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Henry Ford Health System

Henry Ford Health System Publication List – May 2020

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, and Web of Science during the month, and then imported into EndNote for formatting. There are 131 unique citations listed this month, 16 on COVID-19; articles are listed first, followed by conference abstracts and a bibliography of publications on COVID-19. 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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Articles

Administration

Lin JC, **Kavousi Y**, **Sullivan B**, and **Stevens C**. Analysis of Outpatient Telemedicine Reimbursement in an Integrated Healthcare System. *Ann Vasc Surg* 2020; 65:100-106. PMID: 31678131. Full Text

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BACKGROUND: Current reimbursement policy surrounding telemedicine has been cited as a barrier for the adaptation of this care model. The objective of this study is to analyze the reimbursement figures for outpatient telemedicine consultation in vascular surgery. METHODS: Patients first underwent synchronous telemedicine visits after receiving point-of-care ultrasound at one of 3 satellite locations of Henry Ford Health System in Michigan. Visit types included new, return, and postoperative patients. Reimbursement information related to payor, adjustment, denial, paid and outstanding balances were recorded for each telemedicine visit. Then, using an enterprise data warehouse, a retrospective analysis was performed for the aforementioned telemedicine visits. The data were analyzed to determine the outcome of total billed charges, number of denied claims, reimbursement per payor, reimbursement per patient, and out-of-pocket costs to the patients. RESULTS: Among 184 virtual clinical encounters, the payors included Aetna US Healthcare, Blue Advantage, Blue Cross Blue Shield, Cofinity Plan, Health Alliance Plan, HAP Medicare Advantage, Humana Medicare Advantage, Medicaid, Medicare, Molina Medicaid HMO, United Healthcare, Blue Care Network, Aetna Better Health of Michigan, Priority Health, and self-pay. Among the 15 payors, reimbursement ranged from 0% to 67% of the total charges billed. Among the 184 virtual visits, a grand total of $22,145 was collected or an average of $120.35 per virtual encounter. The breakdown of charges billed was 40% adjusted, 41% paid by insurance, 10% paid by patient, and 13% denied. There were 27 total denials (15%). Denial of payment included telehealth and nontelehealth reasons, citing noncovered charges, payment included for other prior services, new patient quality not met, and not covered by payor. The average out-of-pocket cost to patients was $12.59 per visit. CONCLUSIONS: These reimbursement data validate the economic potential within this new platform of healthcare delivery. As our experience with the business model grows, we expect to see an increase in reimbursement from private payors and acceptance from patients. Within a tertiary care system, telemedicine for chronic vascular disease has proven to be a viable means to reach a broader population base, and without significant cost to the patients.

Allergy & Immunology

Luria CJ, **Sitarik AR**, **Havstad S**, **Zoratti EM**, **Kim H**, **Wegienka GR**, **Joseph CLM**, and **Cassidy-Bushrow AE**. Association between asthma symptom scores and perceived stress and trait anxiety in adolescents with asthma. *Allergy Asthma Proc* 2020; 41(3):210-217. PMID: 32375966. Request Article

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Background: Emotional disorders, including depression and anxiety, are more prevalent in individuals with asthma than in the general population and are associated with poor asthma outcomes. Identification of patients with increased levels of stress and anxiety may be helpful when treating asthma and during asthma counseling. Objective: To further characterize the relationship between asthma symptoms and perceived stress and trait anxiety in an adolescent population. Methods: Adolescents (N = 335) ages 14-17 years were recruited to examine the effect of stress on health measures. They were included in the present analysis if they reported current asthma, defined as self-reported clinician-diagnosed asthma plus one or more episodes of asthma in the past year. Asthma symptoms were assessed on a 7-point scale by using a standardized questionnaire that targets nocturnal awakening due to asthma, symptoms on awakening, activity limitation, shortness of breath, time spent wheezing, and short-acting bronchodilator use. Stress was measured by using the Perceived Stress Scale (PSS), and trait anxiety was measured by using the State-Trait Anxiety Inventory. Linear regression was used to associate asthma symptoms with PSS and trait anxiety. Results: Thirty-eight adolescents (11.3%), with mean ± standard deviation age 16.7 ± 0.9 years, reported current asthma. Four of the six asthma symptom assessments had significant associations with PSS: symptoms on awakening ($\beta = 4.82$, $p < 0.001$), nocturnal awakening due to asthma ($\beta = 4.47$, $p < 0.001$), activity limitation ($\beta = 2.78$, $p = 0.005$), and shortness of breath ($\beta = 1.73$, $p = 0.014$). These associations remained significant after adjusting for gender, race, and the body mass index percentile. Trait anxiety had significant associations with nocturnal awakening ($\beta = 9.28$, $p = 0.002$) and symptoms on awakening ($\beta = 8.74$, $p = 0.002$). Associations remained significant after adjusting for gender, race, and body mass index percentile. Conclusion: Asthma symptom severity is associated with increased perceived stress and trait anxiety. Adolescents with asthma may represent a population that is particularly vulnerable to perceived stress and anxiety, which highlights the importance of considering these factors in asthma counseling.

Allergy & Immunology

Ober C, McKennan CG, Magnaye KM, Altman MC, Washington C, 3rd, Stanhope C, Naughton KA, Rosasco MG, Bacharier LB, Billheimer D, Gold DR, Gress L, Hartert T, **Havstad S**, Khurana Hershey GK, Hallmark B, Hogarth DK, Jackson DJ, **Johnson CC**, Kattan M, Lemanske RF, Lynch SV, Mendonca EA, Miller RL, Naureckas ET, O'Connor GT, Seroogy CM, **Wegienka G**, White SR, Wood RA, Wright AL, **Zoratti EM**, Martinez FD, Ownby D, Nicolae DL, **Levin AM**, and Gern JE. Expression quantitative trait locus fine mapping of the 17q12-21 asthma locus in African American children: a genetic association and gene expression study. *Lancet Respir Med* 2020; 8(5):482-492. PMID: 32380068. Full Text

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BACKGROUND: African ancestry is associated with a higher prevalence and greater severity of asthma than European ancestries, yet genetic studies of the most common locus associated with childhood-onset asthma, 17q12-21, in African Americans have been inconclusive. The aim of this study was to leverage both the phenotyping of the Children's Respiratory

and Environmental Workgroup (CREW) birth cohort consortium, and the reduced linkage disequilibrium in African Americans, to fine map the 17q12-21 locus. METHODS: We first did a genetic association study and meta-analysis using 17q12-21 tag single-nucleotide polymorphisms (SNPs) for childhood-onset asthma in 1613 European American and 870 African American children from the CREW consortium. Nine tag SNPs were selected based on linkage disequilibrium patterns at 17q12-21 and their association with asthma, considering the effect allele under an additive model (0, 1, or 2 effect alleles). Results were meta-analysed with publicly available summary data from the EVE consortium (on 4303 European American and 3034 African American individuals) for seven of the nine SNPs of interest. Subsequently, we tested for expression quantitative trait loci (eQTLs) among the SNPs associated with childhood-onset asthma and the expression of 17q12-21 genes in resting peripheral blood mononuclear cells (PBMCs) from 85 African American CREW children and in upper airway epithelial cells from 246 African American CREW children; and in lower airway epithelial cells from 44 European American and 72 African American adults from a case-control study of asthma genetic risk in Chicago (IL, USA). FINDINGS: 17q12-21 SNPs were broadly associated with asthma in European Americans. Only two SNPs (rs2305480 in gasdermin-B [GSDMB] and rs8076131 in ORMDL sphingolipid biosynthesis regulator 3 [ORMDL3]) were associated with asthma in African Americans, at a Bonferroni-corrected threshold of p<0·0055 (for rs2305480_G, odds ratio [OR] 1·36 [95% CI 1·12-1·65], p=0·0014; and for rs8076131_A, OR 1·37 [1·13-1·67], p=0·0010). In upper airway epithelial cells from African American children, genotype at rs2305480 was the most significant eQTL for GSDMB (eQTL effect size [β] 1·35 [95% CI 1·25-1·46], p<0·0001), and to a lesser extent showed an eQTL effect for post-GPI attachment to proteins phospholipase 3 (β 1·15 [1·08-1·22], p<0·0001). No SNPs were eQTLs for ORMDL3. By contrast, in PBMCs, the five core SNPs were associated only with expression of GSDMB and ORMDL3. Genotype at rs12936231 (in zona pellucida binding protein 2) showed the strongest associations across both genes (for GSDMB, eQTLβ 1·24 [1·15-1·32], p<0·0001; and for ORMDL3 (β 1·19 [1·12-1·24], p<0·0001). The eQTL effects of rs2305480 on GSDMB expression were replicated in lower airway cells from African American adults (β 1·29 [1·15-1·44], p<0·0001). INTERPRETATION: Our study suggests that SNPs regulating GSDMB expression in airway epithelial cells have a major role in childhood-onset asthma, whereas SNPs regulating the expression levels of 17q12-21 genes in resting blood cells are not central to asthma risk. Our genetic and gene expression data in African Americans and European Americans indicated GSDMB to be the leading candidate gene at this important asthma locus. FUNDING: National Institutes of Health, Office of the Director.

Allergy & Immunology

Sheehan WJ, Krouse RZ, Calatroni A, Gergen PJ, Gern JE, Gill MA, Gruchalla RS, Khurana Hershey GK, Kattan M, Kercsmar CM, Lamm CI, Little FF, Makhija MM, Searing DA, **Zoratti E**, Busse WW, and Teach SJ. Aeroallergen Sensitization, Serum IgE, and Eosinophilia as Predictors of Response to Omalizumab Therapy during the Fall Season among Children with Persistent Asthma. *J Allergy Clin Immunol Pract* 2020; Epub ahead of print. PMID: 32376491. Full Text

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BACKGROUND: Perennial aeroallergen sensitization is associated with greater asthma morbidity and is required for treatment with omalizumab. OBJECTIVE: To investigate the predictive relationship between the number of aeroallergen sensitizations, total serum IgE, and serum eosinophil count, and response to omalizumab in children and adolescents with asthma treated during the fall season. METHODS: This analysis includes inner-city patients with persistent asthma and recent exacerbations aged 6-20 years comprising the placebo and omalizumab-treated groups in two completed randomized clinical trials, the Inner-City Anti-IgE Therapy for Asthma (ICATA) study and the Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations (PROSE) study. Logistic regression modeled the relationship between greater degrees of markers of allergic inflammation and the primary outcome of fall season asthma exacerbations. RESULTS: The analysis included 761 participants who were 62% male and 59% African American with a median age of 10 years. Fall asthma exacerbations were significantly higher in children with greater numbers of aeroallergen-specific sensitizations in the placebo group (OR 1.33, 95% CI 1.11-1.60, p<0.01), but not in the omalizumab-treated children (OR 1.08, 95% CI 0.91-1.28, p=0.37) indicating a significant differential effect (p<0.01). Likewise, there was a differential effect of omalizumab treatment in children with greater baseline total serum IgE levels (p<0.01) or greater baseline serum eosinophil counts (p<0.01). Multiple aeroallergen sensitization was the best predictor of response to omalizumab; treated participants sensitized to ≥4 different groups of aeroallergens had a 51% reduction in the odds of a fall exacerbation (OR 0.49, 95% CI 0.30-0.81, p<0.01). CONCLUSIONS: In preventing fall season asthma exacerbations, treatment with omalizumab was most beneficial in children with a greater degree of allergic inflammation.

Behavioral Health Services/Psychiatry
Blumenfeld EM, **Gautam M**, **Akinyemi E**, and **Mahr G**. Suicidality in Factitious Disorder. *Prim Care Companion CNS Disord* 2020; 22(3). PMID: 32441497. Request Article

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Behavioral Health Services/Psychiatry
Clark-Sienkiewicz SM, **Hecht LM**, **Pester B**, **Martens K**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Racial Differences in Psychological Symptoms and Eating Behaviors Among Bariatric Surgery Candidates. *J Racial Ethn Health Disparities* 2020; Epub ahead of print. PMID: 32367444. Request Article

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BACKGROUND: Black patients typically lose less weight than White patients following bariatric surgery; however, the reasons for this racial disparity are unclear. The purpose of the current study was to evaluate whether there are differences in psychiatric symptoms and problematic eating behaviors between White and Black patients pursuing bariatric surgery as this may aid in understanding postsurgical weight loss disparities and inform psychosocial assessment of bariatric candidates. METHODS: A retrospective chart review was conducted of participants (N = 284) who completed a psychological evaluation prior to surgery. Information collected included history of binge eating and purging as well as data from measures administered (i.e., the Hospital Anxiety and Depression Scale, the Emotional Eating Scale, and the Yale Food Addiction Scale 2.0). RESULTS: White patients reported higher levels of eating in response to anger/frustration (p = .03) and eating in response to depression (p = .01) than Black patients. White patients also reported more symptoms of food addiction, a difference that was trending toward significance (p = .05). No significant differences were found on measures of anxiety or depression. CONCLUSION: White patients appear to have higher levels of presurgical problematic eating as compared with Black patients pursuing bariatric surgery; thus, these measurements of problematic eating may not explain the racial disparity in outcomes. However, future research should determine whether measures are valid among diverse populations and identify additional factors that may contribute to racial disparities in bariatric outcomes.

Behavioral Health Services/Psychiatry
Khan A, **Gautam M**, **Chawa M**, **Thakrar A**, and **Akinyemi E**. The Intersection of Suicide and Viral Outbreaks. *Prim Care Companion CNS Disord* 2020; 22(3). PMID: 32408398. Request Article

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Behavioral Health Services/Psychiatry
Macki M, Mahajan A, Shatz R, **Air EL**, **Novikova M**, Fakih M, Elmenini J, **Kaur M**, **Bouchard KR**, **Funk BA**, and **Schwalb JM**. Prevalence of Alternative Diagnoses and Implications for Management in Idiopathic Normal Pressure Hydrocephalus Patients. *Neurosurgery* 2020; Epub ahead of print. PMID: 32472677. Full Text

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BACKGROUND: Following Bayes theorem, ventriculomegaly and ataxia confer only a 30% chance of idiopathic Normal Pressure Hydrocephalus (NPH). When coupled with positive responses to best diagnostic testing (extended lumbar drainage), 70% of patients recommended for shunting will not actually have NPH. This is inadequate clinical care. OBJECTIVE: To determine the proportion of alternative and treatable diagnoses in patients referred to a multidisciplinary NPH clinic. METHODS: Patients without previously diagnosed NPH were queried from prospectively collected data. At least 1

neurosurgeon, cognitive neurologist, and neuropsychologist jointly formulated best treatment plans. RESULTS: Of 328 total patients, 45% had an alternative diagnosis; 11% of all patients improved with treatment of an alternative diagnosis. Of 87 patients with treatable conditions, the highest frequency of pathologies included sleep disorders, and cervical stenosis, followed by Parkinson disease. Anti-cholinergic burden was a contributor for multiple patients. Of 142 patients undergoing lumbar puncture, 71% had positive responses and referred to surgery. Compared to NPH patients, mimickers were statistically significantly older with lower Montreal Cognitive Assessment (MoCA) score and worse gait parameters. Overall, 26% of the original patients underwent shunting. Pre-post testing revealed a statistically significant improved MoCA score and gait parameters in those patients who underwent surgery with follow-up. CONCLUSION: Because the Multidisciplinary NPH Clinic selected only 26% for surgery (corroborating 30% in Bayes theorem), an overwhelming majority of patients with suspected NPH will harbor alternative diagnoses. Identification of contributing/confounding conditions will support the meticulous work-up necessary to appropriately manage patients without NPH while optimizing clinical responses to shunting in correctly diagnosed patients.

Behavioral Health Services/Psychiatry
Mun M, and **Akinyemi E**. Representation on the Editorial Boards of Academic Psychiatry Journals: the Gender Difference. *Acad Psychiatry* 2020; Epub ahead of print. PMID: 32458311. Full Text

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Behavioral Health Services/Psychiatry
Patel S, **Gautam M**, and **Mahr G**. COVID-19 and Infection Control: A Perspective From the Psychiatric Ward. *Prim Care Companion CNS Disord* 2020; 22(3). PMID: 32441495. Request Article

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Cardiology and Cardiovascular Research
Ananthasubramaniam K. ASNC Image Guide Registry: Leading the way toward improving quality and patient care in nuclear cardiology. *J Nucl Cardiol* 2020; Epub ahead of print. PMID: 32394401. Full Text

Henry Ford West Bloomfield Hospital, Heart and Vascular Institute, West Bloomfield, MI, 48322, USA. kananth1@hfhs.org.

Cardiology and Cardiovascular Research
Basir MB. Beyond the coronary arteries, should we be shifting our focus to mechanical circulatory support in patients with acute myocardial infarction and cardiogenic shock? *Cardiovasc Revasc Med* 2020; Epub ahead of print. PMID: 32387218. Full Text

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Cardiology and Cardiovascular Research
Butera B, **Klingler D**, **McCord JK**, and **Ananthasubramaniam K**. Interpreting technetium-99m pyrophosphate cardiac scans to diagnose transthyretin cardiac amyloidosis: Need for due diligence. *J Nucl Cardiol* 2020; Epub ahead of print. PMID: 32390109. Full Text

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Cardiology and Cardiovascular Research
Drake DH, De Bonis M, Covella M, Agricola E, Zangrillo A, **Zimmerman KG**, and Cobey FC. Echocardiography in Pandemic: Front-Line Perspective, Expanding Role of Ultrasound, and Ethics of Resource Allocation. *J Am Soc Echocardiogr* 2020; 33(6):683-689. PMID: Not assigned. Full Text

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The grave clinical context of the coronavirus disease 2019 (COVID-19) pandemic must be understood. Italy is immersed in the COVID-19 pandemic. Most of the world will soon follow. The United States currently has the most documented cases of COVID-19 of any nation. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)–associated acute cardiomyopathy is common in critical care patients and is associated with a high mortality rate. Patients with COVID-19 frequently require mechanical support for adequate oxygenation. A severe shortfall of ventilators is predicted. Of equal concern is the projected shortage of trained professionals required to care for patients on mechanical ventilation. Ultrasonography is proving to be a

valuable tool for identifying the pulmonary manifestations and progression of COVID-19. Lung ultrasound also facilitates successful weaning from mechanical ventilation. Ultrasonography of the lung, pleura, and diaphragm are easily mastered by experienced echocardiographers. Echocardiography has an established role for optimal fluid management and recognition of cardiac disease, including SARS-CoV-2-associated acute cardiomyopathy. Cardiologists, anesthesiologists, sonographers, and all providers should be prepared to commit their full spectrum of skills to mitigate the consequences of the pandemic. We should also be prepared to collaborate and cross-train to expand professional services as necessary. During a declared health care crisis, providers must be familiar with the ethical principles, organizational structure, practical application, and gravity of limited resource allocation.

Cardiology and Cardiovascular Research
Gibbs J, and **McCord J**. Chest Pain Evaluation in the Emergency Department: Risk Scores and High-Sensitivity Cardiac Troponin. *Curr Cardiol Rep* 2020; 22(7):49. PMID: 32472247. Full Text

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PURPOSE OF REVIEW: As many as 10 million patients present annually to the emergency department in the USA with symptoms concerning for acute myocardial infarction. The use of risk scores for patients with chest pain or equivalent without ST-segment elevation on the electrocardiogram. The adaptation in the USA of high sensitivity troponin assays requires rethinking of how to best optimize troponin testing within a risk score. RECENT FINDINGS: Patients are risk stratified using a combination of validated risk scores, biomarkers, and both noninvasive and invasive testing. The advent of high-sensitivity troponins has served to augment existing risk scores in the identification of low-risk patients for early discharge, as well as led to the introduction of new rapid rule-out protocols by which acute myocardial infarction can be excluded by biomarker evaluation more quickly. The emergence of machine learning algorithms may further enhance provider's ability to quickly diagnose or exclude myocardial infarction in the emergency department. The addition of high sensitive troponin assays to established emergency department risk scores is providing new opportunities to improve the timeliness and accuracy of the evaluation of patients presenting with a possible myocardial infarction. Utilizing the time between troponin measures as a variable combined with clinical risk factors with new algorithms may further serve to improve diagnostic accuracy.

Cardiology and Cardiovascular Research
Greenbaum AB, Khan JM, Rogers T, Babaliaros VC, **Eng MHK**, **Wang DD**, **Paone G**, and Lederman RJ. First-in-human transcatheter pledget-assisted suture tricuspid annuloplasty for severe tricuspid insufficiency. *Catheter Cardiovasc Interv* 2020; Epub ahead of print. PMID: 32385950. Full Text

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OBJECTIVES: We report the first pledget-assisted suture tricuspid annuloplasty (PASTA) in a patient with torrential tricuspid regurgitation (TR). BACKGROUND: Tricuspid valve regurgitation is a common malignant disease with no commercially available transcatheter therapy. PASTA is a "percutaneous surgical" procedure using pledgeted sutures to create a double-orifice tricuspid valve. METHODS: An 83-year-old man had end-stage TR caused by a defibrillator lead. He consented to undergo PASTA on a compassionate basis. A double-orifice valve was created with pledgeted sutures from percutaneous right ventricular apical access. RESULTS: TR was reduced from torrential to trace. The vena contracta reduced to from 23 to 1 mm and annular area reduced from 1817 to 782 mm(2) . However, the annulus dehisced and required closure with a percutaneous nitinol plug. The patient was discharged home and was alive 6 months later but with persistent symptoms. CONCLUSIONS: The anatomy of a double-orifice valve can eliminate TR but a better solution is required to avoid excessive suture tension on annular tissue.

Cardiology and Cardiovascular Research
Guerrero M, **Wang DD**, Pursnani A, Eleid M, Khalique O, Urena M, Salinger M, Kodali S, Kaptzan T, Lewis B, Kato N, Cajigas HM, Wendler O, Holzhey D, Pershad A, Witzke C, Alnasser S, Tang GHL, Grubb K, Reisman M, Blanke P, Leipsic J, Williamson E, Pellikka PA, Pislaru S, Crestanello J, Himbert D, Vahanian A, Webb J, Hahn RT, Leon M, George I, Bapat V, **O'Neill W**, and Rihal C. A Cardiac Computed Tomography-Based Score to Categorize Mitral Annular Calcification Severity and Predict Valve Embolization. *JACC Cardiovasc Imaging* 2020; Epub ahead of print. PMID: 32417332. Full Text

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OBJECTIVES: This study aims to establish a computed tomography (CT)-based scoring system for grading mitral annular calcification (MAC) severity and potentially aid in predicting valve embolization during transcatheter mitral valve (MV) replacement using balloon-expandable aortic transcatheter heart valves. BACKGROUND: Transcatheter MV replacement is emerging as an alternative treatment for patients with severe MAC who are not surgical candidates. Although cardiac CT is the imaging modality of choice in the evaluation of candidates for valve-in-MAC (ViMAC), a standardized grading system to quantify MAC severity has not been established. METHODS: We performed a multicenter retrospective review of cardiac CT and clinical outcomes of patients undergoing ViMAC. A CT-based MAC score was created using the following features: average calcium thickness (mm), degrees of annulus circumference involved, calcification at one or both fibrous trigones, and calcification of one or both leaflets. Features were assigned points according to severity (total maximum score = 10) and severity grade was assigned based on total points (mild ≤3, moderate 4 to 6, and severe ≥7 points). The association between MAC score and device migration/embolization was evaluated. RESULTS: Of 117 patients in the TMVR in MAC registry, 87 had baseline cardiac CT of adequate quality. Of these, 15 were treated with transatrial access and were not included. The total cohort included 72 (trans-septal = 37, transapical = 35). Mean patient age was 74 ± 12 years, 66.7% were female, and the mean Society of Thoracic Surgery risk score was 15.4% ± 10.5. The mean MAC score was 7.7 ± 1.4. Embolization/migration rates were lower in higher scores: Patients with a MAC score of 7 had valve embolization/migration rate of 12.5%, MAC score ≥8 had a rate of 8.7%, and a MAC score of ≥9 had zero ($p = 0.023$). Patients with a MAC score of ≤6 had 60% embolization/migration rate versus 9.7% in patients with a MAC score ≥7 ($p < 0.001$). In multivariable analysis, a MAC score ≤6 was in independent predictor of valve embolization/migration (odds ratio [OR]: 5.86 [95% CI: 1.00 to 34.26]; $p = 0.049$). CONCLUSIONS: This cardiac CT-based score provides a systematic method to grade MAC severity which may assist in predicting valve embolization/migration during trans-septal or transapical ViMAC procedures.

Cardiology and Cardiovascular Research

Ketcham SW, Adie SK, **Malliett A**, **Abdul-Aziz AA**, **Bitar A**, **Grafton G**, and **Konerman MC**. Coronavirus Disease-2019 in Heart Transplant Recipients in Southeastern Michigan: A Case Series. *J Card Fail* 2020; Epub ahead of print. PMID: 32417380. Full Text

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BACKGROUND: Since coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China, in December 2019, the number of cases has risen exponentially. Clinical characteristics and outcomes among patients with orthotopic heart transplant (OHT) with COVID-19 remain poorly described. METHODS: We performed a retrospective case series of patients with OHT with COVID-19 admitted to 1 of 2 hospitals in Southeastern Michigan between March 21 and April 22, 2020. Clinical data were obtained through review of the electronic medical record. Final date of follow-up was May 7, 2020. Demographic, clinical, laboratory, radiologic, treatment, and mortality data were collected and analyzed. RESULTS: We identified 13 patients with OHT admitted with COVID-19. The mean age of patients was 61 ± 12 years, 100% were black males, and symptoms began 6 ± 4 days before admission. The most common symptoms included subjective fever (92%), shortness of breath (85%), and cough (77%). Six patients (46%) required admission to the intensive care unit. Two patients (15%) died during hospitalization.

CONCLUSIONS: Black men may be at increased risk for COVID-19 among patients with OHT. Presenting signs and symptoms in this cohort are similar to those in the general population. Elevated inflammatory markers on presentation appear to be associated with more severe illness.

Cardiology and Cardiovascular Research
Lemor A, **Basir MB**, Patel K, Kolski B, Kaki A, Kapur N, Riley R, Finley J, Goldsweig A, Aronow HD, Belford PM, Tehrani B, Truesdell AG, Lasorda D, Bharadwaj A, Hanson I, LaLonde T, **Gorgis S**, and **O'Neill W**. Multivessel Versus Culprit-Vessel Percutaneous Coronary Intervention in Cardiogenic Shock. *JACC Cardiovasc Interv* 2020; 13(10):1171-1178. PMID: 32360256. Full Text

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Department of Cardiology, Inova Fairfax Hospital, Falls Church, Virginia.
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OBJECTIVES: This study sought to compare outcomes of patients enrolled in the NCSI (National Cardiogenic Shock Initiative) trial who were treated using a revascularization strategy of percutaneous coronary intervention (PCI) of multivessel PCI (MV-PCI) versus culprit-vessel PCI (CV-PCI). BACKGROUND: In patients with multivessel disease who present with acute myocardial infarction and cardiogenic shock (AMICS), intervening on the nonculprit vessel is controversial. There are conflicting published reports and lack of evidence, particularly in patients treated with early mechanical circulatory support (MCS). METHODS: From July 2016 to December 2019, patients who presented with AMICS to 57 participating hospitals were included in this analysis. All patients were treated using a standard shock protocol emphasizing early MCS, revascularization, and invasive hemodynamic monitoring. Patients with multivessel coronary artery disease (MVCAD) were analyzed according to whether CV-PCI or MV-PCI was undertaken during the index procedure. RESULTS: Of 198 patients with MVCAD, 126 underwent MV-PCI (64%) and 72 underwent CV-PCI (36%). Demographics between the cohorts were similar with respect to age, sex, history of diabetes, prior PCI or coronary artery bypass grafting, and prior history of myocardial infarction. Patients who underwent MV-PCI had a trend toward more severe impairment of cardiac output and worse lactate clearance on presentation, and cardiac performance was significantly worse at 12 h. However, 24 h from PCI, the hemometabolic derangements were similar. Survival and rates of acute kidney injury were not significantly different between groups (69.8% MV-PCI vs. 65.3% CV-PCI; p = 0.51; and 29.9% vs. 34.2%; p = 0.64, respectively). CONCLUSIONS: In patients with MVCAD presenting with AMICS treated with early MCS, revascularization of nonculprit lesions was associated with similar hospital survival and acute kidney injury when compared with culprit-only PCI. Selective nonculprit PCI can be safety performed in AMICS in patients supported with mechanical circulatory support.

