomography (UST) examination at the Karmanos Cancer Institute in Detroit, MI. Standard statistical techniques were employed to measure the associations between the various mammographic- and UST-related density measures and various

participant characteristics such as age, weight and height. The mammographic percent density (MPD) was found to have similar strength associations with UST mean sound speed (Spearman coefficient, rs = 0.722, p < 0.001) and UST median sound speed (rs = 0.737, p < 0.001). Both were stronger than the associations between MPD with two separate measures of UST percent density, a k-means (rs = 0.568, p < 0.001) or a threshold (rs = 0.715, p < 0.001) measure. Segmentation of the UST sound speed images into dense and non-dense volumes showed weak to moderate associations with the mammographically equivalent measures. Relationships were found to be inversely and weakly associated between age and the UST mean sound speed (rs = -0.239, p = 0.002), UST median sound speed (rs = -0.226, p = 0.004) and MPD (rs = -0.204, p = 0.008). Relationships were found to be inversely and moderately associated between body mass index (BMI) and the UST mean sound speed (rs = -0.429, p < 0.001), UST median sound speed (rs = -0.447, p < 0.001) and MPD (rs = -0.489, p < 0.001). The results confirm and strengthen findings presented in previous work indicating that UST sound speed imaging yields viable markers of breast density in a manner consistent with mammography, the current clinical standard. These results lay the groundwork for further studies to assess the role of sound speed imaging in risk prediction.

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

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BACKGROUND AND OBJECTIVE: We explored racial differences in adherence to recommended clotting factor treatment regimens, chronic pain, and quality of life (QoL) among adolescents and young adults (AYAs) diagnosed with moderate or severe hemophilia. METHODS: A convenience sample of hemophilia patients aged 13-25 years completed an online cross-sectional survey in 2012. Chronic pain was measured using the revised Faces Pain Scale (FPS-R) and dichotomized as high (FPS-R >/= 4) or low (FPS-R < 4). QoL was measured with the SF-36. RESULTS: Of 80 AYA participants (79 male), most had severe disease (91 %) and hemophilia A (91 %). Most were white (76 %) and non-Hispanic (88 %). At the univariate level, compared to whites, non-whites were more likely to have produced an inhibitor against clotting factor treatment (74 vs 38 %, p < .01), less likely to have commercial health insurance (16 vs 63 %, p < .001), more likely to report high levels of chronic pain (FPS-R >/= 4) (63 vs 26 %, p < .01), and had lower SF-36 physical composite summary (PCS) scores. Adjusted logistic and quantile regression modeling, respectively, revealed that non-whites were 5.31 (95 % CI 1.62, 17.4; p < .01) times more likely to report high chronic pain and had median PCS scores that were 26.0 (95 % CI 11.0, 40.9; p < .01) points lower than whites. CONCLUSIONS: Targeted efforts to prevent and manage chronic pain among non-white AYAs with moderate or severe hemophilia are necessary. After accounting for demographic and clinical differences, there were no racial differences in adherence to recommended clotting factor treatment regimens; however, non-whites were more than five times more likely to report high levels of chronic pain, which predicted worse overall physical QoL, bodily pain, physical and social functioning, and greater role limitations due to physical health.

Hypertension and Vascular Research
Mali VR, **Pan G**, **Deshpande M**, Thandavarayan RA, **Xu J**, **Yang XP**, and **Palaniyandi SS**. Cardiac mitochondrial respiratory dysfunction and tissue damage in chronic hyperglycemia correlate with reduced aldehyde dehydrogenase-2 activity *PLoS One* 2016; 11(10):e0163158. PMID: 27736868. Full Text

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Aldehyde dehydrogenase (ALDH) 2 is a mitochondrial isozyme of the heart involved in the metabolism of toxic aldehydes produced from oxidative stress. We hypothesized that hyperglycemia-mediated decrease in ALDH2 activity may impair mitochondrial respiration and ultimately result in cardiac damage. A single dose (65 mg/kg; i.p.) streptozotocin injection to rats resulted in hyperglycemia with blood glucose levels of 443 +/- 9 mg/dl versus 121 +/- 7 mg/dl in control animals, p<0.0001, N = 7-11. After 6 months of diabetes mellitus (DM) induction, the rats were sacrificed after recording the functionality of their hearts. Increase in the cardiomyocyte cross sectional area (446 +/-

32 mum2 Vs 221 +/- 10 mum2; p<0.0001) indicated cardiac hypertrophy in DM rats. Both diastolic and systolic dysfunctions were observed with DM rats compared to controls. Most importantly, myocardial ALDH2 activity and levels were reduced, and immunostaining for 4HNE protein adducts was increased in DM hearts compared to controls. The mitochondrial oxygen consumption rate (OCR), an index of mitochondrial respiration, was decreased in mitochondria isolated from DM hearts compared to controls (p<0.0001). Furthermore, the rate of mitochondrial respiration and the increase in carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (FCCP)-induced maximal respiration were also decreased with chronic hyperglycemia. Chronic hyperglycemia reduced mitochondrial OXPHOS proteins. Reduced ALDH2 activity was correlated with mitochondrial dysfunction, pathological remodeling and cardiac dysfunction, respectively. Our results suggest that chronic hyperglycemia reduces ALDH2 activity, leading to mitochondrial respiratory dysfunction and consequently cardiac damage and dysfunction.

Hypertension and Vascular Research
Romero C, **Monu S**, **Cabral G**, **Knight R**, and **Carretero O**. Os 21-02 connecting tubule-glomerular feedback (ctgf) in renal hemodynamics and blood pressure regulation after unilateral nephrectomy (unx) *J Hypertens* 2016; 34 Suppl 1 - ISH 2016 Abstract Book:e235. PMID: 27754097. Abstract

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OBJECTIVE: Renal hemodynamics is critical for regulation of glomerular filtration (GFR), sodium excretion and blood pressure (BP), and it depends on myogenic response, tubuloglomerular feedback (TGF) and connecting tubule-glomerular feedback (CTGF). CTGF dilates afferent arteriole in response to high sodium in connecting tubule (CNT), counteracting and resetting TGF; and increasing the plasma flow and glomerular pressure favoring sodium excretion. CTGF is initiated by epithelial sodium channel (ENaC) activation in CNT and inhibited by ENaC blocker Benzamil. Unilateral nephrectomy (UNx) is accompanied by TGF resetting, increase in renal blood flow (RBF) and single nephron GFR in the remnant kidney, without any changes in systemic BP. We evaluated CTGF role in BP regulation and TGF resetting after UNx. DESIGN AND METHOD: UNx was performed on Sprague-Dawley rats and 24 h later TGF was evaluated in vivo by renal micropuncture using stop flow pressure (Psf) techniques. CTGF was evaluated by intratubularly adding Benzamil during the TGF response. Another set of animals received chronic kidney infusion of Benzamil that started 1 week before UNx. Renal blood flow (RBF) was measured by arterial spin labeling-MRI 24 h before and 24 h after the UNx. Direct BP measurement was performed before and 3 weeks after the UNx. RESULTS: After UNx, TGF resetting was observed (delta-Psf 8 +/- 1 vs. 1 +/- 1 mmHg p < 0.05, Sham vs. Unx) and that was inhibited by Benzamil. RBF increased after the UNx in comparison to sham and this increase was inhibited by chronic infusion of Benzamil (Sham: 305 +/- 59; UNx: 456 +/- 34; UNx + Benzamil 346 +/- 64 ml/min/100 g tissue p < 0.002). Mean BP values were not different between the vehicle or Benzamil infused rats before the UNx, however 3 weeks after the UNx, Benzamil infused rats showed higher mean BP values than vehicle (88 +/- 0.3 vs. 97 +/- 4 mmHg, p < 0.01). CONCLUSIONS: CTGF participates in TGF resetting and BP regulation after UNx. CTGF impairment could be a potential cause of hypertension.

Infectious Diseases
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; 59(5):489-495. 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.

Infectious Diseases
Orenstein R, Dubberke E, Hardi R, Ray A, Mullane K, Pardi DS, and **Ramesh MS**. Safety and durability of rbx2660 (microbiota suspension) for recurrent clostridium difficile infection: Results of the PUNCH CD study *Clin Infect Dis* 2016; 62(5):596-602. PMID: 26565008. Full Text

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BACKGROUND: Managing recurrent Clostridium difficile infection (CDI) presents a significant challenge for clinicians and patients. Fecal microbiota transplantation (FMT) is a highly effective therapy for recurrent CDI, yet availability of a standardized, safe, and effective product has been lacking. Our aim in this study was to assess the safety and effectiveness of RBX2660 (microbiota suspension), a commercially prepared FMT drug manufactured using standardized processes and available in a ready-to-use format. METHODS: Patients with at least 2 recurrent CDI episodes or at least 2 severe episodes resulting in hospitalization were enrolled in a prospective, multicenter open-label study of RBX2660 administered via enema. Intensive surveillance for adverse events (AEs) was conducted daily for 7 days following treatment and then at 30 days, 60 days, 3 months, and 6 months. The primary objective was product-related AEs. A secondary objective was CDI-associated diarrhea resolution at 8 weeks. RESULTS: Of the 40 patients enrolled at 11 centers in the United States between 15 August 2013 and 16 December 2013, 34 received at least 1 dose of RBX2660 and 31 completed 6-month follow-up. Overall efficacy was 87.1% (16 with 1 dose and 11 with 2 doses). Of 188 reported AEs, diarrhea, flatulence, abdominal pain/cramping, and constipation were most common. The frequency and severity of AEs decreased over time. Twenty serious AEs were reported in 7 patients; none were related to RBX2660 or its administration. CONCLUSIONS: Among patients with recurrent or severe CDI, administration of RBX2660 via enema appears to be safe and effective. CLINICAL TRIALS REGISTRATION: NCT01925417.

Infectious Diseases
Suleyman G, **Kenney R**, **Zervos MJ**, and **Weinmann A**. Safety and efficacy of outpatient parenteral antibiotic therapy in an academic infectious disease clinic *J Clin Pharm Ther* 2016;PMID: 27747899. Full Text

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WHAT IS KNOWN AND OBJECTIVE: Outpatient parenteral therapy (OPAT) has become a safe and effective modality for patients requiring intravenous or prolonged antimicrobial therapy since the 1970s. It is being increasingly utilized in various settings; however, studies evaluating the safety and efficacy of clinic-based OPAT are limited. Since 2012, patients being considered for OPAT have required an infectious disease (ID) consultation at our institution. Candidates receiving once-daily antimicrobials who were ineligible for home infusion or nursing home placement as determined by their insurance companies and those who preferred the clinic over nursing home or home infusion were referred to the ID clinic. This study assessed the safety and outcome of patients receiving OPAT in an academic inner-city ID clinic in Detroit, Michigan. METHODS: This was a retrospective cross-sectional study of electronic medical records of patients, identified through clinic records, who received at least 2 days of OPAT from December 2012 to December 2015. Demographics, types of infections, antimicrobial regimen used, adverse events and outcome were evaluated. RESULTS: A total of 122 cases were identified during the study period. Mean age was 62 years with 55% male; 102 (84%) of 122 patients had peripherally inserted central catheter (PICC). Fifty-five per cent of patients participated in the clinic-based OPAT programme for insurance reasons, and 43% preferred the clinic over nursing home or home infusion. The most common infections were bone and joint (36%), followed by skin and soft tissue (18%) and urinary tract infections (12%). Ertapenem (44%) and daptomycin (41%) alone or in combination were used most frequently with 40% of patients receiving at least 4 weeks of treatment. Thirteen patients (11%)

experienced one or more adverse drug events on daptomycin and/or ertapenem; of these, nine (69%) patients were receiving daptomycin monotherapy. Gastrointestinal symptoms (29%), cramping and myalgias (29%) and asymptomatic creatine phosphokinase (CPK) elevation (24%) were the most common adverse events. Three (3%) of 102 patients had PICC-related complications. Fourteen (88%) of 16 patients with adverse events or PICC-related complications required changing or stopping antibiotics; two (2%) had infection-related readmission. Conversely, 113 (93%) of 122 patients who completed treatment were considered cured and none had treatment failure at the end of 30 days of treatment. No patients died as a result of treatment or infection-related complications. WHAT IS NEW AND CONCLUSION: Outpatient parenteral therapy in our academic ID clinic was a safe and effective alternative to home infusion or skilled nursing facilities for patients requiring long-term antibiotics with few adverse events and complications.

Infectious Diseases
Suleyman G, and **Zervos MJ**. Safety and efficacy of commonly used antimicrobial agents in the treatment of enterococcal infections: a review *Expert Opin Drug Saf* 2016; 15(2):153-167. PMID: 26629598. Article request form

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INTRODUCTION: Enterococci have become the second leading cause of nosocomial infections in the U.S, which are associated with higher morbidity, mortality, length of stay, and cost due to escalating resistance to several antimicrobial agents. With limited treatment options, the adverse events associated with the increasing use of available agents must be considered. AREAS COVERED: Safety data about the most commonly used antimicrobial agents to treat enterococcal infections (ampicillin, vancomycin, linezolid, daptomycin, and tigecycline) derived from animal models, clinical trials and post-marketing surveillance are evaluated. However, most of these agents are not FDA approved and have been used for off-label indications in enterococcal infections. EXPERT OPINION: The commonly used antimicrobials to treat enterococcal infections have unique safety profiles and side effects but are generally safe and tolerated in the short-term based on data from clinical trials and post-marketing surveillance. However, serious long-term adverse events may occur, and antibiotic selection should be individualized and based on source of infection, duration, potential drug-related toxicity, and drug-drug interactions to minimize side-effects. Implementing standard precautions and infection control measures, minimizing unnecessary antibiotic exposure, and optimizing treatment and duration with removal of source of infection are essential to prevent the spread of resistance and improve outcomes.

Internal Medicine
Abid Z, Oh SS, Hu D, Sen S, Huntsman S, Eng C, Farber HJ, Rodriguez-Cintron W, Rodriguez-Santana JR, Serebrisky D, Avila PC, Thyne SM, Kim KA, Borrell LN, **Williams LK**, Seibold MA, Burchard EG, and Kumar R. Maternal age and asthma in Latino populations *Clin Exp Allergy* 2016; 46(11):1398-1406. PMID: 27238356. Full Text

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BACKGROUND: Younger maternal age at birth is associated with increased risk of asthma in offspring in European descent populations, but has not been studied in Latino populations. OBJECTIVES: We sought to examine the relationship between maternal age at birth and prevalence of asthma in a nationwide study of Latino children. METHODS: We included 3473 Latino children aged 8-21 years (1696 subjects with physician-diagnosed asthma and 1777 healthy controls) from five US centres and Puerto Rico recruited from July 2008 through November 2011. We

used multiple logistic regression models to examine the effect of maternal age at birth on asthma in offspring overall and in analyses stratified by ethnic subgroup (Mexican American, Puerto Rican and other Latino). Secondary analyses evaluated the effects of siblings, acculturation and income on this relationship. RESULTS: Maternal age < 20 years was significantly associated with decreased odds of asthma in offspring, independent of other risk factors (OR = 0.73, 95% CI: 0.57-0.93). In subgroup analyses, the protective effect of younger maternal age was observed only in Mexican Americans (OR = 0.53, 95% CI: 0.36, 0.79). In Puerto Ricans, older maternal age was associated with decreased odds of asthma (OR = 0.65, 95% CI: 0.44-0.97). In further stratified models, the protective effect of younger maternal age in Mexican Americans was seen only in children without older siblings (OR = 0.44, 95% CI: 0.23-0.81). CONCLUSION AND CLINICAL RELEVANCE: In contrast to European descent populations, younger maternal age was associated with decreased odds of asthma in offspring in Mexican American women. Asthma is common in urban minority populations but the factors underlying the varying prevalence among different Latino ethnicities in the United States is not well understood. Maternal age represents one factor that may help to explain this variability.

Internal Medicine
Alkhatib Y, **Abdel Rahman Z**, and **Kuriakose P**. Clinical impact of metformin in diabetic diffuse large B-cell lymphoma patients: a case-control study *Leuk Lymphoma* 2016:1-5. PMID: 27701994. Article request form

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Molecular studies have shown metformin to have a promising effect in lymphoma; however, there is lack of studies translating this effect into clinical settings. This was a case-control study to assess the clinical effect of metformin in diabetic diffuse large B-cell lymphoma (DLBCL) patients. Case subjects were diabetic on metformin with a new diagnosis of DLBCL. A total of 24 case subjects were identified, and for each case a control was matched. Outcomes of this study were to assess overall response rate, complete remission rate, progression free survival, and overall survival between the two groups. There was a significant increase in overall response rate, complete remission rate, and improved progression free survival in the metformin group compared to the control group, however, no significant overall survival difference was observed. Metformin use might be associated with an improved response rates and progression-free survival in diabetic DLBCL patients.

Internal Medicine
Brant SR, Okou DT, Simpson CL, Cutler DJ, Haritunians T, Bradfield JP, Chopra P, Prince J, Begum F, Kumar A, Huang C, Venkateswaran S, Datta LW, Wei Z, Thomas K, Herrinton LJ, Klapproth JA, Quiros AJ, Seminerio J, Liu Z, Alexander JS, Baldassano RN, Dudley-Brown S, Cross RK, Dassopoulos T, Denson LA, Dhere TA, Dryden GW, Hanson JS, Hou JK, Hussain SZ, Hyams JS, Isaacs KL, Kader H, Kappelman MD, Katz J, Kellermayer R, Kirschner BS, Kuemmerle JF, Kwon JH, Lazarev M, Li E, Mack D, Mannon P, Moulton DE, Newberry RD, Osuntokun BO, Patel AS, Saeed SA, Targan SR, Valentine JF, Wang MH, **Zonca M**, Rioux JD, Duerr RH, Silverberg MS, Cho JH, Hakonarson H, Zwick ME, McGovern DP, and Kugathasan S. Genome-wide association study identifies African-specific susceptibility loci in African Americans with inflammatory bowel disease *Gastroenterology* 2016;PMID: 27693347. Full Text

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BACKGROUND & AIMS: The inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's disease (CD) cause significant morbidity and are increasing in prevalence among all populations, including African Americans. More than 200 susceptibility loci have been identified in populations of predominantly European ancestry, but few loci have been associated with IBD in other ethnicities. METHODS: We performed 2 high-density, genome-wide scans comprising 2345 cases of African Americans with IBD (1646 with CD, 583 with UC, and 116 inflammatory bowel disease unclassified [IBD-U]) and 5002 individuals without IBD (controls, identified from the Health Retirement Study and Kaiser Permanente database). Single-nucleotide polymorphisms (SNPs) associated at $P<5.0 \times 10^{-8}$ in meta-analysis with a nominal evidence ($P<.05$) in each scan were considered to have genome-wide significance. RESULTS: We detected SNPs at HLA-DRB1, and African-specific SNPs at ZNF649 and LSAMP, with associations of genome-wide significance for UC. We detected SNPs at USP25 with associations of genome-wide significance associations for IBD. No associations of genome-wide significance were detected for CD. In addition, 9 genes previously associated with IBD contained SNPs with significant evidence for replication ($P<1.6 \times 10^{-6}$): ADCY3, CXCR6, HLA-DRB1 to HLA-DQA1 (genome-wide significance on conditioning), IL12B, PTGER4, and TNC for IBD;

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IL23R, PTGER4, and SNX20 (in strong linkage disequilibrium with NOD2) for CD; and KCNQ2 (near TNFRSF6B) for UC. Several of these genes, such as TNC (near TNFSF15), CXCR6, and genes associated with IBD at the HLA locus, contained SNPs with unique association patterns with African-specific alleles. CONCLUSIONS: We performed a genome-wide association study of African Americans with IBD and identified loci associated with CD and UC in only this population; we also replicated loci identified in European populations. The detection of variants associated with IBD risk in only people of African descent demonstrates the importance of studying the genetics of IBD and other complex diseases in populations beyond those of European ancestry.

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; 59(5):489-495. 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

Kessler MD, Yerges-Armstrong L, Taub MA, Shetty AC, Maloney K, Jeng LJ, Ruczinski I, **Levin AM**, **Williams LK**, Beaty TH, Mathias RA, Barnes KC, and O'Connor TD. Challenges and disparities in the application of personalized genomic medicine to populations with African ancestry *Nat Commun* 2016; 7:12521. PMID: 27725664. Full Text

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To characterize the extent and impact of ancestry-related biases in precision genomic medicine, we use 642 whole-genome sequences from the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) project to evaluate typical filters and databases. We find significant correlations between estimated African ancestry proportions and the number of variants per individual in all variant classification sets but one. The source of these correlations is highlighted in more detail by looking at the interaction between filtering criteria and the ClinVar and Human Gene Mutation databases. ClinVar's correlation, representing African ancestry-related bias, has changed over

time amidst monthly updates, with the most extreme switch happening between March and April of 2014 (r=0.733 to r=-0.683). We identify 68 SNPs as the major drivers of this change in correlation. As long as ancestry-related bias when using these clinical databases is minimally recognized, the genetics community will face challenges with implementation, interpretation and cost-effectiveness when treating minority populations.

Internal Medicine
Liu Q, **Wu D**, **Han L**, **Deng J**, **Zhou L**, He R, Lu C, and **Mi QS**. Roles of MicroRNAs in psoriasis: immunological functions and potential biomarkers *Exp Dermatol* 2016;PMID: 27783430. Full Text

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MicroRNAs (miRNAs) are small non-coding RNA molecules, which function in RNA silencing and post-transcriptional regulation of gene expression. Psoriasis is an inflammatory skin disease characterized by the dysfunction of keratinocytes, with the immune dysregulation. We reviewed the recent studies on the roles of miRNAs in psoriasis, and showed that miRNAs play key roles in psoriasis, including the regulation of hyperproliferation, cytokine and chemokine production in keratinocyte, as well as mediating immune dysfunction in psoriasis. Furthermore, miRNAs, particularly, circulating miRNAs may serve as novel biomarkers for diagnosis, monitoring therapy response, and reflecting the disease severity. Thus, targeting specific miRNAs may be used to develop new therapeutic methods for psoriasis. This article is protected by copyright. All rights reserved.

Internal Medicine
Mali VR, **Pan G**, **Deshpande M**, Thandavarayan RA, **Xu J**, **Yang XP**, and **Palaniyandi SS**. Cardiac mitochondrial respiratory dysfunction and tissue damage in chronic hyperglycemia correlate with reduced aldehyde dehydrogenase-2 activity *PLoS One* 2016; 11(10):e0163158. PMID: 27736868. Full Text

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Aldehyde dehydrogenase (ALDH) 2 is a mitochondrial isozyme of the heart involved in the metabolism of toxic aldehydes produced from oxidative stress. We hypothesized that hyperglycemia-mediated decrease in ALDH2 activity may impair mitochondrial respiration and ultimately result in cardiac damage. A single dose (65 mg/kg; i.p.) streptozotocin injection to rats resulted in hyperglycemia with blood glucose levels of 443 +/- 9 mg/dl versus 121 +/- 7 mg/dl in control animals, p<0.0001, N = 7-11. After 6 months of diabetes mellitus (DM) induction, the rats were sacrificed after recording the functionality of their hearts. Increase in the cardiomyocyte cross sectional area (446 +/- 32 mum2 Vs 221 +/- 10 mum2; p<0.0001) indicated cardiac hypertrophy in DM rats. Both diastolic and systolic dysfunctions were observed with DM rats compared to controls. Most importantly, myocardial ALDH2 activity and levels were reduced, and immunostaining for 4HNE protein adducts was increased in DM hearts compared to controls. The mitochondrial oxygen consumption rate (OCR), an index of mitochondrial respiration, was decreased in mitochondria isolated from DM hearts compared to controls (p<0.0001). Furthermore, the rate of mitochondrial respiration and the increase in carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (FCCP)-induced maximal respiration were also decreased with chronic hyperglycemia. Chronic hyperglycemia reduced mitochondrial OXPHOS proteins. Reduced ALDH2 activity was correlated with mitochondrial dysfunction, pathological remodeling and cardiac dysfunction, respectively. Our results suggest that chronic hyperglycemia reduces ALDH2 activity, leading to mitochondrial respiratory dysfunction and consequently cardiac damage and dysfunction.

Internal Medicine

Mathias RA, Taub MA, Gignoux CR, Fu W, Musharoff S, O'Connor TD, Vergara C, Torgerson DG, Pino-Yanes M, Shringarpure SS, Huang L, Rafaels N, Boorgula MP, Johnston HR, Ortega VE, **Levin AM**, Song W, Torres R, **Padhukasahasram B**, Eng C, Mejia-Mejia DA, Ferguson T, Qin ZS, Scott AF, Yazdanbakhsh M, Wilson JG, Marrugo J, Lange LA, Kumar R, Avila PC, **Williams LK**, Watson H, Ware LB, Olopade C, Olopade O, Oliveira R, Ober C, Nicolae DL, Meyers D, Mayorga A, Knight-Madden J, Hartert T, Hansel NN, Foreman MG, Ford JG, Faruque MU, Dunston GM, Caraballo L, Burchard EG, Bleecker E, Araujo MI, Herrera-Paz EF, Gietzen K, Grus WE, Bamshad M, Bustamante CD, Kenny EE, Hernandez RD, Beaty TH, Ruczinski I, Akey J, and Barnes KC. A continuum of admixture in the Western Hemisphere revealed by the African Diaspora genome *Nat Commun* 2016; 7:12522. PMID: 27725671. Full Text

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The African Diaspora in the Western Hemisphere represents one of the largest forced migrations in history and had a profound impact on genetic diversity in modern populations. To date, the fine-scale population structure of descendants of the African Diaspora remains largely uncharacterized. Here we present genetic variation from deeply sequenced genomes of 642 individuals from North and South American, Caribbean and West African populations, substantially increasing the lexicon of human genomic variation and suggesting much variation remains to be discovered in African-admixed populations in the Americas. We summarize genetic variation in these populations, quantifying the postcolonial sex-biased European gene flow across multiple regions. Moreover, we refine estimates on the burden of deleterious variants carried across populations and how this varies with African ancestry. Our data are an important resource for empowering disease mapping studies in African-admixed individuals and will facilitate gene discovery for diseases disproportionately affecting individuals of African ancestry.

Internal Medicine
Milling TJ, Jr., and **Kaatz S**. Preclinical and clinical data for factor Xa and "Universal" reversal agents *Am J Emerg Med* 2016;PMID: 27697443. Full Text

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Oral Factor Xa (FXa) inhibitors, a growing class of direct-acting anticoagulants, are frequently used to prevent stroke and systemic embolism in patients with atrial fibrillation and to prevent and treat venous thromboembolism. These drugs reduce the risk of clotting at the expense of increasing the risk of bleeding, and currently they have no specific reversal agent. However, andexanet alfa, a recombinant modified FXa decoy molecule, is in a late-phase clinical trial in bleeding patients, and ciraparantag, a small molecule that appears to reverse many anticoagulants including the FXa inhibitors, is in development. This review summarizes the published data to date on both drugs, which have the potential to change the management approach to patients with FXa inhibitoreassociated major hemorrhage.

Internal Medicine
Zhang X, **Liu Q**, **Wang J**, **Li G**, **Weiland M**, Yu FS, **Mi QS**, Gu J, and **Zhou L**. TIM-4 is differentially expressed in the distinct subsets of dendritic cells in skin and skin-draining lymph nodes and controls skin Langerhans cell homeostasis *Oncotarget* 2016; 7(25):37498-37512. PMID: 27224924. Full Text

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T cell immunoglobulin and mucin-4 (TIM-4), mainly expressed on dendritic cells (DC) and macrophages, plays an essential role in regulating immune responses. Langerhans cells (LC), which are the sole DC subpopulation residing at the epidermis, are potent mediators of immune surveillance and tolerance. However, the significance of TIM-4 on epidermal LCs, along with other cutaneous DCs, remains totally unexplored. For the first time, we discovered that epidermal LCs expressed TIM-4 and displayed an increased level of TIM-4 expression upon migration. We also found that dermal CD207+ DCs and lymph node (LN) resident CD207-CD4+ DCs highly expressed TIM-4, while dermal CD207- DCs and LN CD207-CD4- DCs had limited TIM-4 expressions. Using TIM-4-deficient mice, we further demonstrated that loss of TIM-4 significantly upregulated the frequencies of epidermal LCs and LN resident CD207-CD4+ DCs. In spite of this, the epidermal LCs of TIM-4-deficient mice displayed normal phagocytic and migratory abilities, comparable maturation status upon the stimulation as well as normal repopulation under the inflamed state. Moreover, lack of TIM-4 did not affect dinitrofluorobenzene-induced contact hypersensitivity response. In conclusion, our results indicated that TIM-4 was differentially expressed in the distinct subsets of DCs in skin and skin-draining LNs, and specifically regulated epidermal LC and LN CD207-CD4+ DC homeostasis.

Immunology

Liu Q, **Wu D**, **Han L**, **Deng J**, **Zhou L**, He R, Lu C, and **Mi QS**. Roles of MicroRNAs in psoriasis: immunological functions and potential biomarkers *Exp Dermatol* 2016;PMID: 27783430. Full Text

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MicroRNAs (miRNAs) are small non-coding RNA molecules, which function in RNA silencing and post-transcriptional regulation of gene expression. Psoriasis is an inflammatory skin disease characterized by the dysfunction of keratinocytes, with the immune dysregulation. We reviewed the recent studies on the roles of miRNAs in psoriasis, and showed that miRNAs play key roles in psoriasis, including the regulation of hyperproliferation, cytokine and chemokine production in keratinocyte, as well as mediating immune dysfunction in psoriasis. Furthermore, miRNAs, particularly, circulating miRNAs may serve as novel biomarkers for diagnosis, monitoring therapy response, and reflecting the disease severity. Thus, targeting specific miRNAs may be used to develop new therapeutic methods for psoriasis. This article is protected by copyright. All rights reserved.

Nephrology

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

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BACKGROUND: Diabetic Ketoacidosis (DKA) is a potentially life-threatening emergency that requires prompt diagnosis and treatment. In paediatric populations an end tidal capnography value greater than 36 mmHg was found to be 100 % sensitive in ruling out DKA. METHODS: A cross sectional observational study of adults >/= 17 years of age presenting to the emergency department between January 2014 and May 2014 with glucose > 550 mg/dL. In all patients, nasal capnography and venous blood gas analysis were performed prior to any insulin or intravenous fluid administration. The diagnosis of DKA was based on the presence of anion gap metabolic acidosis, hyperglycaemia and ketonemia. The overall diagnostic performance (area under the curve [AUC]), sensitivity, specificity and likelihood ratios at different end tidal CO_2 (ETCO2) cut-offs were determined. RESULTS: 71 patients were enrolled in the study of which 21 (30 %) met the diagnosis of DKA. The area under the curve for ETCO2 was 0.95 with a 95 % CI of 0.91 to 0.99. Test sensitivity for DKA at ETCO2 level >/=35 mmHg was 100 % (95 % CI, 83.9-100). An ETCO2 level </= 21 mmHg was 100 % specific (95 % CI, 92.9-100.0) for DKA. CONCLUSION: Nasal capnography exhibits favourable diagnostic performance in detecting patients with or without DKA among those who present to the emergency department with a glucometer reading > 550 mg/dL.

Nephrology

Ma J, **Patel A**, and Tinckam K. Donor-specific antibody monitoring: Where is the beef? *Adv Chronic Kidney Dis* 2016; 23(5):317-325. PMID: 27742387. Full Text

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This review paper discusses the impact of de novo donor-specific antibodies (DSA) to donor HLA antigens in kidney transplantation and summarizes the benefits and challenges that exist with DSA monitoring. Post-transplant DSA is associated with worse allograft outcomes and its detection may precede or coincide with clinical, biochemical, and histologic allograft dysfunction. There are no absolute features of DSA testing results that perfectly discriminate between states of disease and health. In a state of antibody-associated graft dysfunction, removal or reduction in DSA may only provide clinical benefit for some. Furthermore, various factors influence test results, and detection of HLA antibodies must be interpreted within the appropriate clinical and laboratory context. The utility of DSA monitoring is further affected by the limited effectiveness of treatment for antibody-mediated rejection. Although DSA monitoring is potentially beneficial in some circumstances, the optimal screening and treatment strategies are still to be defined.

Nephrology
Patel AK, and **Samaniego M**. The struggle for optimization of long-term outcomes after kidney transplantation *Adv Chronic Kidney Dis* 2016; 23(5):280. PMID: 27742380. Full Text

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Nephrology
Prashar R, and **Venkat KK**. Immunosuppression minimization and avoidance protocols: When less is not more *Adv Chronic Kidney Dis* 2016; 23(5):295-300. PMID: 27742383. Full Text

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Kidney transplantation is well established as the best treatment option for end-stage kidney disease. It confers not only a better quality of life but also a significant survival advantage compared to dialysis. However, despite significant improvement in short-term kidney transplant graft survival over the past three decades, long-term graft survival remains suboptimal. Concerns about the possible contribution of chronic calcineurin inhibitor (CNI) nephrotoxicity to late allograft failure and other serious adverse effects of currently used immunosuppressive agents (especially corticosteroids) have led to increasing interest in developing regimens which may better preserve kidney allograft function and minimize other immunosuppression-related problems without increasing the risk of rejection. The availability of newer immunosuppressive agents has provided the opportunity to formulate such regimens. Approaches to this end include minimization, withdrawal, or avoidance of corticosteroids and CNIs. Currently, replacement of a CNI with a mammalian target of rapamycin inhibitor while continuing mycophenolate and discontinuation of corticosteroids within the first post-transplant week is being increasingly utilized. Belatacept-based, CNI-free immunosuppression is an emerging alternative approach to avoiding CNI-mediated nephrotoxicity. We also discuss the evolution, results, and pros and cons of corticosteroid- and CNI minimization protocols. Recent studies suggest that chronic alloimmune damage rather than chronic CNI nephrotoxicity is the major contributor to late kidney allograft failure. The implications of this finding for the use of CNI minimization protocols are also discussed.

Nephrology
Yee J. Increasing access to kidney transplantation: Easy as A-B-O *Adv Chronic Kidney Dis* 2016; 23(5):277-279. PMID: 27742379. Full Text

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

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

Neurology
Gamage NH, Jing L, **Worsham MJ**, and **Ali MM**. Targeted theranostic approach for glioma using dendrimer-based curcumin nanoparticle *J Nanomed Nanotechnol* 2016; 7(4)PMID: 27699139. Full Text

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The delivery of anti-cancer agents to brain tumors represent a challenge because the blood-brain tumor barrier (BBTB) effectively limits the delivery of many agents. A new generation 3 (G3) dendrimer-based curcumin (Curc) conjugate was synthesized. The synthesized G3-Curc conjugate demonstrated full solubility in aqueous media. The in vitro study revealed that G3-Curc nanoparticles were internalized into glioma U-251 cells. Systemic delivery of G3-Curc conjugate led to preferentially accumulation in an orthotopic preclinical glioma model minimizing systemic toxic effect. Multicolor microscopy images of the tumor tissue showed that G3-Curc particles were internalized inside tumor cells selectively and further localized within nuclei. Enhanced bioavailability of G3-Curc conjugate was also observed with improved therapeutic efficacy against different cancers cells.

Neurology

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Angiogenesis, a hallmark of glioblastoma, can potentially be targeted by inhibiting the VEGF pathway using bevacizumab, a humanized monoclonal antibody against VEGF-A. This study was designed to determine the efficacy and safety of these regimens in the cooperative group setting. Eligibility included age >/=18, recurrent or progressive GBM after standard chemoradiation. Treatment was intravenous bevacizumab 10 mg/kg and either irinotecan (CPT) 125 mg/m2 every 2 weeks or temozolomide (TMZ) 75-100 mg/m2 day 1-21 of 28 day cycle. Accrual goal was 57 eligible patients per arm. Primary endpoint was 6 month progression-free survival (6-m PFS); a predetermined rate of >/=35 % to declare efficacy. 60 eligible patients were enrolled on TMZ arm and 57 patients on CPT arm. Median age was 56, median KPS was 80. For TMZ arm, the 6-m-PFS rate was 39 % (23/59); for the CPT arm, the 6-m-PFS rate was 38.6 % (22/57). Objective responses: TMZ arm had 2 (3 %) CR, 9 (16 %) PR; CPT arm had 2 (4 %) CR, 13 (24 %) PR. Overall there was moderate toxicity: TMZ arm with 33 (55 %) grade 3, 11 (18 %) grade 4, and 1 (2 %) grade 5 (fatal) toxicities; CPT arm had 22 (39 %) grade 3, 7 (12 %) grade 4, and 3 (5 %) grade 5 toxicities. The 6-m-PFS surpassed the predetermined efficacy threshold for both arms, corroborating the efficacy of bevacizumab and CPT and confirming activity for bevacizumab and protracted TMZ for recurrent/progressive GBM, even after prior temozolomide exposure. Toxicities were within anticipated frequencies with a moderately high rate of venous thrombosis, moderate hypertension and one intracranial hemorrhage.

Neurology

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In brain tumors, delivering nanoparticles across the blood-tumor barrier presents major hurdles. A clinically relevant MRI contrast agent, GdDOTA and a near-infrared (NIR) fluorescent dye, DL680 were conjugated to a G5 PAMAM dendrimer, thus producing a dual-mode MRI and NIR imaging agent. Systemic delivery of the subsequent nano-sized agent demonstrated glioma-specific accumulation, probably due to the enhanced permeability and retention effect. In vivo MRI detected the agent in glioma tissue, but not in normal contralateral tissue; this observation was validated with in vivo and ex vivo fluorescence imaging. A biodistribution study showed the agent to have accumulated in the glioma tumor and the liver, the latter being the excretion path for a G5 dendrimer-based agent.

Neurology

Modi SY, **Dharaiya D**, **Katramados AM**, and **Mitsias P**. Predictors of prolonged hospital stay in status migrainosus *Neurohospitalist* 2016; 6(4):141-146. PMID: 27695594. Full Text

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BACKGROUND: Patients with status migrainosus often need to be admitted due to the severity of their headaches. Their hospitalization is often prolonged due to poor headache control. Large sample studies looking into the factors associated with prolonged length of stay (pLOS) in status migrainosus are lacking. METHODS: We utilized the Nationwide Inpatient Sample database to identify 4325 patients with primary discharge diagnosis of status migrainosus. Length of inpatient stay (LOS) of more than 6 days (90th percentile of LOS) was defined as pLOS. Patient demographics, hospital characteristics, mood disorders, anxiety disorder, and common medical comorbidities were identified. Multivariable logistic regression was used to identify factors associated with pLOS. RESULTS: We found 402 patients with pLOS. Female gender, African American race, mood disorder, obesity, opioid abuse, congestive heart failure, and chronic renal failure were significant independent predictors of pLOS. Median inflation-adjusted cost of hospitalization was USD$3829 (interquartile range: 2419-5809). CONCLUSION: We were able to identify several factors associated with pLOS in status migrainosus. Most of the factors we found were similar to those known to increase the prevalence and severity of migraine in the general population. Knowledge of these factors may help physicians identify high-risk patients to institute early migraine abortive and prophylactic treatment in order to shorten the length of hospital stay.

Neurology

Romero C, **Monu S**, **Cabral G**, **Knight R**, and **Carretero O**. Os 21-02 connecting tubule-glomerular feedback (ctgf) in renal hemodynamics and blood pressure regulation after unilateral nephrectomy (unx) *J Hypertens* 2016; 34 Suppl 1 - ISH 2016 Abstract Book:e235. PMID: 27754097. Abstract

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OBJECTIVE: Renal hemodynamics is critical for regulation of glomerular filtration (GFR), sodium excretion and blood pressure (BP), and it depends on myogenic response, tubuloglomerular feedback (TGF) and connecting tubule-glomerular feedback (CTGF). CTGF dilates afferent arteriole in response to high sodium in connecting tubule (CNT), counteracting and resetting TGF; and increasing the plasma flow and glomerular pressure favoring sodium excretion. CTGF is initiated by epithelial sodium channel (ENaC) activation in CNT and inhibited by ENaC blocker Benzamil. Unilateral nephrectomy (UNx) is accompanied by TGF resetting, increase in renal blood flow (RBF) and single nephron GFR in the remnant kidney, without any changes in systemic BP. We evaluated CTGF role in BP regulation and TGF resetting after UNx. DESIGN AND METHOD: UNx was performed on Sprague-Dawley rats and 24 h later TGF was evaluated in vivo by renal micropuncture using stop flow pressure (Psf) techniques. CTGF was evaluated by intratubularly adding Benzamil during the TGF response. Another set of animals received chronic kidney infusion of Benzamil that started 1 week before UNx. Renal blood flow (RBF) was measured by arterial spin labeling-MRI 24 h before and 24 h after the UNx. Direct BP measurement was performed before and 3 weeks after the UNx. RESULTS: After UNx, TGF resetting was observed (delta-Psf 8 +/- 1 vs. 1 +/- 1 mmHg p < 0.05, Sham vs. Unx) and that was inhibited by Benzamil. RBF increased after the UNx in comparison to sham and this increase was inhibited by chronic infusion of Benzamil (Sham: 305 +/- 59; UNx: 456 +/- 34; UNx + Benzamil 346 +/- 64 ml/min/100 g tissue p < 0.002). Mean BP values were not different between the vehicle or Benzamil infused rats before the UNx, however 3 weeks after the UNx, Benzamil infused rats showed higher mean BP values than vehicle (88 +/- 0.3 vs. 97 +/- 4 mmHg, p < 0.01). CONCLUSIONS: CTGF participates in TGF resetting and BP regulation after UNx. CTGF impairment could be a potential cause of hypertension.