Cardiology and Cardiovascular Research
Othman H, Seth M, Zein R, Rosman H, Lalonde T, Yamasaki H, **Alaswad K**, Menees D, Mehta RH, Gurm H, and Daher E. Percutaneous Coronary Intervention for Chronic Total Occlusion-The Michigan Experience: Insights From the BMC2 Registry. *JACC Cardiovasc Interv* 2020; Epub ahead of print. PMID: 32417095. Full Text

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OBJECTIVES: The aim of this study was to describe the performance and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) in Michigan. BACKGROUND: CTO PCI has been associated with reduction in angina, but previous registry analyses showed a higher rate of major adverse cardiac events with this procedure. METHODS: To study uptake and outcomes of CTO PCI in Michigan, patients enrolled in the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) registry (2010 to 2017) were evaluated. CTO PCI was defined as intervention in a 100% occluded coronary artery ≥3 months old. RESULTS: Among 210,172 patients enrolled in the registry, 7,389 CTO PCIs (3.5%) were

attempted, with 4,614 (58.3%) achieving post-procedural TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. The proportion of PCIs performed on CTOs increased over the study period (from 2.67% in 2010 to 4.48% in 2017). Thirty of 47 hospitals performed >50 CTO interventions in 2017. Pre-procedural angina class ≤2 was present in one-quarter, and functional assessment for ischemia was performed in 46.6% of patients. Major complications occurred in 245 patients (3.3%) and included death (1.4%), post-procedural stroke (0.4%), cardiac tamponade (0.5%), and urgent coronary artery bypass graft surgery (1.3%). Procedural success improved modestly from 44.5% in 2010 to 54.9% in 2017 (p for trend < 0.001). Rates of in-hospital mortality (p for trend = 0.247) and major adverse cardiac event (p for trend = 0.859) for CTO PCI remained unchanged over the study period. CONCLUSIONS: The rate of CTO PCI in Michigan increased over the study period. Although the success rate of CTO PCI has increased modestly in contemporary practice, it remained far below the >80% reported by select high-volume CTO operators. The rate of periprocedural major adverse cardiac events or death remained unchanged over time. These data suggest room for improvement in the selection and functional assessment of CTO lesions before subjecting patients to the increased procedural risk associated with CTO PCI.

Cardiology and Cardiovascular Research

Reshef E, **Sabbah HN**, and Nussinovitch U. Effects of protective controlled coronary reperfusion on left ventricular remodeling in dogs with acute myocardial infarction: A pilot study. *Cardiovasc Revasc Med* 2020; Epub ahead of print. PMID: 32417208. Full Text

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BACKGROUND: Coronary artery obstruction causes ischemia of cardiac tissue, leading to acute myocardial infarction (AMI). The treatment of choice for reducing acute myocardial ischemic injury is early, effective vascular reperfusion using thrombolytic therapy or primary percutaneous coronary intervention. However, reperfusion can cause cardiomyocyte injury. Currently, there is no effective therapy to prevent cardiac reperfusion-related tissue damage. This study evaluated whether Protective Controlled Coronary Reperfusion (PCCR), selectively delivered to ischemic tissue, is associated with decreased myocardial scarring, contractile deterioration and reperfusion-associated myocardial edema. METHODS: Three hours of cardiac ischemia was induced in 10 mongrel dogs, and followed by either 30-minute PCCR or sham treatment. Cardiac performance was evaluated 2, 4 and 6 months later. Trichrome staining was used to distinguish collagen from viable myocardial tissue and to evaluate mean scar area. RESULTS: One hour following reperfusion, PCCR significantly attenuated the relative increase (edema) in left ventricular end diastolic posterior wall thickness compared with sham treatment. At 6 months follow-up, the PCCR group showed a modest corrected increase in left ventricular ejection fraction (cΔLVEF) in comparison to the sham group where it deteriorated (2.3 ± 10.5% vs. -16.4 ± 10.3%, respectively, p = 0.043). Histomorphometric assessments of the hearts showed the PCCR group had smaller area of scarring, as compared to sham-treated animals (9.0 ± 2.4% vs. 14.0 ± 3.3%, p = 0.047). CONCLUSIONS: In this pilot study, PCCR reduced myocardial edema, modestly increased in cΔLVEF and resulted in a smaller scar area. Further studies are needed to fully ascertain the mechanisms that underlie the potential benefits of PCCR therapy prior to initiating clinical trials in human subjects with AMI.

Cardiology and Cardiovascular Research

Verma S, **Peterson EL**, **Liu B**, **Sabbah HN**, **Williams LK**, and **Lanfear DE**. Effectiveness of beta blockers in patients with and without a history of myocardial infarction. *Eur J Clin Pharmacol* 2020; Epub ahead of print. PMID: 32440720. Full Text

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PURPOSE: Studies demonstrating mortality benefit of beta blockers (BB) after myocardial infarction (MI) were conducted before the era of percutaneous intervention and widespread use of statins. Recent retrospective studies show inconsistent results regarding which subgroups of coronary artery disease (CAD) patients' benefit. Most studies did not account for medication changes over time. We evaluated the association of time-varying BB exposure with death in CAD patients with or without a history of MI. METHODS: This retrospective cohort study included all patients with MI and those with coronary disease but no MI at a single health care system who also had health insurance from January 1, 1997, to June 30, 2011. Pharmacy claims data were used to estimate BB exposure over 6-month rolling windows. The primary endpoint was all-cause death. The effect of BB exposure was tested using time-updated Cox proportional hazards models. RESULTS: We identified

6220 patients with MI and 21,285 patients with CAD but no MI. Among patients who suffered MI, BB exposure was associated with a 31% relative risk reduction in all-cause death (hazard ratio [HR] 0.69, P = 0.001). Among subjects who survived 3 years after MI, BB retained a protective association (HR 0.71, P = 0.001). Among CAD-only patients, BB exposure was also associated with risk reduction (HR 0.85, P = 0.001). CONCLUSION: Among patients with CAD, BB exposure is associated with reduced risk of death. The association is strongest among those who have suffered MI. This favorable association appears durable beyond 3 years.

Cardiology and Cardiovascular Research

Winchester DE, Osborne A, Peacock WF, Bhatt DL, Dehmer GJ, Diercks D, Masoudi FA, **McCord J**, Kontos M, and Levy PD. Closing Gaps in Essential Chest Pain Care Through Accreditation. *J Am Coll Cardiol* 2020; 75(19):2478-2482. PMID: 32408982. Full Text

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Center for Health Policy and Health Services Research

Clark-Sienkiewicz SM, **Hecht LM**, **Pester B**, **Martens K**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Racial Differences in Psychological Symptoms and Eating Behaviors Among Bariatric Surgery Candidates. *J Racial Ethn Health Disparities* 2020; Epub ahead of print. PMID: 32367444. Request Article

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BACKGROUND: Black patients typically lose less weight than White patients following bariatric surgery; however, the reasons for this racial disparity are unclear. The purpose of the current study was to evaluate whether there are differences in psychiatric symptoms and problematic eating behaviors between White and Black patients pursuing bariatric surgery as this may aid in understanding postsurgical weight loss disparities and inform psychosocial assessment of bariatric candidates. METHODS: A retrospective chart review was conducted of participants (N = 284) who completed a psychological evaluation prior to surgery. Information collected included history of binge eating and purging as well as data from measures administered (i.e., the Hospital Anxiety and Depression Scale, the Emotional Eating Scale, and the Yale Food Addiction Scale 2.0). RESULTS: White patients reported higher levels of eating in response to anger/frustration (p = .03) and eating in response to depression (p = .01) than Black patients. White patients also reported more symptoms of food addiction, a difference that was trending toward significance (p = .05). No significant differences were found on measures of anxiety or depression. CONCLUSION: White patients appear to have higher levels of presurgical problematic eating as compared with Black patients pursuing bariatric surgery; thus, these measurements of problematic eating may not explain the racial disparity in outcomes. However, future research should determine whether measures are valid among diverse populations and identify additional factors that may contribute to racial disparities in bariatric outcomes.

Center for Individualized and Genomic Medicine Research

Verma S, **Peterson EL**, **Liu B**, **Sabbah HN**, **Williams LK**, and **Lanfear DE**. Effectiveness of beta blockers in patients with and without a history of myocardial infarction. *Eur J Clin Pharmacol* 2020; Epub ahead of print. PMID: 32440720. Full Text

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PURPOSE: Studies demonstrating mortality benefit of beta blockers (BB) after myocardial infarction (MI) were conducted before the era of percutaneous intervention and widespread use of statins. Recent retrospective studies show inconsistent results regarding which subgroups of coronary artery disease (CAD) patients' benefit. Most studies did not account for medication changes over time. We evaluated the association of time-varying BB exposure with death in CAD patients with or without a history of MI. METHODS: This retrospective cohort study included all patients with MI and those with coronary disease but no MI at a single health care system who also had health insurance from January 1, 1997, to June 30, 2011. Pharmacy claims data were used to estimate BB exposure over 6-month rolling windows. The primary endpoint was all-cause death. The effect of BB exposure was tested using time-updated Cox proportional hazards models. RESULTS: We identified 6220 patients with MI and 21,285 patients with CAD but no MI. Among patients who suffered MI, BB exposure was associated with a 31% relative risk reduction in all-cause death (hazard ratio [HR] 0.69, P = 0.001). Among subjects who survived 3 years after MI, BB retained a protective association (HR 0.71, P = 0.001). Among CAD-only patients, BB exposure was also associated with risk reduction (HR 0.85, P = 0.001). CONCLUSION: Among patients with CAD, BB exposure is associated with reduced risk of death. The association is strongest among those who have suffered MI. This favorable association appears durable beyond 3 years.

Clinical Quality and Safety
Drake DH, De Bonis M, Covella M, Agricola E, Zangrillo A, **Zimmerman KG**, and Cobey FC. Echocardiography in Pandemic: Front-Line Perspective, Expanding Role of Ultrasound, and Ethics of Resource Allocation. *J Am Soc Echocardiogr* 2020; 33(6):683-689. PMID: Not assigned. Full Text

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The grave clinical context of the coronavirus disease 2019 (COVID-19) pandemic must be understood. Italy is immersed in the COVID-19 pandemic. Most of the world will soon follow. The United States currently has the most documented cases of COVID-19 of any nation. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)–associated acute cardiomyopathy is common in critical care patients and is associated with a high mortality rate. Patients with COVID-19 frequently require mechanical support for adequate oxygenation. A severe shortfall of ventilators is predicted. Of equal concern is the projected shortage of trained professionals required to care for patients on mechanical ventilation. Ultrasonography is proving to be a valuable tool for identifying the pulmonary manifestations and progression of COVID-19. Lung ultrasound also facilitates successful weaning from mechanical ventilation. Ultrasonography of the lung, pleura, and diaphragm are easily mastered by experienced echocardiographers. Echocardiography has an established role for optimal fluid management and recognition of cardiac disease, including SARS-CoV-2-associated acute cardiomyopathy. Cardiologists, anesthesiologists, sonographers, and all providers should be prepared to commit their full spectrum of skills to mitigate the consequences of the pandemic. We should also be prepared to collaborate and cross-train to expand professional services as necessary. During a declared health care crisis, providers must be familiar with the ethical principles, organizational structure, practical application, and gravity of limited resource allocation.

Dermatology
Fatima S, **D'Sa H**, **Chaffins ML**, **Menon M**, and **Friedman BJ**. An elderly male with a chronic rash on the right foot. *Indian J Dermatol* 2020; 65(3):222-224. PMID: Not assigned. Full Text

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Dermatology
Gold LS, Bhatia N, Tallman AM, and Rubenstein DS. A Phase IIb, Randomized Clinical Trial of Tapinarof Cream for the Treatment of Plaque Psoriasis: Secondary Efficacy and Patient-Reported Outcomes. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32446832. Request Article

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BACKGROUND: Tapinarof cream is a topical therapeutic aryl hydrocarbon receptor modulating agent (TAMA) under investigation for treatment of psoriasis and atopic dermatitis. METHODS: In a phase IIb, double-blind, vehicle-controlled study, adults with plaque psoriasis were randomized to tapinarof cream 0.5% or 1% once (QD) or twice daily (BID) or vehicle QD or BID for 12 weeks with 4-week follow-up. Efficacy outcomes included Physician Global Assessment (PGA) scores, change in PGA and total target lesion grading scores, and proportion of subjects achieving ≥50%, ≥75%, and ≥90% reductions in Psoriasis Area and Severity Index scores from baseline (PASI50, 75, and 90). RESULTS: At week 12, improvements were

observed in all tapinarof groups versus vehicle in PGA response, change in PGA and total target lesion grading scores, PASI50 (71-92% versus 10-32%), PASI75 (46-65% versus 5-16%), and PASI90 (18-40% versus 0%); all differences were statistically significant with tapinarof 1%QD. Tapinarof responses were apparent from week 2, with significant efficacy at week 8 maintained through week 16. Most adverse events were mild or moderate. LIMITATIONS: Analyses reported require confirmation in larger prospective studies. CONCLUSIONS: Tapinarof may represent an important advance in the development of topical medicines for treatment of psoriasis.

Dermatology
Gold LS, Hansen JB, Patel D, Veverka KA, and Strober B. PGAxBSA composite versus PASI: Comparison across disease severities and as therapeutic response measure for Cal/BD foam in plaque psoriasis. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32430142. Full Text

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BACKGROUND: The product of the Physician Global Assessment and body surface area (PGA×BSA) is simpler to use than the Psoriasis Area and Severity Index (PASI), which lacks sensitivity in patients with mild psoriasis. OBJECTIVE: To compare the PGA×BSA versus the modified PASI (mPASI) for assessing disease severity and therapeutic response to calcipotriol/betamethasone dipropionate (Cal/BD) foam. METHODS: This post hoc analysis evaluated the efficacy of Cal/BD foam in mild, moderate, and severe psoriasis, as assessed by the PGA×BSA and mPASI, using data from 3 randomized controlled trials (NCT01536886, NCT01866163, NCT02132936). Spearman correlation and Bland-Altman plots were used to compare the PGA×BSA with the mPASI. RESULTS: Proportions of patients receiving Cal/BD foam achieving 75% response for PGA×BSA and mPASI at weeks 1, 2, and 4 were similar and significantly greater than with vehicle ($P \leq .002$ at all timepoints); at week 4, mean improvements were 51.0% and 50.7%, respectively. Spearman correlations for mild, moderate, and severe psoriasis were moderate to high between PGA×BSA and mPASI at baseline ($r = .51$, .72, and .86, respectively; $n = 126$, 465, and 58, respectively) and high at week 4 ($r = .80$, .81, and .89, respectively; $n = 121$, 452, and 58, respectively) ($P < .001$). LIMITATIONS: Pooled data from different trials were not prespecified for post hoc analysis. Interrater reliability was not assessed. CONCLUSION: Pooled data analysis showed that the PGA×BSA and mPASI correlation was higher with increasing psoriasis severity.

Dermatology
Huang L, **Li GH**, **Yu Q**, **Xu Y**, **Cvetkovski S**, **Wang X**, **Parajuli N**, **Udo-Inyang I**, Kaplan D, **Zhou L**, Yao Z, and **Mi QS**. Smad2/4 Signaling Pathway Is Critical for Epidermal Langerhans Cell Repopulation Under Inflammatory Condition but Not Required for Their Homeostasis at Steady State. *Front Immunol* 2020; 11:912. PMID: 32457763. Full Text

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Epidermal Langerhans cells (LCs) are skin-resident dendritic cells that are essential for the induction of skin immunity and tolerance. Transforming growth factor-β 1 (TGFβ1) is a crucial factor for LC maintenance and function. However, the underlying TGFβ1 signaling pathways remain unclear. Our previous research has shown that the TGFβ1/Smad3 signaling pathway does not impact LC homeostasis and maturation. In this study, we generated mice with conditional deletions of either individual Smad2, Smad4, or both Smad2 and Smad4 in the LC lineage or myeloid lineage, to further explore the impact of TGFβ1/Smad signaling pathways on LCs. We found that interruption of Smad2 or Smad4 individually or simultaneously in the LC lineage did not significantly impact the maintenance, maturation, antigen uptake, and migration of LCs in vivo or in vitro during steady state. However, the interruption of both Smad2 and Smad4 pathways in the myeloid lineage led to a dramatic inhibition of bone marrow-derived LCs in the inflammatory state. Overall, our data suggest that canonical TGFβ1/Smad2/4 signaling pathways are dispensable for epidermal LC homeostasis and maturation at steady state, but are critical for the long-term LC repopulation directly originating from the bone marrow in the inflammatory state.

Dermatology
Luther CA, **Griffith JL**, **Kurland E**, Al Shabeeb R, Eleryan M, Redbord K, and **Ozog DM**. The Infection Rate of Intralesional Triamcinolone and The Safety of Compounding in Dermatology for Intradermal and Subcutaneous Injection: A Retrospective Chart Review. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32442698. Full Text

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BACKGROUND: Intralesional injection of sterile medications remains a mainstay in dermatology, enabling a tailored, low-cost, in-office therapy. Following the 2012 United States outbreak of fungal meningitis from contaminated intrathecally administered corticosteroids, there has been increased regulation of in-office compounding, regardless of administration route. Studies demonstrating the safety data of in-office corticosteroid compounding for intradermal or subcutaneous use are lacking. OBJECTIVE: To assess the incidence of infection caused by compounded in-office intralesional triamcinolone. METHODS: A retrospective chart review identified subjects that received in-office intralesional corticosteroid injections in 2016. Medical documentation within 30 days of injection was reviewed for suspected infection. RESULTS: Charts of 4370 intralesional triamcinolone injections were assessed, 2780/4370 (64%) being compounded triamcinolone with bacteriostatic saline. Eleven suspected localized infections (0.25%) were identified, with 4/11 in the compounding cohort. Of these, 7/11 occurred after injection of an "inflamed cyst." No hospitalizations or deaths occurred. No temporal/locational relationships were identified. LIMITATIONS: This study was limited to two academic institutions. A 30-day post injection time frame of was used. CONCLUSION: In-office compounding for intralesional dermal and subcutaneous administration is safe when sterile products are used by medical practitioners. There is no increased risk of compounded triamcinolone relative to non-compounded triamcinolone.

Dermatology
Nguyen TV, Damiani G, Orenstein LAV, **Hamzavi I**, and Jemec G. Hidradenitis Suppurativa: An Update on Epidemiology, Phenotypes, Diagnosis, Pathogenesis, Comorbidities and Quality of Life. *J Eur Acad Dermatol Venereol* 2020; Epub ahead of print. PMID: 32460374. Full Text

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that severely impairs patients' quality of life. It is characterized by recurrent painful nodules, abscesses and draining sinus tracts in primarily intertriginous areas. We aimed to review the most up-to-date information regarding the epidemiology, clinical presentation, diagnostic studies, pathogenesis, comorbidities, and quality of life of patients with hidradenitis suppurativa. We performed a systematic search of Medline, Embase database (from inception to September 2019) and review of bibliographies without restrictions on year or language. HS has an estimated global prevalence of 0.00033%-4.1% (but most likely 0.7-1.2% in the European-US population). Patients still experience a significant diagnostic delay, up to several years. In the absence of pathognomonic tests, the diagnosis of HS is made from clinical observation and the disease narrative. Phenotypic variation renders diagnosis and severity assessment difficult. Ultrasound imaging is an emerging assessment tool for deep-seated lesions. The Hurley Staging System is still widely used in severity rating. Follicular hyperkeratosis and dilatation, follicular rupture, and chronic inflammation with architectural tissue changes have been implicated in the pathogenesis of HS. HS has been associated with metabolic syndrome and other risk factors for cardiovascular disease, diabetes mellitus type II, polycystic ovarian syndrome, depression, suicide, and substance use disorders. It has been linked to other immune-mediated diseases such as inflammatory bowel disease and spondyloarthropathy. Pain, pruritus, malodor, low self-esteem, sleep and sexual dysfunctions, and poor mental health are chronic symptoms or consequences of uncontrolled disease. HS is an under-diagnosed and under-treated disease with a profound negative impact on patients' quality of life. In light of its associated comorbidities, an interdisciplinary management approach may be needed to ensure the best outcomes.

Dermatology
Orenstein LAV, Nguyen TV, Damiani G, Sayed C, Jemec GBE, and **Hamzavi I**. Medical and Surgical Management of Hidradenitis Suppurativa: A Review of International Treatment Guidelines and Implementation in General Dermatology Practice. *Dermatology* 2020; Epub ahead of print. PMID: 32408306. Full Text

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BACKGROUND: Hidradenitis suppurativa (HS) is a chronic painful skin disease that severely impairs patients' quality of life. While high-quality trials of HS therapies remain limited, medical knowledge of best treatment practices is rapidly evolving, leading to the recent publication of multiple international treatment guidelines for HS. SUMMARY: This review compares international HS treatment guidelines, describes evidence for effectiveness of common and emerging HS therapies, and provides guidance for integrating evidence-based HS care into practice. Although over 50 medical and procedural treatments are mentioned across international HS guidelines, only adalimumab and infliximab have grade B/weak recommendation or higher across all major guidelines. This review describes the appropriate patient selection and effectiveness of the most commonly used medical and procedural treatments for HS. It also includes recommendations for counseling, dosing, and duration of medical therapies as well as procedure videos for the practicing dermatologist.

Dermatology
Oska S, **Zarbo A**, **Yeager D**, **Friedman BJ**, and **Shwayder T**. Melanoma arising in a patient with ataxia-telangiectasia: A call for full skin examinations in this patient population. *Pediatr Dermatol* 2020; Epub ahead of print. PMID: 32413934. Full Text

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Ataxia-telangiectasia (A-T) is an autosomal recessive, multisystem disorder characterized by cerebellar ataxia and oculocutaneous telangiectasias that present in early childhood. Increased incidence of malignancy is also associated with A-T. Hematopoietic malignancies occur most commonly, with a majority being lymphoid cancers; however, there is a risk for other malignancies, such as breast, gastric, and other solid tumors. Herein, we report the case of a 28-year-old woman with A-T with melanoma.

Dermatology
Ozog D, **Parks-Miller A**, **Kohli I**, **Lyons AB**, **Narla S**, **Torres AE**, **Levesque M**, **Lim HW**, and **Hamzavi IH**. The Importance of Fit-Testing in Decontamination of N95 Respirators: A Cautionary Note. *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32389714. Full Text

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Dermatology
Richard EG, and **Lim HW**. In Memoriam. *Photodermatol Photoimmunol Photomed* 2020; 36(3):171. PMID: 32401395. Full Text

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Dermatology
Torres AE, **Lyons AB**, **Narla S**, **Kohli I**, **Parks-Miller A**, **Ozog D**, **Hamzavi IH**, and **Lim HW**. Ultraviolet-C and other methods of decontamination of filtering facepiece N-95 respirators during the COVID-19 pandemic. *Photochem Photobiol Sci* 2020; Epub ahead of print. PMID: 32412033. Request Article

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During global health emergencies such as the current COVID-19 pandemic, the decontamination of single-use personal protective equipment (PPE) becomes a necessary means to keep up with the growing demand from healthcare workers and patients alike. Many unverified methods are being considered, which can pose the risk of incomplete decontamination and lead to catastrophic results. Several factors come into play when determining the suitability of such methods including the quality of the decontamination technique, the targeted pathogen, cost, ease of installation and use, rate of sterilization, and the surface or material to be sterilized. The germicidal properties of ultraviolet-C are well known. This review will cover the most commonly described methods for the sterilization of N95 respirators, namely, ultraviolet germicidal irradiation, hydrogen peroxide vaporization, microwave-generated steaming, and dry heating. These techniques have been tested previously and

have demonstrated efficacy in reducing or inactivating viral and bacterial pathogens, although testing against SARS-CoV-2 specifically has not been done. Moreover, it must be emphasized that proper disposal after a single use is still ideal under normal circumstances.

Dermatology
Torres AE, **Ozog DM**, **Hamzavi IH**, and **Lim HW**. Notes and Comments on "Proposed Approach for Re-using Surgical Masks in COVID-19 Pandemic". *J Am Acad Dermatol* 2020; Epub ahead of print. PMID: 32446829. Full Text

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Diagnostic Radiology
Dehghani A, **Soltanian-Zadeh H**, and Hossein-Zadeh GA. Global Data-Driven Analysis of Brain Connectivity during Emotion Regulation by EEG Neurofeedback. *Brain Connect* 2020; Epub ahead of print. PMID: 32458692. Request Article

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BACKGROUND: Emotion regulation by neurofeedback involves interactions among multiple brain regions, including prefrontal cortex and subcortical regions in the limbic system. Previous studies focused on connections of specific brain regions like amygdala with other brain regions. New method: EEG neurofeedback is used to upregulate positive emotion through induced happiness by retrieving positive autobiographical memories and fMRI data acquired simultaneously. A global data-driven approach, group independent component analysis (ICA), is applied to fMRI data and functional network connectivity is estimated. This study discovers all connections among independent components involved in emotion regulation. RESULTS: The proposed approach identified all functional networks engaged in positive autobiographical memories and evaluated effects of neurofeedback. The results revealed two pairs of networks with significantly different functional connectivity among emotion regulation blocks (relative to other blocks of experiment) and between experimental and control groups (FDR-corrected for multiple comparisons, q=0.05). Functional network connectivity distribution (FNCD) showed significant connectivity differences between neurofeedback blocks and other blocks, revealing more synchronized brain networks during neurofeedback. During emotion regulation, significant functional connectivity changes were found in and between prefrontal, parietal, temporal, occipital, and limbic networks. Comparison with existing methods: While the results are consistent with those of previous model based studies, some of the connections found in this study were not found previously. These connections are between a) occipital (fusiform, cuneus, middle occipital, and lingual gyrus) and other regions including limbic system/sub-lobar (thalamus, hippocampus, amygdala, caudate, putamen, insula, and ventral striatum), prefrontal/frontal cortex (DLPFC, VLPFC, and OFC), inferior parietal, middle temporal gyrus and b) PCC and hippocampus. CONCLUSIONS: Using fMRI during EEG neurofeedback, this study provided a global insight to brain connectivity for emotion regulation. The brain networks interactions may be used to develop connectivity-based neurofeedback methods and alternative therapeutic approaches, which may be more effective than the traditional activity-based neurofeedback methods.

Diagnostic Radiology
Kaur J, **Davoodi-Bojd E**, **Fahmy LM**, **Zhang L**, **Ding G**, Hu J, **Zhang Z**, **Chopp M**, and **Jiang Q**. Magnetic Resonance Imaging and Modeling of the Glymphatic System. *Diagnostics (Basel)* 2020; 10(6). PMID: 32471025. Full Text

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The glymphatic system is a newly discovered waste drainage pathway in the brain; it plays an important role in many neurological diseases. Ongoing research utilizing various cerebrospinal fluid tracer infusions, either directly or indirectly into the brain parenchyma, is investigating clearance pathways by using distinct imaging techniques. In the present review, we discuss the role of the glymphatic system in various neurological diseases and efflux pathways of brain waste clearance based on current evidence and controversies. We mainly focus on new magnetic resonance imaging (MRI) modeling techniques, along with traditional computational modeling, for a better understanding of the glymphatic system function. Future sophisticated modeling techniques hold the potential to generate quantitative maps for glymphatic system parameters that

could contribute to the diagnosis, monitoring, and prognosis of neurological diseases. The non-invasive nature of MRI may provide a safe and effective way to translate glymphatic system measurements from bench-to-bedside.

Diagnostic Radiology
Mahan MC, **Yu CC**, **Shields R**, **van Holsbeeck M**, and Zaltz I. Impingement-Free Hip Flexion in Asymptomatic Young Adult Women. *J Bone Joint Surg Am* 2020; Epub ahead of print. PMID: 32453117. Full Text

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BACKGROUND: Ultrasound-assisted measurement of hip flexion has demonstrated that hip flexion has been historically overestimated in men. To our knowledge, assessment of hip flexion in women using similar methods has not been reported. Establishing normative values for hip flexion is vital to aid diagnosis, management, and future research. Therefore, we asked 2 questions: (1) At what range of midsagittal hip flexion do soft-tissue impingement and femoroacetabular abutment occur in asymptomatic young adult women? (2) Do radiographic findings on a supine anteroposterior pelvic radiograph correlate with ultrasound-assisted measurements of hip flexion? METHODS: Fifty-five asymptomatic adult women volunteers (107 hips) underwent ultrasound-assisted assessment of hip flexion. Hip flexion was recorded at the initiation of labral contact and at bone-on-bone contact. Recorded motion was correlated with common radiographic measurements of hip morphology as observed on a supine anteroposterior pelvic radiograph. RESULTS: The mean age of the subjects was 26 ± 3 years (range, 21 to 35 years), and the mean body mass index was 23 ± 3 kg/m (range, 17 to 31.6 kg/m). Mean impingement-free and maximum midsagittal passive flexion were 72° ± 8° (95% confidence interval [CI], 70° to 74°) and 101° ± 11° (95% CI, 99° to 103°), respectively. There were no significant correlations between radiographic measurements of hip morphology and ultrasound-measured hip range of motion. CONCLUSIONS: Observed hip flexion in the asymptomatic hips of young women is substantially less than has been historically reported. Morphologic features that are measurable on anteroposterior pelvic radiographs do not correlate with ultrasound-measured hip flexion. Diagnosis of hip disorders and treatments that are designed to alter hip range of motion should be based on normative data. Future studies regarding surgical restoration and/or preservation of hip flexion should be based on an understanding of normal hip range of motion. CLINICAL RELEVANCE: Ultrasound-assisted hip flexion measurement established normative values to guide surgical restoration and/or preservation of hip flexion.