Neurology

Walbert T, Glantz M, **Schultz L**, and Puduvalli VK. Impact of provider level, training and gender on the utilization of palliative care and hospice in neuro-oncology: a North-American survey *J Neurooncol* 2016; 126(2):337-345. PMID: 26518539. Full Text

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Specialized palliative care (PC) services have emerged to address symptoms and provide end-of-life management for patients with brain tumors. The utilization patterns of PC in neuro-oncology are unknown. A 22-question survey was distributed to participants of the society for neuro-oncology annual meeting 2012 (n = 4487). Nonparametric methods including Wilcoxon two-sample and Kruskal-Wallis tests were used to assess differences in responses. 239 (5.3 %) evaluable responses were received; 79 % of respondents were physicians, and 17 % were nurses or midlevel providers. Forty-seven percent were medical or neuro-oncologists, 31 % neurosurgeons and 11 % radiation oncologists. Forty percent had no formal training in PC, 57 % had some formal training and 3 % completed a PC fellowship. Seventy-nine percent practiced in an academic setting. Of the respondents, 57 % referred patients to PC when symptoms required treatment and 18 % at end of life. Only 51 % of all providers felt comfortable dealing with end-of-life issues and symptoms, while 33 % did not. Fifty-one percent preferred a service named "Supportive Care" rather than "Palliative Care" (MDs > midlevel providers, p < 0.001), and 32 % felt that patient expectations for ongoing therapy hindered their ability to make PC referrals. Female gender, formal training in neuro-oncology and PC, and medical versus surgical neuro-oncology training were significantly associated with hospice referral, comfort in dealing with end-of-life issues, and ease of access to PC services. Provider level, specialty, gender, training in PC and neuro-oncology have significant impact on the utilization of PC and hospice in neuro-oncology.

Neurology
Yan T, Venkat P, **Chopp M**, Zacharek A, Ning R, Roberts C, Zhang Y, Lu M, and Chen J. Neurorestorative responses to delayed human mesenchymal stromal cells treatment of stroke in type 2 diabetic rats *Stroke* 2016; 47(11):2850-2858. PMID: 27729575. Full Text

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BACKGROUND AND PURPOSE: Comorbidity of diabetes mellitus and stroke results in worse functional outcome, poor long-term recovery, and extensive vascular damage. We investigated the neurorestorative effects and mechanisms of stroke treatment with human bone marrow-derived mesenchymal stromal cells (hMSCs) in type 2 diabetes mellitus (T2DM) rats. METHODS: Adult male Wistar rats were induced with T2DM, subjected to 2 hours of middle cerebral artery occlusion (MCAo) and treated via tail-vein injection with (1) PBS (n=8) and (2) hMSCs (n=10; 5x106) at 3 days after MCAo. RESULTS: In T2DM rats, hMSCs administered at 3 days after MCAo significantly improves neurological function without affecting blood glucose, infarct volume, and incidence of brain hemorrhage in comparison to T2DM-MCAo PBS-treated rats. Delayed hMSC treatment of T2DM stroke significantly improves blood-brain barrier integrity, increases vascular and arterial density and cerebral vascular perfusion, and promotes neuroblast cell migration and white matter remodeling as indicated by increased doublecortin, axon, myelin, and neurofilament density, respectively. Delayed hMSC treatment significantly increases platelet-derived growth factor expression in the ischemic brain, decreases proinflammatory M1 macrophage and increases anti-inflammatory M2 macrophage compared to PBS-treated T2DM-MCAo rats. In vitro data show that hMSCs increase subventricular zone explant cell migration and primary cortical neuron neurite outgrowth, whereas inhibition of platelet-derived growth factor decreases hMSC-induced subventricular zone cell migration and axonal outgrowth. CONCLUSIONS: In T2DM stroke rats, delayed hMSC treatment significantly improves neurological functional outcome and increases neurorestorative effects and M2 macrophage polarization. Increasing brain platelet-derived growth factor expression may contribute to hMSC-induced neurorestoration.

Neurology
Zhang R, **Zhang Z**, and **Chopp M**. Function of neural stem cells in ischemic brain repair processes *J Cereb Blood Flow Metab* 2016;PMID: 27742890. Full Text

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Hypoxic/ischemic injury is the single most important cause of disabilities in infants, while stroke remains a leading cause of morbidity in children and adults around the world. The injured brain has limited repair capacity, and thereby only modest improvement of neurological function is evident post injury. In rodents, embryonic neural stem cells in the ventricular zone generate cortical neurons, and adult neural stem cells in the ventricular-subventricular zone of the lateral ventricle produce new neurons through animal life. In addition to generation of new neurons, neural stem cells contribute to oligodendrogenesis. Neurogenesis and oligodendrogenesis are essential for repair of injured brain. Much progress has been made in preclinical studies on elucidating the cellular and molecular mechanisms that control and coordinate neurogenesis and oligodendrogenesis in perinatal hypoxic/ischemic injury and the adult ischemic brain. This article will review these findings with a focus on the ventricular-subventricular zone neurogenic niche and discuss potential applications to facilitate endogenous neurogenesis and thereby to improve neurological function post perinatal hypoxic/ischemic injury and stroke.

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; 130(1):1-9. 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
Bydon M, **Macki M**, Kerezoudis P, Sciubba DM, Wolinsky JP, Witham TF, Gokaslan ZL, and Bydon A. The incidence of adjacent segment disease after lumbar discectomy: A study of 751 patients *J Clin Neurosci* 2016;PMID: 27765560. Full Text

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INTRODUCTION: The objective of this study is to determine the incidence and prognostic factors of adjacent segment disease (ASD) following first-time lumbar discectomy (LD). METHODS: We retrospectively reviewed all neurosurgical patients who underwent first-time LD for degenerative lumbar disease from 1990 to 2012. ASD was

defined as a clinical and radiographic progression of degenerative spinal disease that required surgical decompression (with or without fusion) at the level above or below the index discectomy. Adjusted odds ratios were calculated from multivariable logistical regression controlling for sex and age, as well as postoperative sensory deficit, motor deficit, back pain, neurogenic claudication, and radiculopathy. RESULTS: Of the 751 patients who underwent single-level LD, the cumulative reoperation rate for degenerative spinal disease was 10.79%. The incidence of ASD requiring reoperation was 4% over 3.11years. More specifically, the incidence of adjacent level discectomy was 1.86% over 3.45years. The annualized reoperation rate for ASD was 1.35% (1.35 ASD reoperations per 100 person-years). The 63.33% incidence of cranial ASD requiring reoperation was statistically significantly higher than the 40.00% incidence of caudal ASD requiring reoperation. Following multivariable logistical regression, the strongest (and only) statistically significant predictor of ASD requiring reoperation was lower extremity radiculopathy after the index discectomy operation (OR=14.23, p<0.001). CONCLUSIONS: In the first series on ASD following first-time LD without fusion, the rate of reoperation for ASD was 4% and the cumulative reoperation rate 10.79%. Rostral ASD is more common than caudal ASD and lower extremity radiculopathy is the strongest predictor of ASD.

Neurosurgery

Kazimirsky G, **Jiang W**, Slavin S, Ziv-Av A, and **Brodie C**. Mesenchymal stem cells enhance the oncolytic effect of Newcastle disease virus in glioma cells and glioma stem cells via the secretion of TRAIL *Stem Cell Res Ther* 2016; 7(1):149. PMID: 27724977. Full Text

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BACKGROUND: Newcastle disease virus (NDV) is an avian paramyxovirus, which selectively exerts oncolytic effects in cancer cells. Mesenchymal stem cells (MSCs) have been reported to affect tumor growth and deliver anti-tumor agents to experimental glioblastoma (GBM). Here, we explored the effects of NDV-infected MSCs derived from different sources, on glioma cells and glioma stem cells (GSCs) and the mechanisms involved in their effects. METHODS: The glioma cell lines (A172 and U87) and primary GSCs that were generated from GBM tumors were used in this study. MSCs derived from bone marrow, adipose tissue or umbilical cord were infected with NDV (MTH-68/H). The ability of these cells to deliver the virus to glioma cell lines and GSCs and the effects of NDV-infected MSCs on cell death and on the stemness and self-renewal of GSCs were examined. The mechanisms involved in the cytotoxic effects of the NDV-infected MSCs and their influence on the radiation sensitivity of GSCs were examined as well. RESULTS: NDV induced a dose-dependent cell death in glioma cells and a low level of apoptosis and inhibition of self-renewal in GSCs. MSCs derived from bone marrow, adipose and umbilical cord that were infected with NDV delivered the virus to co-cultured glioma cells and GSCs. Conditioned medium of NDV-infected MSCs induced higher level of apoptosis in the tumor cells compared with the apoptosis induced by their direct infection with similar virus titers. These results suggest that factor(s) secreted by the infected MSCs sensitized the glioma cells to the cytotoxic effects of NDV. We identified TRAIL as a mediator of the cytotoxic effects of the infected MSCs and demonstrated that TRAIL synergized with NDV in the induction of cell death in glioma cells and GSCs. Moreover, conditioned medium of infected MSCs enhanced the sensitivity of GSCs to gamma-radiation. CONCLUSIONS: NDV-infected umbilical cord-derived MSCs may provide a novel effective therapeutic approach for targeting GSCs and GBM and for sensitizing these tumors to gamma-radiation.

Neurosurgery

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

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

Neurosurgery

Macki M, Syeda S, Rajjoub K, Kerezoudis P, Bydon A, Wolinsky JP, Witham T, Sciubba DM, Bydon M, and Gokaslan Z. The effect of smoking status on successful arthrodesis after lumbar instrumentation supplemented with rhBMP-2 *World Neurosurg* 2016;PMID: 27756663. Full Text

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INTRODUCTION: The primary objective of this study is to examine the effects smoking status on rhBMP-2 supplementation in spinal fusion constructs. METHODS: Patient records were retrospectively reviewed for a consecutive set of patients who underwent first-time posterolateral, instrumented fusion of the lumbar spine for degenerative spinal disease. All operations included arthrodesis supplementation with rhBMP-2. All patients were followed for at least two years. The primary endpoint of this study was reoperation for pseudarthrosis, instrumentation failure, and/or adjacent segment disease. Following rigorous sensitivity analysis, measure of association was calculated with a multivariable logistic regression controlling for smoking, age, and number of spinal levels fused. RESULTS: Of the 110 patients in the study population, 82 (74.6%) were non-smokers and 28 (25.5%) were smokers. Among perioperative predictors, smokers were younger in age (53.9+/-9.6 vs 61.1+/-13.1, p=0.008) and had shorter length on inpatient hospital stay (4.1+/-1.8 vs 5.3+/-3.0, p=0.039). After a mean follow up of 59 months, the 32% incidence of reoperation for pseudarthrosis, instrumentation failure, and/or adjacent segment among smokers was statistically significantly higher than the 13.4% incidence in non-smokers (p=0.027). Following multivariable logistic regression, the odds of reoperation among smokers was 4.75 times higher than non-smoker (p=0.009, 95% Confidence Interval [1.48-15.24]). CONCLUSION: While rhBMP-2 supplements arthrodesis of instrumented lumbar fusion constructs, smoking status ascertains the strongest predictor of reoperation for pseudarthrosis, instrumentation failure, and/or adjacent segment.

Neurosurgery

Meir R, Betzer O, Motiei M, Kronfeld N, **Brodie C**, and Popovtzer R. Design principles for noninvasive, longitudinal and quantitative cell tracking with nanoparticle-based CT imaging *Nanomedicine* 2016;PMID: 27720990. Full Text

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Contradictory results in clinical trials are preventing the advancement and implementation of cell-based therapy. To explain such results, there is a need to uncover the mystery regarding the fate of the transplanted cells. To answer this need, we developed a technique for noninvasive in vivo cell tracking, which uses gold nanoparticles as contrast agents for CT imaging. Herein, we investigate the design principles of this technique for intramuscular transplantation of therapeutic cells. Longitudinal studies were performed, displaying the ability to track cells over long periods of time. As few as 500 cells could be detected and a way to quantify the number of cells visualized by CT was demonstrated. Moreover, monitoring of cell functionality was demonstrated on a mouse model of Duchenne muscular dystrophy. This cell-tracking technology has the potential to become an essential tool in pre-clinical as well as clinical trials and to advance the future of cell therapy.

Neurosurgery
Pabaney AH, **Rammo RA**, **Tahir RA**, and **Seyfried D**. Development of de novo arteriovenous malformation following ischemic stroke: Case report and review of current literature *World Neurosurg* 2016;PMID: 27671884. Full Text

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BACKGROUND: Arteriovenous malformations (AVMs) are hypothesized to be static, congenital lesions developing as early as 4 weeks of fetal life. New literature has shown that AVMs may represent dynamic and reactive vascular lesions arising from cerebral infarction, inflammation, or trauma. A literature search reveals 17 previously reported cases of new AVM formation after previous negative imaging studies. This reactive development or "second hit" theory suggests that at a molecular level, growth factors may play a vital role in aberrant angiogenesis and maturation of an arteriovenous fistula into an AVM. CASE DESCRIPTION: A 52-year-old female presented with a ruptured left frontal AVM demonstrated by computed tomography angiography and digital subtraction angiography. The patient had suffered an acute ischemic stroke in the similar cerebral vascular territory 8 years prior due to left internal carotid artery occlusion. Detailed neuroimaging at that time failed to reveal any vascular malformation, suggesting that the AVM might have developed in response to initial vascular insult. CONCLUSIONS: We believe that there might exist a subset of AVMs that display dynamic characteristics and could potentially appear, grow, or resolve spontaneously without intervention, especially in the presence of local growth factors and molecular signaling cascades. When combined with a previous cerebral insult such as stroke, trauma, or inflammation, de novo AVM formation may represent a "second hit" with abnormal angiogenesis and vessel formation.

Neurosurgery
Walbert T, Glantz M, **Schultz L**, and Puduvalli VK. Impact of provider level, training and gender on the utilization of palliative care and hospice in neuro-oncology: a North-American survey *J Neurooncol* 2016; 126(2):337-345. PMID: 26518539. Full Text

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Specialized palliative care (PC) services have emerged to address symptoms and provide end-of-life management for patients with brain tumors. The utilization patterns of PC in neuro-oncology are unknown. A 22-question survey was distributed to participants of the society for neuro-oncology annual meeting 2012 (n = 4487). Nonparametric methods including Wilcoxon two-sample and Kruskal-Wallis tests were used to assess differences in responses. 239 (5.3 %) evaluable responses were received; 79 % of respondents were physicians, and 17 % were nurses or midlevel providers. Forty-seven percent were medical or neuro-oncologists, 31 % neurosurgeons and 11 % radiation oncologists. Forty percent had no formal training in PC, 57 % had some formal training and 3 % completed a PC fellowship. Seventy-nine percent practiced in an academic setting. Of the respondents, 57 % referred patients to PC when symptoms required treatment and 18 % at end of life. Only 51 % of all providers felt comfortable dealing with

end-of-life issues and symptoms, while 33 % did not. Fifty-one percent preferred a service named "Supportive Care" rather than "Palliative Care" (MDs > midlevel providers, p < 0.001), and 32 % felt that patient expectations for ongoing therapy hindered their ability to make PC referrals. Female gender, formal training in neuro-oncology and PC, and medical versus surgical neuro-oncology training were significantly associated with hospice referral, comfort in dealing with end-of-life issues, and ease of access to PC services. Provider level, specialty, gender, training in PC and neuro-oncology have significant impact on the utilization of PC and hospice in neuro-oncology.

Obstetrics, Gynecology and Women's Health Services
Eziefule AA, **Elshatanoufy S**, Thakur M, and Rocha FG. Propofol-related infusion syndrome in the peripartum period *AJP Rep* 2016; 6(4):e368-e371. PMID: 27738550. Full Text

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Background Propofol is a widely known, commonly used drug. Complications can occur with the use of this drug, including propofol-related infusion syndrome (PRIS). PRIS, in the obstetric population, has not been documented; however, we report a case of a patient who developed PRIS after an emergent cesarean delivery of a preterm infant. Case Study A 35-year-old multigravida woman presented complaining of leakage of fluid and decreased fetal movement. Her pregnancy was complicated by methadone maintenance therapy due to a history of opioid abuse. Complications after admission for prolonged monitoring and a prolonged fetal heart tone deceleration was noted with no recovery despite intrauterine resuscitation. An emergent cesarean delivery was performed using general anesthesia and endotracheal intubation after which she developed aspiration pneumonia. She was admitted to the intensive care unit and reintubation and sedation were required secondary to respiratory distress. Sedation was achieved using propofol infusion. She subsequently developed changes in her electrocardiogram, an increase of her serum creatinine, creatinine protein kinase, lipase, amylase, and triglycerides, making the diagnosis of PRIS. Conclusion PRIS should be included in the differential diagnosis of intubated or postoperative patients in the obstetric population.

Obstetrics, Gynecology and Women's Health Services
Feldman AM, **Zhang Z**, **Buekers T**, and **Elshaikh MA**. Management of gynaecologic plasmacytoma: A review article *J Obstet Gynaecol* 2016:1-6. PMID: 27760483. Article request form

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In contrast to multiple myeloma (MM) which exhibits diffuse bone marrow and other organ involvement, solitary plasmacytomas carry a favourable prognosis. Extramedullary plasmacytomas (EMP) are a unique form of plasma cell neoplasms. These tumours are rare in the female reproductive tract. Only 24 cases of gynaecologic plasmacytomas were reported to date (7 cases were solitary plasmacytomas and 17 cases were either part of disseminated MM with involvement of a gynaecologic organ or were lacking complete work-up to rule out MM). The standard care of gynaecologic solitary EMP is surgical resection alone when feasible. Adjuvant radiation therapy may be considered for adverse prognostic factors such as positive resection margins. MM with gynaecologic organ involvement should be managed with systemic therapy and defer local therapies to symptomatic progression.

Obstetrics, Gynecology and Women's Health Services
Mazloomdoost D, Kanter G, Chan RC, Deveaneau N, Wyman AM, Von Bargen EC, Chaudhry Z, **Elshatanoufy S**, Miranne JM, Chu CM, Pauls RN, Arya LA, and Antosh DD. Social networking and internet use among pelvic floor patients: a multicenter survey *Am J Obstet Gynecol* 2016; 215(5):654.e651-654.e610. PMID: 27319368. Full Text

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BACKGROUND: Internet resources are becoming increasingly important for patients seeking medical knowledge. It is imperative to understand patient use and preferences for using the Internet and social networking websites to optimize patient education. OBJECTIVES: The purpose of this study was to evaluate social networking and Internet use among women with pelvic floor complaints to seek information for their conditions as well as describe the likelihood, preferences, and predictors of website usage. STUDY DESIGN: This was a cross-sectional, multicenter study of women presenting to clinical practices of 10 female pelvic medicine and reconstructive surgery fellowship programs across the United States, affiliated with the Fellows' Pelvic Research Network. New female patients presenting with pelvic floor complaints, including urinary incontinence, pelvic organ prolapse, and fecal incontinence were eligible. Participants completed a 24 item questionnaire designed by the authors to assess demographic information, general Internet use, preferences regarding social networking websites, referral patterns, and resources utilized to learn about their pelvic floor complaints. Internet use was quantified as high (>/=4 times/wk), moderate (2-3 times/wk), or minimal (</=1 time/wk). Means were used for normally distributed data and medians for data not meeting this assumption. Fisher's exact and chi2 tests were used to evaluate the associations between variables and Internet use. RESULTS: A total of 282 surveys were analyzed. The majority of participants, 83.3%, were white. The mean age was 55.8 years old. Referrals to urogynecology practices were most frequently from obstetrician/gynecologists (39.9%) and primary care providers (27.8%). Subjects were well distributed geographically, with the largest representation from the South (38.0%). Almost one third (29.9%) were most bothered by prolapse complaints, 22.0% by urgency urinary incontinence, 20.9% by stress urinary incontinence, 14.9% by urgency/frequency symptoms, and 4.1% by fecal incontinence. The majority, 75.0%, described high Internet use, whereas 8.5% moderately and 4.8% minimally used the Internet. Women most often used the Internet for personal motivations including medical research (76.4%), and 42.6% reported Google to be their primary search engine. Despite this, only 4.9% primarily used the Internet to learn about their pelvic floor condition, more commonly consulting an obstetrician-gynecologist for this information (39.4%). The majority (74.1%) held a social networking account, and 45.9% visited these daily. Nearly half, 41.7%, expressed the desire to use social networking websites to learn about their condition. Women <65 years old were significantly more likely to have high Internet use (83.4% vs 68.8%, P = .018) and to desire using social networking websites to learn about their pelvic floor complaint (P = .008). The presenting complaint was not associated with Internet use (P = .905) or the desire to use social networking websites to learn about pelvic floor disorders (P = .201). CONCLUSION: Women presenting to urogynecology practices have high Internet use and a desire to learn about their conditions via social networking websites. Despite this, obstetrician-gynecologists remain a common resource for information. Nonetheless, urogynecology practices and national organizations would likely benefit from increasing their Internet resources for patient education in pelvic floor disorders, though patients should be made aware of available resources.

Ophthalmology and Eye Care Services

Elfersy AJ, Prinzi RA, Peracha ZH, Kim DD, Crandall DA, **Darnley-Fisch DA**, and **Imami NR**. IOP elevation after cataract surgery: Results for residents and senior staff at henry ford health system *J Glaucoma* 2016; 25(10):802-806. PMID: 27027228. Full Text

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PURPOSE: To determine the incidence of intraocular pressure (IOP) elevation on postoperative day 1 (POD1) after cataract surgery performed by resident surgeons compared with attending surgeons and to examine the influence of associated variables on the incidence of postoperative IOP elevation. PATIENTS AND METHODS: Retrospective review of 2472 consecutive 2.2 to 2.8 mm temporal clear corneal cataract extractions by phacoemulsification performed by either residents or attending surgeons at Henry Ford Health System. Fellow eyes were excluded, resulting in 1847 eyes. IOP measurements of >40, >30, and >23 mm Hg were noted along with incremental IOP elevations of >/=10 and 20 mm Hg over preoperative/baseline IOP. Associated variables included: age, sex, diabetes mellitus, hypertension, glaucoma, glaucoma suspect, uveitis, prior ocular trauma, and vitreous loss at surgery. RESULTS: Resident-performed cataract surgery was associated with statistically significant higher rates of IOP elevation in all categories and in all clinical situations known to be associated with postoperative IOP spike, that is, vitreous loss at surgery, prior ocular trauma, and preexisting glaucoma. CONCLUSIONS: The incidence of postoperative day 1 IOP elevation after phacoemulsification performed by resident surgeons was 2 to 5 times that of experienced cataract surgeons. Variables including vitreous loss at surgery, prior ocular trauma, preexisting glaucoma, glaucoma suspect status, and male sex were significant contributors. Consideration for prophylactic IOP lowering is advised in high-risk patients.

Orthopaedics
Baumer TG, **Chan D**, **Mende V**, **Dischler J**, **Zauel R**, **van Holsbeeck M**, **Siegal DS**, **Divine G**, **Moutzouros V**, and **Bey MJ**. Effects of rotator cuff pathology and physical therapy on in vivo shoulder motion and clinical outcomes in patients with a symptomatic full-thickness rotator cuff tear *Orthop J Sports Med* 2016; 4(9)PMID: 27734020. Full Text

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BACKGROUND: Physical therapy (PT) is often prescribed for patients with rotator cuff tears. The extent to which PT influences strength, range of motion (ROM), and patient-reported outcomes has been studied extensively, but the effect of PT on in vivo joint kinematics is not well understood. PURPOSE: To assess the influence of symptomatic rotator cuff pathology and the effects of PT on shoulder motion, strength, and patient-reported outcomes. STUDY DESIGN: Controlled laboratory study. METHODS: Twenty-five patients with a symptomatic rotator cuff tear and 25 age-matched asymptomatic control subjects were recruited. Shoulder motion was measured using a biplane radiography imaging system, strength was assessed with a Biodex dynamometer, and patient-reported outcomes were assessed using the Western Ontario Rotator Cuff Index and visual analog scale (VAS) pain scores. Data were acquired from the patients before and after 8 weeks of physical therapy. Data were acquired at 1 time point for the control subjects. RESULTS: Compared with the control subjects, patients with a symptomatic rotator cuff tear had significantly worse pain/function scores (P < .01); less ROM (P < .01); lower abduction (ABD), external rotation (ER), and internal rotation (IR) strength (P < .01); less scapulothoracic posterior tilt (P = .05); and lower glenohumeral joint elevation (P < .01). Physical therapy resulted in improved pain/function scores (P < .01), increased ROM (P < .02), increased scapulothoracic posterior tilt (P = .05), increased glenohumeral joint elevation (P = .01), and decreased acromiohumeral distance (AHD) (P = .02). CONCLUSION: Compared with age-matched controls, patients had worse pain/function scores, less ROM, and lower ABD, ER, and IR strength. Patients also had less scapulothoracic anteroposterior tilt, less glenohumeral joint elevation, and an altered glenohumeral joint contact path. PT resulted in improved pain/function scores, increased ROM, greater posterior scapulothoracic tilt, increased glenohumeral joint elevation, an increased range of superoinferior joint contact, and a lower mean AHD. Of these differences, PT only returned scapulothoracic tilt to control levels. CLINICAL RELEVANCE: This study documents the effects of PT on shoulder motion and conventional clinical outcomes. It is expected that understanding how changes in joint motion are associated with conventional clinical outcomes will lead to improved nonoperative interventions for patients with rotator cuff tears.

Orthopaedics
Fradet A, and **Fitzgerald J**. INPPL1 gene mutations in opsismodysplasia *J Hum Genet* 2016;PMID: 27708270. Article request form

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The INPPL1 (inositol polyphosphate phosphatase-like 1) gene encodes the inositol phosphatase, SHIP2 (for src homology 2 domain-containing inositol phosphatase 2). SHIP2 functions to dephosphorylate, and negatively regulate, the lipid second messenger phosphatidylinositol (3,4,5)P3. SHIP2 has been well studied in the area of insulin resistance and obesity but has roles in cancer and other disorders. Recently, it was reported that mutations in INPPL1 cause opsismodysplasia, a rare, autosomal recessive severe skeletal dysplasia. This review focuses on the mutations associated with opsismodysplasia and explores the role of INPPL1/ SHIP2 in skeletal development.Journal of Human Genetics advance online publication, 6 October 2016; doi:10.1038/jhg.2016.119.

Orthopaedics
Frisch N, **Wessell NM**, **Charters M**, **Peterson E**, Cann B, **Greenstein A**, and **Silverton CD**. Effect of body mass index on blood transfusion in total hip and knee arthroplasty *Orthopedics* 2016; 39(5):e844-849. PMID: 27172370. Article request form

Perioperative blood management remains a challenge during total hip arthroplasty (THA) and total knee arthroplasty (TKA). The purpose of this study was to systematically examine the relationship between body mass index (BMI) and perioperative blood transfusion during THA and TKA while attempting to resolve conflicting results in previously published studies. The authors retrospectively evaluated 2399 patients, 896 of whom underwent THA and 1503 of whom underwent TKA. Various outcome variables were assessed for their relationship to BMI, which was stratified using the World Health Organization classification scheme (normal, <25 kg/m(2); overweight, 25-30 kg/m(2); obese, >30 kg/m(2)). Among patients undergoing THA, transfusion rates were 34.8%, 27.6%, and 21.9% for normal, overweight, and obese patients, respectively (P=.002). Among patients undergoing TKA, transfusion rates were 17.3%, 11.4%, and 8.3% for normal, overweight, and obese patients, respectively (P=.002). Patients with an elevated BMI have decreased rates of blood transfusion following both THA and TKA. This same cohort also loses a significantly decreased percentage of estimated blood volume. No trends were identified for a relationship between BMI and deep venous thrombosis, pulmonary embolism, myocardial infarction, discharge location, length of stay, 30-day readmission rate, and preoperative hemoglobin level. Elevated BMI was significantly associated with increased estimated blood loss in patients undergoing THA and those undergoing TKA. There was a statistically significant trend toward increased deep surgical-site infection in patients undergoing THA (P=.043). Patients with increased BMI have lower rates of blood transfusion and lose a significantly smaller percentage of estimated blood volume following THA and TKA. [Orthopedics.2016; 39(5):e844-e849.].

Otolaryngology – Head and Neck Surgery
Duke WS, Holsinger FC, Kandil E, Richmon JD, **Singer MC**, and Terris DJ. Remote access robotic facelift thyroidectomy: A multi-institutional experience *World J Surg* 2016;PMID: 27738835. Full Text

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BACKGROUND: Robotic facelift thyroidectomy (RFT) was developed as a new surgical approach to the thyroid gland using a remote incision site. Early favorable results led to this confirmatory multi-institutional experience. METHODS: Prospectively collected data on consecutive patients undergoing RFT in five North American academic endocrine surgical practices were compiled. Surgical indications, operative times, final pathology, nodule size, complications, and postoperative management (drain use and length of hospital stay) were evaluated. RESULTS: A total of 102 RFT procedures were undertaken in 90 patients. All but one of the patients (98.9 %) were female, and the mean age was 41.9 +/- 13.1 years (range 12-69 years). The indication for surgery was nodular disease in 91.2 % of cases; 8.8 % were completion procedures performed for a diagnosis of cancer. The mean size of the largest nodule was 1.9 cm (range 0-5.6 cm). The mean total operative time for a thyroid lobectomy was 162 min (range 82-265 min). No permanent complications occurred. There were 4 cases (3.9 %) of transient recurrent laryngeal nerve weakness, no cases of hypocalcemia, and 3 (2.9 %) hematomas. There were no conversions to an anterior cervical approach. The majority of patients were managed on an outpatient basis (61.8 %) and without a drain (65.7 %). CONCLUSIONS: RFT is technically feasible and safe in selected patients. RFT can continue to be offered to carefully selected patients as a way to avoid a visible cervical scar. Future prospective studies to compare this novel approach to other remote access approaches are warranted.

Otolaryngology – Head and Neck Surgery
Miller A, Hall F, and **Ahsan S**. Chronic otitis media with effusion following radiation therapy *Ear Nose Throat J* 2016; 95(10-11):E26-e31. PMID: 27792830. Full Text

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The incidence of chronic otitis media with effusion (COME) after radiotherapy for nasopharyngeal or sinonasal tumors is relatively high. It is often a difficult-to-treat problem in these patients. In this retrospective study, we sought to describe the clinical course of COME in 51 patients-33 men and 18 women, aged 39 to 90 years (mean: 58.9 +/- 15)-who had been referred to the Henry Ford Health System in Detroit between 2001 and 2011 for management of a tumor that had involved either the nasopharyngeal area or the sinonasal area. The median length of follow-up from the time of cancer diagnosis was 32 months. Of the 51 patients, 23 (45.1%) developed COME before, during, or after radiation therapy. Of these 23 patients, 13 (56.5%) did not experience any improvement after treatment with various combinations of therapies, including myringotomy, tympanostomy tube placement, otic drops, oral antibiotics, and corticosteroid nasal sprays. No patient- or tumor-specific factors were found to be significantly associated with the incidence of COME after irradiation to the sinonasal area. Older age and squamous cell tumor pathology were found to be significant factors for the resolution of COME after it had developed, whereas treatments with tympanostomy tubes and ear drops were not. Because of the high incidence of COME after radiotherapy and the high rate of COME's failure to resolve after tympanostomy tube insertion, we suggest that these patients require an alternative treatment.

Otolaryngology – Head and Neck Surgery
Yaremchuk K. Palatal procedures for obstructive sleep apnea *Otolaryngol Clin North Am* 2016;PMID: 27720460. Full Text

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Uvulopalatopharyngoplasty was the first surgical procedure described, other than tracheostomy, for the treatment of obstructive sleep apnea (OSA) in 1981. It was recognized then that there were responders who were cured of OSA with the procedure and others that were not. It took many years for a staging system to be described that categorized patients based on Mallampati score, tonsil size, and body mass index to better predict success rates. It was recognized that individuals with retro-palatal obstruction as the cause of the airway obstruction responded well but that the morbidity associated with the inpatient procedure was often problematic.

Palliative Medicine
Palmer TR. Re: A trial of shuangbai san for treating primary liver cancer patients with cancer pain *J Pain Symptom Manage* 2016;PMID: 27713032. Full Text

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Pathology
Feldman AM, **Zhang Z**, **Buekers T**, and **Elshaikh MA**. Management of gynaecologic plasmacytoma: A review article *J Obstet Gynaecol* 2016:1-6. PMID: 27760483. Article request form

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In contrast to multiple myeloma (MM) which exhibits diffuse bone marrow and other organ involvement, solitary plasmacytomas carry a favourable prognosis. Extramedullary plasmacytomas (EMP) are a unique form of plasma cell neoplasms. These tumours are rare in the female reproductive tract. Only 24 cases of gynaecologic plasmacytomas were reported to date (7 cases were solitary plasmacytomas and 17 cases were either part of disseminated MM with involvement of a gynaecologic organ or were lacking complete work-up to rule out MM). The standard care of gynaecologic solitary EMP is surgical resection alone when feasible. Adjuvant radiation therapy may be considered for adverse prognostic factors such as positive resection margins. MM with gynaecologic organ involvement should be managed with systemic therapy and defer local therapies to symptomatic progression.

Pathology

Kouba EJ, Eble JN, Simper N, Grignon DJ, Wang M, Zhang S, Wang L, Martignoni G, **Williamson SR**, Brunelli M, Luchini C, Calio A, and Cheng L. High fidelity of driver chromosomal alterations among primary and metastatic renal cell carcinomas: implications for tumor clonal evolution and treatment *Mod Pathol* 2016; 29(11):1347-1357. PMID: 27469331. Full Text

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Recent studies have demonstrated considerable genomic heterogeneity in both primary and metastatic renal cell carcinoma (RCC). This mutational diversity has serious implications for the development and implementation of targeted molecular therapies. We evaluated 39 cases of primary RCC tumors with their matched metastatic tumors to determine if the hallmark chromosomal anomalies of these tumors are preserved over the course of disease progression. Thirty-nine matched pairs of primary and metastatic RCCs (20 clear cell RCC, 16 papillary RCC, and 3 chromophobe RCC) were analyzed. All clear cell RCC and papillary RCC tumors were evaluated for chromosome 3p deletion, trisomy 7 and 17 using fluorescence in situ hybridization. Chromophobe RCC tumors were evaluated for genetic alterations in chromosomes 1, 2, 6, 10, and 17. Of the 20 clear cell RCC tumors, 18 primary tumors (90%) showed a deletion of chromosome 3p and were disomic for chromosomes 7 and 17. All molecular aberrations were conserved within the matched metastatic tumor. Of the 16 papillary RCC tumors, 10 primary tumors (62%) showed trisomy for both chromosomes 7 and 17 without 3p deletion. These molecular aberrations and others were conserved in the paired metastatic tumors. Of the three chromophobe RCC tumors, multiple genetic anomalies were identified in chromosomes 1, 2, 6, 10, and 17. These chromosomal aberrations were conserved in the matched metastatic tumors. Our results demonstrated genomic fidelity among the primary and metastatic lesions in RCCs. These findings may have important clinical and diagnostic implications.

Pathology

Kryvenko ON, **Williamson SR**, Trpkov K, **Gupta NS**, Athanazio D, Selig MK, Smith PT, Magi-Galluzzi C, and Jorda M. Small cell-like glandular proliferation of prostate: a rare lesion not related to small cell prostate cancer *Virchows Arch* 2016;PMID: 27743032. Full Text

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Small cell-like change (SCLC) is a rare prostate lesion which has been described in only two previous studies (total of eight cases). Its relation to possible neuroendocrine differentiation remained unclear. We evaluated 11 SCLC cases with immunohistochemistry and electron microscopy. SCLC was characterized by crowded hyperchromatic small nuclei with scant cytoplasm, rosette-like structures, finely granular chromatin with indistinct nucleoli, and lack of mitoses, apoptoses, and necroses. In nine cases, SCLC was admixed with high-grade cancer, and in two cases, it represented a separate intraductal process, spatially remote from a low-volume Gleason score 6 (grade group 1) cancer. Only 2/11 SCLC labeled for synaptophysin, chromogranin, and serotonin, although 6/11 were at least focally positive for TTF1. Staining for NKX3.1 and pancytokeratin was typically weak, focal, and markedly reduced compared

to the adjacent cancer. SCLC was positive for ERG in 1/8 and for racemase in 6/10 cases, again typically in a focal and weak fashion. There was no immunoreactivity with CD56, p63, or HMWCK. Ki-67 highlighted only rare nuclei (<1 %). No neuroendocrine granules were demonstrated by electron microscopy in four cases that showed no immunoreactivity for neuroendocrine markers. In summary, SCLC is more frequently found in high-grade prostate cancer, but it may also be encountered as a noninvasive lesion in Gleason score 6 (grade group 1) cancer. Importantly, it does not appear to indicate neuroendocrine differentiation. The low-grade cytology, the lack of mitoses and apoptoses, and the minimal Ki-67 reactivity are findings to support its discrimination from a small cell carcinoma.

Pathology
Smith SC, Trpkov K, Chen YB, Mehra R, Sirohi D, Ohe C, Cani AK, Hovelson DH, Omata K, McHugh JB, Jochum W, Colecchia M, Amin M, Divatia MK, Hes O, Menon S, Werneck da Cunha I, Tripodi S, Brimo F, Gill AJ, Osunkoya AO, Magi-Galluzzi C, Sibony M, **Williamson SR**, Nesi G, Picken MM, Maclean F, Agaimy A, Cheng L, Epstein JI, Reuter VE, Tickoo SK, Tomlins SA, and Amin MB. Tubulocystic carcinoma of the kidney with poorly differentiated foci: A frequent morphologic pattern of fumarate hydratase-deficient renal cell carcinoma *Am J Surg Pathol* 2016; 40(11):1457-1472. PMID: 27635946. Full Text

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An emerging group of high-grade renal cell carcinomas (RCCs), particularly carcinomas arising in the hereditary leiomyomatosis renal cell carcinoma syndrome (HLRCC), show fumarate hydratase (FH) gene mutation and loss of function. On the basis of similar cytomorphology and clinicopathologic features between these tumors and cases described as tubulocystic carcinomas with poorly differentiated foci (TC-PD) of infiltrative adenocarcinoma, we hypothesized a relationship between these entities. First, 29 RCCs with morphology of TC-PD were identified retrospectively and assessed for FH expression and aberrant succination (2SC) by immunohistochemistry (IHC), with targeted next-generation sequencing of 409 genes-including FH-performed on a subset. The 29 TC-PD RCCs included 21 males and 8 females, aged 16 to 86 years (median, 46), with tumors measuring 3 to 21 cm (median, 9) arising in the right (n=16) and left (n=13) kidneys. Family history or stigmata of HLRCC were identifiable only retrospectively in 3 (12%). These tumors were aggressive, with 79% showing perinephric extension, nodal involvement in 41%, and metastasis in 86%. Of these, 16 (55%) demonstrated loss of FH by IHC (14/14 with positive 2SC). In contrast, 5 (17%) showed a wild-type immunoprofile of FH+/2SC-. An intriguing group of 8 (28%) showed variable FH+/- positivity, but with strong/diffuse 2SC+. Next-generation sequencing revealed 8 cases with FH mutations, including 5 FH-/2SC+ and 3 FH+/-/2SC+ cases, but none in FH+/2SC- cases. Secondly, we retrospectively reviewed the morphology of 2 well-characterized cohorts of RCCs with FH-deficiency determined by IHC or sequencing (n=23 and n=9), unselected for TC-PD pattern, identifying the TC-PD morphology in 10 (31%). We conclude that RCCs with TC-PD morphology are enriched for FH deficiency, and we recommend additional workup, including referral to genetic counseling, for prospective cases. In addition, based on these and other observations, we propose the term "FH-deficient RCC" as a provisional term for tumors with a combination of suggestive morphology and immunophenotype but where genetic confirmation is unavailable upon diagnosis. This term will serve as a

provisional nomenclature that will enable triage of individual cases for genetic counseling and testing, while designating these cases for prospective studies of their relationship to HLRCC.