Diagnostic Radiology
Mallon S, **Patel S**, Wright J, and **Griffith B**. Ectopic parathyroid adenoma in the pyriform sinus: Case report. *Applied Radiology* 2020; 49(3):48J-48L. PMID: Not assigned. Request Article

Diagnostic Radiology
Poyiadji N, **Cormier P**, **Patel PY**, **Hadied MO**, **Bhargava P**, **Khanna K**, **Nadig J**, **Keimig T**, **Spizarny D**, **Reeser N**, **Klochko C**, **Peterson EL**, and **Song T**. Acute Pulmonary Embolism and COVID-19. *Radiology* 2020; Epub ahead of print. PMID: 32407256. Full Text

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Diagnostic Radiology
Sisodiya SM, Whelan CD, Hatton SN, Huynh K, Altmann A, Ryten M, Vezzani A, Caligiuri ME, Labate A, Gambardella A, Ives-Deliperi V, Meletti S, Munsell BC, Bonilha L, Tondelli M, Rebsamen M, Rummel C, Vaudano AE, Wiest R, Balachandra AR, Bargalló N, Bartolini E, Bernasconi A, Bernasconi N, Bernhardt B, Caldairou B, Carr SJA, Cavalleri GL, Cendes F, Concha L, Desmond PM, Domin M, Duncan JS, Focke NK, Guerrini R, Hamandi K, Jackson GD, Jahanshad N, Kälviäinen R, Keller SS, Kochunov P, Kowalczyk MA, Kreilkamp BAK, Kwan P, Lariviere S, Lenge M, Lopez SM, Martin P, Mascalchi M, Moreira JCV, Morita-Sherman ME, Pardoe HR, Pariente JC, Raviteja K, Rocha CS, Rodríguez-Cruces R, Seeck M, Semmelroch M, Sinclair B, **Soltanian-Zadeh H**, Stein DJ, Striano P, Taylor PN, Thomas RH, Thomopoulos SI, Velakoulis D, Vivash L, Weber B, Yasuda CL, Zhang J, Thompson PM, and McDonald CR. The ENIGMA-Epilepsy working group: Mapping disease from large data sets. *Hum Brain Mapp* 2020; Epub ahead of print. PMID: 32468614. Full Text

Epilepsy is a common and serious neurological disorder, with many different constituent conditions characterized by their electro clinical, imaging, and genetic features. MRI has been fundamental in advancing our understanding of brain processes in the epilepsies. Smaller-scale studies have identified many interesting imaging phenomena, with implications both for understanding pathophysiology and improving clinical care. Through the infrastructure and concepts now well-established by the ENIGMA Consortium, ENIGMA-Epilepsy was established to strengthen epilepsy neuroscience by greatly increasing sample sizes, leveraging ideas and methods established in other ENIGMA projects, and generating a body of collaborating scientists and clinicians to drive forward robust research. Here we review published, current, and future projects, that include

structural MRI, diffusion tensor imaging (DTI), and resting state functional MRI (rsfMRI), and that employ advanced methods including structural covariance, and event-based modeling analysis. We explore age of onset- and duration-related features, as well as phenomena-specific work focusing on particular epilepsy syndromes or phenotypes, multimodal analyses focused on understanding the biology of disease progression, and deep learning approaches. We encourage groups who may be interested in participating to make contact to further grow and develop ENIGMA-Epilepsy.

Diagnostic Radiology

Zong W, **Lee JK**, **Liu C**, **Carver EN**, **Feldman AM**, **Janic B**, **Elshaikh MA**, **Pantelic MV**, **Hearshen D**, **Chetty IJ**, **Movsas B**, and **Wen N**. A Deep Dive into Understanding Tumor Foci Classification using Multiparametric MRI Based on Convolutional Neural Network. *Med Phys* 2020; Epub ahead of print. PMID: 32449176. Full Text

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PURPOSE: Deep learning models have had a great success in disease classifications using large data pools of skin cancer images or lung X-rays. However, data scarcity has been the roadblock of applying deep learning models directly on prostate multiparametric MRI (mpMRI). Although model interpretation has been heavily studied for natural images for the past few years, there has been a lack of interpretation of deep learning models trained on medical images. In this paper, an efficient convolutional neural network (CNN) was developed and the model interpretation at various convolutional layers was systematically analyzed to improve the understanding of how CNN interprets multimodality medical images and the predictive powers of features at each layer. The problem of small sample size was addressed by feeding the intermediate features into a traditional classification algorithm known as weighted extreme learning machine (wELM), with imbalanced distribution among output categories taken into consideration. METHODS: The training data collection used a retrospective set of prostate MR studies, from SPIE-AAPM-NCI PROSTATEx Challenges held in 2017. Three hundred twenty biopsy samples of lesions from 201 prostate cancer patients were diagnosed and identified as clinically significant (malignant) or not significant (benign). All studies included T2-weighted (T2W), proton density-weighted (PD-W), dynamic contrast enhanced (DCE) and diffusion-weighted (DW) imaging. After registration and lesion-based normalization, a CNN with four convolutional layers were developed and trained on 10-fold cross validation. The features from intermediate layers were then extracted as input to wELM to test the discriminative power of each individual layer. The best performing model from the 10 folds was chosen to be tested on the holdout cohort from two sources. Feature maps after each convolutional layer were then visualized to monitor the trend, as the layer propagated. Scatter plotting was used to visualize the transformation of data distribution. Finally, a class activation map was generated to highlight the region of interest based on the model perspective. RESULTS: Experimental trials indicated that the best input for CNN was a modality combination of T2W, apparent diffusion coefficient (ADC) and DWIb50. The convolutional features from CNN paired with a weighted extreme learning classifier showed substantial performance compared to a CNN end-to-end training model. The feature map visualization reveals similar findings on natural images where lower layers tend to learn lower level features such as edges, intensity changes, etc, while higher layers learn more abstract and task-related concept such as the lesion region. The generated saliency map revealed that the model was able to focus on the region of interest where the lesion resided and filter out background information, including prostate boundary, rectum, etc. CONCLUSIONS: This work designs a customized workflow for the small and imbalanced data set of prostate mpMRI where features were extracted from a deep learning model and then analyzed by a traditional machine learning classifier. In addition, this work contributes to revealing how deep learning models interpret mpMRI for prostate cancer patients stratification.

Emergency Medicine

Doyle MP, **McCarty JP**, and **Lazzara AA**. Case Study of Phrenic Nerve Paralysis: "I Can't Breathe!". *J Emerg Med* 2020; Epub ahead of print. PMID: 32354588. Full Text

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BACKGROUND: The anatomic course of the phrenic nerve runs in the fascia covering the anterior scalene muscle. Interscalene blocks are commonly performed by an anesthesiologist for shoulder surgery, such as a rotator cuff repair, total shoulder replacement, humeral fracture, or other arm surgery. Phrenic nerve palsy or paralysis is a known complication from interscalene block and is covered in multiple case reports and series in both Anesthesia and Neurosurgical literature, but only one case report in the Emergency Medicine literature. CASE REPORT: This case involves a 57-year-old man who had an uncomplicated arthroscopic rotator cuff repair with placement of interscalene block under care of anesthesia. He was discharged with a pain pump in place and then subsequently presented to the Emergency Department (ED) later that same day for evaluation of dyspnea. Using point-of-care ultrasound, his right diaphragm did not appear to be moving. Chest x-ray study revealed an elevated right hemidiaphragm. He was diagnosed with iatrogenic right phrenic nerve paralysis from interscalene block. WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?: Emergent diagnosis of phrenic nerve paralysis in the ED is complicated by a distressed patient and need for quick intervention. Most formal tests for this diagnosis are not immediately available to emergency physicians. Ultrasound is a rapid and reproducible, noninvasive

resource with high sensitivity and specificity, making it an ideal imaging modality for the emergent evaluation of possible phrenic nerve palsy or paralysis.

Emergency Medicine

Fadel R, **Morrison AR**, **Vahia A**, **Smith ZR**, **Chaudhry Z**, **Bhargava P**, **Miller J**, **Kenney RM**, **Alangaden G**, and **Ramesh MS**. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32427279. Full Text

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BACKGROUND: There is no proven antiviral or immunomodulatory therapy for COVID-19. The disease progression associated with the pro-inflammatory host response prompted us to examine the role of early corticosteroid therapy in patients with moderate to severe COVID-19. METHODS: We conducted a single pre-test, single post-test quasi-experiment in a multi-center health system in Michigan from March 12 to March 27, 2020. Adult patients with confirmed moderate to severe COVID were included. A protocol was implemented on March 20, 2020 using early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days. Outcomes of standard of care (SOC) and early corticosteroid groups were evaluated, with a primary composite endpoint of escalation of care from ward to ICU, new requirement for mechanical ventilation, and mortality. All patients had at least 14 days of follow-up. RESULTS: We analyzed 213 eligible subjects, 81 (38%) and 132 (62%) in SOC and early corticosteroid groups, respectively.The composite endpoint occurred at a significantly lower rate in the early corticosteroid group (34.9% vs. 54.3%, p=0.005). This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (8 vs. 5 days, $p < 0.001$). Multivariate regression analysis demonstrated an independent reduction in the composite endpoint at 14-days controlling for other factors (aOR: 0.41; 95% CI [0.22 - 0.77]). CONCLUSION: An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.

Emergency Medicine

Kalayci A, Peacock WF, Nagurney JT, Hollander JE, Levy PD, Singer AJ, Shapiro NI, Cheng RK, Cannon CM, Blomkalns AL, Walters EL, Christenson RH, Chen-Tournoux A, **Nowak RM**, Lurie MD, Pang PS, Kastner P, Masson S, Gibson CM, Gaggin HK, and Januzzi JL, Jr. Echocardiographic assessment of insulin-like growth factor binding protein-7 and early identification of acute heart failure. *ESC Heart Fail* 2020; Epub ahead of print. PMID: 32406612. Full Text

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Department of Pathology, University of Maryland School of Medicine, Baltimore, MD, USA.
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Department of Emergency Medicine, Henry Ford Health System, Detroit, MI, USA.
Division of Cardiology, Torrance Memorial Medical Center, Torrance, CA, USA.
Department of Emergency Medicine, Indiana University School of Medicine & Indianapolis EMS, Indianapolis, Indiana, USA.
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AIMS: Concentrations of insulin-like growth factor binding protein-7 (IGFBP7) have been linked to abnormal cardiac structure and function in patients with chronic heart failure (HF), but cardiovascular correlates of the biomarker in patients with more acute presentations are lacking. We aimed to determine the relationship between IGFBP7 concentrations and cardiac

structure and to evaluate the impact of IGFBP7 on the diagnosis of acute HF among patients with acute dyspnoea. METHODS AND RESULTS: In this pre-specified subgroup analysis of the International Collaborative of N-terminal pro-B-type Natriuretic Peptide Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department (ICON-RELOADED) study, we included 271 patients with and without acute HF. All patients presented to an emergency department with acute dyspnoea, had blood samples for IGFBP7 measurement, and detailed echocardiographic evaluation. Higher IGFBP7 concentrations were associated with numerous cardiac abnormalities, including increased left atrial volume index (LAVi; r = 0.49, P < 0.001), lower left ventricular ejection fraction (r = -0.27, P < 0.001), lower right ventricular fractional area change (r = -0.31, P < 0.001), and higher tissue Doppler E/e' ratio (r = 0.44, P < 0.001). In multivariable linear regression analyses, increased LAVi (P = 0.01), lower estimated glomerular filtration rate (P = 0.008), higher body mass index (P = 0.001), diabetes (P = 0.009), and higher concentrations of amino-terminal pro-B-type natriuretic peptide (NT-proBNP, P = 0.02) were independently associated with higher IGFBP7 concentrations regardless of other variables. Furthermore, IGFBP7 (odds ratio = 12.08, 95% confidence interval 2.42-60.15, P = 0.02) was found to be independently associated with the diagnosis of acute HF in the multivariable logistic regression analysis. CONCLUSIONS: Among acute dyspnoeic patients with and without acute HF, increased IGFBP7 concentrations are associated with a range of cardiac structure and function abnormalities. Independent association with increased LAVi suggests elevated left ventricular filling pressure is an important trigger for IGFBP7 expression and release. IGFBP7 may enhance the diagnosis of acute HF.

Emergency Medicine

Townsend SR, **Rivers EP**, and Duseja R. CMS Measure Stewards' Assessment of the Infectious Diseases Society of America's Position Paper on SEP-1. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32374387. Full Text

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The Infectious Diseases Society of America has not met their burden of proof to establish that SEP-1 has increased unnecessary antibiotic usage. Strategies recommending delay in antibiotic administration for additional diagnostics in severe sepsis have not been shown to be safe.

Endrocrinology and Metabolism

Agarwal S, Kanapka LG, Raymond JK, Walker A, Gerard-Gonzalez A, **Kruger D**, Redondo MJ, Rickels MR, Shah VN, Butler A, Gonzalez J, Verdejo AS, Gal RL, Willi S, and Long JA. Racial-Ethnic Inequity in Young Adults with Type 1 Diabetes. *J Clin Endocrinol Metab* 2020; Epub ahead of print. PMID: 32382736. Full Text

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CONTEXT: Minority young adults (YA) currently represent the largest growing population with type 1 diabetes (T1D) and experience very poor outcomes. Modifiable drivers of disparities need to be identified, but are not well-studied. OBJECTIVE: To describe racial-ethnic disparities among YA with T1D, and identify drivers of glycemic disparity other than socioeconomic status (SES). DESIGN: Cross-sectional multi-center collection of patient and chart-reported variables, including SES, social determinants of health, and diabetes-specific factors, with comparison between White, Black, and Hispanic YA and multi-level modeling to identify variables that account for glycemic disparity apart from SES. SETTING: Six diabetes centers across the U.S. PARTICIPANTS: 300 YA with T1D (18-28 yrs: 33% Non-Hispanic White, 32% Non-Hispanic Black, and 34% Hispanic). MAIN OUTCOME: Racial-ethnic disparity in HbA1c levels. RESULTS: Black and Hispanic YA had lower SES, higher HbA1c levels, and much lower diabetes technology use than White YA (p<0.001). Black YA differed from Hispanic, reporting higher diabetes distress and lower self-management (p<0.001). After accounting for SES, differences in HbA1c levels disappeared between White and Hispanic YA, while they remained for Black YA (+ 2.26% [24 mmol/mol], p<0.001). Diabetes technology use, diabetes distress, and disease self-management accounted for a significant portion of the remaining Black-White glycemic disparity. CONCLUSION: This study demonstrated large racial-ethnic inequity in YA with T1D, especially among

Black participants. Our findings reveal key opportunities for clinicians to potentially mitigate glycemic disparity in minority YA by promoting diabetes technology use, connecting with social programs, and tailoring support for disease self-management and diabetes distress to promote resilience.

Endrocrinology and Metabolism
Agarwal S, Kanapka LG, Raymond JK, Walker A, Gerard-Gonzalez A, **Kruger D**, Redondo MJ, Rickels MR, Shah VN, Butler A, Gonzalez J, Verdejo AS, Gal RL, Willi S, and Long JA. Racial-Ethnic Inequity in Young Adults with Type 1 Diabetes. *J Clin Endocrinol Metab* 2020; Epub ahead of print. PMID: 32382736. Full Text

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CONTEXT: Minority young adults (YA) currently represent the largest growing population with type 1 diabetes (T1D) and experience very poor outcomes. Modifiable drivers of disparities need to be identified, but are not well-studied. OBJECTIVE: To describe racial-ethnic disparities among YA with T1D, and identify drivers of glycemic disparity other than socioeconomic status (SES). DESIGN: Cross-sectional multi-center collection of patient and chart-reported variables, including SES, social determinants of health, and diabetes-specific factors, with comparison between White, Black, and Hispanic YA and multi-level modeling to identify variables that account for glycemic disparity apart from SES. SETTING: Six diabetes centers across the U.S. PARTICIPANTS: 300 YA with T1D (18-28 yrs: 33% Non-Hispanic White, 32% Non-Hispanic Black, and 34% Hispanic). MAIN OUTCOME: Racial-ethnic disparity in HbA1c levels. RESULTS: Black and Hispanic YA had lower SES, higher HbA1c levels, and much lower diabetes technology use than White YA ($p<0.001$). Black YA differed from Hispanic, reporting higher diabetes distress and lower self-management ($p<0.001$). After accounting for SES, differences in HbA1c levels disappeared between White and Hispanic YA, while they remained for Black YA (+ 2.26% [24 mmol/mol], $p<0.001$). Diabetes technology use, diabetes distress, and disease self-management accounted for a significant portion of the remaining Black-White glycemic disparity. CONCLUSION: This study demonstrated large racial-ethnic inequity in YA with T1D, especially among Black participants. Our findings reveal key opportunities for clinicians to potentially mitigate glycemic disparity in minority YA by promoting diabetes technology use, connecting with social programs, and tailoring support for disease self-management and diabetes distress to promote resilience.

Endrocrinology and Metabolism
Rao SD, **Miragaya J**, **Parikh N**, **Honasoge M**, **Springer K**, **Van Harn M**, and **Divine GW**. Effect of vitamin D nutrition on disease indices in patients with primary hyperparathyroidism. *J Steroid Biochem Mol Biol* 2020; 201. PMID: 32407867. Request Article

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In patients with primary hyperparathyroidism, the size of the adenoma is a major determinant of biochemical indices, disease severity, and manner of presentation. However, the large variation in adenoma weight, both within and between populations and a steady decline in parathyroid adenoma weights over time remain largely unexplained. Based on the results in a small number of patients almost two decades ago we proposed that vitamin D nutritional status of the patient explains both the disease manifestations and much of the variation in adenoma size. Accordingly, we examined the relationship between vitamin D nutrition, as assessed by serum levels of 25-hydroxyvitamin D, and parathyroid gland weight, the best available index of disease severity, in a large number of patients ($n = 440$) with primary hyperparathyroidism. A significant inverse relationship was found between serum 25-hydroxyvitamin D level and log adenoma weight ($r = -0.361$; $p < 0.001$). Also, the adenoma

weight was significantly related directly to serum PTH, calcium, and alkaline phosphatase as dependent variables. In patients with vitamin D deficiency (defined as serum 25-hydroxyvitamin D levels 15 ng/mL or lower), gland weight, PTH, AP, and adjusted calcium were each significantly higher than in patients with 25-hydroxyvitamin D levels of 16 ng/mL or higher, but serum 1,25-dihydroxyvitamin D levels were similar in both groups. We interpret this to mean that suboptimal vitamin D nutrition stimulates parathyroid adenoma growth by a mechanism unrelated to 1,25-dihydroxyvitamin D deficiency. We conclude that variable vitamin D nutritional status in the population may partly explain the differences in disease presentation.

Family Medicine
Park B, Budzynska K, Almasri N, Islam S, Alyas F, Carolan RL, Abraham BE, Castro-Camero PA, Shreve ME, Rees DA, and Lamerato L. Tight versus standard blood pressure control on the incidence of myocardial infarction and stroke: an observational retrospective cohort study in the general ambulatory setting. *BMC Fam Pract* 2020; 21(1):91. PMID: 32416722. Full Text

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BACKGROUND: The 2017 American College of Cardiology and American Heart Association guideline defined hypertension as blood pressure (BP) ≥ 130/80 mmHg compared to the traditional definition of ≥140/90 mmHg. This change raised much controversy. We conducted this study to compare the impact of tight (TBPC) versus standard BP control (SBPC) on the incidence of myocardial infarction (MI) and stroke. METHODS: We retrospectively identified all hypertensive patients in an ambulatory setting based on the diagnostic code for 1 year at our institution who were classified by the range of BP across 3 years into 2 groups of TBPC (< 130 mmHg) and SBPC (130-139 mmHg). We compared the incidence of new MI and stroke between the 2 groups across a 2-year follow-up. Multivariate analysis was done to identify independent predictors for the incidence of new MI and stroke. RESULTS: Of 5640 study patients, the TBPC group showed significantly less incidence of stroke compared to the SBPC group (1.5% vs. 2.7%, P < 0.010). No differences were found in MI incidence between the 2 groups (0.6% vs. 0.8%, P = 0.476). Multivariate analysis showed that increased age independently increased the incidence of both MI (OR 1.518, 95% CI 1.038-2.219) and stroke (OR 1.876, 95% CI 1.474-2.387), and TBPC independently decreased the incidence of stroke (OR 0.583, 95% CI 0.374-0.910) but not of MI. CONCLUSIONS: Our observational study suggests that TBPC may be beneficial in less stroke incidence compared to SBPC but it didn't seem to affect the incidence of MI. Our study is limited by its retrospective design with potential confounders.

Gastroenterology
Caines A, **Allo G**, and **Siddiqui Y**. Gastric varices from metastatic ovarian cancer with splenic involvement. *Practical Gastroenterology* 2020; 44(2):40-44. PMID: Not assigned. Request Article

Left-sided portal hypertension (LSPH), also known as splenoportal hypertension, is a rare but life-threatening cause of upper gastrointestinal bleeding. LSPH often occurs in non-cirrhotic patients as a consequence of splenic vein obstruction. We present a case of isolated gastric varices due to mass effect on the splenic vein and likely tumor thrombus due to metastatic ovarian cancer.

Gastroenterology
Loomba R, Wong R, Fraysse J, Shreay S, Li S, Harrison S, and **Gordon SC**. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. *Aliment Pharmacol Ther* 2020; 51(11):1149-1159. PMID: 32372515. Full Text

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BACKGROUND: Risk factors and timing associated with disease progression and mortality in nonalcoholic fatty liver disease (NAFLD) are poorly understood. AIMS: To evaluate the impact of disease severity, demographics and comorbidities on risk of

mortality and time to progression in a large, real-world cohort of diagnosed NAFLD patients. METHODS: Claims data from a 20% Medicare representative sample between 2007 and 2015 were analysed retrospectively. Adults were categorised into disease severity groups: NAFLD/nonalcoholic steatohepatitis (NASH) alone, compensated cirrhosis, decompensated cirrhosis, liver transplant or hepatocellular carcinoma. Cumulative incidence of mortality and disease progression were calculated for each group and multivariate analyses performed adjusting for demographics, comorbidities and disease severity. RESULTS: A total of 10 826 456, patients were assessed and the prevalence of NAFLD was 5.7% (N = 621 253). Among patients with NAFLD, 71.1% had NAFLD/NASH alone and 28.9% had NAFLD cirrhosis. Overall, 85.5% of patients had hypertension, 84.1% dyslipidemia, 68.7% had cardiovascular disease and 55.5% diabetes. The cumulative risk of progression of NAFLD to cirrhosis, and compensated cirrhosis to decompensated cirrhosis was 39% and 45%, respectively, over 8 years of follow-up. The independent predictors of progression included cardiovascular disease, renal impairment, dyslipidemia and diabetes. The cumulative risk of mortality for NAFLD, NAFLD cirrhosis, decompensated cirrhosis and hepatocellular carcinoma was 12.6%, 31.1%, 51.4% and 76.2%, respectively. CONCLUSIONS: The present report (a) demonstrates that NAFLD is grossly underdiagnosed in real-world clinical settings and (b) provides new evidence on the progression rates of NAFLD and risk factors of mortality across the spectrum of severity of NAFLD and cirrhosis.

Gastroenterology

Satapathy SK, **Gonzalez HC**, Vanatta J, Dyer A, Angel W, Nouer SS, Kocak M, Kedia SK, Jiang Y, Clark I, Yadak N, Nezakagtoo N, Helmick R, Horton P, Campos L, Agbim U, Maliakkal B, Maluf D, Nair S, Halford HH, and Eason JD. A pilot study of ex-vivo MRI-PDFF of donor livers for assessment of steatosis and predicting early graft dysfunction. *PLoS One* 2020; 15(5). PMID: 32407331. Full Text

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BACKGROUND: The utility of ex vivo Magnetic resonance imaging proton density fat fraction (MRI-PDFF) in donor liver fat quantification is unknown. PURPOSE: To evaluate the diagnostic accuracy and utility in predicting early allograft dysfunction (EAD) of ex vivo MRI-PDFF measurement of fat in deceased donor livers using histology as the gold standard. METHODS: We performed Ex vivo, 1.5 Tesla MRI-PDFF on 33 human deceased donor livers before implantation, enroute to the operating room. After the exclusion of 4 images (technical errors), 29 MRI images were evaluable. Histology was evaluable in 27 of 29 patients. EAD was defined as a peak value of aminotransferase >2000 IU/mL during the first week or an INR of ≥1.6 or bilirubin ≥10 mg/dL at day 7. RESULTS: MRI-PDFF values showed a strong positive correlation (Pearson's correlation coefficient) when histology (macro-steatosis) was included (r = 0.78, 95% confidence interval 0.57-0.89, p<0.0001). The correlation appeared much stronger when macro plus micro-steatosis were included (r = 0.87, 95% confidence interval 0.72-0.94, p<0.0001). EAD was noted in 7(25%) subjects. AUC (Area Under the Curve) for macro steatosis (histology) predicted EAD in 73% (95% CI: 48-99), micro plus macro steatosis in 76% (95% CI: 49-100). AUC for PDFF values predicted EAD in 67(35-98). Comparison of the ROC curves in a multivariate model revealed, adding MRI PDFF values to macro steatosis increased the ability of the model in predicting EAD (AUC: 79%, 95% CI: 59-99), and addition of macro plus micro steatosis based on histology predicted EAD even better (AUC: 90%: 79-100, P = 0.054). CONCLUSION: In this pilot study, MRI-PDFF imaging showed potential utility in quantifying hepatic steatosis ex-vivo donor liver evaluation and the ability to predict EAD related to severe allograft steatosis in the recipient.

Global Health Initiative

Rock JP, **Prentiss T**, Mo SM, Myat Hnin Aye NS, **Asmaro K**, Win AT, Phyu AM, Maung TM, Khaing EE, Naung Z, Park KB, Hlaing K, and Myaing W. Traumatic Brain Injury in Myanmar: Preliminary Results and Development of an Adjunct Electronic Medical Record. *World Neurosurg* 2020; Epub ahead of print. PMID: 32413564. Full Text

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BACKGROUND: The treatment of traumatic brain injury (TBI) in Myanmar is a major health issue. Comprehensive appreciation of the pathology is limited given the lack of granular metadata available. In this proof-of-concept study, we analyzed demographic data on TBI generated from a novel prospective, online database in a low-to-middle income country (LMIC). METHODS: Neurosurgery residents were given an electronic tablet for data entry onto an online database. Metadata-driven data capture was carried prospectively by the trained residents and the information was reviewed weekly by the supervising team in the United States. RESULTS: Complete data was available on 242/253 (96%) patients. Age at admission was 37 years (range 16-85) and length of stay was 3.53 days (1-21). Etiologies included motorcycle accidents, falls, assaults, pedestrian vehicular injuries and industrial accidents. Dispositions were primarily to home (211). Average Glasgow Coma Score (GCS) at admission was 12.97. There was a 68% mortality rate of patients directly admitted to NOGH with GCS <8 versus 75% for patients transferred in from other facilities. Surgery was performed on 30 patients (12.4%). CONCLUSIONS: Despite a lack of formal training in electronic medical records or research, the resident team was able to capture the majority of admissions with granular-level data. This helped shed light on the etiology and severity of TBI in Myanmar. As a result, more effective transport systems and access to trauma care must be achieved. Accessible regional trauma centers with investment in intensive care units, operative care, anesthesia, and imaging resources is necessary.

Hematology/Oncology

Balanchivadze N, and **Donthireddy V**. Hematology/Oncology Fellowship Emergency Restructuring in Response to the COVID-19 Pandemic-Henry Ford Hospital, Michigan. *JCO Oncol Pract* 2020; Epub ahead of print. PMID: 32407178. Full Text

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The COVID-19 pandemic has wreaked havoc and created challenges in various subspecialty training programs, including hematology/oncology fellowship programs. The challenge of social distancing, providing care for those infected by COVID-19, continuing appropriate treatment of time-sensitive diseases, and the looming threat of health care worker infections required swift planning and restructuring of training programs. The Accreditation Council for Graduate Medical Education provided leeway to tackle the challenges faced by institutions and training programs in the setting of the COVID-19 pandemic. Currently, there is no established guideline specific to hematology and oncology fellowship programs. While understanding that there is no one-size-fits-all, shared experiences can assist training programs to incorporate best practices and customize their programs to provide an active educational environment that balances patient care needs, didactics, scholarly activities, and wellbeing during the process of rapid changes and adaptation. We share our hematology/oncology fellowship program's restructuring approach in response to the COVID-19 pandemic.