Pathology
Williamson SR, Delahunt B, Magi-Galluzzi C, Algaba F, Egevad L, Ulbright TM, Tickoo SK, Srigley JR, Epstein JI, and Berney DM. The WHO 2016 classification of testicular germ cell tumours: A review and update from the ISUP testis consultation panel *Histopathology* 2016;PMID: 27747907. Full Text

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Since the last World Health Organization (WHO) Classification scheme for tumours of the urinary tract and male genital organs, there have been a number of advances in the understanding, classification, immunohistochemistry, and genetics of testicular germ cell tumours. The updated 2016 draft classification was discussed at an International Society of Urological Pathology (ISUP) Consultation on Testicular and Penile Cancer. This review addresses the main updates to germ cell tumour classification. Major changes include a pathogenetically derived classification using germ cell neoplasia in situ (GCNIS) as a new name for the precursor lesion, as well as distinction of prepubertal (non-GCNIS-derived) from postpubertal-type tumours (GCNIS-derived), acknowledging the existence of rare benign prepubertal-type teratomas in the postpubertal testis. Spermatocytic tumour is adopted as a replacement for spermatocytic seminoma to avoid potential confusion with the unrelated usual seminoma. The spectrum of trophoblastic tumours arising in the setting of testicular germ cell tumour continues to expand, to include epithelioid and placental site trophoblastic tumours analogous to those of the gynecologic tract. Currently, reporting of anaplasia (seminoma or spermatocytic tumour) or immaturity (teratoma) are not required, as these do not have demonstrable prognostic importance. In contrast, overgrowth of a teratomatous component (somatic-type malignancy) and sarcomatous change in spermatocytic tumour indicate more aggressive behavior and should be reported. This article is protected by copyright. All rights reserved.

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; 59(5):489-495. 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.

Pharmacy
Ganti BR, Marini BL, Nagel J, Bixby D, and Perissinotti AJ. Impact of antibacterial prophylaxis during reinduction chemotherapy for relapse/refractory acute myeloid leukemia *Support Care Cancer* 2016;PMID: 27738797. Full Text

Department of Pharmacy Services and College of Pharmacy, University of Michigan Health System, 1111 E. Catherine St., Rm 330, Ann Arbor, MI, 48109, USA.
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PURPOSE: This study evaluated the impact of antibacterial prophylaxis with levofloxacin in relapsed/refractory acute myeloid leukemia (AML) patients. METHODS: This was a retrospective, single-center, cohort study. Adult patients with relapsed/refractory AML admitted for reinduction chemotherapy between November 1, 2006 and June 15, 2015 were screened for inclusion. A protocol initiating levofloxacin prophylaxis was implemented on December 1, 2013. Patients receiving hypomethylating agents (decitabine/azacitidine) were not administered antibacterial prophylaxis and thus not included in this analysis. Patients receiving broad spectrum antibiotics on day 1 of reinduction chemotherapy or receiving another antibacterial agent for prophylaxis were also excluded. Ninety-seven patients were included in the control group (no prophylaxis), while 48 patients received levofloxacin prophylaxis. Patients in the prophylaxis group received levofloxacin 500 mg once daily on day 1 of chemotherapy and continued until neutrophil recovery (or hospital discharge or death). RESULTS: There was a reduction in the rate of bacteremia in the prophylaxis group (37.5 %) compared to the control group (53.6 %, p = 0.0789), largely due to a reduction in gram-negative bacteremia (2.1 vs. 21.6 % respectively, p = 0.001). No difference was found between prophylaxis and the control groups in the incidence of neutropenic fever, incidence of multidrug resistance, length of hospital or ICU stay, or mortality. CONCLUSIONS: Levofloxacin prophylaxis reduced the rate of infections overall in adult patients with relapsed/refractory AML, without increasing rates of multidrug-resistant organisms.

Pharmacy
Suleyman G, **Kenney R**, **Zervos MJ**, and **Weinmann A**. Safety and efficacy of outpatient parenteral antibiotic therapy in an academic infectious disease clinic *J Clin Pharm Ther* 2016;PMID: 27747899. Full Text

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WHAT IS KNOWN AND OBJECTIVE: Outpatient parenteral therapy (OPAT) has become a safe and effective modality for patients requiring intravenous or prolonged antimicrobial therapy since the 1970s. It is being increasingly utilized in various settings; however, studies evaluating the safety and efficacy of clinic-based OPAT are limited. Since 2012, patients being considered for OPAT have required an infectious disease (ID) consultation at our institution. Candidates receiving once-daily antimicrobials who were ineligible for home infusion or nursing home placement as determined by their insurance companies and those who preferred the clinic over nursing home or home infusion were referred to the ID clinic. This study assessed the safety and outcome of patients receiving OPAT in an academic inner-city ID clinic in Detroit, Michigan. METHODS: This was a retrospective cross-sectional study of electronic medical records of patients, identified through clinic records, who received at least 2 days of OPAT from December 2012 to December 2015. Demographics, types of infections, antimicrobial regimen used, adverse events and outcome were evaluated. RESULTS: A total of 122 cases were identified during the study period. Mean age was 62 years with 55% male; 102 (84%) of 122 patients had peripherally inserted central catheter (PICC). Fifty-five per cent of patients participated in the clinic-based OPAT programme for insurance reasons, and 43% preferred the clinic over nursing home or home infusion. The most common infections were bone and joint (36%), followed by skin and soft tissue (18%) and urinary tract infections (12%). Ertapenem (44%) and daptomycin (41%) alone or in combination were used most frequently with 40% of patients receiving at least 4 weeks of treatment. Thirteen patients (11%) experienced one or more adverse drug events on daptomycin and/or ertapenem; of these, nine (69%) patients were receiving daptomycin monotherapy. Gastrointestinal symptoms (29%), cramping and myalgias (29%) and asymptomatic creatine phosphokinase (CPK) elevation (24%) were the most common adverse events. Three (3%) of 102 patients had PICC-related complications. Fourteen (88%) of 16 patients with adverse events or PICC-related

complications required changing or stopping antibiotics; two (2%) had infection-related readmission. Conversely, 113 (93%) of 122 patients who completed treatment were considered cured and none had treatment failure at the end of 30 days of treatment. No patients died as a result of treatment or infection-related complications. WHAT IS NEW AND CONCLUSION: Outpatient parenteral therapy in our academic ID clinic was a safe and effective alternative to home infusion or skilled nursing facilities for patients requiring long-term antibiotics with few adverse events and complications.

Physical Therapy
Baumer TG, **Chan D**, **Mende V**, **Dischler J**, **Zauel R**, **van Holsbeeck M**, **Siegal DS**, **Divine G**, **Moutzouros V**, and **Bey MJ**. Effects of rotator cuff pathology and physical therapy on in vivo shoulder motion and clinical outcomes in patients with a symptomatic full-thickness rotator cuff tear *Orthop J Sports Med* 2016; 4(9)PMID: 27734020. Full Text

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Department of Physical Therapy, Henry Ford Health System, Detroit, Michigan, USA.
Department of Radiology, Henry Ford Health System, Detroit, Michigan, USA.
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BACKGROUND: Physical therapy (PT) is often prescribed for patients with rotator cuff tears. The extent to which PT influences strength, range of motion (ROM), and patient-reported outcomes has been studied extensively, but the effect of PT on in vivo joint kinematics is not well understood. PURPOSE: To assess the influence of symptomatic rotator cuff pathology and the effects of PT on shoulder motion, strength, and patient-reported outcomes. STUDY DESIGN: Controlled laboratory study. METHODS: Twenty-five patients with a symptomatic rotator cuff tear and 25 age-matched asymptomatic control subjects were recruited. Shoulder motion was measured using a biplane radiography imaging system, strength was assessed with a Biodex dynamometer, and patient-reported outcomes were assessed using the Western Ontario Rotator Cuff Index and visual analog scale (VAS) pain scores. Data were acquired from the patients before and after 8 weeks of physical therapy. Data were acquired at 1 time point for the control subjects. RESULTS: Compared with the control subjects, patients with a symptomatic rotator cuff tear had significantly worse pain/function scores ($P < .01$); less ROM ($P < .01$); lower abduction (ABD), external rotation (ER), and internal rotation (IR) strength ($P < .01$); less scapulothoracic posterior tilt ($P = .05$); and lower glenohumeral joint elevation ($P < .01$). Physical therapy resulted in improved pain/function scores ($P < .01$), increased ROM ($P < .02$), increased scapulothoracic posterior tilt ($P = .05$), increased glenohumeral joint elevation ($P = .01$), and decreased acromiohumeral distance (AHD) ($P = .02$). CONCLUSION: Compared with age-matched controls, patients had worse pain/function scores, less ROM, and lower ABD, ER, and IR strength. Patients also had less scapulothoracic anteroposterior tilt, less glenohumeral joint elevation, and an altered glenohumeral joint contact path. PT resulted in improved pain/function scores, increased ROM, greater posterior scapulothoracic tilt, increased glenohumeral joint elevation, an increased range of superoinferior joint contact, and a lower mean AHD. Of these differences, PT only returned scapulothoracic tilt to control levels. CLINICAL RELEVANCE: This study documents the effects of PT on shoulder motion and conventional clinical outcomes. It is expected that understanding how changes in joint motion are associated with conventional clinical outcomes will lead to improved nonoperative interventions for patients with rotator cuff tears.

Plastic Surgery
Meier EM, Wu B, **Siddiqui A**, **Tepper DG**, Longaker MT, and Lam MT. Mechanical stimulation increases knee meniscus gene RNA-level expression in adipose-derived stromal cells *Plast Reconstr Surg Glob Open* 2016; 4(9):e864. PMID: 27757329. Full Text

Department of Biomedical Engineering, Wayne State University, Detroit, Mich.; Department of Plastic Surgery, Henry Ford Health System, Detroit, Mich.; and Hagey Laboratory for Pediatric Regenerative Medicine, Department of Surgery, Plastic and Reconstructive Surgery, Stanford University School of Medicine, Stanford, Calif.

Efforts have been made to engineer knee meniscus tissue for injury repair, yet most attempts have been unsuccessful. Creating a cell source that resembles the complex, heterogeneous phenotype of the meniscus cell remains difficult. Stem cell differentiation has been investigated, mainly using bone marrow mesenchymal cells and biochemical means for differentiation, resulting in no solution. Mechanical stimulation has been investigated to an extent with no conclusion. Here, we explore the potential for and effectiveness of mechanical stimulation to induce the meniscal phenotype in adipose-derived stromal cells. METHODS: Human adipose-derived stromal cells were chosen for their fibrogenic nature and conduciveness for chondrogenesis. Biochemical and mechanical stimulation were investigated. Biochemical stimulation included fibrogenic and chondrogenic media. For mechanical stimulation, a custom-built device was used to apply constant, cyclical, uniaxial strain for up to 6 hours. Strain and frequency

varied. RESULTS: Under biochemical stimulation, both fibrogenic (collagen I, versican) and chondrogenic (collagen II, Sox9, aggrecan) genes were expressed by cells exposed to either fibrogenic or chondrogenic biochemical factors. Mechanical strain was found to preferentially promote fibrogenesis over chondrogenesis, confirming that tensile strain is an effective fibrogenic cue. Three hours at 10% strain and 1 Hz in chondrogenic media resulted in the highest expression of fibrochondrogenic genes. Although mechanical stimulation did not seem to affect protein level expression, biochemical means did affect protein level presence of collagen fibers. CONCLUSION: Mechanical stimulation can be a useful differentiation tool for mechanoresponsive cell types as long as biochemical factors are also integrated.

Psychiatry
Park G, and **Prabhakar D**. Inviting police officers to grand rounds *Acad Psychiatry* 2016; 40(1):194-195. PMID: 26691142. Full Text

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Public Health Sciences
Abid Z, Oh SS, Hu D, Sen S, Huntsman S, Eng C, Farber HJ, Rodriguez-Cintron W, Rodriguez-Santana JR, Serebrisky D, Avila PC, Thyne SM, Kim KA, Borrell LN, **Williams LK**, Seibold MA, Burchard EG, and Kumar R. Maternal age and asthma in Latino populations *Clin Exp Allergy* 2016; 46(11):1398-1406. PMID: 27238356. Full Text

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BACKGROUND: Younger maternal age at birth is associated with increased risk of asthma in offspring in European descent populations, but has not been studied in Latino populations. OBJECTIVES: We sought to examine the relationship between maternal age at birth and prevalence of asthma in a nationwide study of Latino children. METHODS: We included 3473 Latino children aged 8-21 years (1696 subjects with physician-diagnosed asthma and 1777 healthy controls) from five US centres and Puerto Rico recruited from July 2008 through November 2011. We used multiple logistic regression models to examine the effect of maternal age at birth on asthma in offspring overall and in analyses stratified by ethnic subgroup (Mexican American, Puerto Rican and other Latino). Secondary analyses evaluated the effects of siblings, acculturation and income on this relationship. RESULTS: Maternal age < 20 years was significantly associated with decreased odds of asthma in offspring, independent of other risk factors (OR = 0.73, 95% CI: 0.57-0.93). In subgroup analyses, the protective effect of younger maternal age was observed only in Mexican Americans (OR = 0.53, 95% CI: 0.36, 0.79). In Puerto Ricans, older maternal age was associated with decreased odds of asthma (OR = 0.65, 95% CI: 0.44-0.97). In further stratified models, the protective effect of younger maternal age in Mexican Americans was seen only in children without older siblings (OR = 0.44, 95% CI: 0.23-0.81). CONCLUSION AND CLINICAL RELEVANCE: In contrast to European descent populations, younger maternal age was associated with decreased odds of asthma in offspring in Mexican American women. Asthma is common in urban minority populations but the factors underlying the varying prevalence among different Latino ethnicities in the United States is not well understood. Maternal age represents one factor that may help to explain this variability.

Public Health Sciences

Bansal N, Szpiro A, Masoudi F, Greenlee RT, Smith DH, Magid DJ, Gurwitz JH, Reynolds K, Tabada GH, Sung SH, Dighe A, **Cassidy-Bushrow A**, Garcia-Montilla R, Hammill S, Hayes J, Kadish A, Sharma P, Varosy P, Vidaillet H, and Go AS. Kidney function and appropriateness of device therapies in adults with implantable cardioverter defibrillators *Heart* 2016;PMID: 27742796. Full Text

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Kaiser Permanente Northwest Center for Health Research, Portland, Oregon, USA.
Kaiser Permanente Colorado Institute for Health Research, Oakland, California, USA.
Meyers Primary Care Institute, Worcester, Massachusetts, USA.
Kaiser Permanente Southern California Department of Research and Evaluation, Pasadena, California, USA.
Kaiser Permanente Northern California Division of Research, Oakland, California, USA.
Henry Ford Hospital, Detroit, Michigan, USA.
Mayo Clinic, Rochester, Minnesota, USA.
Touro College, New York, USA.

OBJECTIVE: Patients with chronic kidney disease (CKD) have higher risk of sudden cardiac death; however, they may not receive implantable cardioverter defibrillators (ICDs), in part due to higher risk of complications. We evaluated whether CKD is associated with greater risk of device-delivered shocks/antitachycardia pacing (ATP) therapies among patients receiving a primary prevention ICD. METHODS: We studied participants in the observational Cardiovascular Research Network Longitudinal Study of Implantable Cardioverter Defibrillators. CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2. Outcomes included all delivered shocks/ATPs therapies and type of shock/ATP therapies (inappropriate or appropriate, determined by physician adjudication) within the 3 years. We evaluated the associations between CKD and time to first device therapy, burden of device therapy, and inappropriate versus appropriate device therapy, adjusting for demographics, comorbidity, laboratory values and medication use. RESULTS: Among 2161 participants, 1066 (49.3%) had CKD (eGFR 44+/-11 mL/min/1.73 m2) at ICD implantation. During mean of 2.26+/-0.89 years, 9.8% and 18.5% of participants had at least one inappropriate and appropriate shock/ATP therapies, respectively. CKD was not associated with time to first shock/ATP therapies (adjusted HR 0.87, 95% CI 0.73 to 1.05), overall burden of shock/ATP therapies (adjusted relative rate 0.93, 95% CI 0.74 to 1.17) or inappropriate versus appropriate shock/ATP therapies (adjusted relative risk 0.88, 95% CI 0.68 to 1.14) compared with not having CKD. CONCLUSIONS: In adults receiving a primary prevention ICD, mild-to-moderate CKD was not associated with the timing, burden or appropriateness of subsequent device therapy. Potential concern for inappropriate ICD-delivered therapies should not preclude ICDs among eligible patients with CKD.

Public Health Sciences

Baumer TG, **Chan D**, **Mende V**, **Dischler J**, **Zauel R**, **van Holsbeeck M**, **Siegal DS**, **Divine G**, **Moutzouros V**, and **Bey MJ**. Effects of rotator cuff pathology and physical therapy on in vivo shoulder motion and clinical outcomes in patients with a symptomatic full-thickness rotator cuff tear *Orthop J Sports Med* 2016; 4(9)PMID: 27734020. Full Text

Bone and Joint Center, Henry Ford Health System, Detroit, Michigan, USA.
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elevation (P < .01). Physical therapy resulted in improved pain/function scores (P < .01), increased ROM (P < .02), increased scapulothoracic posterior tilt (P = .05), increased glenohumeral joint elevation (P = .01), and decreased acromiohumeral distance (AHD) (P = .02). CONCLUSION: Compared with age-matched controls, patients had worse pain/function scores, less ROM, and lower ABD, ER, and IR strength. Patients also had less scapulothoracic anteroposterior tilt, less glenohumeral joint elevation, and an altered glenohumeral joint contact path. PT resulted in improved pain/function scores, increased ROM, greater posterior scapulothoracic tilt, increased glenohumeral joint elevation, an increased range of superoinferior joint contact, and a lower mean AHD. Of these differences, PT only returned scapulothoracic tilt to control levels. CLINICAL RELEVANCE: This study documents the effects of PT on shoulder motion and conventional clinical outcomes. It is expected that understanding how changes in joint motion are associated with conventional clinical outcomes will lead to improved nonoperative interventions for patients with rotator cuff tears.

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; 59(5):489-495. PMID: 27544457. Full Text

Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan; Department of Pediatrics, Henry Ford Health System, Detroit, Michigan. Electronic address: mconnol1@hfhs.org.
Department of Internal Medicine, Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan.
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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.

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

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

Public Health Sciences

Kessler MD, Yerges-Armstrong L, Taub MA, Shetty AC, Maloney K, Jeng LJ, Ruczinski I, **Levin AM**, **Williams LK**, Beaty TH, Mathias RA, Barnes KC, and O'Connor TD. Challenges and disparities in the application of personalized genomic medicine to populations with African ancestry *Nat Commun* 2016; 7:12521. PMID: 27725664. Full Text

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To characterize the extent and impact of ancestry-related biases in precision genomic medicine, we use 642 whole-genome sequences from the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) project to evaluate typical filters and databases. We find significant correlations between estimated African ancestry proportions and the number of variants per individual in all variant classification sets but one. The source of these correlations is highlighted in more detail by looking at the interaction between filtering criteria and the ClinVar and Human Gene Mutation databases. ClinVar's correlation, representing African ancestry-related bias, has changed over time amidst monthly updates, with the most extreme switch happening between March and April of 2014 (r=0.733 to r=-0.683). We identify 68 SNPs as the major drivers of this change in correlation. As long as ancestry-related bias when using these clinical databases is minimally recognized, the genetics community will face challenges with implementation, interpretation and cost-effectiveness when treating minority populations.

Public Health Sciences

Mathias RA, Taub MA, Gignoux CR, Fu W, Musharoff S, O'Connor TD, Vergara C, Torgerson DG, Pino-Yanes M, Shringarpure SS, Huang L, Rafaels N, Boorgula MP, Johnston HR, Ortega VE, **Levin AM**, Song W, Torres R, **Padhukasahasram B**, Eng C, Mejia-Mejia DA, Ferguson T, Qin ZS, Scott AF, Yazdanbakhsh M, Wilson JG, Marrugo J, Lange LA, Kumar R, Avila PC, **Williams LK**, Watson H, Ware LB, Olopade C, Olopade O, Oliveira R, Ober C, Nicolae DL, Meyers D, Mayorga A, Knight-Madden J, Hartert T, Hansel NN, Foreman MG, Ford JG, Faruque MU, Dunston GM, Caraballo L, Burchard EG, Bleecker E, Araujo MI, Herrera-Paz EF, Gietzen K, Grus WE, Bamshad M,

Bustamante CD, Kenny EE, Hernandez RD, Beaty TH, Ruczinski I, Akey J, and Barnes KC. A continuum of admixture in the Western Hemisphere revealed by the African Diaspora genome *Nat Commun* 2016; 7:12522. PMID: 27725671. [Full Text](#)

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The African Diaspora in the Western Hemisphere represents one of the largest forced migrations in history and had a profound impact on genetic diversity in modern populations. To date, the fine-scale population structure of descendants of the African Diaspora remains largely uncharacterized. Here we present genetic variation from deeply

sequenced genomes of 642 individuals from North and South American, Caribbean and West African populations, substantially increasing the lexicon of human genomic variation and suggesting much variation remains to be discovered in African-admixed populations in the Americas. We summarize genetic variation in these populations, quantifying the postcolonial sex-biased European gene flow across multiple regions. Moreover, we refine estimates on the burden of deleterious variants carried across populations and how this varies with African ancestry. Our data are an important resource for empowering disease mapping studies in African-admixed individuals and will facilitate gene discovery for diseases disproportionately affecting individuals of African ancestry.

Public Health Sciences

Reynolds K, Go AS, Leong TK, Boudreau DM, **Cassidy-Bushrow AE**, Fortmann SP, Goldberg RJ, Gurwitz JH, Magid DJ, Margolis KL, McNeal CJ, Newton KM, Novotny R, Quesenberry CP, Jr., Rosamond WD, Smith DH, VanWormer JJ, Vupputuri S, Waring SC, Williams MS, and Sidney S. Trends in incidence of hospitalized acute myocardial infarction in the cardiovascular research network (CVRN) *Am J Med* 2016;PMID: 27751900. Full Text

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BACKGROUND: Monitoring trends in cardiovascular events can provide key insights into the effectiveness of prevention efforts. Leveraging data from electronic health records provides a unique opportunity to examine contemporary, community-based trends in acute myocardial infarction hospitalizations. METHODS: We examined trends in hospitalized acute myocardial infarction incidence among adults aged >/=25 years in 13 U.S. health plans in the Cardiovascular Research Network. The first hospitalization per member for acute myocardial infarction overall and for ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction was identified by ICD-9 primary discharge codes in each calendar year from 2000 through 2008. Age- and sex-adjusted incidence was calculated per 100,000 person-years using direct adjustment with 2000 U.S. census data. RESULTS: Between 2000 and 2008, we identified 125,435 acute myocardial infarction hospitalizations. Age- and sex-adjusted incidence rates (per 100,000 person-years) of acute myocardial infarction declined an average 3.8%/year from 230.5 in 2000 to 168.6 in 2008. Incidence of ST-segment elevation myocardial infarction declined 8.7%/year from 104.3 in 2000 to 51.7 in 2008 while incidence of non-ST-segment elevation myocardial infarction increased from 126.1 to 129.4 between 2000 and 2004 and then declined thereafter to 116.8 in 2008. Age- and sex-specific incidence rates generally reflected similar patterns, with relatively larger declines in ST-segment elevation myocardial infarction rates in women compared with men. As compared to 2000, the age-adjusted incidence of ST-segment elevation myocardial infarction in 2008 was 48% lower among men and 61% lower among women. CONCLUSIONS AND RELEVANCE: Among a large, diverse, multicenter community-based insured population, there were significant declines in incidence of hospitalized acute myocardial infarction and the more serious ST-segment elevation myocardial infarctions between 2000 and 2008. Declines in ST-segment elevation myocardial infarctions were most pronounced among women. While ecologic in nature, these secular declines likely reflect, at least in part, results of improvement in primary prevention efforts.

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; 33(13):1306-1312. 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
Schulman KL, **Lamerato LE**, Dalal MR, Sung J, Jhaveri M, Koren A, Mallya UG, and Foody JM. Development and validation of algorithms to identify statin intolerance in a US administrative database *Value Health* 2016; 19(6):852-860. PMID: 27712714. Full Text

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OBJECTIVES: To develop and validate algorithms to define statin intolerance (SI) in an administrative database using electronic medical records (EMRs) as the reference comparison. METHODS: One thousand adults with one or more qualifying changes in statin therapy and one or more previous diagnoses of hyperlipidemia, hypercholesterolemia, or mixed dyslipidemia were identified from the Henry Ford Health System administrative database. Data regarding statin utilization, comorbidities, and adverse effects were extracted from the administrative database and corresponding EMR. Patients were stratified by cardiovascular (CV) risk. SI was classified as absolute intolerance or titration intolerance on the basis of changes in statin utilization and/or the occurrence of adverse effects and laboratory testing for creatine kinase. Measures of concordance (Cohen's kappa [kappa]) and accuracy (sensitivity, specificity, positive predictive value [PPV], and negative predictive value) were calculated for the administrative database algorithms. RESULTS: Half of the sample population was white, 52.9% were women, mean age was 60.6 years, and 35.7% were at high CV risk. SI was identified in 11.5% and 14.0%, absolute intolerance in 2.2% and 3.1%, and titration intolerance in 9.7% and 11.8% of the patients in the EMR and the administrative database, respectively. The algorithm identifying any SI had substantial concordance (kappa = 0.66) and good sensitivity (78.1%), but modest PPV (64.0%). The titration intolerance algorithm performed better (kappa = 0.74; sensitivity 85.4%; PPV 70.1%) than the absolute intolerance algorithm (kappa = 0.40; sensitivity 50%; PPV 35.5%) and performed best in the high CV-risk group (n = 353), with robust concordance (kappa = 0.73) and good sensitivity (80.9%) and PPV (75.3%). CONCLUSIONS: Conservative but comprehensive algorithms are available to identify SI in administrative databases for application in real-world research. These are the first validated algorithms for use in administrative databases available to decision makers.

Public Health Sciences
Takahashi K, **Obeid J**, **Burmeister CS**, **Bruno DA**, **Kazimi MM**, **Yoshida A**, **Abouljoud MS**, and **Schnickel GT**. Intrahepatic cholangiocarcinoma in the liver explant after liver transplantation: Histological differentiation and prognosis *Ann Transplant* 2016; 21:208-215. PMID: 27068242. Full Text

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BACKGROUND: The aim of this study was to evaluate the outcome of patients with intrahepatic cholangiocarcinoma (ICCA) incidentally found in the explanted liver after liver transplantation. MATERIAL AND METHODS: We retrospectively reviewed 1188 recipients undergoing liver transplantation from August 2003 to August 2014; 13 patients were found to have ICCA (1.1%). Recurrence-free survival (RFS) rate was compared between ICCA patients and the matched cohort of 39 patients with hepatocellular carcinoma (HCC). We also investigate the relevance of clinical and pathological parameters in recurrence of ICCA. RESULTS: ICCA patients showed significantly higher recurrence rate with lower 1-year and 3-year RFS rates than HCC patients (recurrence rate, 12.8% vs. 54.8%; 1-year and 3-year RFS rates, 94% and 84% vs. 67% and 42%). Of the 13 ICCA patients, 4 were diagnosed with a well-differentiated ICCA and 9 with a moderately-differentiated ICCA. There was no recurrence among those with a well-differentiated ICCA, whereas 78% recurred in the moderately-differentiated group. The median RFS time for the moderately-differentiated group was 13.0 months, yielding RFS rates of 56% at 1 year and 22% at 3 years. CONCLUSIONS: Liver transplantation in patients with a well-differentiated ICCA yielded excellent outcomes as compared to patients with a moderately-differentiated ICCA. This may allow consideration of transplantation in the setting of a well-differentiated ICCA, and obviate the need for adjuvant systemic treatment. Conversely, a moderately-differentiated ICCA carries a poor prognosis with a prohibitively high recurrence rate and poor survival. Liver transplantation should remain a contraindication in this group.

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

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BACKGROUND: Diabetic Ketoacidosis (DKA) is a potentially life-threatening emergency that requires prompt diagnosis and treatment. In paediatric populations an end tidal capnography value greater than 36 mmHg was found to be 100 % sensitive in ruling out DKA. METHODS: A cross sectional observational study of adults >/= 17 years of age presenting to the emergency department between January 2014 and May 2014 with glucose > 550 mg/dL. In all patients, nasal capnography and venous blood gas analysis were performed prior to any insulin or intravenous fluid administration. The diagnosis of DKA was based on the presence of anion gap metabolic acidosis, hyperglycaemia and ketonemia. The overall diagnostic performance (area under the curve [AUC]), sensitivity, specificity and likelihood ratios at different end tidal CO_2 (ETCO2) cut-offs were determined. RESULTS: 71 patients were enrolled in the study of which 21 (30 %) met the diagnosis of DKA. The area under the curve for ETCO2 was 0.95 with a 95 % CI of 0.91 to 0.99. Test sensitivity for DKA at ETCO2 level >/=35 mmHg was 100 % (95 % CI, 83.9-100). An ETCO2 level </= 21 mmHg was 100 % specific (95 % CI, 92.9-100.0) for DKA. CONCLUSION: Nasal capnography exhibits favourable diagnostic performance in detecting patients with or without DKA among those who present to the emergency department with a glucometer reading > 550 mg/dL.

Pulmonary
Girard TD, Alhazzani W, Kress JP, **Ouellette DR**, Schmidt GA, Truwit JD, Burns SM, Epstein SK, Esteban A, Fan E, Ferrer M, Fraser GL, Gong M, Hough C, Mehta S, Nanchal R, Patel S, Pawlik AJ, Sessler CN, Strom T, Schweickert W, Wilson KC, and Morris PE. An official american thoracic society/American college of chest physicians clinical practice guideline: Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests *Am J Respir Crit Care Med* 2016;PMID: 27762595. Full Text

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BACKGROUND: Interventions that lead to earlier liberation from mechanical ventilation can improve patient outcomes. This guideline, a collaborative effort between the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST), provides evidence-based recommendations to optimize liberation from mechanical ventilation in critically ill adults. METHODS: Two methodologists performed evidence syntheses to summarize available evidence relevant to key questions about liberation from mechanical ventilation. The methodologists appraised the certainty in the evidence (i.e., the quality of evidence) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and summarized the results in evidence profiles. The guideline panel then formulated recommendations after considering the balance of desirable consequences (benefits) versus undesirable consequences (burdens, adverse effects, and costs), the certainty in the evidence, and the feasibility and acceptability of various interventions. Recommendations were rated as strong or conditional. RESULTS: The guideline panel made four conditional recommendations related to rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. The recommendations were for acutely hospitalized adults mechanically ventilated for >24 hours to receive protocolized rehabilitation directed toward early mobilization; be managed with a ventilator liberation protocol; be assessed with a cuff leak test if they meet extubation criteria but are deemed high risk for post-extubation stridor; and be administered systemic steroids for at least 4 hours before extubation if they fail the cuff leak test. CONCLUSION: The ATS/CHEST recommendations are intended to support healthcare professionals in their decisions related to liberating critically ill adults from mechanical ventilation.

Pulmonary

Schmidt GA, Girard TD, Kress JP, Morris PE, **Ouellette DR**, Alhazzani W, Burns SM, Epstein SK, Esteban A, Fan E, Ferrer M, Fraser GL, Gong M, Hough C, Mehta S, Nanchal R, Patel S, Pawlik AJ, Sessler CN, Strom T, Schweickert W, Wilson KC, and Truwit JD. Official executive summary of an American thoracic society/american college of chest physicians clinical practice guideline: Liberation from mechanical ventilation in critically ill adults *Am J Respir Crit Care Med* 2016;PMID: 27762608. Full Text

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BACKGROUND: This clinical practice guideline addresses six questions related to liberation from mechanical ventilation in critically ill adults. It is the result of a collaborative effort between the American Thoracic Society (ATS) and American College of Chest Physicians (CHEST). METHODS: A multi-disciplinary panel posed six clinical questions in a Population, Intervention, Comparator and Outcomes (PICO) format. A comprehensive literature search and evidence synthesis was performed for each question, which included appraising the certainty in the evidence (i.e., the quality of evidence) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The Evidence-to-Decision Framework was applied to each question, requiring the panel to evaluate and weigh the: importance of the problem, confidence in the evidence, certainty about how much the public value the main outcomes, magnitude and balance of desirable and undesirable outcomes, resources and costs associated with the intervention, impact on health disparities, and acceptability and feasibility of the intervention. RESULTS: Evidence-based recommendations were formulated and graded, initially by subcommittees and then modified following full panel discussions. The recommendations were confirmed by confidential electronic voting; approval required that at least 80% of the panel members agree with the recommendation. CONCLUSION: The panel provides recommendations regarding liberation from mechanical ventilation. The details regarding the evidence and rationale for each recommendation are presented in the American Journal of Respiratory and Critical Care Medicine and CHEST.

Pulmonary

Shah SK, **Jennings JH**, **Diaz-Mendoza JI**, **Yessayan L**, **Ray C**, and **Simoff MJ**. Removal of self-expanding metallic stents *J Bronchology Interv Pulmonol* 2016; 23(4):279-282. PMID: 27764006. Full Text

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BACKGROUND: Despite their safety profile, self-expanding metallic stents (SEMS) have been difficult to remove. We aim to describe our experience in removal of SEMS at Henry Ford Hospital with a specific emphasis on safety. METHODS: We reviewed the charts of all patients who underwent removal of a SEMS at Henry Ford Hospital between 2003 and 2013. We recorded demographic information, indication for initial stent placement, indication for stent removal, time to stent removal, procedure of removal, and any complications. RESULTS: In all, 19 stents were removed in 16 separate procedures in 14 patients. The median age was 62 years, and 50% of the patients were female. Stents were removed at a median of 35 days (range, 2 to 595 d). No complications occurred in 10/16 (62.5%) procedures. In the remaining 5 patients, complications were not directly related to the stent removal, and serious complications were mostly related to severity of underlying lung disease. Of the 10 procedures done as outpatients, 70% were discharged immediately after the procedure. CONCLUSIONS: Removal of SEMS can be done safely. Routine postoperative ventilation and intensive care unit monitoring is not required. In the absence of severe underlying lung disease, patients can safely be discharged if there are no immediate postprocedure complications.

Radiation Oncology
Chetvertkov MA, **Siddiqui F**, Kim J, **Chetty I**, **Kumarasiri A**, **Liu C**, and **Gordon JJ**. Use of regularized principal component analysis to model anatomical changes during head and neck radiation therapy for treatment adaptation and response assessment *Med Phys* 2016; 43(10):5307. PMID: 27782712. Article request form

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PURPOSE: To develop standard (SPCA) and regularized (RPCA) principal component analysis models of anatomical changes from daily cone beam CTs (CBCTs) of head and neck (H&N) patients and assess their potential use in adaptive radiation therapy, and for extracting quantitative information for treatment response assessment. METHODS: Planning CT images of ten H&N patients were artificially deformed to create "digital phantom" images, which modeled systematic anatomical changes during radiation therapy. Artificial deformations closely mirrored patients' actual deformations and were interpolated to generate 35 synthetic CBCTs, representing evolving anatomy over 35 fractions. Deformation vector fields (DVFs) were acquired between pCT and synthetic CBCTs (i.e., digital phantoms) and between pCT and clinical CBCTs. Patient-specific SPCA and RPCA models were built from these synthetic and clinical DVF sets. EigenDVFs (EDVFs) having the largest eigenvalues were hypothesized to capture the major anatomical deformations during treatment. RESULTS: Principal component analysis (PCA) models achieve variable results, depending on the size and location of anatomical change. Random changes prevent or degrade PCA's ability to detect underlying systematic change. RPCA is able to detect smaller systematic changes against the background of random fraction-to-fraction changes and is therefore more successful than SPCA at capturing systematic changes early in treatment. SPCA models were less successful at modeling systematic changes in clinical patient images, which contain a wider range of random motion than synthetic CBCTs, while the regularized approach was able to extract major modes of motion. CONCLUSIONS: Leading EDVFs from the both PCA approaches have the potential to capture systematic anatomical change during H&N radiotherapy when systematic changes are large enough with respect to random fraction-to-fraction changes. In all cases the RPCA approach appears to be more reliable at capturing systematic changes, enabling dosimetric consequences to be projected once trends are established early in a treatment course, or based on population models.

Radiation Oncology
Elshaikh MA. Adult comorbidity evaluation 27 score in endometrial cancer patient *Am J Obstet Gynecol* 2016;PMID: 27640945. Full Text

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Radiation Oncology
Feldman AM, **Zhang Z**, **Buekers T**, and **Elshaikh MA**. Management of gynaecologic plasmacytoma: A review article *J Obstet Gynaecol* 2016:1-6. PMID: 27760483. Article request form

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In contrast to multiple myeloma (MM) which exhibits diffuse bone marrow and other organ involvement, solitary plasmacytomas carry a favourable prognosis. Extramedullary plasmacytomas (EMP) are a unique form of plasma cell neoplasms. These tumours are rare in the female reproductive tract. Only 24 cases of gynaecologic plasmacytomas were reported to date (7 cases were solitary plasmacytomas and 17 cases were either part of disseminated MM with involvement of a gynaecologic organ or were lacking complete work-up to rule out MM). The standard care of gynaecologic solitary EMP is surgical resection alone when feasible. Adjuvant radiation therapy may be considered for adverse prognostic factors such as positive resection margins. MM with gynaecologic organ involvement should be managed with systemic therapy and defer local therapies to symptomatic progression.

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Purpose or Objective: The development of a synthetic CT (synCT) derived from MR images is necessary to support MRonly treatment planning. While we have previously developed a synCT solution for the brain, no clear quality assurance workflow currently exists for synCT validation. This work uses a novel MR-CT compatible 3D anthropomorphic skull phantom (Fig 1A) to evaluate the uncertainty in an MR-only workflow in the brain. Material and Methods: MR images of the phantom were acquired on a 1.0T High-Field Open MR-Simulator (Philips Medical Systems, Cleveland, OH). Triple echo ultra-short echo time combined with mDixon (UTE/Dixon), T1-FFE, T2- TSE, and FLAIR images MR images were acquired using an 8- channel head coil. Bone-enhanced images were generated via an optimal weighted combination of inverted UTE and water/fat maps automatically generated from mDixon. Images were then semi-automatically segmented using Gaussian mixture modeling before generating synCTs via a previously described region-specific, voxel-based, weighted summation method. SynCTs were validated by calculating the mean absolute error (MAE) between SynCT and CT-SIM. DRRs from CT-SIM and SynCT were generated of the phantom and geometric fidelity was assessed via bounding box and landmark analysis. On-board planar (MV/KV) and volumetric (CBCT) images were acquired of the phantom and rigid registration was compared between datasets across three linear accelerator platforms. Results: The MAE of the synCT for the skull phantom (Fig 1E) was 131 HU. Embedded landmarks between the phantom CTSIM DRRs and SynCT DRRs for both right lateral and anterior projections were <1 mm (1G). However, slight image intensity variations were observed across the DRRs in the synCT as compared to the CT-SIM. Bounding box analysis of the skull revealed that anterior-posterior DRRs were <1 mm different between synCT and CT-SIM while lateral DRRs had a slightly higher uncertainty in the anterior-posterior dimension (~2 mm). MV and KV planar image registrations were within 0.7 mm for all linear accelerators. CBCT/CT-SIM and CBCT/SynCT rigid registrations were <0.4 mm different. Conclusion: DRRs yielded comparable geometry between CT and synCT. Future work will involve an intensity normalization for synCT DRRs. Image registrations were within clinically acceptable ranges. Efforts are needed to combine geometric and dosimetric errors of the entire synCT pipeline; establishing QA workflows to quantify these uncertainties are necessary for MR-only treatment planning. (Figure Presented).

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OBJECTIVE: The aim of the study was to characterize the impact of adjuvant therapy on survival in women with stage I/II uterine carcinosarcoma after primary surgery. METHODS: We reviewed records of 118 consecutively treated women with 2009 International Federation of Gynecology and Obstetrics stage I/II uterine carcinosarcoma who underwent hysterectomy between 1990 and 2014 at 4 academic institutions. Patients were categorized by adjuvant treatment group into observation, chemotherapy only, radiation only, and combined chemotherapy and radiation. Survival analyses were conducted using Kaplan-Meier and Cox proportional hazards models. RESULTS: Median follow-up was 28 months (range, 1-244 months). Lymphadenectomy was performed in 94 patients (80%). Postoperative management included observation (n = 37 [31%]), chemotherapy alone (n = 19 [16%]), radiation therapy (RT) alone (n = 24 [20%]), and combined RT and chemotherapy (n = 38 [32%]). Radiation therapy modality

included vaginal brachytherapy in 22 patients, pelvic external beam RT in 21 patients, and combination in 19 patients. In 58% of women, chemotherapy consisted of carboplatin/paclitaxel. Median overall survival for all women was 97 months. On univariate analysis, adjuvant treatment group was associated with improved overall survival (hazard ratio [HR], 0.74; confidence interval [CI], 0.58-0.96; p = 0.02), freedom from vaginal recurrence (HR, 0.55; CI, 0.37-0.82]; p = 0.004), and freedom from any recurrence (HR, 0.70; CI, 0.54-0.92; p = 0.01). Pairwise comparisons demonstrated a significant benefit to chemoradiation over other adjuvant treatments. Adjuvant treatment group remained a significant covariate for all 3 end points on multivariate analysis as well. In addition, lymphadenectomy improved overall survival on multivariate analysis (HR, 0.24; CI, 0.09-0.61; p = 0.003). Of patients under observation only who had a recurrence, 8 (44%) of 18 had a recurrence in the vagina as the sole site of recurrence. By contrast, of women who received vaginal brachytherapy, significantly fewer had a recurrence in the vagina (1/42 [2.3%]; p < 0.003, log-rank test). CONCLUSIONS: In women with early-stage uterine carcinosarcoma, our data suggest superior survival end points with combined RT and chemotherapy. The frequency of vaginal recurrence suggests a role for incorporating vaginal brachytherapy in the adjuvant management of this disease.