Hematology/Oncology

Dhanju S, Upadhyaya K, Rice CA, Pegan SD, **Media J**, **Valeriote FA**, and Crich D. Synthesis, Cytotoxicity, and Genotoxicity of 10-Aza-9-oxakalkitoxin, an N,N,O-Trisubstituted Hydroxylamine Analog, or Hydroxalog, of a Marine Natural Product. *J Am Chem Soc* 2020; 142(20):9147-9151. PMID: 32364709. Request Article

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We describe the synthesis of 10-aza-9-oxakalkitoxin, an N,N,O-trisubstituted hydroxylamine-based analog, or hydroxalog, of the cytotoxic marine natural product kalkitoxin in which the -NMe-O- moiety replaces a -CHMe-CH(2)- unit in the backbone of the natural product. 10-Aza-9-oxakalkitoxin displays potent and selective cytotoxicity (IC(50) 2.4 ng mL(-1)) comparable to that of kalkitoxin itself (IC(50) 3.2 ng mL(-1)) against the human hepato-carcinoma cell line HepG2 over both the human leukemia cell line CEM and the normal hematopoietic CFU-GM. Like kalkitoxin, and contrary to the common expectation for hydroxylamines, 10-aza-9-oxakalkitoxin is not mutagenic.

Hematology/Oncology

Nagasaka M, Ge Y, Sukari A, **Kukreja G**, and Ou SI. A user's guide to lorlatinib. *Crit Rev Oncol Hematol* 2020; 151. PMID: 32416346. Full Text

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Rearrangements of the ALK gene are found in approximately 5% of non-small-cell lung cancer. It is of particular importance to test for this rearrangement in patients with metastatic lung adenocarcinoma because these tumors are highly sensitive to therapy with ALK-targeted inhibitors. Lorlatinib is a reversible potent third generation tyrosine kinase inhibitor that is highly selective and targets ALK and ROS1. It was developed to target resistant ALK mutants including the most common G1202R. Lorlatinib has excellent central nervous system (CNS) penetration and its efficacy has also been demonstrated even in patients with intracranial metastases after progression on second generation ALK inhibitors. Potential toxicities include neurocognitive effects and hyperlipidemia. "A User's Guide to Lorlatinib" reviews the mechanism of action, pharmacology and clinical trial data. Also covering the management of adverse events, this "guide" has been prepared to be a practical reference tool to both clinicians and basic researchers.

Hematology/Oncology
Onwubiko I, **Kasperek G**, **Laforest RA**, **Philip SG**, **Kuriakose P**, and **Otrock ZK**. Predictors of response and outcome of patients with acquired haemophilia A. *Haemophilia* 2020; Epub ahead of print. PMID: 32469118. Full Text

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Hematology/Oncology
Sukari A, **Kukreja G**, Nagasaka M, Shukairy MK, Yoo G, Lin HS, Hotaling J, and Kim H. The role of immune checkpoint inhibitors in anaplastic thyroid cancer (Case Series). *Oral Oncol* 2020; Epub ahead of print. PMID: 32402656. Full Text

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Anaplastic thyroid carcinoma (ATC) is a rare type of thyroid neoplasm. However, it is one of the most aggressive forms of malignancy accounting for approximately 50% of mortality associated with all thyroid cancers. Here we report two cases of ATC treated with immune checkpoint inhibitors. Next generation sequencing identified BRAFV600E mutation in one of the patients who also derived benefit from BRAF targeted therapy. We here discuss these cases highlighting the importance of expert pathological review, utilizing molecular testing to identify the underlying genetic targets for personalized therapy, and the potential role of PD-1 inhibitors for the treatment of ATC.

Hematology/Oncology
Yu Y, Brown Wade N, Hwang AE, Nooka AK, Fiala MA, Mohrbacher A, Peters ES, Pawlish K, Bock C, Van Den Berg DJ, Rand KA, Stram D, Conti DV, Auclair D, Colditz GA, Mehta J, Haiman CA, Terebelo H, **Janakiraman N**, Singhal S, Chiu B, Vij R, Bernal-Mizrachi L, Zonder JA, Huff CA, Lonial S, Orlowski RZ, Cozen W, and Ailawadhi S. Variability in Cytogenetic Testing for Multiple Myeloma: A Comprehensive Analysis From Across the United States. *JCO Oncol Pract* 2020; Epub ahead of print. PMID: 32469686. Request Article

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PURPOSE: Multiple myeloma (MM) treatment has changed tremendously, with significant improvement in patient out-comes. One group with a suboptimal benefit is patients with high-risk cytogenetics, as tested by conventional karyotyping or fluorescence in situ hybridization (FISH). Methodology for these tests has been published, but not necessarily standardized. METHODS: We address variability in the testing and reporting methodology for MM cytogenetics in the United States using the ongoing African American Multiple Myeloma Study (AAMMS). We evaluated clinical and cytogenetic data from 1,221 patients (1,161 with conventional karyotyping and 976 with FISH) tested between 1998 and 2016 across 58 laboratories nationwide. RESULTS: Interlab and intralab variability was noted for the number of cells analyzed for karyotyping, with a significantly higher number of cells analyzed in patients in whom cytogenetics were normal (P 5.0025). For FISH testing, CD138-positive cell enrichment was used in 29.7% of patients and no enrichment in 50% of patients, whereas the remainder had unknown status. A significantly smaller number of cells was analyzed for patients in which CD138 cell enrichment was used compared with those without such enrichment (median, 50 v 200; P, .0001). A median of 7 loci probes (range, 1-16) were used for FISH testing across all laboratories, with variability in the loci probed even within a given laboratory. Chromosome 13-related abnormalities were the most frequently tested abnormality (n5956; 97.9%), and t(14;16) was the least frequently tested abnormality (n 5 119; 12.2%). CONCLUSIONS: We report significant variability in cytogenetic testing across the United States for MM, potentially leading to variability in risk stratification, with possible clinical implications and personalized treatment approaches.

Hospital Medicine
Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, Dager WE, Deitelzweig SB, **Ellsworth S**, Garcia D, **Kaatz S**, and Minichiello T. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2020; Epub ahead of print. PMID: 32440883. Full Text

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Coronavirus disease 2019 (COVID-19) is a viral infection that can, in severe cases, result in cytokine storm, systemic inflammatory response and coagulopathy that is prognostic of poor outcomes. While some, but not all, laboratory findings appear similar to sepsis-associated disseminated intravascular coagulopathy (DIC), COVID-19- induced coagulopathy (CIC) appears to be more prothrombotic than hemorrhagic. It has been postulated that CIC may be an uncontrolled immunothrombotic response to COVID-19, and there is growing evidence of venous and arterial thromboembolic events in these critically ill patients. Clinicians around the globe are challenged with rapidly identifying reasonable diagnostic, monitoring and anticoagulant strategies to safely and effectively manage these patients. Thoughtful use of proven, evidence-based approaches must be carefully balanced with integration of rapidly emerging evidence and growing experience. The goal of this document is to provide guidance from the Anticoagulation Forum, a North American organization of anticoagulation providers, regarding use of anticoagulant therapies in patients with COVID-19. We discuss in-hospital and post-discharge venous thromboembolism (VTE) prevention, treatment of suspected but unconfirmed VTE, laboratory monitoring of COVID-19, associated anticoagulant therapies, and essential elements for optimized transitions of care specific to patients with COVID-19.

Hospital Medicine
Barnes GD, Li Y, Gu X, Haymart B, Kline-Rogers E, Ali MA, Kozlowski J, **Krol G**, Froehlich JB, and **Kaatz S**. Periprocedural Bridging Anticoagulation in Patients with Venous Thromboembolism: A Registry-based Cohort Study. *J Thromb Haemost* 2020; Epub ahead of print. PMID: 32428998. Full Text

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BACKGROUND: Use of bridging anticoagulation increases a patient's bleeding risk without clear evidence of thrombotic prevention among warfarin-treated patients with atrial fibrillation. Contemporary use of bridging anticoagulation among warfarin-treated patients with venous thromboembolism (VTE) have not been studied. METHODS: We identified warfarin-treated patients with VTE who temporarily stopped warfarin for a surgical procedure between 2010 and 2018 at six health systems. Using the 2012 American College of Chest Physicians (ACCP) guideline, we assessed use of periprocedural bridging anticoagulation based on recurrent VTE risk. Recurrent VTE risk and 30-day outcomes (bleeding, thromboembolism, emergency department visit) were each assessed using logistic regression adjusted for multiple procedures per patient. RESULTS: During the study period, 789 warfarin-treated patients with VTE underwent 1529 procedures (median 2, IQR 1-4). Unadjusted use of bridging anticoagulation was more common in patients at high-risk for VTE recurrence (99/171, 57.9%) than for patients at moderate (515/1078, 47.8%) or low risk of recurrence (134/280, 47.86%). Bridging anticoagulation use was higher in high-risk patients compared to low- or moderate-risk patients in both unadjusted (p=0.013) and patient-level cluster-adjusted analyses (p=0.031). Adherence to ACCP guidelines in high- and low-risk patients did not change during the study period (OR 0.98 per year, 95% CI 0.91-1.05). Adverse events were rare and not statistically different between the two treatment groups. CONCLUSIONS: Bridging anticoagulation was commonly overused among low-risk patients and underused among high-risk patients treated with warfarin for VTE. Adverse events were rare and not different between the two treatment groups.

Infectious Diseases
Bakthavatchalam YD, Shankar A, Muniyasamy R, Peter JV, **Marcus Z**, Triplicane Dwarakanathan H, Gunasekaran K, Iyadurai R, and Veeraraghavan B. Levonadifloxacin, a recently approved benzoquinolizine fluoroquinolone, exhibits potent in vitro activity against contemporary Staphylococcus aureus isolates and Bengal Bay clone isolates collected from a large Indian tertiary care hospital. *J Antimicrob Chemother* 2020; Epub ahead of print. PMID: 32361727. Full Text

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OBJECTIVES: Levonadifloxacin (WCK 771; IV) and its prodrug alalevonadifloxacin (WCK 2349; oral) are benzoquinolizine fluoroquinolones, recently approved in India for the treatment of acute bacterial skin and skin structure infections with concurrent bacteraemia and diabetic foot infections. Ahead of its market launch, the present study aimed to assess the in vitro activity of levonadifloxacin against contemporary Staphylococcus aureus isolates collected from a large tertiary care hospital in India. Additionally, levonadifloxacin activity was tested against hVISA and Bengal Bay clone MRSA isolates. METHODS: Non-duplicate S. aureus (n = 793) isolates collected at Christian Medical College hospital, Vellore, India during 2013-19 were included in the study. MRSA isolates were identified using a cefoxitin disc diffusion assay. MICs of levonadifloxacin and comparator antibiotics were determined using the broth microdilution method. Mutations in QRDRs were identified for selected levofloxacin-non-susceptible isolates. MLST profiling was undertaken to detect the Bengal Bay clone. RESULTS: Among the 793 isolates, 441 (55.6%) were MRSA and 626 (78.9%) were non-susceptible to levofloxacin. Levonadifloxacin showed MIC50 and MIC90 values of 0.25 and 0.5 mg/L, respectively, for all S. aureus, which included hVISA and Bengal Bay clone MRSA. The potency of levonadifloxacin was 16 times superior compared with levofloxacin. CONCLUSIONS: The present study demonstrated potent activity of levonadifloxacin against contemporary S. aureus isolates, which included MRSA isolates, hVISA isolates, Bengal Bay clone isolates and a high proportion of quinolone-non-susceptible isolates. The potent activity of levonadifloxacin observed in this study supports its clinical use for the treatment of S. aureus infections.

Infectious Diseases
Fadel R, **Morrison AR**, **Vahia A**, **Smith ZR**, **Chaudhry Z**, **Bhargava P**, **Miller J**, **Kenney RM**, **Alangaden G**, and **Ramesh MS**. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32427279. Full Text

Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.
Pharmacy, Henry Ford Hospital, Detroit, MI, USA.
Infectious Diseases, Henry Ford Hospital, Detroit, MI, USA.
Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: There is no proven antiviral or immunomodulatory therapy for COVID-19. The disease progression associated with the pro-inflammatory host response prompted us to examine the role of early corticosteroid therapy in patients

with moderate to severe COVID-19. METHODS: We conducted a single pre-test, single post-test quasi-experiment in a multi-center health system in Michigan from March 12 to March 27, 2020. Adult patients with confirmed moderate to severe COVID were included. A protocol was implemented on March 20, 2020 using early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days. Outcomes of standard of care (SOC) and early corticosteroid groups were evaluated, with a primary composite endpoint of escalation of care from ward to ICU, new requirement for mechanical ventilation, and mortality. All patients had at least 14 days of follow-up. RESULTS: We analyzed 213 eligible subjects, 81 (38%) and 132 (62%) in SOC and early corticosteroid groups, respectively.The composite endpoint occurred at a significantly lower rate in the early corticosteroid group (34.9% vs. 54.3%, p=0.005). This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (8 vs. 5 days, p < 0.001). Multivariate regression analysis demonstrated an independent reduction in the composite endpoint at 14-days controlling for other factors (aOR: 0.41; 95% CI [0.22 - 0.77]). CONCLUSION: An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.

Infectious Diseases
Morrison A, **Brar I**, **Willens D**, and **Thomas E**. Collaboration Improves PrEP Care for Providers and Patients. *Am J Med* 2020; 133(5):e212. PMID: 32450956. Full Text

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Infectious Diseases
Poyiadji N, **Cormier P**, **Patel PY**, **Hadied MO**, **Bhargava P**, **Khanna K**, **Nadig J**, **Keimig T**, **Spizarny D**, **Reeser N**, **Klochko C**, **Peterson EL**, and **Song T**. Acute Pulmonary Embolism and COVID-19. *Radiology* 2020; Epub ahead of print. PMID: 32407256. Full Text

From the Department of Radiology, Henry Ford Health System, Detroit, MI (N.P., P.C., P.Y.P, M.O.H., K.K., J.N., T.K., D.S., N.R., C.K., T.S.); Department of Internal Medicine, Division of Infectious Diseases, Henry Ford Health System. Detroit, MI (P.B.); Department of Public Health Sciences, Henry Ford Health System. Detroit, MI (E.L.P.).

Infectious Diseases
Ramireddy S, **Gudipati S**, and **Zervos M**. Expect the Unexpected: A Rare Case of Pseudomonas aerguinosa Endocarditis. *IDCases* 2020; 21. PMID: 32399394. Full Text

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Infective endocarditis (IE) caused by Pseudomonas aeruginosa is extremely uncommon. Reported cases have usually been associated with intravenous drug use, prosthetic heart valves, and/or implanted cardiac devices. Traditionally, successful treatment has necessitated a combination of antimicrobial(s) and valve replacement. Yet, P. aeruginosa IE remains difficult to manage, especially in cases where valve replacement may not be an immediate option. We present such a case of P. aeruginosa IE, highlighting that medical management with 2 antipseudomonal synergistic agents may be an alternative to surgery in particularly complicated cases.

Infectious Diseases
Swegal W, **Deeb R**, Greene J, **Peterson E**, **Perri MB**, **Bardossy AC**, **Zervos M**, and **Jones LR**. Changes in Nasal Staphylococcus Colonization and Infection Rates After Nasal Surgery. *Facial Plast Surg Aesthet Med* 2020; Epub ahead of print. PMID: 32392437. Full Text

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Background: The relationship between nasal flora and infection rates in patients undergoing nasal surgery is of interest. This relationship has been studied though changes that may take place due to surgery have never been elucidated. Objective: To assess colonization rates and changes in colonization patterns of methicillin-resistant or methicillin-sensitive Staphylococcus aureus (MRSA/MSSA) in nasal flora in patients undergoing nasal surgery and to determine whether colonization is a risk factor for postoperative infection. Methods: Patients undergoing nasal surgery including septoplasty, rhinoplasty, or nasal valve

repair were recruited prospectively. Patients completed a survey preoperatively concerning risk factors of postoperative infection. Nasal swabs and cultures were done preoperatively and at 1 week postoperatively. Patients were assessed for surgical site infections postoperatively. Results: Fifty-five patients completed both preoperative and postoperative nasal swabs. Preoperative to postoperative colonization rates increased for MRSA (2-5%) and MSSA (22-36%). Of the 55 patients, 11 had a change in nasal flora postoperatively, 9 of whom were colonized with a Staphylococcus aureus strain. However, MSSA/MRSA colonization either preoperatively or postoperatively was not associated with surgical site infections. Gender was the only variable found to be associated with postoperative infection ($p = 0.007$) with all four infections occurring in females. Conclusions: MSSA and MRSA do not appear to be major risk factors for surgical site infection in nasal surgery, whereas prior nasal surgery is a risk factor. This is the first report of a change in nasal colonization after nasal surgery. This could have implications for antibiotic prophylaxis in select nasal surgery cases.

Internal Medicine

Barkoudah E, Piazza G, Hecht TEH, Grant P, Deitelzweig S, Fang MC, Fanikos J, Kao CK, Barnes GD, Chen T, Ramishvili T, Schnipper JL, Goldstein JN, Ruff CT, **Kaatz S**, Schwartz A, Connors JM, and Goldhaber SZ. Extended Venous Thromboembolism Prophylaxis in Medically Ill Patients: An NATF Anticoagulation Action Initiative. *Am J Med* 2020; 133 Suppl 1:1-27. PMID: 32362349. Full Text

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Brigham and Women's Hospital, Boston, Mass; Massachusetts College of Pharmacy and Health Science, Boston.
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Christiana Care Health System, Newark, Del.
Henry Ford Hospital, Detroit, Mich; Wayne State University, Detroit, Mich.
North American Thrombosis Forum, Brookline, Mass.

Hospitalized patients with acute medical illnesses are at risk for venous thromboembolism (VTE) during and after a hospital stay. Risk factors include physical immobilization and underlying pathophysiologic processes that activate the coagulation pathway and are still present after discharge. Strategies for optimal pharmacologic VTE thromboprophylaxis are evolving, and recommendations for VTE prophylaxis can be further refined to protect high-risk patients after hospital discharge. An early study of extended VTE prophylaxis with a parenteral agent in medically ill patients yielded inconclusive results with regard to efficacy and bleeding. In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial, extended use of betrixaban halved symptomatic VTE, decreased hospital readmission, and reduced stroke and major adverse cardiovascular events compared with standard enoxaparin prophylaxis. Based on findings from APEX, the Food and Drug Administration approved betrixaban in 2017 for extended VTE prophylaxis in acute medically ill patients. In the Reducing Post-Discharge Venous Thrombo-Embolism Risk (MARINER) study, extended use of rivaroxaban halved symptomatic VTE in high-risk medical patients compared with placebo. In 2019, rivaroxaban was approved for extended thromboprophylaxis in high-risk medical patients, thus making available a new strategy for in-hospital and post-discharge VTE prevention. To address the critical unmet need for VTE prophylaxis in medically ill patients at the time of hospital discharge, the North American Thrombosis Forum (NATF) is launching the Anticoagulation Action Initiative, a comprehensive consensus document that provides practical guidance and straightforward, patient-centered recommendations for VTE prevention during hospitalization and after discharge.

Internal Medicine

Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, Dager WE, Deitelzweig SB, **Ellsworth S**, Garcia D, **Kaatz S**, and Minichiello T. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis* 2020; Epub ahead of print. PMID: 32440883. Full Text

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Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
UC Davis Medical Center, Sacramento, CA, USA.
Ochsner Health System, New Orleans, LA, USA.
Henry Ford Hospital, Detroit, MI, USA.

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Coronavirus disease 2019 (COVID-19) is a viral infection that can, in severe cases, result in cytokine storm, systemic inflammatory response and coagulopathy that is prognostic of poor outcomes. While some, but not all, laboratory findings appear similar to sepsis-associated disseminated intravascular coagulopathy (DIC), COVID-19- induced coagulopathy (CIC) appears to be more prothrombotic than hemorrhagic. It has been postulated that CIC may be an uncontrolled immunothrombotic response to COVID-19, and there is growing evidence of venous and arterial thromboembolic events in these critically ill patients. Clinicians around the globe are challenged with rapidly identifying reasonable diagnostic, monitoring and anticoagulant strategies to safely and effectively manage these patients. Thoughtful use of proven, evidence-based approaches must be carefully balanced with integration of rapidly emerging evidence and growing experience. The goal of this document is to provide guidance from the Anticoagulation Forum, a North American organization of anticoagulation providers, regarding use of anticoagulant therapies in patients with COVID-19. We discuss in-hospital and post-discharge venous thromboembolism (VTE) prevention, treatment of suspected but unconfirmed VTE, laboratory monitoring of COVID-19, associated anticoagulant therapies, and essential elements for optimized transitions of care specific to patients with COVID-19.

Internal Medicine
Barnes GD, Li Y, Gu X, Haymart B, Kline-Rogers E, Ali MA, Kozlowski J, **Krol G**, Froehlich JB, and **Kaatz S**. Periprocedural Bridging Anticoagulation in Patients with Venous Thromboembolism: A Registry-based Cohort Study. *J Thromb Haemost* 2020; Epub ahead of print. PMID: 32428998. Full Text

Department of Internal Medicine, Frankel Cardiovascular Center, University of Michigan, Ann Arbor, MI, USA.
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Division of Hospital Medicine, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: Use of bridging anticoagulation increases a patient's bleeding risk without clear evidence of thrombotic prevention among warfarin-treated patients with atrial fibrillation. Contemporary use of bridging anticoagulation among warfarin-treated patients with venous thromboembolism (VTE) have not been studied. METHODS: We identified warfarin-treated patients with VTE who temporarily stopped warfarin for a surgical procedure between 2010 and 2018 at six health systems. Using the 2012 American College of Chest Physicians (ACCP) guideline, we assessed use of periprocedural bridging anticoagulation based on recurrent VTE risk. Recurrent VTE risk and 30-day outcomes (bleeding, thromboembolism, emergency department visit) were each assessed using logistic regression adjusted for multiple procedures per patient. RESULTS: During the study period, 789 warfarin-treated patients with VTE underwent 1529 procedures (median 2, IQR 1-4). Unadjusted use of bridging anticoagulation was more common in patients at high-risk for VTE recurrence (99/171, 57.9%) than for patients at moderate (515/1078, 47.8%) or low risk of recurrence (134/280, 47.86%). Bridging anticoagulation use was higher in high-risk patients compared to low- or moderate-risk patients in both unadjusted (p=0.013) and patient-level cluster-adjusted analyses (p=0.031). Adherence to ACCP guidelines in high- and low-risk patients did not change during the study period (OR 0.98 per year, 95% CI 0.91-1.05). Adverse events were rare and not statistically different between the two treatment groups. CONCLUSIONS: Bridging anticoagulation was commonly overused among low-risk patients and underused among high-risk patients treated with warfarin for VTE. Adverse events were rare and not different between the two treatment groups.

Internal Medicine
Fadel R, **Morrison AR**, **Vahia A**, **Smith ZR**, **Chaudhry Z**, **Bhargava P**, **Miller J**, **Kenney RM**, **Alangaden G**, and **Ramesh MS**. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32427279. Full Text

Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.
Pharmacy, Henry Ford Hospital, Detroit, MI, USA.
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Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: There is no proven antiviral or immunomodulatory therapy for COVID-19. The disease progression associated with the pro-inflammatory host response prompted us to examine the role of early corticosteroid therapy in patients with moderate to severe COVID-19. METHODS: We conducted a single pre-test, single post-test quasi-experiment in a multi-center health system in Michigan from March 12 to March 27, 2020. Adult patients with confirmed moderate to severe COVID were included. A protocol was implemented on March 20, 2020 using early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days. Outcomes of standard of care (SOC) and early corticosteroid groups

were evaluated, with a primary composite endpoint of escalation of care from ward to ICU, new requirement for mechanical ventilation, and mortality. All patients had at least 14 days of follow-up. RESULTS: We analyzed 213 eligible subjects, 81 (38%) and 132 (62%) in SOC and early corticosteroid groups, respectively.The composite endpoint occurred at a significantly lower rate in the early corticosteroid group (34.9% vs. 54.3%, p=0.005). This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (8 vs. 5 days, p < 0.001). Multivariate regression analysis demonstrated an independent reduction in the composite endpoint at 14-days controlling for other factors (aOR: 0.41; 95% CI [0.22 - 0.77]). CONCLUSION: An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.

Internal Medicine

Huang L, **Li GH**, **Yu Q**, **Xu Y**, **Cvetkovski S**, **Wang X**, **Parajuli N**, **Udo-Inyang I**, Kaplan D, **Zhou L**, Yao Z, and **Mi QS**. Smad2/4 Signaling Pathway Is Critical for Epidermal Langerhans Cell Repopulation Under Inflammatory Condition but Not Required for Their Homeostasis at Steady State. *Front Immunol* 2020; 11:912. PMID: 32457763. Full Text

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Epidermal Langerhans cells (LCs) are skin-resident dendritic cells that are essential for the induction of skin immunity and tolerance. Transforming growth factor-β 1 (TGFβ1) is a crucial factor for LC maintenance and function. However, the underlying TGFβ1 signaling pathways remain unclear. Our previous research has shown that the TGFβ1/Smad3 signaling pathway does not impact LC homeostasis and maturation. In this study, we generated mice with conditional deletions of either individual Smad2, Smad4, or both Smad2 and Smad4 in the LC lineage or myeloid lineage, to further explore the impact of TGFβ1/Smad signaling pathways on LCs. We found that interruption of Smad2 or Smad4 individually or simultaneously in the LC lineage did not significantly impact the maintenance, maturation, antigen uptake, and migration of LCs in vivo or in vitro during steady state. However, the interruption of both Smad2 and Smad4 pathways in the myeloid lineage led to a dramatic inhibition of bone marrow-derived LCs in the inflammatory state. Overall, our data suggest that canonical TGFβ1/Smad2/4 signaling pathways are dispensable for epidermal LC homeostasis and maturation at steady state, but are critical for the long-term LC repopulation directly originating from the bone marrow in the inflammatory state.

Internal Medicine

Lin JC, **Kavousi Y**, **Sullivan B**, and **Stevens C**. Analysis of Outpatient Telemedicine Reimbursement in an Integrated Healthcare System. *Ann Vasc Surg* 2020; 65:100-106. PMID: 31678131. Full Text

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BACKGROUND: Current reimbursement policy surrounding telemedicine has been cited as a barrier for the adaptation of this care model. The objective of this study is to analyze the reimbursement figures for outpatient telemedicine consultation in vascular surgery. METHODS: Patients first underwent synchronous telemedicine visits after receiving point-of-care ultrasound at one of 3 satellite locations of Henry Ford Health System in Michigan. Visit types included new, return, and postoperative patients. Reimbursement information related to payor, adjustment, denial, paid and outstanding balances were recorded for each telemedicine visit. Then, using an enterprise data warehouse, a retrospective analysis was performed for the aforementioned telemedicine visits. The data were analyzed to determine the outcome of total billed charges, number of denied claims, reimbursement per payor, reimbursement per patient, and out-of-pocket costs to the patients. RESULTS: Among 184 virtual clinical encounters, the payors included Aetna US Healthcare, Blue Advantage, Blue Cross Blue Shield, Cofinity Plan, Health Alliance Plan, HAP Medicare Advantage, Humana Medicare Advantage, Medicaid, Medicare, Molina Medicaid HMO, United Healthcare, Blue Care Network, Aetna Better Health of Michigan, Priority Health, and self-pay. Among the 15 payors, reimbursement ranged from 0% to 67% of the total charges billed. Among the 184 virtual visits, a grand total of $22,145 was collected or an average of $120.35 per virtual encounter. The breakdown of charges billed was 40% adjusted, 41% paid by insurance, 10% paid by patient, and 13% denied. There were 27 total denials (15%). Denial of payment included telehealth and nontelehealth reasons, citing noncovered charges, payment included for other prior services, new patient quality not met, and not covered by payor. The average out-of-pocket cost to patients was $12.59 per visit. CONCLUSIONS: These reimbursement data validate the economic potential within this new platform of healthcare delivery. As our experience with the business model grows, we expect to see an increase in reimbursement from private payors and acceptance from

patients. Within a tertiary care system, telemedicine for chronic vascular disease has proven to be a viable means to reach a broader population base, and without significant cost to the patients.