Radiation Oncology
Kim JH, **Brown SL**, and **Kolozsvary A**. Methods to mitigate injury from radiation exposure by administering cxcr4 antagonist during decisive treatment window *Google Patents* 2016;PMID: Not assigned. Full Text

Mitigating radiation induced injury to a mammal that has been exposed to radiation by administering a pharmaceutically effective amount of a composition comprising at least one CXCR4 antagonist to the mammal at least once within a decisive treatment window wherein the window opens 48 hours after exposure.

Radiation Oncology
Mahmoud O, Hathout L, Shaaban SG, **Elshaikh MA**, Beriwal S, and Small W, Jr. Can chemotherapy boost the survival benefit of adjuvant radiotherapy in early stage cervical cancer with intermediate risk factors? A population based study *Gynecol Oncol* 2016;PMID: 27769525. Full Text

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PURPOSE: The Gynecologic Oncology group (GOG) 0263 trial is currently exploring whether adding chemotherapy to adjuvant radiotherapy improves recurrence-free and/or overall survival in stage IB-IIA cervical cancer patients with pathologic intermediate-risk factors. Using the National Cancer Data Base, we evaluated the benefit of adjuvant chemoradiotherapy over adjuvant radiotherapy alone in the community practice setting. MATERIALS: The analysis included 869 stage IB-IIA cervical cancer patients who underwent radical hysterectomy retrieving intermediate-risk factors justifying adjuvant therapy. Adjuvant chemoradiotherapy and adjuvant radiotherapy were delivered in 440 and 429 patients, respectively. Chi-square test assessed the distribution of variables in each group and the overall survival was estimated using the Kaplan-Meier method. Proportional hazard models were performed to evaluate the impact of the different prognostic factors on survival and propensity score analysis adjusted variables imbalanced distribution. RESULTS: Adding chemotherapy to ART did not show a survival benefit at 48months median follow-up; the 5-year overall survival was 87% and 81% (p=0.6) in the adjuvant chemoradiotherapy and adjuvant radiotherapy groups, respectively. On univariate analysis, age older than 60, a higher comorbidity score, and stage IIA were significantly associated with worse survival, while none of the other covariates were significant prognosticator on multivariate analysis. The same findings held after propensity score analysis. CONCLUSION: Our analysis could not detect a significant survival benefit for adjuvant chemoradiotherapy over adjuvant radiotherapy in women with intermediate-risk factors. Until GOG 0263 results become available, the benefits of adjuvant chemoradiotherapy should be considered on an individual basis within a multidisciplinary approach.

Radiation Oncology

Wahl AO, Gaffney DK, Jhingran A, Yashar CM, Biagioli M, **Elshaikh MA**, Jolly S, Kidd E, Lee LJ, Li L, Moore DH, Rao GG, Williams NL, and Small W, Jr. Acr appropriateness criteria(r) adjuvant management of early-stage endometrial cancer *Oncology (Williston Park)* 2016; 30(9)PMID: 27633412. Full Text

These consensus guidelines on adjuvant radiotherapy for early-stage endometrial cancer were developed from an expert panel convened by the American College of Radiology. The American College of Radiology Appropriateness Criteria(R) are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer-reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method; and Grading of Recommendations Assessment, Development, and Evaluation, or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment. After a review of the published literature, the panel voted on three variants to establish best practices for the utilization of imaging, radiotherapy, and chemotherapy after primary surgery for early-stage endometrial cancer.

Radiation Oncology

Wen N, **Lu S**, **Kim J**, **Qin Y**, **Huang Y**, **Zhao B**, **Liu C**, and **Chetty IJ**. Precise film dosimetry for stereotactic radiosurgery and stereotactic body radiotherapy quality assurance using Gafchromic EBT3 films *Radiat Oncol* 2016; 11(1):132. PMID: 27716323. Full Text

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PURPOSE: The purpose of this study is to evaluate the dosimetric uncertainty associated with Gafchromic (EBT3) films and establish a practical and efficient film dosimetry protocol for Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT). METHOD AND MATERIALS: EBT3 films were irradiated at each of seven different dose levels between 1 and 15 Gy with open fields and standard deviations of dose maps were calculated at each color channel for evaluation. A scanner non-uniform response correction map was built by registering and comparing film doses to the reference ion chamber array-based dose map delivered with the same doses. To determine the temporal dependence of EBT3 films, the average correction factors of different dose levels as a function of time were evaluated up to 4 days after irradiation. An integrated film dosimetry protocol was developed for dose calibration, calibration curve fitting, dose mapping, and profile/gamma analysis. Patient specific quality assurance (PSQA) was performed for 83 SRS/SBRT treatment plans, and analysis of the measurements and calculations are presented here. RESULTS: The scanner response varied within 1 % for the field sizes less than 5 x 5 cm2, and up to 5 % for the field sizes of 10 x 10 cm2 for all color channels. The scanner correction method was able to remove visually evident, irregular detector responses for larger field sizes. The dose response of the film changed rapidly (~10 %) in the first two hours and became smooth plateaued afterwards, ~3 % change between 2 and 24 h. The uncertainties were approximately 1.5, 1.7 and 4.8 % over the dose range of 3~15 Gy for the red, green and blue channels. The green channel showed very high sensitivity and low uncertainty in the dose range between 10 and 15 Gy, which is suitable for SRS/SBRT commissioning and PSQA. The difference between the calculated dose and measured dose of ion chamber measurement at isocenter was -0.64 +/- 2.02 for all plans, corresponding to a 95 % confidence interval of (-1.09, -0.26). The percentage of points passing the 3 %/1 mm gamma criteria in absolute dose, averaged over all tests was 95.0 +/- 4.2. CONCLUSION: We have developed the EBT3 films based dosimetry protocol to obtain absolute dose values. The overall uncertainty has been established to be 1.5 % for SRS and SBRT PSQA.

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Radiology
Baumer TG, **Chan D**, **Mende V**, **Dischler J**, **Zauel R**, **van Holsbeeck M**, **Siegal DS**, **Divine G**, **Moutzouros V**, and **Bey MJ**. Effects of rotator cuff pathology and physical therapy on in vivo shoulder motion and clinical outcomes in patients with a symptomatic full-thickness rotator cuff tear *Orthop J Sports Med* 2016; 4(9)PMID: 27734020. Full Text

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BACKGROUND: Physical therapy (PT) is often prescribed for patients with rotator cuff tears. The extent to which PT influences strength, range of motion (ROM), and patient-reported outcomes has been studied extensively, but the effect of PT on in vivo joint kinematics is not well understood. PURPOSE: To assess the influence of symptomatic rotator cuff pathology and the effects of PT on shoulder motion, strength, and patient-reported outcomes. STUDY DESIGN: Controlled laboratory study. METHODS: Twenty-five patients with a symptomatic rotator cuff tear and 25 age-matched asymptomatic control subjects were recruited. Shoulder motion was measured using a biplane radiography imaging system, strength was assessed with a Biodex dynamometer, and patient-reported outcomes were assessed using the Western Ontario Rotator Cuff Index and visual analog scale (VAS) pain scores. Data were acquired from the patients before and after 8 weeks of physical therapy. Data were acquired at 1 time point for the control subjects. RESULTS: Compared with the control subjects, patients with a symptomatic rotator cuff tear had significantly worse pain/function scores (P < .01); less ROM (P < .01); lower abduction (ABD), external rotation (ER), and internal rotation (IR) strength (P < .01); less scapulothoracic posterior tilt (P = .05); and lower glenohumeral joint elevation (P < .01). Physical therapy resulted in improved pain/function scores (P < .01), increased ROM (P < .02), increased scapulothoracic posterior tilt (P = .05), increased glenohumeral joint elevation (P = .01), and decreased acromiohumeral distance (AHD) (P = .02). CONCLUSION: Compared with age-matched controls, patients had worse pain/function scores, less ROM, and lower ABD, ER, and IR strength. Patients also had less scapulothoracic anteroposterior tilt, less glenohumeral joint elevation, and an altered glenohumeral joint contact path. PT resulted in improved pain/function scores, increased ROM, greater posterior scapulothoracic tilt, increased glenohumeral joint elevation, an increased range of superoinferior joint contact, and a lower mean AHD. Of these differences, PT only returned scapulothoracic tilt to control levels. CLINICAL RELEVANCE: This study documents the effects of PT on shoulder motion and conventional clinical outcomes. It is expected that understanding how changes in joint motion are associated with conventional clinical outcomes will lead to improved nonoperative interventions for patients with rotator cuff tears.

Radiology
Griffith B, and Jain R. Perfusion imaging in neuro-oncology: Basic techniques and clinical applications *Magn Reson Imaging Clin N Am* 2016; 24(4):765-779. PMID: 27742116. Full Text

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Perfusion imaging is a method for assessing the flow of blood occurring at the tissue level and can be accomplished by both CT and MR perfusion techniques. The use of perfusion imaging has increased substantially in the past decade, particularly in neuro-oncologic imaging, where it is has been used for brain tumor grading and directing biopsies or targeted therapy, as well as for the evaluation of treatment response and disease progression. This article discusses the basic principles and techniques of perfusion imaging, as well as its applications in neuro-oncology.

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

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

Radiology

Pinkney DM, Mychajlowycz M, and **Shah BA**. A prospective comparative study to evaluate the displacement of four commercially available breast biopsy markers *Br J Radiol* 2016; 89(1065):20160149. PMID: 27376410. Full Text

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OBJECTIVE: Radiopaque markers are commonly deployed following breast biopsies to indicate the location of the targeted lesion. A frequently encountered complication is the displacement of these markers. This study compared the degree of displacement among four newer generation markers after stereotactic core needle biopsy. METHODS: 80 consecutive biopsies were performed at three breast centre sites. The markers included: HydroMARK((R)) (Mammotome, Cincinnati, OH), MammoMARK (Mammotome, Cincinnati, OH), MammoStar (Mammotome, Cincinnati, OH) and SecurMark((R)) (Hologic, Bedford, MA). Each marker was composed of a radiopaque core with a unique polymeric encasing component. Post-procedure mammograms were obtained and the degree of marker displacement was measured. RESULTS: MammoMARK exhibited the greatest mean net displacement, followed by HydroMARK((R)), SecurMark((R)) and MammoStar (13.9, 7.7, 5.8 and 4.7 mm, respectively), although these differences did not reach statistical significance (p = 0.398). 73% of the markers did not displace at all. However, in the 19 of 22 markers in which displacement occurred, the distance from the biopsy cavity was >10 mm. No statistically significant contributing factors to predict displacement were found. CONCLUSION: Newer generation biopsy markers perform comparably with one another. However, clinically significant and unpredictable marker displacement persists. Compared with multiple similar studies of older generation bare metallic markers, the overall displacement rate of newer generation markers seems to be lower, possibly owing to the use of polymeric embedding agents that self-expand within the biopsy cavity. ADVANCES IN KNOWLEDGE: This article compares the post-procedure displacement of breast biopsy markers, which have not been evaluated or discussed in detail since markers with polymeric embedding agents gained widespread use.

Radiology

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

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

Radiology

Zdrenghea M, Bagacean C, Renaudineau Y, Salaun PY, **Marin H**, Pop D, and Tempescul A. Isolated cardiac richter syndrome: A case report *Ann Hematol* 2016;PMID: 27696201. Full Text

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Research Administration
Brigolin C, **McKenty N**, **Pindolia K**, and **Wolf B**. Differential gene expression during early development in brains of wildtype and biotinidase-deficient mice *Mol Genet Metab Rep* 2016; 9:35-41. PMID: 27752475. Full Text

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Biotinidase deficiency is an autosomal recessively inherited disorder characterized by neurological and cutaneous abnormalities. Untreated individuals with biotinidase deficiency cannot recycle biotin from biocytin (N-biotinyl--lysine), the proteolytic digestion product of protein-bound biotin. Biotin therapy can markedly resolve symptoms, or can prevent the development of symptoms if initiated early. To understand better the pathogenesis of the neurological problems in the disorder in humans, we have compared gene transcription changes during the first week post-birth in the brains of biotinidase-deficient, transgenic, knock-out mice at days 1 and 8 and compared to changes in wildtype mice at the same times. The knockout pups that were not supplemented with unconjugated biotin became symptomatic by day 8 and exhibiting failure to thrive. Wildtype pups remained asymptomatic under the same experimental conditions. We compared all four possible combinations and noted the most significant up- and down-regulated genes in the knockout animals at Day 8 compared to those at Day 1, reflecting the changes in gene expression over the first week of development. These alterations involved neurological development and immunological function pathways and provide some clues to avenues for further research. At this time, these preliminary analyses provide us with limited, but new information. However, with the development of new algorithms and programs examining various mechanisms and pathways in the central nervous system, these analyses may help us to understand better the role of biotinidase and the pathogenesis of biotinidase deficiency.

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

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PURPOSE: Segmentation of the hippocampus from magnetic resonance (MR) images is a key task in the evaluation of mesial temporal lobe epilepsy (mTLE) patients. Several automated algorithms have been proposed although manual segmentation remains the benchmark. Choosing a reliable algorithm is problematic since structural definition pertaining to multiple edges, missing and fuzzy boundaries, and shape changes varies among mTLE subjects. Lack of statistical references and guidance for quantifying the reliability and reproducibility of automated techniques has further detracted from automated approaches. The purpose of this study was to develop a systematic and statistical approach using a large dataset for the evaluation of automated methods and establish a method that would achieve results better approximating those attained by manual tracing in the epileptogenic hippocampus. METHODS: A template database of 195 (81 males, 114 females; age range 32-67 yr, mean 49.16 yr) MR images of mTLE patients was used in this study. Hippocampal segmentation was accomplished manually and by two well-known tools (FreeSurfer and hammer) and two previously published methods developed at their institution [Automatic brain structure segmentation (ABSS) and LocalInfo]. To establish which method was better performing for mTLE cases, several voxel-based, distance-based, and volume-based performance metrics were considered. Statistical validations of the results using automated techniques were compared with the results of benchmark manual segmentation.

Extracted metrics were analyzed to find the method that provided a more similar result relative to the benchmark. RESULTS: Among the four automated methods, ABSS generated the most accurate results. For this method, the Dice coefficient was 5.13%, 14.10%, and 16.67% higher, Hausdorff was 22.65%, 86.73%, and 69.58% lower, precision was 4.94%, -4.94%, and 12.35% higher, and the root mean square (RMS) was 19.05%, 61.90%, and 65.08% lower than LocalInfo, FreeSurfer, and hammer, respectively. The Bland-Altman similarity analysis revealed a low bias for the ABSS and LocalInfo techniques compared to the others. CONCLUSIONS: The ABSS method for automated hippocampal segmentation outperformed other methods, best approximating what could be achieved by manual tracing. This study also shows that four categories of input data can cause automated segmentation methods to fail. They include incomplete studies, artifact, low signal-to-noise ratio, and inhomogeneity. Different scanner platforms and pulse sequences were considered as means by which to improve reliability of the automated methods. Other modifications were specially devised to enhance a particular method assessed in this study.

Sleep Medicine
Jarrin DC, Chen IY, Ivers H, **Drake CL**, and Morin CM. Temporal stability of the ford insomnia response to stress test (FIRST) *J Clin Sleep Med* 2016; 12(10):1373-1378. PMID: 27568895. Full Text

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STUDY OBJECTIVES: The Ford Insomnia Response to Stress Test (FIRST) is a self-report tool that measures sleep reactivity (i.e., vulnerability to experience situational insomnia under stressful conditions). Sleep reactivity has been termed a "trait-like" vulnerability; however, evidence of its long-term stability is lacking. The main objective of the current psychometric study was to investigate the temporal stability of the FIRST over two 6-mo intervals in a population-based sample of adults with and without insomnia. The temporal stability of the FIRST was also compared with the temporal stability of other scales associated with insomnia (trait-anxiety, arousability). METHODS: Participants included 1,122 adults (mean age = 49.9 y, standard deviation = 14.8; 38.8% male) presenting with an insomnia syndrome (n = 159), insomnia symptoms (n = 152), or good sleep (n = 811). Participants completed the FIRST, the State-Trait Anxiety Inventory (trait-anxiety), and the Arousal Predisposition Scale (arousability) on three different occasions: baseline and at 6- and 12-mo follow-up. Intraclass correlation coefficients (ICCs) were computed for all scales (baseline to 6 mo and 6 to 12 mo). RESULTS: The FIRST yielded strong temporal stability from baseline to 6 mo among those with insomnia syndrome (ICC = 0.81), symptoms (ICC = 0.78), and good sleep (ICC = 0.81). Similar results were observed for 6 to 12 mo among those with insomnia syndrome (ICC = 0.74), insomnia symptoms (ICC = 0.82), and good sleep (ICC = 0.84). The stability of the FIRST was not comparable with the stability of trait-anxiety, but was somewhat comparable with the stability of arousability. CONCLUSIONS: Overall, the FIRST is a temporally reliable stable scale over 6-mo intervals. Future research is needed to corroborate the stability and trait-like measures of sleep reactivity with physiological, behavioural and personality measures.

Sleep Medicine
Komada Y, Breugelmans R, **Drake CL**, Nakajima S, Tamura N, Tanaka H, Inoue S, and Inoue Y. Social jetlag affects subjective daytime sleepiness in school-aged children and adolescents: A study using the Japanese version of the Pediatric Daytime Sleepiness Scale (PDSS-J) *Chronobiol Int* 2016:1-9. PMID: 27715324. Article request form

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The aim of this study was to elucidate the level of daytime sleepiness in Japanese school-aged children and adolescents, and to examine associated factors including sleep loss and social jetlag using the Japanese version of the Pediatric Daytime Sleepiness Scale (PDSS-J). After the linguistic validation of the PDSS-J with a multi-step translation methodology, consisting of forward translation, back translation, expert review and cognitive debriefing interviews, we conducted a psychometric validation for 492 students aged 11-16 years (46.7% boys) of public elementary school, junior high school and high school, using the PDSS-J, the Karolinska Sleepiness Scale (KSS), and bedtimes and wake-up times on school days and free days. Internal consistency (Cronbach's alpha) of the PDSS-J was 0.77, and the test-retest reliability demonstrated by the intraclass coefficient was 0.88. Multivariate logistic regression analysis revealed that both short sleep duration and social jetlag were identified as factors

associated with daytime sleepiness, after adjustment for age and sex. PDSS-J scores were significantly higher in the group with large social jetlag with or without sufficient sleep duration than in the group with sufficient sleep duration and small social jetlag. The PDSS-J is an important tool for assessing daytime sleepiness, given its ease of administration and robust psychometric properties. The impact of not only sleep loss but also social jetlag on daytime sleepiness among school-aged children and adolescents must be fully taken into account.

Marques DR, Allen Gomes A, **Drake CL**, Roth T, and de Azevedo MH. Assessing stress-induced sleep reactivity in college students: The European Portuguese version of the Ford insomnia response to stress test (FIRST) *Behav Sleep Med* 2016:1-12. PMID: 27712109. Article request form

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OBJECTIVE AND BACKGROUND: Over the past few years, the comprehensive models of insomnia have exhibited impressive developments. However, there is scarce knowledge on predisposing or vulnerability factors for insomnia. One of the most promising constructs to aid in filling this gap is stress-induced sleep reactivity assessed through self-report. Our aim was to study the psychometric properties of the European Portuguese version of the Ford Insomnia Response to Stress Test (FIRST). PARTICIPANTS: We recruited a large sample of students attending medical school (N = 699). METHODS: Several analyses were carried out such as internal consistency, construct validity, and discriminant groups' analysis. RESULTS: It was observed that FIRST-PT shows good internal consistency (Cronbach s alpha = .81) and validity indicators. Interestingly, and contrary to what was observed in the previously published studies on psychometric properties of the FIRST, it was observed that a two-factor solution (Factor I = rumination, Factor II = worry) was the most adequate one to explain the correlation matrix, accounting for approximately 44% of the total variance. CONCLUSIONS: The FIRST-PT proved to be a useful and reliable tool to measure stress-induced sleep reactivity. However, these results should be replicated in other groups, particularly clinical samples, in order to verify the stability of its factorial dimension.

Palagini L, Mauri M, Dell'Osso L, Riemann D, and **Drake CL**. Trait- and pre-sleep-state-dependent arousal in insomnia disorders: what role may sleep reactivity and sleep-related metacognitions play? A pilot study *Sleep Medicine* 2016; 25:42-48. PMID: Not yet assigned. Full Text

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Objective Research into the cause of chronic insomnia has identified hyperarousal as a key factor, which is likely to have both trait and state components. Sleep-related cognition, metacognition, and sleep reactivity also play an important role in insomnia. Our aim was to investigate how these insomnia-related constructs are associated with trait predisposition and pre-sleep arousal in subjects with an insomnia disorder. Methods Fifty-three individuals with insomnia disorder (according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (F = 33; 52 + 10)) and 30 healthy controls (F = 18; 51.8 + 12 years) were evaluated with a set of questionnaires, including the Ford Insomnia Response to Stress Test (FIRST), Metacognition Questionnaire – Insomnia (MCQI), Arousal Predisposition Scale (APS), and Pre-sleep Arousal Scale (PSAS). Statistical analyses included multiple regression to elucidate the independent determinants of APS and PSAS. Results Participants with insomnia presented higher FIRST, MCQI, APS, PSAS scores (p-values <0.001) than healthy controls. In insomnia, APS and cognitive PSAS were best determined by MCQI (respectively, B = 0.09, p = 0.001, B = 0.08, p = 0.02), somatic PSAS by cognitive arousal (PSAS B = 0.35, p = 0.004) Conclusions This study suggests that in insomnia disorders, trait predisposition toward hyperarousal and pre-sleep-cognitive-state-dependent arousal may be closely related to sleep-related metacognitive processes. Sleep-related metacognitive processes may be associated with trait hyperarousal within the framework of a mutual relationship, and could, in turn, modulate cognitive pre-sleep-state arousal. A broad range of cognitive and metacognitive processes should be considered when dealing with subjects with insomnia.

Roehrs TA, and **Roth T**. Hyperarousal in insomnia and hypnotic dose escalation *Sleep Med* 2016; 23:16-20. PMID: 27692272. Full Text

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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.

Surgery
Kabbani LS, **Wasilenko S**, **Nypaver TJ**, **Weaver MR**, **Taylor AR**, **Abdul-Nour K**, **Borgi J**, and **Shepard AD**. Socioeconomic disparities affect survival after aortic dissection *J Vasc Surg* 2016; 64(5):1239-1245. PMID: 27374067. Full Text

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

Surgery
Karamanos E, **Dulchavsky S**, Beale E, Inaba K, and Demetriades D. Diabetes mellitus in patients presenting with adhesive small bowel obstruction: Delaying surgical intervention results in worse outcomes *World J Surg* 2016; 40(4):863-869. PMID: 26566780. Full Text

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INTRODUCTION: The impact of diabetes mellitus (DM) on outcomes in patients undergoing emergency laparotomy for adhesive small bowel obstruction (ASBO) remains unknown. METHODS: Low-risk (ASA class of I and II) patients requiring emergency operation for ASBO were identified using the ACS NSQIP database. Propensity score matching

was used to match patients with DM to those without DM in a ratio of 1:3. Mortality, infectious complications, acute renal failure (ARF), and myocardial infarction (MI) were compared between the two groups. The impact of delaying OR >/= 24 h was also analyzed in the two groups. RESULTS: A total of 1,608 patients were matched, 402 with DM and 1,204 without DM. Overall, patients with DM were significantly more likely to develop infections, ARF and MI. Diabetes had no negative impact on outcomes if the operation was performed within 24 h of admission. However, delaying surgery >24, significantly increased infections, ARF and MI. CONCLUSIONS: DM in low-risk patients has no negative impact on outcomes in patients undergoing surgery for ASBO within 24 h. However, delaying surgery >24 h resulted in worse outcomes.

Surgery

Karamanos E, **Schmoekel N**, **Blyden D**, **Falvo A**, and **Rubinfeld I**. Association of unplanned reintubation with higher mortality in old, frail patients: A national surgical quality-improvement program analysis *Perm J* 2016; 20(4)PMID: 27768568. Article request form

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BACKGROUND: Unplanned postoperative reintubation increases the risk of mortality, but associated factors are unclear. OBJECTIVE: To elucidate factors associated with increased mortality risk in patients with unplanned postoperative reintubation. DESIGN: Retrospective study. Patients older than 40 years who underwent unplanned reintubation from 2005 to 2010 were identified using the American College of Surgeons National Surgical Quality Improvement Program database. Multiple regression models were used to examine the impact on mortality of factors that included the modified frailty index (mFI) we developed, American Society of Anesthesiologists (ASA) score, age decile, and days to reintubation. MAIN OUTCOME MEASURE: Mortality. RESULTS: A total of 17,051 postoperative reintubations in adults were analyzed. Overall mortality was 29.4% (n = 5009). On postoperative day 1, 4434 patients were reintubated and 878 (19.8%) died. On postoperative day 7 and beyond, 6329 patients were reintubated and 2215 (35.0%) died. Increasing mFI resulted in increasing incidence of mortality (mFI of 0 = 20.5% mortality vs mFI of 0.37-0.45 = 41.7% mortality). As ASA score increased from 1 to 5, reintubation was associated with a mortality of 12.1% to 41.6%, respectively. Similarly, increasing age decile was associated with increasing incidence of mortality (40-49 years, 17.9% vs 80-89 years, 42.1%). After adjustment for confounding factors, mFI, ASA score, age decile, and increasing number of days to reintubation were independently and significantly associated with increased mortality in the study population. CONCLUSION: Among patients who underwent unplanned reintubation, older and more frail patients had an increased risk of mortality.

Surgery
Likosky DS, Paugh TA, **Harrington SD**, Wu X, Rogers MA, Dickinson TA, DeLucia A, 3rd, Benedetti BR, Prager RL, Zhang M, and **Paone G**. Prediction of transfusions after isolated coronary artery bypass grafting surgical procedures *Ann Thorac Surg* 2016;PMID: 27726856. Full Text

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BACKGROUND: Although blood transfusions are common and have been associated with adverse sequelae after cardiac surgical procedures, few contemporaneous models exist to support clinical decision making. This study developed a preoperative clinical decision support tool to predict perioperative red blood cell transfusions in the

setting of isolated coronary artery bypass grafting. METHODS: We performed a multicenter, observational study of 20,377 patients undergoing isolated coronary artery bypass grafting among patients at 39 hospitals participating in the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative's PERFusion measures and outcomes (PERForm) registry between 2011 and 2015. Candidates' preoperative risk factors were identified based on previous work and clinical input. The study population was randomly divided into a 70% development sample and a 30% validation sample. A generalized linear mixed-effect model was developed to predict perioperative red blood cell transfusion. The model's performance was assessed for calibration and discrimination. Sensitivity analysis was performed to assess the robustness of the model in different clinical subgroups. RESULTS: Transfusions occurred in 36.8% of patients. The final regression model included 16 preoperative variables. The correlation between the observed and expected transfusions was 1.0. The risk prediction model discriminated well (receiver operator characteristic [ROC]development, 0.81; ROCvalidation, 0.82) and had satisfactory calibration (correlation between observed and expected rates was r = 0.999). The model performance was confirmed across medical centers and clinical subgroups. CONCLUSIONS: Our risk prediction model uses 16 readily obtainable preoperative variables. This model, which provides a patient-specific estimate of the need for transfusion, offers clinicians a guide for decision making and evaluating the effectiveness of blood management strategies.

Surgery
Qazi Y, Shaffer D, Kaplan B, **Kim D**, Luan FL, Peddi VR, Shihab F, Tomlanovich S, Yilmaz S, McCague K, Patel D, and Mulgaonkar S. Efficacy and safety of everolimus plus low-dose tacrolimus versus mycophenolate mofetil plus standard-dose tacrolimus in de novo renal transplant recipients: 12-month data *Am J Transplant* 2016;PMID: 27775865. Full Text

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In this 12-month, multicenter, randomized, open-label, non-inferiority study, de novo renal transplant recipients (RTxRs) were randomized (1:1) to receive everolimus plus low-dose tacrolimus (EVR+LTac) or mycophenolate mofetil plus standard-dose Tac (MMF+STac) with induction therapy (basiliximab or rabbit anti-thymocyte globulin). Non-inferiority of composite efficacy failure rate (tBPAR/graft loss/death/loss to follow-up) in EVR+LTac versus MMF+STac, was missed by 1.4% considering the non-inferiority margin of 10% (24.6% vs 20.4%; 4.2% [-3.0, 11.4]). Incidence of tBPAR (19.1% vs 11.2%; P<0.05) was significantly higher, while graft loss (1.3% vs 3.9%; P<0.05) and composite of graft loss/death/lost to follow-up (6.1% vs 10.5%, P = 0.05) were significantly lower in EVR+LTac versus MMF+STac groups, respectively. Mean eGFR was similar between EVR+LTac and MMF+STac groups (63.1 [22.0] vs 63.1 [19.5] mL/min/1.73 m2) and safety was comparable. In conclusion, EVR+LTac missed non-inferiority versus MMF+STac based on the 10% non-inferiority margin. Further studies evaluating optimal immunosuppression for improved efficacy will guide appropriate dosing and target-levels of EVR and LTac in RTxRs. This article is protected by copyright. All rights reserved.

Surgery
Takahashi K, **Obeid J**, **Burmeister CS**, **Bruno DA**, **Kazimi MM**, **Yoshida A**, **Aboujoud MS**, and **Schnickel GT**. Intrahepatic cholangiocarcinoma in the liver explant after liver transplantation: Histological differentiation and prognosis *Ann Transplant* 2016; 21:208-215. PMID: 27068242. Full Text

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BACKGROUND: The aim of this study was to evaluate the outcome of patients with intrahepatic cholangiocarcinoma (ICCA) incidentally found in the explanted liver after liver transplantation. MATERIAL AND METHODS: We retrospectively reviewed 1188 recipients undergoing liver transplantation from August 2003 to August 2014; 13 patients were found to have ICCA (1.1%). Recurrence-free survival (RFS) rate was compared between ICCA patients

and the matched cohort of 39 patients with hepatocellular carcinoma (HCC). We also investigate the relevance of clinical and pathological parameters in recurrence of ICCA. RESULTS: ICCA patients showed significantly higher recurrence rate with lower 1-year and 3-year RFS rates than HCC patients (recurrence rate, 12.8% vs. 54.8%; 1-year and 3-year RFS rates, 94% and 84% vs. 67% and 42%). Of the 13 ICCA patients, 4 were diagnosed with a well-differentiated ICCA and 9 with a moderately-differentiated ICCA. There was no recurrence among those with a well-differentiated ICCA, whereas 78% recurred in the moderately-differentiated group. The median RFS time for the moderately-differentiated group was 13.0 months, yielding RFS rates of 56% at 1 year and 22% at 3 years. CONCLUSIONS: Liver transplantation in patients with a well-differentiated ICCA yielded excellent outcomes as compared to patients with a moderately-differentiated ICCA. This may allow consideration of transplantation in the setting of a well-differentiated ICCA, and obviate the need for adjuvant systemic treatment. Conversely, a moderately-differentiated ICCA carries a poor prognosis with a prohibitively high recurrence rate and poor survival. Liver transplantation should remain a contraindication in this group.

Surgery

Varban OA, Greenberg CC, Schram J, Ghaferi AA, Thumma JR, **Carlin AM**, and Dimick JB. Surgical skill in bariatric surgery: Does skill in one procedure predict outcomes for another? *Surgery* 2016; 160(5):1172-1181. PMID: 27324569. Full Text

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BACKGROUND: Recent data establish a strong link between peer video ratings of surgical skill and clinical outcomes with laparoscopic gastric bypass. Whether skill for one bariatric procedure can predict outcomes for another related procedure is unknown. METHODS: Twenty surgeons voluntarily submitted videos of a standard laparoscopic gastric bypass procedure, which was blindly rated by 10 or more peers using a modified version of the Objective Structured Assessment of Technical Skills. Surgeons were divided into quartiles for skill in performing gastric bypass, and within 30 days of sleeve gastrectomy, their outcomes were compared. Multivariate logistic regression analysis was utilized to adjust for patient risk factors. RESULTS: Surgeons with skill ratings in the top (n = 5), middle (n = 10, middle 2 combined), and bottom (n = 5) quartiles for laparoscopic gastric bypass saw similar rates of surgical and medical complications after laparoscopic sleeve gastrectomy (top 5.7%, middle 6.4%, bottom 5.5%, P = .13). Furthermore, surgeons' skill ratings did not correlate with rates of reoperation, readmission, and emergency department visits. Top-rated surgeons had significantly faster operating room times for sleeve gastrectomy (top 76 minutes, middle 90 minutes, bottom 88 minutes; P < .001) and a higher annual volume of bariatric cases per year (top 240, middle 147, bottom 105; P = .001). CONCLUSION: Video ratings of surgical skill with laparoscopic gastric bypass do not predict outcomes of laparoscopic sleeve gastrectomy. Evaluation of surgical skill with one procedure may not apply to other related procedures and may require independent assessment of surgical technical proficiency.

Surgery

Xuereb L, **Go PH**, **Kaur B**, **Akrawe S**, **Nemeh HW**, **Borgi J**, **Williams CT**, **Paone G**, and **Morgan JA**. Impact of preoperative atrial fibrillation on postoperative thromboembolic events after left ventricular assist device implantation *Ann Thorac Surg* 2016; 102(5):1543-1549. PMID: 27469338. Full Text

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BACKGROUND: The incidence of atrial fibrillation (AF) among patients undergoing left ventricular assist device (LVAD) implantation is high. However, the impact of AF on clinical outcomes has not been clarified. We reviewed our 9-year experience of continuous flow (CF) LVADs to determine the impact of preoperative AF on stroke, device thrombosis, and survival. METHODS: Between March 2006 and May 2015, 231 patients underwent implantation of 240 CF LVADs, 127 (52.9%) as bridge to transplantation and 113 (47.1%) as destination therapy. Effect of AF on postoperative outcomes was assessed by using Kaplan-Meier survival and Cox proportional hazard regression. RESULTS: There were 78 patients (32.5%) with preoperative AF with a mean age of 55.7 +/- 11.4 years. A similar

incidence of stroke was found in patients with and without AF, 12.8% versus 16.0%, respectively (p = 0.803). Survival was similar, with 1-, 6-, 12-, and 24-month survivals of 96.2%, 91.7%, 84.5%, and 69.2%, respectively, for AF patients, versus 93.1%, 85.0%, 79.4%, and 74.1%, respectively, for non-AF patients (p = 0.424). Preoperative AF was not a significant independent predictor of survival with the use of Cox proportional hazard regression (hazard ratio 1.08, 95% confidence interval: 0.66 to 1.76). CONCLUSIONS: Preoperative AF was associated with a similar incidence of postoperative stroke, device thrombosis, and survival. On the basis of these data, it seems unnecessary to perform a left atrial appendage ligation or to alter postoperative anticoagulation in patients with AF undergoing LVAD implantation.

Urology
Abdollah F, Moschini M, **Sood A**, **Sammon J**, **Dalela D**, **Hsu L**, Beyer B, Haese A, Graefen M, Gandaglia G, Montorsi F, Briganti A, and **Menon M**. When should a positive surgical margin ring a bell? An analysis of a multi-institutional robot-assisted laparoscopic radical prostatectomy database *J Endourol* 2016; 30(2):201-207. PMID: 26415003. Full Text

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OBJECTIVE: The impact of positive surgical margin (SM) on cancer control outcomes in prostate cancer patients is a subject of continuous debate. We test the hypothesis that the impact of SM on clinical recurrence (CR) rate may vary based on the other clinical/pathologic characteristics of the tumor. MATERIALS AND METHODS: We focused on 5290 patients treated with robot-assisted radical prostatectomy and pelvic node dissection, between 2002 and 2013, at three tertiary care centers. Regression tree analysis stratified patients into risk groups based on their tumor characteristics and the corresponding CR rate. Kaplan-Meier log-rank and multivariable Cox regression models tested the relationship between SM status and CR rate in each tree-generated risk group. RESULTS: Mean (median) follow-up time was 47.7 (39.0) months. Regression tree analysis that considered all available covariates, except SM status, divided patients based on their CR risk into the following risk groups: (1) high risk (any pT3b/pT4 disease); (2) intermediate risk (</=pT3a disease and pGS 8-10); (3) low risk (</=pT3a, pGS </=7, and prostate-specific antigen [PSA] >9 ng/mL); and (4) very low risk (</=pT3a, pGS </=7, and PSA </=9 ng/mL). Positive SM had a significant detrimental impact on CR risk only in two groups: intermediate risk (p < 0.001) and high risk (p = 0.01). These observations were confirmed by multivariable analyses. CONCLUSIONS: Our findings show that positive SM had a detrimental impact on CR only in a minority of patients (15%), specifically in those with advanced pathologic stage and/or pathologically poorly differentiated tumor. For all the remaining patients (85%), positive SM by itself did not increase the risk of CR.

Urology
Day KC, Lorenzatti Hiles G, Kozminsky M, Dawsey SJ, Paul A, Broses LJ, Shah R, Kunju LP, Hall C, **Palanisamy N**, Daignault-Newton S, El-Sawy L, Wilson SJ, Chou A, Ignatoski KM, Keller ET, Thomas DG, Nagrath S, Morgan TM, and Day ML. HER2 and EGFR overexpression support metastatic progression of prostate cancer to bone *Cancer Res* 2016;PMID: 27793843. Full Text

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Activation of the epidermal growth factor receptors EGFR (ErbB1) and HER2 (ErbB2) drive the progression of multiple cancer types through complex mechanisms that are still not fully understood. In this study, we report that

HER2 expression is elevated in bone metastases of prostate cancer independently of gene amplification. An examination of HER2 and NF-kappaB receptor (RANK) coexpression revealed increased levels of both proteins in aggressive prostate tumors and metastatic deposits. Inhibiting HER2 expression in bone tumor xenografts reduced proliferation and RANK expression while maintaining EGFR expression. In examining the role of EGFR in tumor-initiating cells (TIC), we found that EGFR expression was required for primary and secondary sphere formation of prostate cancer cells. EGFR expression was also observed in circulating tumor cells (CTC) during prostate cancer metastasis. Dual inhibition of HER2 and EGFR resulted in significant inhibition of tumor xenograft growth, further supporting the significance of these receptors in prostate cancer progression. Overall, our results indicate that EGFR promotes survival of prostate TIC and CTC that metastasize to bone, whereas HER2 supports the growth of prostate cancer cells once they are established at metastatic sites.

Urology
Smith SC, **Palanisamy N**, Martin E, Almenara J, McHugh JB, Choi EK, Lucas DR, Betz BL, Thomas D, and Patel RM. The utility of ETV1, ETV4, and ETV5 RNA in situ hybridization in the diagnosis of CIC-DUX4 sarcomas *Histopathology* 2016;PMID: 27790742. Full Text

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AIMS: A recently characterized group of undifferentiated small round cell sarcomas harbours fusions of the genes CIC and DUX4. Studies report a distinctive gene expression profile for these sarcomas, including expression of E26 transformation specific (ETS)-family protooncogenic transcription factors ETV1, ETV4, and ETV5. To test the utility of an ancillary diagnostic technique for these tumors, we evaluated chromogenic RNA in situ hybridization assays for ETV1, ETV4, and ETV5, as diagnostic adjuncts for this emerging group of highly malignant sarcomas. METHODS AND RESULTS: We tested 6 confirmed CIC-DUX4 sarcomas and 105 lesions in the differential, including 48 Ewing sarcomas for expression of ETV1, ETV4, and ETV5, scoring expression utilizing a previously validated scale. ETV1 and ETV4 were positive in 5/6 cases, while ETV5 was positive in 6/6. No Ewing sarcoma or other sarcoma tested, showed co-expression of these transcripts, while one ETV1, ETV4, ETV5 positive previously unclassified round cell sarcoma, was identified as harboring a CIC rearrangement by break-apart FISH. CONCLUSION: We identified overexpression of ETV1, ETV4, and ETV5 transcripts in situ in CIC-DUX4 sarcomas using a robust assay in routine archival sections. One previously unclassified round cell sarcoma showed ETV1/4/5 positivity, and was proven to harbor a CIC rearrangement by break-apart FISH. The sensitivity and specificity observed with our in situ hybridization assay implies potential utility as an ancillary diagnostic technique, particularly when faced with limited biopsy samples. This article is protected by copyright. All rights reserved.

Urology
Sood A, **Abdollah F**, and **Menon M**. Je le pansai, Dieu le guerit *Eur Urol* 2016;PMID: 27720535. Full Text

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Urology
Wang L, **Diaz M**, **Stricker H**, **Peabody JO**, **Menon M**, and **Rogers CG**. Erratum to: Adding a newly trained surgeon into a high-volume robotic prostatectomy group: are outcomes compromised? *J Robot Surg* 2016;PMID: 27743311. Full Text

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