Internal Medicine
Morrison A, **Brar I**, **Willens D**, and **Thomas E**. Collaboration Improves PrEP Care for Providers and Patients. *Am J Med* 2020; 133(5):e212. PMID: 32450956. Full Text

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Infectious Diseases, Henry Ford Hospital, Detroit, Michigan.
Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Pharmacy, Henry Ford Hospital, Detroit, Michigan.

Internal Medicine
Ramireddy S, **Gudipati S**, and **Zervos M**. Expect the Unexpected: A Rare Case of Pseudomonas aerguinosa Endocarditis. *IDCases* 2020; 21:e00787. PMID: 32399394. Full Text

Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI, 48202, United States.
Henry Ford Macomb Hospital, 15855 19 Mile Road, Clinton Township, MI, 48038, United States.

Infective endocarditis (IE) caused by Pseudomonas aeruginosa is extremely uncommon. Reported cases have usually been associated with intravenous drug use, prosthetic heart valves, and/or implanted cardiac devices. Traditionally, successful treatment has necessitated a combination of antimicrobial(s) and valve replacement. Yet, P. aeruginosa IE remains difficult to manage, especially in cases where valve replacement may not be an immediate option. We present such a case of P. aeruginosa IE, highlighting that medical management with 2 antipseudomonal synergistic agents may be an alternative to surgery in particularly complicated cases.

Neurology
Aldrich EF, Higashida R, Hmissi A, Le EJ, Macdonald RL, Marr A, **Mayer SA**, Roux S, and Bruder N. Thick and diffuse cisternal clot independently predicts vasospasm-related morbidity and poor outcome after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2020; Epub ahead of print. PMID: 32442971. Full Text

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OBJECTIVE: Aneurysmal subarachnoid hemorrhage (aSAH) is associated with significant morbidity and mortality. The presence of thick, diffuse subarachnoid blood may portend a worse clinical course and outcome, independently of other known prognostic factors such as age, aneurysm size, and initial clinical grade. METHODS: In this post hoc analysis, patients with aSAH undergoing surgical clipping (n = 383) or endovascular coiling (n = 189) were pooled from the placebo arms of the Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS)-2 and CONSCIOUS-3 randomized, double-blind, placebo-controlled phase 3 studies, respectively. Patients without and with thick, diffuse SAH (≥ 4 mm thick and involving ≥ 3 basal cisterns) on admission CT scans were compared. Clot size was centrally adjudicated. All-cause mortality and vasospasm-related morbidity at 6 weeks and Glasgow Outcome Scale-Extended (GOSE) scores at 12 weeks after aSAH were assessed. The effect of the thick and diffuse cisternal aSAH on vasospasm-related morbidity and mortality, and on poor clinical outcome at 12 weeks, was evaluated using logistic regression models. RESULTS: Overall, 294 patients (51.4%) had thick and diffuse aSAH. Compared to patients with less hemorrhage burden, these patients were older (median age 55 vs 50 years) and more often had World Federation of Neurosurgical Societies (WFNS) grade III-V SAH at admission (24.1% vs 16.5%). At 6 weeks, all-cause mortality and vasospasm-related morbidity occurred in 36.1% (95% CI 30.6%-41.8%) of patients with thick, diffuse SAH and in 14.7% (95% CI 10.8%-19.5%) of those without thick, diffuse SAH. Individual event rates were 7.5% versus 2.5% for all-cause death, 19.4% versus 6.8% for new cerebral infarct, 28.2% versus 9.4% for delayed ischemic neurological deficit, and 24.8% versus 10.8% for rescue therapy due to cerebral vasospasm, respectively. Poor clinical outcome (GOSE score ≥ 4) was observed in 32.7% (95% CI 27.3%-38.3%) and 16.2% (95% CI 12.1%-21.1%) of patients with and without thick, diffuse SAH, respectively. CONCLUSIONS: In a large, centrally adjudicated population of patients with aSAH, WFNS grade at admission and thick, diffuse SAH independently predicted vasospasm-related morbidity and poor 12-week clinical outcome. Patients with thick, diffuse cisternal SAH may be an important cohort to target in future clinical trials of treatment for vasospasm.

Neurology

Ali A. Delay in OnabotulinumtoxinA Treatment During the COVID-19 Pandemic-Perspectives from a Virus Hotspot. *Headache* 2020; 60(6):1183-1186. PMID: 32359098. Full Text

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The COVID-19 pandemic has undoubtedly changed our practice of medicine. With our collective resources and attention focused on caring for those afflicted with the disease, other medical conditions have temporarily but understandably faced constraint. For migraine patients who often require in-person visits for infusions and procedures, this has become particularly challenging. Here, we share our experience in navigating this exigency amidst a local surge of COVID-19.

Neurology

Aloizou AM, Siokas V, Mentis AFA, Dastamani M, Sokratous M, Xiromerisiou G, **Mitsias PD**, Hadjigeorgiou GM, and Dardiotis E. Advancements in the Treatment of Cerebrovascular Complications of Cancer. *Curr Treat Options Neurol* 2020; 22(6). PMID: Not assigned. Full Text

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Purpose of review: To present the new guidelines and therapeutic options regarding cerebrovascular complications of cancer, mainly ischemic stroke, cerebral venous thrombosis (CVT), and leptomeningeal carcinomatosis (LMC). Recent findings: A temporal trend study (2019) revealed that clinicians are still reluctant to apply thrombolysis to cancer patients, although two new studies (2018) reported no increased mortality. Several clinical trials on direct oral anticoagulants (DOACs) showed their superiority or, at least, non-inferiority compared with low molecular weight heparins in the treatment of venous thromboembolism (VTE) (2018–2019). These trials helped in formulating the new guidelines that are being published and the decisions made for cancer-associated thrombosis (CAT) as a whole. A new DOAC antidote was also officially released (US 2018, Europe 2019). Summary: Thrombolysis is safe in a malignancy setting, thus cancer per se should not be considered a contraindication for thrombolysis. Clinical trials assessing the newest DOACs for cancer-associated arterial thrombosis are scarce; however, based on data from VTE studies, the newest DOACs seem to be safe for CAT in patients that are not in high risk of bleeding or suffering from certain malignancies. The treatment should not be ceased after 6 months, but rather continued as long as the cancer remains active. Decompressive craniectomy should maintain its place in patients with CVST in risk of herniation. Last, the future also holds much promise on the role of novel compounds to be used in LMC.

Neurology

Bergman D, **Modh A**, **Schultz L**, **Snyder J**, **Mikkelsen T**, **Shah M**, Ryu S, **Siddiqui MS**, and **Walbert T**. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol* 2020; Epub ahead of print. PMID: 32444980. Full Text

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PURPOSE: Outcomes for patients with recurrent high-grade glioma (HGG) progressing on bevacizumab (BEV) are dismal. Fractionated stereotactic radiosurgery (FSRS) has been shown to be feasible and safe when delivered in this setting, but prospective evidence is lacking. This single-institution randomized trial compared FSRS plus BEV-based chemotherapy versus BEV-based chemotherapy alone for BEV-resistant recurrent malignant glioma. MATERIALS AND METHODS: HGG patients on BEV with tumor progression after 2 previous treatments were randomized to 1) FSRS plus BEV-based chemotherapy or 2) BEV-based chemotherapy with irinotecan, etoposide, temozolomide, or carboplatin. FSRS was delivered as 32 Gy (8 Gy × 4 fractions within 2 weeks) to the gross target volume and 24 Gy (6 Gy × 4 fractions) to the clinical target volume (fluid-attenuated inversion recovery abnormality). The primary endpoints were local control (LC) at 2 months and progression-free survival (PFS). RESULTS: Of the 35 patients enrolled, 29 had glioblastoma (WHO IV) and 6 had anaplastic glioma (WHO III). The median number of prior recurrences was 3. Patients treated with FSRS had significantly improved PFS (5.1 vs 1.8 months, $P < .001$) and improved LC at 2 months (82% [14/17] vs 27% [4/15], $P = .002$). The overall median survival was 6.6 months (7.2 months with FSRS vs 4.8 months with chemotherapy alone, $P = .11$). CONCLUSIONS: FSRS combined with BEV-based chemotherapy in recurrent HGG patients progressing on BEV is feasible and improves LC and PFS when compared to treatment with BEV-based chemotherapy alone.

Neurology
Delly F, Syed MJ, Lisak RP, and Zutshi D. Myasthenic crisis in COVID-19. *J Neurol Sci* 2020; 414:116888. PMID: 32413767. Full Text

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• Myasthenic crises is a potentially severe complication of COVID-19. • Hydroxychloroquine can aggravate myasthenia crises. • IVIg is a potential treatment for both Myasthenic crises and COVID-19. • IVIg treatment may cause thrombosis in susceptible patients.

Neurology
Francis R, Singh PK, Singh S, **Giri S**, and Kumar A. Glycolytic inhibitor 2-deoxyglucose suppresses inflammatory response in innate immune cells and experimental staphylococcal endophthalmitis. *Exp Eye Res* 2020; Epub ahead of print. PMID: 32454039. Request Article

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Previously, we have shown that Staphylococcus (S) aureus induces a glycolytic response in retinal residential (microglia) and infiltrated cells (neutrophils and macrophages) during endophthalmitis. In this study, we sought to investigate the physiological role of glycolysis in bacterial endophthalmitis using a glycolytic inhibitor, 2-deoxyglucose (2DG). Our data showed that 2DG treatment attenuated the inflammatory responses of mouse bone marrow-derived macrophages (BMDM) and neutrophils (BMDN) when challenged with either live or heat-killed S. aureus (HKSA). Among the inflammatory mediators, 2DG caused a significant reduction in levels of cytokines (TNF-α, IL-1β, IL-6) and chemokines (CXCL1 and CXCL2). Western blot analysis of 2DG treated cells showed downregulation of bacterial-induced MEK/ERK pathways. In vivo, intravitreal administration of 2DG both pre- and post-bacterial infection resulted in a significant reduction in intraocular inflammation in C57BL/6 mouse eyes and downregulation of ERK phosphorylation in retinal tissue. Collectively, our study demonstrates that 2DG attenuates inflammatory response in bacterial endophthalmitis and cultured innate immune cells via inhibition of ERK signaling. Thus glycolytic inhibitors in combination with antibiotics could mitigate inflammation-mediated tissue damage in ocular infections.

Neurology
Kaur J, **Davoodi-Bojd E**, **Fahmy LM**, **Zhang L**, **Ding G**, Hu J, **Zhang Z**, **Chopp M**, and **Jiang Q**. Magnetic Resonance Imaging and Modeling of the Glymphatic System. *Diagnostics (Basel)* 2020; 10(6). PMID: 32471025. Full Text

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The glymphatic system is a newly discovered waste drainage pathway in the brain; it plays an important role in many neurological diseases. Ongoing research utilizing various cerebrospinal fluid tracer infusions, either directly or indirectly into the brain parenchyma, is investigating clearance pathways by using distinct imaging techniques. In the present review, we discuss the role of the glymphatic system in various neurological diseases and efflux pathways of brain waste clearance based on current evidence and controversies. We mainly focus on new magnetic resonance imaging (MRI) modeling techniques, along with traditional computational modeling, for a better understanding of the glymphatic system function. Future sophisticated modeling techniques hold the potential to generate quantitative maps for glymphatic system parameters that could contribute to the diagnosis, monitoring, and prognosis of neurological diseases. The non-invasive nature of MRI may provide a safe and effective way to translate glymphatic system measurements from bench-to-bedside.

Neurology
LeWitt PA, Kymes S, and Hauser RA. Parkinson Disease and Orthostatic Hypotension in the Elderly: Recognition and Management of Risk Factors for Falls. *Aging Dis* 2020; 11(3):679-691. PMID: 32489712. Full Text

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Parkinson disease (PD) is often associated with postural instability and gait dysfunction that can increase the risk for falls and associated consequences, including injuries, increased burden on healthcare resources, and reduced quality of life. Patients with PD have nearly twice the risk for falls and associated bone fractures compared with their general population counterparts of similar age. Although the cause of falls in patients with PD may be multifactorial, an often under-recognized factor is neurogenic orthostatic hypotension (nOH). nOH is a sustained decrease in blood pressure upon standing whose symptomology can include dizziness/lightheadedness, weakness, fatigue, and syncope. nOH is due to dysfunction of the autonomic nervous system compensatory response to standing and is a consequence of the neurodegenerative processes of PD. The symptoms associated with orthostatic hypotension (OH)/nOH can increase the risk of falls, and healthcare professionals may not be aware of the real-world clinical effect of nOH, the need for routine screening, or the value of early diagnosis of nOH when treating elderly patients with PD. nOH is easily missed and, importantly, healthcare providers may not realize that there are effective treatments for nOH symptoms that could help lessen the fall risk resulting from the condition. This review discusses the burden of, and key risk factors for, falls among patients with PD, with a focus on practical approaches for the recognition, assessment, and successful management of OH/nOH. In addition, insights are provided as to how fall patterns can suggest fall etiology, thereby influencing the choice of intervention.

Neurology
Macki M, Mahajan A, Shatz R, **Air EL**, **Novikova M**, Fakih M, Elmenini J, **Kaur M**, **Bouchard KR**, **Funk BA**, and **Schwalb JM**. Prevalence of Alternative Diagnoses and Implications for Management in Idiopathic Normal Pressure Hydrocephalus Patients. *Neurosurgery* 2020; Epub ahead of print. PMID: 32472677. Full Text

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BACKGROUND: Following Bayes theorem, ventriculomegaly and ataxia confer only a 30% chance of idiopathic Normal Pressure Hydrocephalus (NPH). When coupled with positive responses to best diagnostic testing (extended lumbar drainage), 70% of patients recommended for shunting will not actually have NPH. This is inadequate clinical care. OBJECTIVE: To determine the proportion of alternative and treatable diagnoses in patients referred to a multidisciplinary NPH clinic. METHODS: Patients without previously diagnosed NPH were queried from prospectively collected data. At least 1 neurosurgeon, cognitive neurologist, and neuropsychologist jointly formulated best treatment plans. RESULTS: Of 328 total patients, 45% had an alternative diagnosis; 11% of all patients improved with treatment of an alternative diagnosis. Of 87 patients with treatable conditions, the highest frequency of pathologies included sleep disorders, and cervical stenosis, followed by Parkinson disease. Anti-cholinergic burden was a contributor for multiple patients. Of 142 patients undergoing lumbar puncture, 71% had positive responses and referred to surgery. Compared to NPH patients, mimickers were statistically significantly older with lower Montreal Cognitive Assessment (MoCA) score and worse gait parameters. Overall, 26% of the original patients underwent shunting. Pre-post testing revealed a statistically significant improved MoCA score and gait parameters in those patients who underwent surgery with follow-up. CONCLUSION: Because the Multidisciplinary NPH Clinic selected only 26% for surgery (corroborating 30% in Bayes theorem), an overwhelming majority of patients with suspected NPH will harbor alternative diagnoses. Identification of contributing/confounding conditions will support the meticulous work-up necessary to appropriately manage patients without NPH while optimizing clinical responses to shunting in correctly diagnosed patients.

Neurology
Nejad-Davarani SP, **Zakariaei N**, Chen Y, Haacke EM, **Hurst NJ**, **Siddiqui MS**, **Schultz LR**, **Snyder JM**, **Walbert T**, and **Glide-Hurst C**. Rapid Multi-contrast Brain Imaging on a 0.35T MR-linac. *Med Phys* 2020; Epub ahead of print. PMID: 32434276. Request Article

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PURPOSE: Magnetic resonance-guided radiation therapy (MRgRT) has shown great promise for localization and real-time tumor monitoring. However, to date, quantitative imaging has been limited for low field MRgRT. This work benchmarks quantitative T1, R2* and Proton Density (PD)-mapping in phantom on a 0.35T MR-linac and implements a novel acquisition method, STrategically Acquired Gradient Echo (STAGE). To further validate STAGE in a clinical setting, a pilot study was undertaken in a cohort of brain tumor patients to elucidate opportunities for longitudinal functional imaging with an MR-linac in the brain. METHODS: STAGE (two triple-echo gradient echo (GRE) acquisitions) was optimized for a 0.35T low-field MR-linac. Simulations were performed to choose two flip angles to optimize signal-to-noise ratio (SNR) and T1-mapping precision. Tradeoffs between SNR, scan time, and spatial resolution for whole-brain coverage were evaluated in healthy volunteers. Data were inputted into a STAGE processing pipeline to yield 4 qualitative images (T1-weighted, enhanced T1-weighted, proton-density (PD) weighted, and simulated FLuid-Attenuated Inversion Recovery (sFLAIR)), and 3 quantitative datasets (T1, PD, and R2*). A benchmarking ISMRM/NIST phantom consisting of vials with variable NiCl(2) and MnCl(2) concentrations was scanned using variable flip angles (VFA) (2-60 degrees) and inversion recovery (IR) methods at 0.35T. STAGE and VFA T1 values of vials were compared to IR T1 values. As measures of agreement with reference values and repeatability, relative error (RE) and coefficient of variability (CV) were calculated, respectively, for quantitative MR values within the phantom vials (spheres). To demonstrate feasibility, longitudinal STAGE data (pre-treatment, weekly, and ~2 months post-treatment) were acquired in an IRB-approved pilot study of brain tumor cases via the generation of temporal and differential quantitative MRI maps. RESULTS: In the phantom, RE of measured STAGE and VFA T1 relative to IR reference values were 7.0 ± 2.5% and 9.5 ± 2.2%, respectively. RE for the PD vials was 8.1%±6.8% and CV for phantom R2* measurements was 10.1% ± 9.9%. Simulations and volunteer experiments yielded final STAGE parameters of FA=50°/10°, 1x1x3 mm(3) resolution, TR=40ms, TE=5/20/34ms in 10 minutes (64 slices). In the pilot study of brain tumor patients, differential maps for R2* and T1 maps were sensitive to local tumor changes and appeared similar to 3T follow up MRI datasets. CONCLUSION: Quantitative T1, R2*, and PD mapping are promising at 0.35T agreeing well with reference data. STAGE phantom data offer quantitative representations comparable to traditional methods in a fraction of the acquisition time. Initial feasibility of implementing STAGE at 0.35T in a patient brain tumor cohort suggests that detectable changes can be observed over time. With confirmation in a larger cohort, results may be implemented to identify areas of recurrence and facilitate adaptive radiation therapy.

Neurology

Zhang Y, **Zhang Y**, **Chopp M**, **Zhang ZG**, **Mahmood A**, and **Xiong Y**. Mesenchymal Stem Cell-Derived Exosomes Improve Functional Recovery in Rats After Traumatic Brain Injury: A Dose-Response and Therapeutic Window Study. *Neurorehabil Neural Repair* 2020; Epub ahead of print. PMID: 32462980. Full Text

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Background. Mesenchymal stem cell (MSC)-derived exosomes play a critical role in regenerative medicine. Objective. To determine the dose- and time-dependent efficacy of exosomes for treatment of traumatic brain injury (TBI). Methods. Male rats were subjected to a unilateral moderate cortical contusion. In the dose-response study, animals received a single intravenous injection of exosomes (50, 100, 200 µg per rat) or vehicle, with treatment initiated at 1 day after injury. In the therapeutic window study, animals received a single intravenous injection of 100 µg exosomes or vehicle starting at 1, 4, or 7 days after injury. Neurological functional tests were performed weekly after TBI for 5 weeks. Spatial learning was measured on days 31 to 35 after TBI using the Morris water maze test. Results. Compared with the vehicle, regardless of the dose and delay in treatment, exosome treatment significantly improved sensorimotor and cognitive function, reduced hippocampal neuronal cell loss, promoted angiogenesis and neurogenesis, and reduced neuroinflammation. Exosome treatment at 100 µg per rat exhibited a significant therapeutic effect compared with the 50- or 200-µg exosome groups. The time-dependent exosome treatment data demonstrated that exosome treatment starting at 1 day post-TBI provided a significantly greater improvement in functional and histological outcomes than exosome treatments at the other 2 delayed treatments. Conclusions. These results indicate that exosomes have a wide range of effective doses for treatment of TBI with a therapeutic window of at least 7 days postinjury. Exosomes may provide a novel therapeutic intervention in TBI.

Neurosurgery

Bergman D, **Modh A**, **Schultz L**, **Snyder J**, **Mikkelsen T**, **Shah M**, Ryu S, **Siddiqui MS**, and **Walbert T**. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol* 2020; Epub ahead of print. PMID: 32444980. Full Text

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PURPOSE: Outcomes for patients with recurrent high-grade glioma (HGG) progressing on bevacizumab (BEV) are dismal. Fractionated stereotactic radiosurgery (FSRS) has been shown to be feasible and safe when delivered in this setting, but prospective evidence is lacking. This single-institution randomized trial compared FSRS plus BEV-based chemotherapy versus BEV-based chemotherapy alone for BEV-resistant recurrent malignant glioma. MATERIALS AND METHODS: HGG patients on BEV with tumor progression after 2 previous treatments were randomized to 1) FSRS plus BEV-based chemotherapy or 2) BEV-based chemotherapy with irinotecan, etoposide, temozolomide, or carboplatin. FSRS was delivered as 32 Gy (8 Gy × 4 fractions within 2 weeks) to the gross target volume and 24 Gy (6 Gy × 4 fractions) to the clinical target volume (fluid-attenuated inversion recovery abnormality). The primary endpoints were local control (LC) at 2 months and progression-free survival (PFS). RESULTS: Of the 35 patients enrolled, 29 had glioblastoma (WHO IV) and 6 had anaplastic glioma (WHO III). The median number of prior recurrences was 3. Patients treated with FSRS had significantly improved PFS (5.1 vs 1.8 months, P < .001) and improved LC at 2 months (82% [14/17] vs 27% [4/15], P = .002). The overall median survival was 6.6 months (7.2 months with FSRS vs 4.8 months with chemotherapy alone, P = .11). CONCLUSIONS: FSRS combined with BEV-based chemotherapy in recurrent HGG patients progressing on BEV is feasible and improves LC and PFS when compared to treatment with BEV-based chemotherapy alone.

Neurosurgery
Chen J, Mitra A, Li S, Song S, Nguyen BN, Chen JS, Shin JH, Gough NR, Lin P, Obias V, He AR, Yao Z, **Malta TM**, **Noushmehr H**, Latham PS, Su X, Rashid A, Mishra B, Wu RC, and Mishra L. Targeting the E3 Ubiquitin Ligase PJA1 Enhances Tumor-Suppressing TGFβ Signaling. *Cancer Res* 2020; 80(9):1819-1832. PMID: 32127355. Full Text

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RING-finger E3 ligases are instrumental in the regulation of inflammatory cascades, apoptosis, and cancer. However, their roles are relatively unknown in TGFβ/SMAD signaling. SMAD3 and its adaptors, such as β2SP, are important mediators of TGFβ signaling and regulate gene expression to suppress stem cell-like phenotypes in diverse cancers, including hepatocellular carcinoma (HCC). Here, PJA1, an E3 ligase, promoted ubiquitination and degradation of phosphorylated SMAD3 and impaired a SMAD3/β2SP-dependent tumor-suppressing pathway in multiple HCC cell lines. In mice deficient for SMAD3 (Smad3 (+/-)), PJA1 overexpression promoted the transformation of liver stem cells. Analysis of genes regulated by PJA1 knockdown and TGFβ1 signaling revealed 1,584 co-upregulated genes and 1,280 co-downregulated genes, including many implicated in cancer. The E3 ligase inhibitor RTA405 enhanced SMAD3-regulated gene expression and reduced growth of HCC cells in culture and xenografts of HCC tumors, suggesting that inhibition of PJA1 may be beneficial in treating HCC or preventing HCC development in at-risk patients.Significance: These findings provide a novel mechanism regulating the tumor suppressor function of TGFβ in liver carcinogenesis.

Neurosurgery
Macki M, Mahajan A, Shatz R, **Air EL**, **Novikova M**, Fakih M, Elmenini J, **Kaur M**, **Bouchard KR**, **Funk BA**, and **Schwalb JM**. Prevalence of Alternative Diagnoses and Implications for Management in Idiopathic Normal Pressure Hydrocephalus Patients. *Neurosurgery* 2020; Epub ahead of print. PMID: 32472677. Full Text

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BACKGROUND: Following Bayes theorem, ventriculomegaly and ataxia confer only a 30% chance of idiopathic Normal Pressure Hydrocephalus (NPH). When coupled with positive responses to best diagnostic testing (extended lumbar drainage), 70% of patients recommended for shunting will not actually have NPH. This is inadequate clinical care. OBJECTIVE: To determine the proportion of alternative and treatable diagnoses in patients referred to a multidisciplinary NPH clinic. METHODS: Patients without previously diagnosed NPH were queried from prospectively collected data. At least 1 neurosurgeon, cognitive neurologist, and neuropsychologist jointly formulated best treatment plans. RESULTS: Of 328 total patients, 45% had an alternative diagnosis; 11% of all patients improved with treatment of an alternative diagnosis. Of 87 patients with treatable conditions, the highest frequency of pathologies included sleep disorders, and cervical stenosis, followed by Parkinson disease. Anti-cholinergic burden was a contributor for multiple patients. Of 142 patients undergoing lumbar puncture, 71% had positive responses and referred to surgery. Compared to NPH patients, mimickers were statistically significantly older with lower Montreal Cognitive Assessment (MoCA) score and worse gait parameters. Overall, 26% of the original patients underwent shunting. Pre-post testing revealed a statistically significant improved MoCA score and gait parameters in those patients who underwent surgery with follow-up. CONCLUSION: Because the Multidisciplinary NPH Clinic selected only 26% for surgery (corroborating 30% in Bayes theorem), an overwhelming majority of patients with suspected NPH will harbor alternative diagnoses. Identification of contributing/confounding conditions will support the meticulous work-up necessary to appropriately manage patients without NPH while optimizing clinical responses to shunting in correctly diagnosed patients.

Neurosurgery

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PURPOSE: Magnetic resonance-guided radiation therapy (MRgRT) has shown great promise for localization and real-time tumor monitoring. However, to date, quantitative imaging has been limited for low field MRgRT. This work benchmarks quantitative T1, R2* and Proton Density (PD)-mapping in phantom on a 0.35T MR-linac and implements a novel acquisition method, STrategically Acquired Gradient Echo (STAGE). To further validate STAGE in a clinical setting, a pilot study was undertaken in a cohort of brain tumor patients to elucidate opportunities for longitudinal functional imaging with an MR-linac in the brain. METHODS: STAGE (two triple-echo gradient echo (GRE) acquisitions) was optimized for a 0.35T low-field MR-linac. Simulations were performed to choose two flip angles to optimize signal-to-noise ratio (SNR) and T1-mapping precision. Tradeoffs between SNR, scan time, and spatial resolution for whole-brain coverage were evaluated in healthy volunteers. Data were inputted into a STAGE processing pipeline to yield 4 qualitative images (T1-weighted, enhanced T1-weighted, proton-density (PD) weighted, and simulated FLuid-Attenuated Inversion Recovery (sFLAIR)), and 3 quantitative datasets (T1, PD, and R2*). A benchmarking ISMRM/NIST phantom consisting of vials with variable NiCl(2) and MnCl(2) concentrations was scanned using variable flip angles (VFA) (2-60 degrees) and inversion recovery (IR) methods at 0.35T. STAGE and VFA T1 values of vials were compared to IR T1 values. As measures of agreement with reference values and repeatability, relative error (RE) and coefficient of variability (CV) were calculated, respectively, for quantitative MR values within the phantom vials (spheres). To demonstrate feasibility, longitudinal STAGE data (pre-treatment, weekly, and ~2 months post-treatment) were acquired in an IRB-approved pilot study of brain tumor cases via the generation of temporal and differential quantitative MRI maps. RESULTS: In the phantom, RE of measured STAGE and VFA T1 relative to IR reference values were 7.0 ± 2.5% and 9.5 ± 2.2%, respectively. RE for the PD vials was 8.1%±6.8% and CV for phantom R2* measurements was 10.1% ± 9.9%. Simulations and volunteer experiments yielded final STAGE parameters of FA=50°/10°, 1x1x3 mm(3) resolution, TR=40ms, TE=5/20/34ms in 10 minutes (64 slices). In the pilot study of brain tumor patients, differential maps for R2* and T1 maps were sensitive to local tumor changes and appeared similar to 3T follow up MRI datasets. CONCLUSION: Quantitative T1, R2*, and PD mapping are promising at 0.35T agreeing well with reference data. STAGE phantom data offer quantitative representations comparable to traditional methods in a fraction of the acquisition time. Initial feasibility of implementing STAGE at 0.35T in a

patient brain tumor cohort suggests that detectable changes can be observed over time. With confirmation in a larger cohort, results may be implemented to identify areas of recurrence and facilitate adaptive radiation therapy.

Neurosurgery
Rock JP, **Prentiss T**, Mo SM, Myat Hnin Aye NS, **Asmaro K**, Win AT, Phyu AM, Maung TM, Khaing EE, Naung Z, Park KB, Hlaing K, and Myaing W. Traumatic Brain Injury in Myanmar: Preliminary Results and Development of an Adjunct Electronic Medical Record. *World Neurosurg* 2020; Epub ahead of print. PMID: 32413564. Full Text

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BACKGROUND: The treatment of traumatic brain injury (TBI) in Myanmar is a major health issue. Comprehensive appreciation of the pathology is limited given the lack of granular metadata available. In this proof-of-concept study, we analyzed demographic data on TBI generated from a novel prospective, online database in a low-to-middle income country (LMIC). METHODS: Neurosurgery residents were given an electronic tablet for data entry onto an online database. Metadata-driven data capture was carried prospectively by the trained residents and the information was reviewed weekly by the supervising team in the United States. RESULTS: Complete data was available on 242/253 (96%) patients. Age at admission was 37 years (range 16-85) and length of stay was 3.53 days (1-21). Etiologies included motorcycle accidents, falls, assaults, pedestrian vehicular injuries and industrial accidents. Dispositions were primarily to home (211). Average Glasgow Coma Score (GCS) at admission was 12.97. There was a 68% mortality rate of patients directly admitted to NOGH with GCS <8 versus 75% for patients transferred in from other facilities. Surgery was performed on 30 patients (12.4%). CONCLUSIONS: Despite a lack of formal training in electronic medical records or research, the resident team was able to capture the majority of admissions with granular-level data. This helped shed light on the etiology and severity of TBI in Myanmar. As a result, more effective transport systems and access to trauma care must be achieved. Accessible regional trauma centers with investment in intensive care units, operative care, anesthesia, and imaging resources is necessary.

Neurosurgery
Zhang Y, **Zhang Y**, **Chopp M**, **Zhang ZG**, **Mahmood A**, and **Xiong Y**. Mesenchymal Stem Cell-Derived Exosomes Improve Functional Recovery in Rats After Traumatic Brain Injury: A Dose-Response and Therapeutic Window Study. *Neurorehabil Neural Repair* 2020; Epub ahead of print. PMID: 32462980. Full Text

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Background. Mesenchymal stem cell (MSC)-derived exosomes play a critical role in regenerative medicine. Objective. To determine the dose- and time-dependent efficacy of exosomes for treatment of traumatic brain injury (TBI). Methods. Male rats were subjected to a unilateral moderate cortical contusion. In the dose-response study, animals received a single intravenous injection of exosomes (50, 100, 200 µg per rat) or vehicle, with treatment initiated at 1 day after injury. In the therapeutic window study, animals received a single intravenous injection of 100 µg exosomes or vehicle starting at 1, 4, or 7 days after injury. Neurological functional tests were performed weekly after TBI for 5 weeks. Spatial learning was measured on days 31 to 35 after TBI using the Morris water maze test. Results. Compared with the vehicle, regardless of the dose and delay in treatment, exosome treatment significantly improved sensorimotor and cognitive function, reduced hippocampal neuronal cell loss, promoted angiogenesis and neurogenesis, and reduced neuroinflammation. Exosome treatment at 100 µg per rat exhibited a significant therapeutic effect compared with the 50- or 200-µg exosome groups. The time-dependent exosome treatment data demonstrated that exosome treatment starting at 1 day post-TBI provided a significantly greater improvement in functional and histological outcomes than exosome treatments at the other 2 delayed treatments. Conclusions. These results indicate that exosomes have a wide range of effective doses for treatment of TBI with a therapeutic window of at least 7 days postinjury. Exosomes may provide a novel therapeutic intervention in TBI.

Obstretrics, Gynecology and Women's Health Services
Hong L, **Smith N**, **Keerthy M**, **Lee-Griffith M**, **Garcia R**, **Shaman M**, and **Goyert G**. Severe COVID-19 infection in pregnancy requiring intubation without preterm delivery: A case report. *Case Rep Womens Health* 2020; 27. PMID: 32382516. Full Text

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BACKGROUND: Coronavirus-2019 (COVID-19) is a global health crisis, but there is limited guidance for the critical care management of pregnant patients experiencing respiratory collapse. We describe our management of a peri-viable pregnant patient requiring intubation; discussion includes pharmacologic interventions, mechanical ventilation adjustments, and

consideration of fetal interventions, including delivery timing. CASE: A 36-year-old, gravida 2, para 1 woman positive for COVID-19 at 23 weeks of gestation with severe disease required admission to the intensive care unit and intubation. She completed 5 days of hydroxychloroquine and 7 days of prednisone. She was successfully intubated after 8 days and discharged home in a stable condition without preterm delivery on hospital day 11. CONCLUSION: Fortunately, the patient responded to aggressive respiratory support with intubation and mechanical ventilation early upon presentation. It is unclear whether our institution's empiric use of hydroxychloroquine and prednisone facilitated her recovery. We hope that our report helps other institutions navigate the complex care surrounding pregnant patients with severe COVID-19 pneumonia requiring intensive care.

Ophthalmology and Eye Care Services

Barbosa J, Syeda S, Rodriguez-Torres Y, **Le K**, and Lin X. Quantifying vitreous inflammation in uveitis: an optical coherence tomography prospective study. *Can J Ophthalmol* 2020; Epub ahead of print. PMID: 32439194. Full Text

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OBJECTIVE: To quantify vitreous inflammation in a uveitis cohort using optical coherence tomography and correlate findings to gold-standard Nussenblatt scores. DESIGN: Prospective cohort study. PARTICIPANTS: 36 eyes from 19 patients primarily with pan uveitis. METHODS: Study participants were scanned with optical coherence tomography and evaluated by 2 independent graders using open-source ImageJ software. Graders characterized the mean intensity of the vitreous in a 67 500-pixel box immediately above the internal limiting membrane and over the fovea and divided it by the mean intensity of the retinal pigment epithelial layer (RPE). The vitreous to retinal pigment epithelial layer ratio (VIT/RPE) ratios were correlated to Nussenblatt vitreous haze scores recorded by an independent uveitis specialist blinded to the graders' reads. Grader 1 measured intensity a second time after a 48-hour washout period, and the intraclass correlation coefficients (2,1) were calculated for intra- and intergrader reliability. RESULTS: 21 (58.3%) eyes had a Nussenblatt score of 0, 9 (25.0%) had a score of 0.5, and the remaining 6 (16.7%) had a score ranging from 1 to 4. The r values for VIT/RPE intensity ratio regressed against Nussenblatt scores were 0.670, 0.672, and 0.660 for grader 1 read 1, grader 1 read 2, and grader 2 read 1, respectively ($p < 0.001$ for all linear correlations). The intragrader reliability was 0.999 ($p < 0.001$) and intergrader reliability was 1.000 ($p < 0.001$). CONCLUSION: The VIT/RPE intensity ratio is a clinically relevant measure that reliably captures inflammation in uveitis and correlates well with gold-standard Nussenblatt scores.

Ophthalmology and Eye Care Services

Hosseinzadeh Z, Hauser S, Singh Y, Pelzl L, Schuster S, Sharma Y, Höflinger P, Zacharopoulou N, Stournaras C, **Rathbun DL**, Zrenner E, Schöls L, and Lang F. Decreased Na(+)/K(+) ATPase Expression and Depolarized Cell Membrane in Neurons Differentiated from Chorea-Acanthocytosis Patients. *Sci Rep* 2020; 10(1):8391. PMID: 32439941. Full Text

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Loss of function mutations of the chorein-encoding gene VPS13A lead to chorea-acanthocytosis (ChAc), a neurodegenerative disorder with accelerated suicidal neuronal cell death, which could be reversed by lithium. Chorein upregulates the serum and glucocorticoid inducible kinase SGK1. Targets of SGK1 include the Na(+)/K(+)-ATPase, a pump required for cell survival. To explore whether chorein-deficiency affects Na(+)/K(+) pump capacity, cortical neurons were differentiated from iPSCs generated from fibroblasts of ChAc patients and healthy volunteers. Na(+)/K(+) pump capacity was estimated from K(+)-induced whole cell outward current (pump capacity). As a result, the pump capacity was completely abolished in the presence of Na(+)/K(+) pump-inhibitor ouabain (100 µM), was significantly smaller in ChAc neurons than in control neurons, and was significantly increased in ChAc neurons by lithium treatment (24 hours 2 mM). The effect of lithium was reversed by SGK1-inhibitor GSK650394 (24 h 10 µM). Transmembrane potential (V(m)) was significantly less negative in ChAc neurons than in control neurons, and was significantly increased in ChAc neurons by lithium treatment (2 mM, 24 hours). The effect of lithium on V(m) was virtually abrogated by ouabain. Na(+)/K(+) α1-subunit transcript levels and protein abundance were significantly

lower in ChAc neurons than in control neurons, an effect reversed by lithium treatment (2 mM, 24 hours). In conclusion, consequences of chorein deficiency in ChAc include impaired Na(+)/K(+) pump capacity.

Ophthalmology and Eye Care Services
Sekhar S, Ramesh P, Bassetto G, Zrenner E, Macke JH, and **Rathbun DL**. Characterizing Retinal Ganglion Cell Responses to Electrical Stimulation Using Generalized Linear Models. *Front Neurosci* 2020; 14:378. PMID: 32477044. Full Text

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The ability to preferentially stimulate different retinal pathways is an important area of research for improving visual prosthetics. Recent work has shown that different classes of retinal ganglion cells (RGCs) have distinct linear electrical input filters for low-amplitude white noise stimulation. The aim of this study is to provide a statistical framework for characterizing how RGCs respond to white-noise electrical stimulation. We used a nested family of Generalized Linear Models (GLMs) to partition neural responses into different components-progressively adding covariates to the GLM which captured non-stationarity in neural activity, a linear dependence on the stimulus, and any remaining non-linear interactions. We found that each of these components resulted in increased model performance, but that even the non-linear model left a substantial fraction of neural variability unexplained. The broad goal of this paper is to provide a much-needed theoretical framework to objectively quantify stimulus paradigms in terms of the types of neural responses that they elicit (linear vs. non-linear vs. stimulus-independent variability). In turn, this aids the prosthetic community in the search for optimal stimulus parameters that avoid indiscriminate retinal activation and adaptation caused by excessively large stimulus pulses, and avoid low fidelity responses (low signal-to-noise ratio) caused by excessively weak stimulus pulses.

Orthopedics/Bone and Joint
Khalil LS, **Cross AG**, Savoie FH, 3rd, and **Makhni EC**. Primary Repair of Proximal Ulnar Collateral Ligament Ruptures in Pediatric Overhead Athletes. *Arthrosc Tech* 2020; 9(5):e639-e643. PMID: 32489838. Full Text

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Ulnar collateral ligament (UCL) injury is commonly seen in overhead throwing athletes resulting from the repetitive valgus stress placed on the medial elbow. UCL injuries (attenuation, insufficiency, or rupture) can result in medial elbow pain, a loss of pitch velocity and accuracy, and increased fatigue. Diagnosis can be made by performing a thorough physical examination along with imaging if indicated, such as ultrasound or magnetic resonance imaging. Treatment options include nonoperative in recreational athletes or those whose primary positions in sport are not high-volume throwing, such as position players in baseball. If nonoperative treatment fails, or the patient has potential for future high-level overhead activity such as a baseball pitcher, surgical repair or reconstruction may be indicated. This article describes our surgical technique for UCL repair in pediatric baseball pitchers.

Orthopedics/Bone and Joint
Lawrence RL, Braman JP, and Ludewig PM. Shoulder kinematics impact subacromial proximities: a review of the literature. *Braz J Phys Ther* 2020; 24(3):219-230. PMID: 31377124. Full Text

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BACKGROUND: Alterations in glenohumeral and scapulothoracic kinematics have been theorized to contribute to rotator cuff pathology by impacting the magnitude of the subacromial space. OBJECTIVE: The purpose of this review is to summarize what is currently known about the relationship between shoulder kinematics and subacromial proximities. CONCLUSIONS: A

variety of methods have been used to quantify subacromial proximities including photographs, MR imaging, ultrasonography, and single- and bi-plane radiographs. Changes in glenohumeral and scapulothoracic kinematics are associated with changes in subacromial proximities. However, the magnitude and direction of a particular motion's impact on subacromial proximities often vary between studies, which likely reflects different methodologies and subject populations. Glenohumeral elevation angle has been consistently found to impact subacromial proximities. Plane of humeral elevation also impacts subacromial proximities but to a lesser degree than the elevation angle. The impact of decreased scapulothoracic upward rotation on subacromial proximities is not absolute, but instead depends on the angle of humerothoracic elevation. The effects of scapular dyskinesis and humeral and scapular axial rotations on subacromial proximities are less clear. Future research is needed to further investigate the relationship between kinematics and subacromial proximities using more homogenous groups, determine the extent to which compression and other factors contribute to rotator cuff pathology, and develop accurate and reliable clinical measures of shoulder motion.

Orthopedics/Bone and Joint
Mahan MC, **Yu CC**, **Shields R**, **van Holsbeeck M**, and Zaltz I. Impingement-Free Hip Flexion in Asymptomatic Young Adult Women. *J Bone Joint Surg Am* 2020; Epub ahead of print. PMID: 32453117. Full Text

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BACKGROUND: Ultrasound-assisted measurement of hip flexion has demonstrated that hip flexion has been historically overestimated in men. To our knowledge, assessment of hip flexion in women using similar methods has not been reported. Establishing normative values for hip flexion is vital to aid diagnosis, management, and future research. Therefore, we asked 2 questions: (1) At what range of midsagittal hip flexion do soft-tissue impingement and femoroacetabular abutment occur in asymptomatic young adult women? (2) Do radiographic findings on a supine anteroposterior pelvic radiograph correlate with ultrasound-assisted measurements of hip flexion? METHODS: Fifty-five asymptomatic adult women volunteers (107 hips) underwent ultrasound-assisted assessment of hip flexion. Hip flexion was recorded at the initiation of labral contact and at bone-on-bone contact. Recorded motion was correlated with common radiographic measurements of hip morphology as observed on a supine anteroposterior pelvic radiograph. RESULTS: The mean age of the subjects was 26 ± 3 years (range, 21 to 35 years), and the mean body mass index was 23 ± 3 kg/m (range, 17 to 31.6 kg/m). Mean impingement-free and maximum midsagittal passive flexion were 72° ± 8° (95% confidence interval [CI], 70° to 74°) and 101° ± 11° (95% CI, 99° to 103°), respectively. There were no significant correlations between radiographic measurements of hip morphology and ultrasound-measured hip range of motion. CONCLUSIONS: Observed hip flexion in the asymptomatic hips of young women is substantially less than has been historically reported. Morphologic features that are measurable on anteroposterior pelvic radiographs do not correlate with ultrasound-measured hip flexion. Diagnosis of hip disorders and treatments that are designed to alter hip range of motion should be based on normative data. Future studies regarding surgical restoration and/or preservation of hip flexion should be based on an understanding of normal hip range of motion. CLINICAL RELEVANCE: Ultrasound-assisted hip flexion measurement established normative values to guide surgical restoration and/or preservation of hip flexion.

Orthopedics/Bone and Joint
Makhni EC, **Gulledge CM**, **Kuhlmann NA**, and **Muh SJ**. Open Acromioclavicular Joint Reconstruction With Semitendinosus Allograft Utilizing the Cerclage Technique. *Arthrosc Tech* 2020; 9(4):e505-e511. PMID: 32368471. Full Text

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Acromioclavicular (AC) joint injuries most commonly occur in young males after a direct injury at the acromion. General consensus stresses nonoperative treatment for type I and II injuries and surgical treatment for types IV through VI, whereas management of type III injuries is more controversial. If surgery is indicated, there are multiple techniques including hook plate, screw fixation, coracoclavicular fixation, and anatomic and nonanatomic reconstruction. The overall complication rate is high (14%), regardless of technique. In this Technical Note, we outline a technique for open repair of a chronic AC joint separation using a semitendinosus allograft using the cerclage for enhanced fixation.

Otolaryngology
Amit M, **Tam S**, Bader T, Sorkin A, and Benov A. Pausing cancer screening during the severe acute respiratory syndrome coronavirus 2pandemic: Should we revisit the recommendations? *Eur J Cancer* 2020; 134:86-89. PMID: 32473542. Full Text

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• The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which originated in Wuhan, China in late 2019, has become a major concern all over the world. • Shortly after the pandemic declaration, medical boards and societies released guidelines stating that medical professionals should use their clinical judgement when scheduling elective surgeries and procedures. • These delays in cancer screening, should not go unnoticed and this “knee-jerk” response should be revisited. • If the current situation last, we anticipate that thousands of cases will be diagnosed late or in some cases will be missed.

Otolaryngology
Macki M, Mahajan A, Shatz R, **Air EL**, **Novikova M**, Fakih M, Elmenini J, **Kaur M**, **Bouchard KR**, **Funk BA**, and **Schwalb JM**. Prevalence of Alternative Diagnoses and Implications for Management in Idiopathic Normal Pressure Hydrocephalus Patients. *Neurosurgery* 2020; Epub ahead of print. PMID: 32472677. Full Text

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BACKGROUND: Following Bayes theorem, ventriculomegaly and ataxia confer only a 30% chance of idiopathic Normal Pressure Hydrocephalus (NPH). When coupled with positive responses to best diagnostic testing (extended lumbar drainage), 70% of patients recommended for shunting will not actually have NPH. This is inadequate clinical care. OBJECTIVE: To determine the proportion of alternative and treatable diagnoses in patients referred to a multidisciplinary NPH clinic. METHODS: Patients without previously diagnosed NPH were queried from prospectively collected data. At least 1 neurosurgeon, cognitive neurologist, and neuropsychologist jointly formulated best treatment plans. RESULTS: Of 328 total patients, 45% had an alternative diagnosis; 11% of all patients improved with treatment of an alternative diagnosis. Of 87 patients with treatable conditions, the highest frequency of pathologies included sleep disorders, and cervical stenosis, followed by Parkinson disease. Anti-cholinergic burden was a contributor for multiple patients. Of 142 patients undergoing lumbar puncture, 71% had positive responses and referred to surgery. Compared to NPH patients, mimickers were statistically significantly older with lower Montreal Cognitive Assessment (MoCA) score and worse gait parameters. Overall, 26% of the original patients underwent shunting. Pre-post testing revealed a statistically significant improved MoCA score and gait parameters in those patients who underwent surgery with follow-up. CONCLUSION: Because the Multidisciplinary NPH Clinic selected only 26% for surgery (corroborating 30% in Bayes theorem), an overwhelming majority of patients with suspected NPH will harbor alternative diagnoses. Identification of contributing/confounding conditions will support the meticulous work-up necessary to appropriately manage patients without NPH while optimizing clinical responses to shunting in correctly diagnosed patients.

Otolaryngology
Swegal W, **Deeb R**, Greene J, **Peterson E**, **Perri MB**, **Bardossy AC**, **Zervos M**, and **Jones LR**. Changes in Nasal Staphylococcus Colonization and Infection Rates After Nasal Surgery. *Facial Plast Surg Aesthet Med* 2020; Epub ahead of print. PMID: 32392437. Full Text

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Background: The relationship between nasal flora and infection rates in patients undergoing nasal surgery is of interest. This relationship has been studied though changes that may take place due to surgery have never been elucidated. Objective: To assess colonization rates and changes in colonization patterns of methicillin-resistant or methicillin-sensitive Staphylococcus aureus (MRSA/MSSA) in nasal flora in patients undergoing nasal surgery and to determine whether colonization is a risk factor for postoperative infection. Methods: Patients undergoing nasal surgery including septoplasty, rhinoplasty, or nasal valve repair were recruited prospectively. Patients completed a survey preoperatively concerning risk factors of postoperative infection. Nasal swabs and cultures were done preoperatively and at 1 week postoperatively. Patients were assessed for surgical site infections postoperatively. Results: Fifty-five patients completed both preoperative and postoperative nasal

swabs. Preoperative to postoperative colonization rates increased for MRSA (2-5%) and MSSA (22-36%). Of the 55 patients, 11 had a change in nasal flora postoperatively, 9 of whom were colonized with a Staphylococcus aureus strain. However, MSSA/MRSA colonization either preoperatively or postoperatively was not associated with surgical site infections. Gender was the only variable found to be associated with postoperative infection ($p = 0.007$) with all four infections occurring in females. Conclusions: MSSA and MRSA do not appear to be major risk factors for surgical site infection in nasal surgery, whereas prior nasal surgery is a risk factor. This is the first report of a change in nasal colonization after nasal surgery. This could have implications for antibiotic prophylaxis in select nasal surgery cases.

Otolaryngology
Yoo F, Kuan EC, Batra PS, Chan CK, Tajudeen BA, and Craig JR. Predictors of rhinorrhea response after posterior nasal nerve cryoablation for chronic rhinitis. *Int Forum Allergy Rhinol* 2020; Epub ahead of print. PMID: 32445248. Full Text

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BACKGROUND: Posterior nasal nerve (PNN) cryoablation has shown promise in improving rhinorrhea due to allergic and nonallergic rhinitis (NAR). Early case series have shown meaningful clinical improvement in 75-80% of patients, but variables predicting PNN cryoablation success have not been studied. The purpose of this study was to evaluate whether disease features and ipratropium nasal spray response predicted rhinorrhea response after PNN cryoablation. METHODS: A multi-institutional retrospective case-control study of 55 patients who underwent PNN cryoablation for bilateral rhinorrhea due to allergic, nonallergic, or mixed rhinitis was conducted at 3 tertiary medical centers. Patients received a 1-month trial of ipratropium spray. Runny Nose Scores (RNSs) of 0-5 from the 22-item Sino-Nasal Outcome Test were collected prospectively, before and after PNN cryoablation. RESULTS: The mean age of subjects was 55.3 years and 54.6% were women. Mean follow-up was 170 days. NAR comprised 62% of patients. Of the 48 patients who trialed ipratropium spray, 33 (69%) had some response and 15 (31%) had no response. Mean overall preprocedural RNS was 4.2 ± 1.0. After PNN cryoablation, there was a ≥1-point decrease in RNS in 39 patients (71%). Only ipratropium spray (INS) response predicted cryoablation success. For ipratropium spray responders, 28 of 33 (85%) had improved RNS after cryoablation, whereas 5 of 15 (33%) nonresponders improved ($p = 0.001$). CONCLUSION: In chronic rhinitis patients, rhinorrhea response to ipratropium was predictive of rhinorrhea improvement after PNN cryoablation. This study has important implications for preoperative counseling and guiding patient expectations when considering PNN cryoablation.

Otolaryngology
Zhao EE, Koochakzadeh S, Nguyen SA, **Yoo F**, Pecha P, and Schlosser RJ. Orbital complications of acute bacterial rhinosinusitis in the pediatric population: A systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol* 2020; 135:110078. PMID: 32408012. Full Text

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OBJECTIVES: Assess characteristics and outcomes of orbital complications of acute bacterial rhinosinusitis (ABRS) in the pediatric population and evaluate trends over time. METHODS: A literature search of pediatric orbital complications was performed in the following databases: Ovid MEDLINE, Scopus, and Cochrane Database of Systematic Reviews. Studies reporting data for at least 10 subjects with orbital complications of sinusitis under 18 years old were included. Studies were grouped by publication year; before 2010 and after and including 2010. Studies that only included patients with subperiosteal abscess (SPA) were grouped in a separate category. Data collected include demographics, Chandler class complications, intra-operative culture, treatment, and outcomes. Meta-analysis of proportion was performed to compare data from studies published before 2010 and data published in 2010 and after. RESULTS: Thirty-five studies met inclusion criteria. No significant difference was observed over time in gender of subjects in the all Chandler complications or SPA only groups ($P > 0.72$). The proportion of subjects presenting with Chandler IV complications decreased from 6.8% to 2.9% in recent studies ($P = 0.019$). The proportion of subjects treated surgically decreased from 45.2% to 21.7% in the all Chandler complications group ($P < 0.0001$) and from 90.0% to 47.9% in the SPA only group, $P < 0.0001$. The proportion of S. pneumoniae positive cultures decreased from 20.5% to 9.1% ($P = 0.02$). CONCLUSION: The demographics of pediatric patients treated for orbital complications of ABRS in published literature has been stable. Patients reported in more recently published studies are less likely to present with orbital abscess and more likely to receive conservative treatment. The proportion of positive Streptococcus pneumoniae cultures have decreased.

Otolaryngology
Zhao K, Kim K, **Craig JR**, and Palmer JN. Using 3D printed sinonasal models to visualize and optimize personalized sinonasal sinus irrigation strategies. *Rhinology* 2020; Epub ahead of print. PMID: 32441708. Request Article

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BACKGROUND: Topical sinus irrigations (neti-pot, squeeze bottles) play a critical role in the management of sinonasal disease. However, due to intricate nasal anatomy, penetration of topical irrigations to targeted sinus regions may be highly variable, and difficult to objectively predict. Variables, including head positions, injection angles, flow rates, etc. may vary significantly depending on the individual's anatomy. OBJECTIVE: The purpose of this study was to propose a novel idea: using a 3D printed model of sinonasal cavities to visualize and develop a patient-specific irrigation strategy. METHODS: As a proof of concept, 3D replicas of one patient's sinonasal cavities pre- and post-surgery were printed with a Form2 SLA 3D printer based on their CT scans. The setup included rubber/silicon seals attached to the model's nostrils to create a watertight seal with the irrigation device and food color dye added for better visualization of irrigation results. RESULTS: Irrigations were performed on the 3D models with various head positions, injection angles, and flow rates, and were successful to determine the optimal strategy to targeted sinuses. Significant differences were observed between different targeted sinuses and between pre and post-surgery models. CONCLUSION: With more affordable 3D printing, this technology may potentially improve patient care and patient education, allowing clinicians and patients to develop a personalized irrigation strategy and have visual confirmation.

Pathology
Caines A, **Allo G**, and **Siddiqui Y**. Gastric varices from metastatic ovarian cancer with splenic involvement. *Pract Gastroenterol* 2020; 44(2):40-44. PMID: Not assigned. Request Article

Left-sided portal hypertension (LSPH), also known as splenoportal hypertension, is a rare but life-threatening cause of upper gastrointestinal bleeding. LSPH often occurs in non-cirrhotic patients as a consequence of splenic vein obstruction. We present a case of isolated gastric varices due to mass effect on the splenic vein and likely tumor thrombus due to metastatic ovarian cancer.

Pathology
Fatima S, **D'Sa H**, **Chaffins ML**, **Menon M**, and **Friedman BJ**. An elderly male with a chronic rash on the right foot. *Indian J Dermatol* 2020; 65(3):222-224. PMID: Not assigned. Full Text

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Pathology
Favazza LA, Parseghian CM, Kaya C, Nikiforova MN, Roy S, Wald AI, Landau MS, Proksell SS, Dueker JM, Johnston ER, Brand RE, Bahary N, Gorantla VC, Rhee JC, Pingpank JF, Choudry HA, Lee K, Paniccia A, Ongchin MC, Zureikat AH, Bartlett DL, and Singhi AD. KRAS amplification in metastatic colon cancer is associated with a history of inflammatory bowel disease and may confer resistance to anti-EGFR therapy. *Mod Pathol* 2020; Epub ahead of print. PMID: 32376853. Full Text

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Mutations in RAS occur in 30-50% of metastatic colorectal carcinomas (mCRCs) and correlate with resistance to anti-EGFR therapy. Consequently, mCRC biomarker guidelines state RAS mutational testing should be performed when considering EGFR inhibitor treatment. However, a small subset of mCRCs are reported to harbor RAS amplification. In order to elucidate the clinicopathologic features and anti-EGFR treatment response associated with RAS amplification, we retrospectively reviewed a large cohort of mCRC patients that underwent targeted next-generation sequencing and copy number analysis for

KRAS, NRAS, HRAS, BRAF, and PIK3CA. Molecular testing was performed on 1286 consecutive mCRC from 1271 patients as part of routine clinical care, and results were correlated with clinicopathologic findings, mismatch repair (MMR) status and follow-up. RAS amplification was detected in 22 (2%) mCRCs and included: KRAS, NRAS, and HRAS for 15, 5, and 2 cases, respectively (6-21 gene copies). Patients with a KRAS-amplified mCRC were more likely to report a history of inflammatory bowel disease ($p < 0.001$). In contrast, mutations in KRAS were associated with older patient age, right-sided colonic origin, low-grade differentiation, mucinous histology, and MMR proficiency ($p \leq 0.017$). Four patients with a KRAS-amplified mCRC and no concomitant RAS/BRAF/PIK3CA mutations received EGFR inhibitor-based therapy, and none demonstrated a clinicoradiographic response. The therapeutic impact of RAS amplification was further evaluated using a separate, multi-institutional cohort of 23 patients. Eight of 23 patients with KRAS-amplified mCRC received anti-EGFR therapy and all 8 patients exhibited disease progression on treatment. Although the number of KRAS-amplified mCRCs is limited, our data suggest the clinicopathologic features associated with mCRC harboring a KRAS amplification are distinct from those associated with a KRAS mutation. However, both alterations seem to confer EGFR inhibitor resistance and, therefore, RAS testing to include copy number analyses may be of consideration in the treatment of mCRC.

Pathology
Onwubiko I, **Kasperek G**, **Laforest RA**, **Philip SG**, **Kuriakose P**, and **Otrock ZK**. Predictors of response and outcome of patients with acquired haemophilia A. *Haemophilia* 2020; Epub ahead of print. PMID: 32469118. Full Text

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Pathology
Oska S, **Zarbo A**, **Yeager D**, **Friedman BJ**, and **Shwayder T**. Melanoma arising in a patient with ataxia-telangiectasia: A call for full skin examinations in this patient population. *Pediatr Dermatol* 2020; Epub ahead of print. PMID: 32413934. Full Text

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Ataxia-telangiectasia (A-T) is an autosomal recessive, multisystem disorder characterized by cerebellar ataxia and oculocutaneous telangiectasias that present in early childhood. Increased incidence of malignancy is also associated with A-T. Hematopoietic malignancies occur most commonly, with a majority being lymphoid cancers; however, there is a risk for other malignancies, such as breast, gastric, and other solid tumors. Herein, we report the case of a 28-year-old woman with A-T with melanoma.

Pathology
van Leenders G, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, Litjens G, McKenney JK, Melamed J, Mottet N, Paner GP, Samaratunga H, Schoots IG, Simko JP, Tsuzuki T, Varma M, Warren AY, Wheeler TM, **Williamson SR**, and Iczkowski KA. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2020; Epub ahead of print. PMID: 32459716. Full Text

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Five years after the last prostatic carcinoma grading consensus conference of the International Society of Urological Pathology (ISUP), accrual of new data and modification of clinical practice require an update of current pathologic grading guidelines. This manuscript summarizes the proceedings of the ISUP consensus meeting for grading of prostatic carcinoma held in September 2019, in Nice, France. Topics brought to consensus included the following: (1) approaches to reporting of Gleason patterns 4 and 5 quantities, and minor/tertiary patterns, (2) an agreement to report the presence of invasive cribriform carcinoma, (3) an agreement to incorporate intraductal carcinoma into grading, and (4) individual versus aggregate grading of systematic and multiparametric magnetic resonance imaging-targeted biopsies. Finally, developments in the field of artificial intelligence in the grading of prostatic carcinoma and future research perspectives were discussed.

Pathology

Williamson SR, Cardili L, **Whiteley LJ**, **Sanchez J**, and **Kis O**. Sclerosing TSC1 Mutated Renal Cell Carcinoma: An Unusual Pattern Mimicking MITF Family Translocation Renal Cell Carcinoma. *Genes Chromosomes Cancer* 2020; Epub ahead of print. PMID: 32418252. Full Text

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The tuberous sclerosis genes and MTOR are increasingly being found to have important roles in novel subtypes of renal cancer, particularly emerging entities eosinophilic solid and cystic renal cell carcinoma (RCC) and high-grade oncocytic renal tumor (HOT) / RCC with eosinophilic and vacuolated cytoplasm. We report a unique renal neoplasm in a 66 year-old woman that initially mimicked MITF family translocation RCC due to mixed clear and eosinophilic cells, extensive stromal hyalinization, and psammoma bodies, yet which was negative for TFE3 and TFEB fluorescence in situ hybridization (FISH) and a next generation sequencing (NGS) gene fusion assay. Cytoplasmic stippling triggered consideration of TSC-associated neoplasms, and a targeted next generation sequencing assay revealed a variant in exon 21 of TSC1 resulting in c.2626G > T p.(Glu876*) truncating mutation. This report adds to the morphologic spectrum of TSC-related renal neoplasms, including prominent stromal hyalinization as a potentially deceptive pattern. Due to the overlap in cytoplasmic stippling between eosinophilic solid and cystic RCC and HOT / RCC with eosinophilic and vacuolated cytoplasm, it is debatable which category this example would best fit. Further understanding of these entities and other renal neoplasms with alterations in the TSC genes will elucidate whether they should be considered a family of tumors. This article is protected by copyright. All rights reserved.

Pharmacy

Alosaimy S, **Sabagha NL**, Lagnf AM, Zasowski EJ, Morrisette T, Jorgensen SCJ, Trinh TD, Mynatt RP, and Rybak MJ. Monotherapy with Vancomycin or Daptomycin versus Combination Therapy with β-Lactams in the Treatment of Methicillin-Resistant Staphylococcus Aureus Bloodstream Infections: A Retrospective Cohort Analysis. *Infect Dis Ther* 2020; 9(2):325-339. PMID: 32248513. Full Text

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BACKGROUND: Methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections (BSI) are associated with high morbidity and mortality. More in vitro, in vivo, and clinical data suggest that vancomycin (VAN) or daptomycin (DAP) combination therapy with β-lactams (BL) improves outcomes of MRSA infections. We hypothesize that BL combination with VAN or DAP would reduce the odds of clinical failure compared to VAN or DAP monotherapy. METHODS: A retrospective cohort study of adult patients ≥ 18 years treated with VAN or DAP for MRSA BSI from 2006 to 2019 at Detroit Medical Center. Combination therapy (CT) was defined as VAN or DAP plus any BL for ≥ 24 h within 72 h of index culture. Monotherapy (MT) was defined as ≥ 72 h VAN or DAP within 72 h of index culture and no BL for ≥ 24 h up to 7 days following VAN/DAP initiation. Primary outcome was composite endpoint of clinical failure defined as: (1) 30-day mortality, (2) 60-day recurrence, or (3) persistent bacteremia (PB). PB was defined as bacteremia > 5 days. Multivariable logistic regression was used to evaluate the association between CT and the primary outcome. RESULTS: Overall, 597 patients were included in this analysis, 153 in the MT group and 444 in the CT group. CT was independently associated with reduced odds of clinical failure (adjusted odds ratio, 0.523; 95% confidence interval, 0.348-0.787). The composite endpoint was driven by 60-day recurrence and PB but not 30-day mortality. There were no difference in adverse events including nephrotoxicity between the two study arms.

CONCLUSIONS: In hospitalized adults with MRSA BSI, CT with any BL was independently associated with improved clinical outcomes and may ultimately be selected as preferred therapy.

Pharmacy
Fadel R, **Morrison AR**, **Vahia A**, **Smith ZR**, **Chaudhry Z**, **Bhargava P**, **Miller J**, **Kenney RM**, **Alangaden G**, and **Ramesh MS**. Early Short Course Corticosteroids in Hospitalized Patients with COVID-19. *Clin Infect Dis* 2020; Epub ahead of print. PMID: 32427279. Full Text

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BACKGROUND: There is no proven antiviral or immunomodulatory therapy for COVID-19. The disease progression associated with the pro-inflammatory host response prompted us to examine the role of early corticosteroid therapy in patients with moderate to severe COVID-19. METHODS: We conducted a single pre-test, single post-test quasi-experiment in a multi-center health system in Michigan from March 12 to March 27, 2020. Adult patients with confirmed moderate to severe COVID were included. A protocol was implemented on March 20, 2020 using early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days. Outcomes of standard of care (SOC) and early corticosteroid groups were evaluated, with a primary composite endpoint of escalation of care from ward to ICU, new requirement for mechanical ventilation, and mortality. All patients had at least 14 days of follow-up. RESULTS: We analyzed 213 eligible subjects, 81 (38%) and 132 (62%) in SOC and early corticosteroid groups, respectively.The composite endpoint occurred at a significantly lower rate in the early corticosteroid group (34.9% vs. 54.3%, p=0.005). This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (8 vs. 5 days, p < 0.001). Multivariate regression analysis demonstrated an independent reduction in the composite endpoint at 14-days controlling for other factors (aOR: 0.41; 95% CI [0.22 - 0.77]). CONCLUSION: An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.

Pharmacy
Morrison A, **Brar I**, **Willens D**, and **Thomas E**. Collaboration Improves PrEP Care for Providers and Patients. *Am J Med* 2020; 133(5):e212. PMID: 32450956. Full Text

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Plastic Surgery
Morrison A, **Brar I**, **Willens D**, and **Thomas E**. Collaboration Improves PrEP Care for Providers and Patients. *Am J Med* 2020; 133(5):e212. PMID: 32450956. Full Text

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Public Health Sciences
Bergman D, **Modh A**, **Schultz L**, **Snyder J**, **Mikkelsen T**, **Shah M**, Ryu S, **Siddiqui MS**, and **Walbert T**. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol* 2020; Epub ahead of print. PMID: 32444980. Full Text

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PURPOSE: Outcomes for patients with recurrent high-grade glioma (HGG) progressing on bevacizumab (BEV) are dismal. Fractionated stereotactic radiosurgery (FSRS) has been shown to be feasible and safe when delivered in this setting, but

prospective evidence is lacking. This single-institution randomized trial compared FSRS plus BEV-based chemotherapy versus BEV-based chemotherapy alone for BEV-resistant recurrent malignant glioma. MATERIALS AND METHODS: HGG patients on BEV with tumor progression after 2 previous treatments were randomized to 1) FSRS plus BEV-based chemotherapy or 2) BEV-based chemotherapy with irinotecan, etoposide, temozolomide, or carboplatin. FSRS was delivered as 32 Gy (8 Gy × 4 fractions within 2 weeks) to the gross target volume and 24 Gy (6 Gy × 4 fractions) to the clinical target volume (fluid-attenuated inversion recovery abnormality). The primary endpoints were local control (LC) at 2 months and progression-free survival (PFS). RESULTS: Of the 35 patients enrolled, 29 had glioblastoma (WHO IV) and 6 had anaplastic glioma (WHO III). The median number of prior recurrences was 3. Patients treated with FSRS had significantly improved PFS (5.1 vs 1.8 months, P < .001) and improved LC at 2 months (82% [14/17] vs 27% [4/15], P = .002). The overall median survival was 6.6 months (7.2 months with FSRS vs 4.8 months with chemotherapy alone, P = .11). CONCLUSIONS: FSRS combined with BEV-based chemotherapy in recurrent HGG patients progressing on BEV is feasible and improves LC and PFS when compared to treatment with BEV-based chemotherapy alone.

Public Health Sciences

Darst BF, Wan P, Sheng X, Bensen JT, Ingles SA, **Rybicki BA**, Nemesure B, John EM, Fowke JH, Stevens VL, Berndt SI, Huff CD, Strom SS, Park JY, Zheng W, Ostrander EA, Walsh PC, Srivastava S, Carpten J, Sellers TA, Yamoah K, Murphy AB, Sanderson M, Crawford DC, Gapstur SM, Bush WS, Aldrich MC, Cussenot O, Yeager M, Petrovics G, Cullen J, **Neslund-Dudas C**, Kittles RA, Xu J, Stern MC, Kote-Jarai Z, Govindasami K, Chokkalingam AP, Multigner L, Parent ME, Menegaux F, Cancel-Tassin G, Kibel AS, Klein EA, Goodman PJ, Drake BF, Hu JJ, Clark PE, Blanchet P, Casey G, Hennis AJM, Lubwama A, Thompson IM, Jr., Leach R, Gundell SM, Pooler L, Xia L, Mohler JL, Fontham ETH, Smith GJ, Taylor JA, Eeles RA, Brureau L, Chanock SJ, Watya S, Stanford JL, Mandal D, Isaacs WB, Cooney K, Blot WJ, Conti DV, and Haiman CA. A Germline Variant at 8q24 Contributes to Familial Clustering of Prostate Cancer in Men of African Ancestry. *Eur Urol* 2020; Epub ahead of print. PMID: 32409115. Full Text

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Although men of African ancestry have a high risk of prostate cancer (PCa), no genes or mutations have been identified that contribute to familial clustering of PCa in this population. We investigated whether the African ancestry-specific PCa risk variant at 8q24, rs72725854, is enriched in men with a PCa family history in 9052 cases, 143 cases from high-risk families, and 8595 controls of African ancestry. We found the risk allele to be significantly associated with earlier age at diagnosis, more aggressive disease, and enriched in men with a PCa family history (32% of high-risk familial cases carried the variant vs 23% of cases without a family history and 12% of controls). For cases with two or more first-degree relatives with PCa who had at least one family member diagnosed at age <60 yr, the odds ratios for TA heterozygotes and TT homozygotes were 3.92 (95% confidence interval [CI] = 2.13-7.22) and 33.41 (95% CI = 10.86-102.84), respectively. Among men with a PCa family history, the absolute risk by age 60 yr reached 21% (95% CI = 17-25%) for TA heterozygotes and 38% (95% CI = 13-65%) for TT homozygotes. We estimate that in men of African ancestry, rs72725854 accounts for 32% of the total familial risk explained by all known PCa risk variants. PATIENT SUMMARY: We found that rs72725854, an African ancestry-specific risk variant, is more common in men with a family history of prostate cancer and in those diagnosed with prostate cancer at younger ages. Men of African ancestry may benefit from the knowledge of their carrier status for this genetic risk variant to guide decisions about prostate cancer screening.

Public Health Sciences

Davis M, Martini R, Newman L, Elemento O, White J, Verma A, **Datta I**, **Adrianto I**, **Chen Y**, Gardner K, Kim HG, Colomb WD, Eltoum IE, Frost AR, Grizzle WE, Sboner A, Manne U, and Yates C. Identification of Distinct Heterogenic Subtypes and Molecular Signatures Associated with African Ancestry in Triple Negative Breast Cancer Using Quantified Genetic Ancestry Models in Admixed Race Populations. *Cancers (Basel)* 2020; 12(5). PMID: 32414099. Full Text

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Triple negative breast cancers (TNBCs) are molecularly heterogeneous, and the link between their aggressiveness with African ancestry is not established. We investigated primary TNBCs for gene expression among self-reported race (SRR) groups of African American (AA, n = 42) and European American (EA, n = 33) women. RNA sequencing data were analyzed to measure changes in genome-wide expression, and we utilized logistic regressions to identify ancestry-associated gene expression signatures. Using SNVs identified from our RNA sequencing data, global ancestry was estimated. We identified 156 African ancestry-associated genes and found that, compared to SRR, quantitative genetic analysis was a more robust method to identify racial/ethnic-specific genes that were differentially expressed. A subset of African ancestry-specific genes that were upregulated in TNBCs of our AA patients were validated in TCGA data. In AA patients, there was a higher incidence of basal-like two tumors and altered TP53, NFB1, and AKT pathways. The distinct distribution of TNBC subtypes and altered oncologic pathways show that the ethnic variations in TNBCs are driven by shared genetic ancestry. Thus, to appreciate the molecular diversity of TNBCs, tumors from patients of various ancestral origins should be evaluated.

Public Health Sciences
Dotiwala Z, Casciano J, Davis JR, Fox K, Gopalan G, Rastogi S, **Lamerato L**, and Mathur SK. Effect of clinically significant thresholds of eosinophil elevation on health care resource use in asthma. *Ann Allergy Asthma Immunol* 2020; Epub ahead of print. PMID: 32371242. Full Text

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BACKGROUND: Blood eosinophil counts correlate with exacerbations, but there is a lack of consensus on a clinically relevant definition of eosinophil count elevation. OBJECTIVE: To analyze health care resource use among patients with elevated blood eosinophil counts defined at 150 cells/μL or greater and 300 cells/μL or greater. METHODS: Data on patients who received a diagnosis of asthma between 2007 and 2016 were extracted from EMRClaims + database. Patients were defined as having elevated eosinophil counts if any test result during 3 months before follow-up found blood eosinophil count of 150 cells/μL or more or 300 cells/μL or more. Hospitalizations, emergency department visits, outpatient visits, and associated costs were compared. With logistic regression, likelihood of hospitalization was assessed in the presence of eosinophil elevation. RESULTS: Among 3687 patients who met the study criteria, 1152 received a test within 3 months before the follow-up period, of whom 644 (56%) had elevated eosinophil counts of 150 cells/μL or greater and 322 (29%) had eosinophil counts of 300 cells/μL or greater. Overall, the mean (SD) number of hospitalizations for patients with elevated eosinophil counts vs the comparator was significantly greater (0.29 [0.92] vs 0.17 [0.57], P < .001 at ≥150 cells/μL and 0.30 [0.95] vs 0.18 [0.61] at ≥300 cells/μL, P = .001). The total mean cost was significantly greater for patients with elevated eosinophil counts (at ≥150 cells/μL: $10,262 vs $7149, P < .001 and at ≥300 cells/μL: $9966 vs $7468, P = .003). CONCLUSION: Patients with asthma incurred greater health care resource use when their blood eosinophil counts were elevated at 150 cells/μL or greater and 300 cells/μL or greater as measured within 3 months of follow-up.

Public Health Sciences
Ghanem AI, **Modh A**, **Burmeister C**, Mahmoud O, and **Elshaikh MA**. Does the Interval Between Hysterectomy and Start of Adjuvant Radiation Treatment Influence Survival in Women With Endometrial Carcinoma?: A National Cancer Database analysis. *Am J Clin Oncol* 2020; Epub ahead of print. PMID: 32398405. Full Text

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OBJECTIVE: The objective of this study was to analyze the impact of the time interval (TI) between hysterectomy and initiation of adjuvant radiation treatment (ART) on overall survival (OS) among women with early stage endometrial carcinoma (EC) using the National Cancer Database (NCDB). MATERIALS AND METHODS: The NCDB was queried for women with the International Federation of Gynecology and Obstetrics (FIGO) stage I to II EC who underwent hysterectomy followed by ART. We examined the prognostic impact of TI on OS using the cutoff ≤8 or >8 weeks to initiate radiation treatment (RT). Two

groups of patients were created. Kaplan-Meier curves were created for OS analysis. Predictors of OS were identified. RESULTS: A total 16,520 women were identified. The median follow-up time for the entire cohort was 59.1 months. Median age was 63 years, and 82% were FIGO stage I. Pelvic external beam RT alone was used in 9569 (58%) and vaginal brachytherapy alone in 4265 women (26%). In total, 10,040 women (61%) received RT ≤8 weeks. Delay in initiating RT >8 weeks was associated with shorter 5-year OS (P=0.048). Independent predictors of shorter OS includes older age, African American race, higher comorbidity burden, higher tumor grade, the presence of lymphovascular invasion and stage II tumors. Although TI in initiating RT was a significant predictor for OS in univariate analysis, its independent significance of OS was lost on multivariate analysis (P=0.28). CONCLUSION: Our study suggests that TI between hysterectomy and initiation of ART was not an independent predictor of OS in women with early stage EC.

Public Health Sciences

Luria CJ, **Sitarik AR**, **Havstad S**, **Zoratti EM**, **Kim H**, **Wegienka GR**, **Joseph CLM**, and **Cassidy-Bushrow AE**. Association between asthma symptom scores and perceived stress and trait anxiety in adolescents with asthma. *Allergy Asthma Proc* 2020; 41(3):210-217. PMID: 32375966. Request Article

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Background: Emotional disorders, including depression and anxiety, are more prevalent in individuals with asthma than in the general population and are associated with poor asthma outcomes. Identification of patients with increased levels of stress and anxiety may be helpful when treating asthma and during asthma counseling. Objective: To further characterize the relationship between asthma symptoms and perceived stress and trait anxiety in an adolescent population. Methods: Adolescents (N = 335) ages 14-17 years were recruited to examine the effect of stress on health measures. They were included in the present analysis if they reported current asthma, defined as self-reported clinician-diagnosed asthma plus one or more episodes of asthma in the past year. Asthma symptoms were assessed on a 7-point scale by using a standardized questionnaire that targets nocturnal awakening due to asthma, symptoms on awakening, activity limitation, shortness of breath, time spent wheezing, and short-acting bronchodilator use. Stress was measured by using the Perceived Stress Scale (PSS), and trait anxiety was measured by using the State-Trait Anxiety Inventory. Linear regression was used to associate asthma symptoms with PSS and trait anxiety. Results: Thirty-eight adolescents (11.3%), with mean ± standard deviation age 16.7 ± 0.9 years, reported current asthma. Four of the six asthma symptom assessments had significant associations with PSS: symptoms on awakening ($\beta = 4.82$, $p < 0.001$), nocturnal awakening due to asthma ($\beta = 4.47$, $p < 0.001$), activity limitation ($\beta = 2.78$, $p = 0.005$), and shortness of breath ($\beta = 1.73$, $p = 0.014$). These associations remained significant after adjusting for gender, race, and the body mass index percentile. Trait anxiety had significant associations with nocturnal awakening ($\beta = 9.28$, $p = 0.002$) and symptoms on awakening ($\beta = 8.74$, $p = 0.002$). Associations remained significant after adjusting for gender, race, and body mass index percentile. Conclusion: Asthma symptom severity is associated with increased perceived stress and trait anxiety. Adolescents with asthma may represent a population that is particularly vulnerable to perceived stress and anxiety, which highlights the importance of considering these factors in asthma counseling.

Public Health Sciences

Macki M, Mahajan A, Shatz R, **Air EL**, **Novikova M**, Fakih M, Elmenini J, **Kaur M**, **Bouchard KR**, **Funk BA**, and **Schwalb JM**. Prevalence of Alternative Diagnoses and Implications for Management in Idiopathic Normal Pressure Hydrocephalus Patients. *Neurosurgery* 2020; Epub ahead of print. PMID: 32472677. Full Text

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BACKGROUND: Following Bayes theorem, ventriculomegaly and ataxia confer only a 30% chance of idiopathic Normal Pressure Hydrocephalus (NPH). When coupled with positive responses to best diagnostic testing (extended lumbar drainage), 70% of patients recommended for shunting will not actually have NPH. This is inadequate clinical care. OBJECTIVE: To determine the proportion of alternative and treatable diagnoses in patients referred to a multidisciplinary NPH clinic. METHODS: Patients without previously diagnosed NPH were queried from prospectively collected data. At least 1 neurosurgeon, cognitive neurologist, and neuropsychologist jointly formulated best treatment plans. RESULTS: Of 328 total patients, 45% had an alternative diagnosis; 11% of all patients improved with treatment of an alternative diagnosis. Of 87 patients with treatable conditions, the highest frequency of pathologies included sleep disorders, and cervical stenosis, followed by Parkinson disease. Anti-cholinergic burden was a contributor for multiple patients. Of 142 patients undergoing lumbar puncture, 71% had positive responses and referred to surgery. Compared to NPH patients, mimickers were statistically significantly older with lower Montreal Cognitive Assessment (MoCA) score and worse gait parameters. Overall, 26% of the

original patients underwent shunting. Pre-post testing revealed a statistically significant improved MoCA score and gait parameters in those patients who underwent surgery with follow-up. CONCLUSION: Because the Multidisciplinary NPH Clinic selected only 26% for surgery (corroborating 30% in Bayes theorem), an overwhelming majority of patients with suspected NPH will harbor alternative diagnoses. Identification of contributing/confounding conditions will support the meticulous work-up necessary to appropriately manage patients without NPH while optimizing clinical responses to shunting in correctly diagnosed patients.

Public Health Sciences

Nejad-Davarani SP, **Zakariaei N**, Chen Y, Haacke EM, **Hurst NJ**, **Siddiqui MS**, **Schultz LR**, **Snyder JM**, **Walbert T**, and **Glide-Hurst C**. Rapid Multi-contrast Brain Imaging on a 0.35T MR-linac. *Med Phys* 2020; Epub ahead of print. PMID: 32434276. Request Article

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PURPOSE: Magnetic resonance-guided radiation therapy (MRgRT) has shown great promise for localization and real-time tumor monitoring. However, to date, quantitative imaging has been limited for low field MRgRT. This work benchmarks quantitative T1, R2* and Proton Density (PD)-mapping in phantom on a 0.35T MR-linac and implements a novel acquisition method, STrategically Acquired Gradient Echo (STAGE). To further validate STAGE in a clinical setting, a pilot study was undertaken in a cohort of brain tumor patients to elucidate opportunities for longitudinal functional imaging with an MR-linac in the brain. METHODS: STAGE (two triple-echo gradient echo (GRE) acquisitions) was optimized for a 0.35T low-field MR-linac. Simulations were performed to choose two flip angles to optimize signal-to-noise ratio (SNR) and T1-mapping precision. Tradeoffs between SNR, scan time, and spatial resolution for whole-brain coverage were evaluated in healthy volunteers. Data were inputted into a STAGE processing pipeline to yield 4 qualitative images (T1-weighted, enhanced T1-weighted, proton-density (PD) weighted, and simulated FLuid-Attenuated Inversion Recovery (sFLAIR)), and 3 quantitative datasets (T1, PD, and R2*). A benchmarking ISMRM/NIST phantom consisting of vials with variable NiCl(2) and MnCl(2) concentrations was scanned using variable flip angles (VFA) (2-60 degrees) and inversion recovery (IR) methods at 0.35T. STAGE and VFA T1 values of vials were compared to IR T1 values. As measures of agreement with reference values and repeatability, relative error (RE) and coefficient of variability (CV) were calculated, respectively, for quantitative MR values within the phantom vials (spheres). To demonstrate feasibility, longitudinal STAGE data (pre-treatment, weekly, and ~2 months post-treatment) were acquired in an IRB-approved pilot study of brain tumor cases via the generation of temporal and differential quantitative MRI maps. RESULTS: In the phantom, RE of measured STAGE and VFA T1 relative to IR reference values were 7.0 ± 2.5% and 9.5 ± 2.2%, respectively. RE for the PD vials was 8.1%±6.8% and CV for phantom R2* measurements was 10.1% ± 9.9%. Simulations and volunteer experiments yielded final STAGE parameters of FA=50°/10°, 1x1x3 mm(3) resolution, TR=40ms, TE=5/20/34ms in 10 minutes (64 slices). In the pilot study of brain tumor patients, differential maps for R2* and T1 maps were sensitive to local tumor changes and appeared similar to 3T follow up MRI datasets. CONCLUSION: Quantitative T1, R2*, and PD mapping are promising at 0.35T agreeing well with reference data. STAGE phantom data offer quantitative representations comparable to traditional methods in a fraction of the acquisition time. Initial feasibility of implementing STAGE at 0.35T in a patient brain tumor cohort suggests that detectable changes can be observed over time. With confirmation in a larger cohort, results may be implemented to identify areas of recurrence and facilitate adaptive radiation therapy.

Public Health Sciences

Ober C, McKennan CG, Magnaye KM, Altman MC, Washington C, 3rd, Stanhope C, Naughton KA, Rosasco MG, Bacharier LB, Billheimer D, Gold DR, Gress L, Hartert T, **Havstad S**, Khurana Hershey GK, Hallmark B, Hogarth DK, Jackson DJ, **Johnson CC**, Kattan M, Lemanske RF, Lynch SV, Mendonca EA, Miller RL, Naureckas ET, O'Connor GT, Seroogy CM, **Wegienka G**, White SR, Wood RA, Wright AL, **Zoratti EM**, Martinez FD, Ownby D, Nicolae DL, **Levin AM**, and Gern JE. Expression quantitative trait locus fine mapping of the 17q12-21 asthma locus in African American children: a genetic association and gene expression study. *Lancet Respir Med* 2020; 8(5):482-492. PMID: 32380068. Full Text

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BACKGROUND: African ancestry is associated with a higher prevalence and greater severity of asthma than European ancestries, yet genetic studies of the most common locus associated with childhood-onset asthma, 17q12-21, in African Americans have been inconclusive. The aim of this study was to leverage both the phenotyping of the Children's Respiratory and Environmental Workgroup (CREW) birth cohort consortium, and the reduced linkage disequilibrium in African Americans, to fine map the 17q12-21 locus. METHODS: We first did a genetic association study and meta-analysis using 17q12-21 tag single-nucleotide polymorphisms (SNPs) for childhood-onset asthma in 1613 European American and 870 African American children from the CREW consortium. Nine tag SNPs were selected based on linkage disequilibrium patterns at 17q12-21 and their association with asthma, considering the effect allele under an additive model (0, 1, or 2 effect alleles). Results were meta-analysed with publicly available summary data from the EVE consortium (on 4303 European American and 3034 African American individuals) for seven of the nine SNPs of interest. Subsequently, we tested for expression quantitative trait loci (eQTLs) among the SNPs associated with childhood-onset asthma and the expression of 17q12-21 genes in resting peripheral blood mononuclear cells (PBMCs) from 85 African American CREW children and in upper airway epithelial cells from 246 African American CREW children; and in lower airway epithelial cells from 44 European American and 72 African American adults from a case-control study of asthma genetic risk in Chicago (IL, USA). FINDINGS: 17q12-21 SNPs were broadly associated with asthma in European Americans. Only two SNPs (rs2305480 in gasdermin-B [GSDMB] and rs8076131 in ORMDL sphingolipid biosynthesis regulator 3 [ORMDL3]) were associated with asthma in African Americans, at a Bonferroni-corrected threshold of p<0·0055 (for rs2305480_G, odds ratio [OR] 1·36 [95% CI 1·12-1·65], p=0·0014; and for rs8076131_A, OR 1·37 [1·13-1·67], p=0·0010). In upper airway epithelial cells from African American children, genotype at rs2305480 was the most significant eQTL for GSDMB (eQTL effect size [β] 1·35 [95% CI 1·25-1·46], p<0·0001), and to a lesser extent showed an eQTL effect for post-GPI attachment to proteins phospholipase 3 (β 1·15 [1·08-1·22], p<0·0001). No SNPs were eQTLs for ORMDL3. By contrast, in PBMCs, the five core SNPs were associated only with expression of GSDMB and ORMDL3. Genotype at rs12936231 (in zona pellucida binding protein 2) showed the strongest associations across both genes (for GSDMB, eQTLβ 1·24 [1·15-1·32], p<0·0001; and for ORMDL3 (β 1·19 [1·12-1·24], p<0·0001). The eQTL effects of rs2305480 on GSDMB expression were replicated in lower airway cells from African American adults (β 1·29 [1·15-1·44], p<0·0001). INTERPRETATION: Our study suggests that SNPs regulating GSDMB expression in airway epithelial cells have a major role in childhood-onset asthma, whereas SNPs regulating the expression levels of 17q12-21 genes in resting blood cells are not central to asthma risk. Our genetic and gene expression data in African Americans and European Americans indicated GSDMB to be the leading candidate gene at this important asthma locus. FUNDING: National Institutes of Health, Office of the Director.

Public Health Sciences

Park B, Budzynska K, Almasri N, Islam S, Alyas F, Carolan RL, Abraham BE, Castro-Camero PA, Shreve ME, Rees DA, and Lamerato L. Tight versus standard blood pressure control on the incidence of myocardial infarction and stroke: an observational retrospective cohort study in the general ambulatory setting. *BMC Fam Pract* 2020; 21(1):91. PMID: 32416722. Full Text

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BACKGROUND: The 2017 American College of Cardiology and American Heart Association guideline defined hypertension as blood pressure (BP) ≥ 130/80 mmHg compared to the traditional definition of ≥140/90 mmHg. This change raised much controversy. We conducted this study to compare the impact of tight (TBPC) versus standard BP control (SBPC) on the incidence of myocardial infarction (MI) and stroke. METHODS: We retrospectively identified all hypertensive patients in an ambulatory setting based on the diagnostic code for 1 year at our institution who were classified by the range of BP across 3 years into 2 groups of TBPC (< 130 mmHg) and SBPC (130-139 mmHg). We compared the incidence of new MI and stroke between the 2 groups across a 2-year follow-up. Multivariate analysis was done to identify independent predictors for the incidence of new MI and stroke. RESULTS: Of 5640 study patients, the TBPC group showed significantly less incidence of stroke compared to the SBPC group (1.5% vs. 2.7%, P < 0.010). No differences were found in MI incidence between the 2 groups (0.6% vs. 0.8%, P = 0.476). Multivariate analysis showed that increased age independently increased the incidence of both MI (OR 1.518, 95% CI 1.038-2.219) and stroke (OR 1.876, 95% CI 1.474-2.387), and TBPC independently decreased the incidence of stroke (OR 0.583, 95% CI 0.374-0.910) but not of MI. CONCLUSIONS: Our observational study suggests that TBPC may be beneficial in less stroke incidence compared to SBPC but it didn't seem to affect the incidence of MI. Our study is limited by its retrospective design with potential confounders.

Public Health Sciences
Poyiadji N, **Cormier P**, **Patel PY**, **Hadied MO**, **Bhargava P**, **Khanna K**, **Nadig J**, **Keimig T**, **Spizarny D**, **Reeser N**, **Klochko C**, **Peterson EL**, and **Song T**. Acute Pulmonary Embolism and COVID-19. *Radiology* 2020; Epub ahead of print. PMID: 32407256. Full Text

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Public Health Sciences
Rao SD, **Miragaya J**, **Parikh N**, **Honasoge M**, **Springer K**, **Van Harn M**, and **Divine GW**. Effect of vitamin D nutrition on disease indices in patients with primary hyperparathyroidism. *J Steroid Biochem Mol Biol* 2020; 201. PMID: 32407867. Request Article

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In patients with primary hyperparathyroidism, the size of the adenoma is a major determinant of biochemical indices, disease severity, and manner of presentation. However, the large variation in adenoma weight, both within and between populations and a steady decline in parathyroid adenoma weights over time remain largely unexplained. Based on the results in a small number of patients almost two decades ago we proposed that vitamin D nutritional status of the patient explains both the disease manifestations and much of the variation in adenoma size. Accordingly, we examined the relationship between vitamin D nutrition, as assessed by serum levels of 25-hydroxyvitamin D, and parathyroid gland weight, the best available index of disease severity, in a large number of patients (n = 440) with primary hyperparathyroidism. A significant inverse relationship was found between serum 25-hydroxyvitamin D level and log adenoma weight (r = -0.361; p < 0.001). Also, the adenoma weight was significantly related directly to serum PTH, calcium, and alkaline phosphatase as dependent variables. In patients with vitamin D deficiency (defined as serum 25-hydroxyvitamin D levels 15 ng/mL or lower), gland weight, PTH, AP, and adjusted calcium were each significantly higher than in patients with 25-hydroxyvitamin D levels of 16 ng/mL or higher, but serum 1,25-dihydroxyvitamin D levels were similar in both groups. We interpret this to mean that suboptimal vitamin D nutrition stimulates parathyroid adenoma growth by a mechanism unrelated to 1,25-dihydroxyvitamin D deficiency. We conclude that variable vitamin D nutritional status in the population may partly explain the differences in disease presentation.

Public Health Sciences
Swegal W, **Deeb R**, Greene J, **Peterson E**, **Perri MB**, **Bardossy AC**, **Zervos M**, and **Jones LR**. Changes in Nasal Staphylococcus Colonization and Infection Rates After Nasal Surgery. *Facial Plast Surg Aesthet Med* 2020; Epub ahead of print. PMID: 32392437. Full Text

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Background: The relationship between nasal flora and infection rates in patients undergoing nasal surgery is of interest. This relationship has been studied though changes that may take place due to surgery have never been elucidated. Objective: To assess colonization rates and changes in colonization patterns of methicillin-resistant or methicillin-sensitive Staphylococcus aureus (MRSA/MSSA) in nasal flora in patients undergoing nasal surgery and to determine whether colonization is a risk factor for postoperative infection. Methods: Patients undergoing nasal surgery including septoplasty, rhinoplasty, or nasal valve repair were recruited prospectively. Patients completed a survey preoperatively concerning risk factors of postoperative infection. Nasal swabs and cultures were done preoperatively and at 1 week postoperatively. Patients were assessed for surgical site infections postoperatively. Results: Fifty-five patients completed both preoperative and postoperative nasal swabs. Preoperative to postoperative colonization rates increased for MRSA (2-5%) and MSSA (22-36%). Of the 55 patients, 11 had a change in nasal flora postoperatively, 9 of whom were colonized with a Staphylococcus aureus strain. However, MSSA/MRSA colonization either preoperatively or postoperatively was not associated with surgical site infections. Gender was the only variable found to be associated with postoperative infection ($p = 0.007$) with all four infections occurring in females. Conclusions: MSSA and MRSA do not appear to be major risk factors for surgical site infection in nasal surgery, whereas prior nasal surgery is a risk factor. This is the first report of a change in nasal colonization after nasal surgery. This could have implications for antibiotic prophylaxis in select nasal surgery cases.

Public Health Sciences
Verma S, **Peterson EL**, **Liu B**, **Sabbah HN**, **Williams LK**, and **Lanfear DE**. Effectiveness of beta blockers in patients with and without a history of myocardial infarction. *Eur J Clin Pharmacol* 2020; Epub ahead of print. PMID: 32440720. Full Text

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PURPOSE: Studies demonstrating mortality benefit of beta blockers (BB) after myocardial infarction (MI) were conducted before the era of percutaneous intervention and widespread use of statins. Recent retrospective studies show inconsistent results regarding which subgroups of coronary artery disease (CAD) patients' benefit. Most studies did not account for medication changes over time. We evaluated the association of time-varying BB exposure with death in CAD patients with or without a history of MI. METHODS: This retrospective cohort study included all patients with MI and those with coronary disease but no MI at a single health care system who also had health insurance from January 1, 1997, to June 30, 2011. Pharmacy claims data were used to estimate BB exposure over 6-month rolling windows. The primary endpoint was all-cause death. The effect of BB exposure was tested using time-updated Cox proportional hazards models. RESULTS: We identified 6220 patients with MI and 21,285 patients with CAD but no MI. Among patients who suffered MI, BB exposure was associated with a 31% relative risk reduction in all-cause death (hazard ratio [HR] 0.69, $P = 0.001$). Among subjects who survived 3 years after MI, BB retained a protective association (HR 0.71, $P = 0.001$). Among CAD-only patients, BB exposure was also associated with risk reduction (HR 0.85, $P = 0.001$). CONCLUSION: Among patients with CAD, BB exposure is associated with reduced risk of death. The association is strongest among those who have suffered MI. This favorable association appears durable beyond 3 years.

Pulmonary and Critical Care Medicine
Reaume M, Farishta M, Costello JA, Gibb T, and Melgar TA. Analysis of lawsuits related to diagnostic errors from point-of-care ultrasound in internal medicine, paediatrics, family medicine and critical care in the USA. *Postgrad Med J* 2020; Epub ahead of print. PMID: 32457206. Full Text

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PURPOSE: The purpose of this study is to identify the extent of diagnostic error lawsuits related to point-of-care ultrasound (POCUS) in internal medicine, paediatrics, family medicine and critical care, of which little is known. METHODS: We conducted a retrospective review of the Westlaw legal database for indexed state and federal lawsuits involving the diagnostic use of POCUS in internal medicine, paediatrics, family medicine and critical care. Retrieved cases were reviewed independently by three physicians to identify cases relevant to our study objective. A lawyer secondarily reviewed any cases with discrepancies between the three reviewers. RESULTS: Our search criteria returned 131 total cases. Ultrasound was mentioned in relation to the lawsuit claim in 70 of the cases returned. In these cases, the majority were formal ultrasounds performed and reviewed by the radiology department, echocardiography studies performed by cardiologists or obstetrical ultrasounds. There were no cases of internal medicine, paediatrics, family medicine or critical care physicians being subjected to adverse legal action for their diagnostic use of POCUS. CONCLUSION: Our results suggest that concerns regarding the potential for lawsuits related to POCUS in the fields of internal medicine, paediatrics, family medicine and critical care are not substantiated by indexed state and federal filed lawsuits.

Pulmonary and Critical Care Medicine
Wahidi MM, Shojaee S, Lamb CR, Ost D, Maldonado F, Eapen G, Caroff DA, Stevens MP, **Ouellette DR**, Lilly C, Gardner DD, Glisinski K, Pennington K, and Alalawi R. The Use of Bronchoscopy During the COVID-19 Pandemic: CHEST/AABIP Guideline and Expert Panel Report. *Chest* 2020; Epub ahead of print. PMID: 32361152. Full Text

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BACKGROUND: The coronavirus disease 2019 (COVID-19) has swept the globe and is causing significant morbidity and mortality. Given that the virus is transmitted via droplets, open airway procedures such as bronchoscopy pose a significant risk to health-care workers (HCWs). The goal of this guideline was to examine the current evidence on the role of bronchoscopy during the COVID-19 pandemic and the optimal protection of patients and HCWs. RESEARCH QUESTION: ▪▪▪ STUDY DESIGN AND METHODS: A group of approved panelists developed key clinical questions by using the Population, Intervention, Comparator, and Outcome (PICO) format that addressed specific topics on bronchoscopy related to COVID-19 infection and transmission. MEDLINE (via PubMed) was systematically searched for relevant literature and references were screened for inclusion. Validated evaluation tools were used to assess the quality of studies and to grade the level of evidence to support each recommendation. When evidence did not exist, suggestions were developed based on consensus using the modified Delphi process. RESULTS: The systematic review and critical analysis of the literature based on six PICO questions resulted in six statements: one evidence-based graded recommendation and 5 ungraded consensus-based statements. INTERPRETATION: The evidence on the role of bronchoscopy during the COVID-19 pandemic is sparse. To maximize protection of patients and HCWs, bronchoscopy should be used sparingly in the evaluation and management of patients with suspected or confirmed COVID-19 infections. In an area where community transmission of COVID-19 infection is present, bronchoscopy should be deferred for nonurgent indications, and if necessary to perform, HCWs should wear personal protective equipment while performing the procedure even on asymptomatic patients.

Radiation Oncology
Bergman D, **Modh A**, **Schultz L**, **Snyder J**, **Mikkelsen T**, **Shah M**, Ryu S, **Siddiqui MS**, and **Walbert T**. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol* 2020; Epub ahead of print. PMID: 32444980. Full Text

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PURPOSE: Outcomes for patients with recurrent high-grade glioma (HGG) progressing on bevacizumab (BEV) are dismal. Fractionated stereotactic radiosurgery (FSRS) has been shown to be feasible and safe when delivered in this setting, but prospective evidence is lacking. This single-institution randomized trial compared FSRS plus BEV-based chemotherapy versus BEV-based chemotherapy alone for BEV-resistant recurrent malignant glioma. MATERIALS AND METHODS: HGG patients on BEV with tumor progression after 2 previous treatments were randomized to 1) FSRS plus BEV-based chemotherapy or 2) BEV-based chemotherapy with irinotecan, etoposide, temozolomide, or carboplatin. FSRS was delivered as 32 Gy (8 Gy × 4 fractions within 2 weeks) to the gross target volume and 24 Gy (6 Gy × 4 fractions) to the clinical target volume (fluid-attenuated inversion recovery abnormality). The primary endpoints were local control (LC) at 2 months and progression-free survival (PFS). RESULTS: Of the 35 patients enrolled, 29 had glioblastoma (WHO IV) and 6 had anaplastic glioma (WHO III). The median number of prior recurrences was 3. Patients treated with FSRS had significantly improved PFS (5.1 vs 1.8 months, P < .001) and improved LC at 2 months (82% [14/17] vs 27% [4/15], P = .002). The overall median survival was 6.6 months (7.2 months with FSRS vs 4.8 months with chemotherapy alone, P = .11). CONCLUSIONS: FSRS combined with BEV-based chemotherapy in recurrent HGG patients progressing on BEV is feasible and improves LC and PFS when compared to treatment with BEV-based chemotherapy alone.

Radiation Oncology

Elshaikh MA, **Modh A**, Jhingran A, Biagioli MC, Coleman RL, Gaffney DK, Harkenrider MM, Heskett K, Jolly S, Kidd E, Lee LJ, Li L, Portelance L, Sherertz T, Venkatessan AM, Wahl AO, Yashar CM, and Small W, Jr. Executive summary of the American Radium Society® Appropriate Use Criteria for management of uterine carcinosarcoma. *Gynecol Oncol* 2020; Epub ahead of print. PMID: 32475772. Full Text

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OBJECTIVE: Uterine carcinosarcomas (UCS) represent a rare but aggressive subset of endometrial cancers, comprising <5% of uterine malignancies. To date, limited prospective trials exist from which evidence-based management of this rare malignancy can be developed. METHODS: The American Radium Society Appropriate Use Criteria presented in this manuscript are evidence-based guidelines developed by a multidisciplinary expert panel for management of women with UCS. An extensive analysis of current medical literature from peer-reviewed journals was performed. A well-established methodology (modified Delphi) was used to rate the appropriate use of imaging and treatment procedures for the management of UCS. These guidelines are intended for the use of all practitioners who desire information about the management of UCS. RESULTS: The majority of patients with UCS will present with advanced extra uterine disease, with 10% presenting with metastatic disease. They have worse survival outcomes when compared to uterine high-grade endometrioid adenocarcinomas. The primary treatment for non-metastatic UCS is complete surgical staging with total hysterectomy, salpingo-oophorectomy and lymph node staging. Patients with UCS appear to benefit from adjuvant multimodality therapy to reduce the chance of tumor recurrence with the potential to improve overall survival. CONCLUSION: Women diagnosed with uterine UCS should undergo complete surgical staging. Adjuvant multimodality therapies should be considered in the treatment of both early- and advanced stage patients. Long-term surveillance is indicated as many of these women may recur. Prospective clinical studies of women with UCS are necessary for optimal management.

Radiation Oncology

Ghanem AI, **Modh A**, **Burmeister C**, Mahmoud O, and **Elshaikh MA**. Does the Interval Between Hysterectomy and Start of Adjuvant Radiation Treatment Influence Survival in Women With Endometrial Carcinoma?: A National Cancer Database analysis. *Am J Clin Oncol* 2020; Epub ahead of print. PMID: 32398405. Full Text

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OBJECTIVE: The objective of this study was to analyze the impact of the time interval (TI) between hysterectomy and initiation of adjuvant radiation treatment (ART) on overall survival (OS) among women with early stage endometrial carcinoma (EC) using the National Cancer Database (NCDB). MATERIALS AND METHODS: The NCDB was queried for women with the International Federation of Gynecology and Obstetrics (FIGO) stage I to II EC who underwent hysterectomy followed by ART. We examined the prognostic impact of TI on OS using the cutoff ≤8 or >8 weeks to initiate radiation treatment (RT). Two groups of patients were created. Kaplan-Meier curves were created for OS analysis. Predictors of OS were identified. RESULTS: A total 16,520 women were identified. The median follow-up time for the entire cohort was 59.1 months. Median age was 63 years, and 82% were FIGO stage I. Pelvic external beam RT alone was used in 9569 (58%) and vaginal brachytherapy alone in 4265 women (26%). In total, 10,040 women (61%) received RT ≤8 weeks. Delay in initiating RT >8 weeks was associated with shorter 5-year OS (P=0.048). Independent predictors of shorter OS includes older age, African American race, higher comorbidity burden, higher tumor grade, the presence of lymphovascular invasion and stage II tumors. Although TI in initiating RT was a significant predictor for OS in univariate analysis, its independent significance of OS was lost on multivariate analysis (P=0.28). CONCLUSION: Our study suggests that TI between hysterectomy and initiation of ART was not an independent predictor of OS in women with early stage EC.

Radiation Oncology

Laucis AM, Jagsi R, Griffith KA, Dominello MM, **Walker EM**, Abu-Isa EI, Dilworth JT, Vicini F, Kocheril PG, Browne CH, Mietzel MA, Moran JM, Hayman JA, and Pierce LJ. The Role of Facility Variation on Racial Disparities in Use of Hypofractionated Whole Breast Radiotherapy. *Int J Radiat Oncol Biol Phys* 2020; Epub ahead of print. PMID: 32376311. Full Text

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INTRODUCTION: Hypofractionated radiotherapy is a less burdensome and less costly approach that is efficacious for most patients with early-stage breast cancer. Concerns about racial disparities in adoption of medical advances motivate investigation of the use of hypofractionated radiation in diverse populations. The goal of our study was to determine whether hypofractionated whole breast radiotherapy after breast conserving surgery was being similarly used across racial groups in the state of METHODS AND MATERIALS: A prospectively collected statewide quality consortium database from 25 institutions was queried for breast cancer patients who completed hypofractionated (HF) or conventionally fractionated (CF) whole breast radiotherapy (RT) from 1/2012-12/2018. We used patient-level multivariable modeling to evaluate associations between HF use and race, controlling for patient and facility factors, and multilevel modeling to account for patient clustering within facilities. RESULTS: Of 9,634 patients analyzed, 81% self-reported race as White, 17% as Black and 2% as Asian, similar to statewide and national distributions. 31.7% of Whites were treated at teaching centers compared to 66.7% of Blacks and 64.8% of Asians. In 2018, HF was utilized in 72.7% of Whites versus 56.7% of Blacks and 67.6% of Asians (p=0.0411). On patient-level multivariable analysis, Black and Asian races were significantly associated with a lower likelihood of HF receipt (p<0.001), despite accounting for treatment year, age, laterality, BMI, breast volume, comorbidities, stage, triple-negative status, IMRT use, teaching center treatment, and 2011 ASTRO Hypofractionation Guideline eligibility. On multilevel analysis, race was no longer significantly associated with HF receipt. CONCLUSIONS: We observed that Black and Asian patients receive hypofractionated RT less often than Whites, despite more frequent treatment at teaching centers. Multilevel modeling eliminated this disparity, suggesting that differences in facility-specific HF use appear to have contributed. Further inquiry is needed to determine if reduction of facility-level variation may reduce disparities in accessing HF treatment.

Radiation Oncology

Nejad-Davarani SP, **Zakariaei N**, Chen Y, Haacke EM, **Hurst NJ**, **Siddiqui MS**, **Schultz LR**, **Snyder JM**, **Walbert T**, and **Glide-Hurst C**. Rapid Multi-contrast Brain Imaging on a 0.35T MR-linac. *Med Phys* 2020; Epub ahead of print. PMID: 32434276. Request Article

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PURPOSE: Magnetic resonance-guided radiation therapy (MRgRT) has shown great promise for localization and real-time tumor monitoring. However, to date, quantitative imaging has been limited for low field MRgRT. This work benchmarks quantitative T1, R2* and Proton Density (PD)-mapping in phantom on a 0.35T MR-linac and implements a novel acquisition method, STrategically Acquired Gradient Echo (STAGE). To further validate STAGE in a clinical setting, a pilot study was undertaken in a cohort of brain tumor patients to elucidate opportunities for longitudinal functional imaging with an MR-linac in the brain. METHODS: STAGE (two triple-echo gradient echo (GRE) acquisitions) was optimized for a 0.35T low-field MR-linac. Simulations were performed to choose two flip angles to optimize signal-to-noise ratio (SNR) and T1-mapping precision. Tradeoffs between SNR, scan time, and spatial resolution for whole-brain coverage were evaluated in healthy volunteers. Data were inputted into a STAGE processing pipeline to yield 4 qualitative images (T1-weighted, enhanced T1-weighted, proton-density (PD) weighted, and simulated FLuid-Attenuated Inversion Recovery (sFLAIR)), and 3 quantitative datasets (T1, PD, and R2*). A benchmarking ISMRM/NIST phantom consisting of vials with variable NiCl(2) and MnCl(2) concentrations was scanned using variable flip angles (VFA) (2-60 degrees) and inversion recovery (IR) methods at 0.35T. STAGE and VFA T1 values of vials were compared to IR T1 values. As measures of agreement with reference values and repeatability, relative error (RE) and coefficient of variability (CV) were calculated, respectively, for quantitative MR values within the phantom vials (spheres). To demonstrate feasibility, longitudinal STAGE data (pre-treatment, weekly, and ~2 months post-treatment) were acquired in an IRB-approved pilot study of brain tumor cases via the generation of temporal and differential quantitative MRI maps. RESULTS: In the phantom, RE of measured STAGE and VFA T1 relative to IR reference values were 7.0 ± 2.5% and 9.5 ± 2.2%, respectively. RE for the PD vials was 8.1%±6.8% and CV for phantom R2* measurements was 10.1% ± 9.9%. Simulations and volunteer experiments yielded final STAGE parameters of FA=50°/10°, 1x1x3 mm(3) resolution, TR=40ms, TE=5/20/34ms in 10 minutes (64 slices). In the pilot study of brain tumor patients, differential maps for R2* and T1 maps were sensitive to local tumor changes and appeared similar to 3T follow up MRI datasets. CONCLUSION: Quantitative T1, R2*, and PD mapping are promising at 0.35T agreeing well with reference data. STAGE phantom data offer quantitative representations comparable to traditional methods in a fraction of the acquisition time. Initial feasibility of implementing STAGE at 0.35T in a patient brain tumor cohort suggests that detectable changes can be observed over time. With confirmation in a larger cohort, results may be implemented to identify areas of recurrence and facilitate adaptive radiation therapy.

Radiation Oncology

Wen N, Cao Y, and Cai J. Editorial: Magnetic Resonance Imaging for Radiation Therapy. *Front Oncol* 2020; 10:483. PMID: 32351888. Full Text

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Radiation Oncology

Xiao C, **Hurst N**, and **Movsas B**. The State of the Science in Patient-Reported Outcomes for Patients with Lung Cancer. *Semin Respir Crit Care Med* 2020; 41(3):377-385. PMID: 32450592. Full Text

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Traditionally, clinicians have assumed the primary responsibility for evaluating disease- and treatment-related outcomes. In the past few decades, however, a series of recommendations and standards promulgated by professional societies and regulatory agencies have resulted in increased use of patient-reported outcome (PRO) measures in cancer clinical trials. PROs, such as quality of life (QOL) measures, are important in establishing overall treatment effectiveness in cancer clinical trials, and they can inform clinical decision making. This article discusses the current state of the science in PRO research for patients with lung cancer, the cancer type with the highest incidence rate and the lowest survival rate worldwide. The discussion focuses on (1) PRO and survival; (2) electronic PRO reporting and interventions; (3) PROs and immunotherapy; (4) PRO, biomarkers, and precision health; (5) key issues in applying PROs in clinical trials; and (6) future directions for research.

Radiation Oncology

Zong W, **Lee JK**, **Liu C**, **Carver EN**, **Feldman AM**, **Janic B**, **Elshaikh MA**, **Pantelic MV**, **Hearshen D**, **Chetty IJ**, **Movsas B**, and **Wen N**. A Deep Dive into Understanding Tumor Foci Classification using Multiparametric MRI Based on Convolutional Neural Network. *Med Phys* 2020; Epub ahead of print. PMID: 32449176. Full Text

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PURPOSE: Deep learning models have had a great success in disease classifications using large data pools of skin cancer images or lung X-rays. However, data scarcity has been the roadblock of applying deep learning models directly on prostate multiparametric MRI (mpMRI). Although model interpretation has been heavily studied for natural images for the past few years, there has been a lack of interpretation of deep learning models trained on medical images. In this paper, an efficient convolutional neural network (CNN) was developed and the model interpretation at various convolutional layers was systematically analyzed to improve the understanding of how CNN interprets multimodality medical images and the predictive powers of features at each layer. The problem of small sample size was addressed by feeding the intermediate features into a traditional classification algorithm known as weighted extreme learning machine (wELM), with imbalanced distribution among output categories taken into consideration. METHODS: The training data collection used a retrospective set of prostate MR studies, from SPIE-AAPM-NCI PROSTATEx Challenges held in 2017. Three hundred twenty biopsy samples of lesions from 201 prostate cancer patients were diagnosed and identified as clinically significant (malignant) or not significant (benign). All studies included T2-weighted (T2W), proton density-weighted (PD-W), dynamic contrast enhanced (DCE) and diffusion-weighted (DW) imaging. After registration and lesion-based normalization, a CNN with four convolutional layers were developed and trained on 10-fold cross validation. The features from intermediate layers were then extracted as input to wELM to test the discriminative power of each individual layer. The best performing model from the 10 folds was chosen to be tested on the holdout cohort from two sources. Feature maps after each convolutional layer were then visualized to monitor the trend, as the layer propagated. Scatter plotting was used to visualize the transformation of data distribution. Finally, a class activation map was generated to highlight the region of interest based on the model perspective. RESULTS: Experimental trials indicated that the best input for CNN was a modality combination of T2W, apparent diffusion coefficient (ADC) and DWIb50. The convolutional features from CNN paired with a weighted extreme learning classifier showed substantial performance compared to a CNN end-to-end training model. The feature map visualization reveals similar findings on natural images where lower layers tend to learn lower level features such as edges, intensity changes, etc, while higher layers learn more abstract and task-related concept such as the lesion region. The generated saliency map revealed that the model was able to focus on the region of interest where the lesion resided and filter out background information, including prostate boundary, rectum, etc. CONCLUSIONS: This work designs a customized workflow for the small and imbalanced data set of prostate mpMRI where features were extracted from a deep learning model and then analyzed by a traditional machine learning classifier. In addition, this work contributes to revealing how deep learning models interpret mpMRI for prostate cancer patients stratification.

Research Administration

Dehghani A, **Soltanian-Zadeh H**, and Hossein-Zadeh GA. Global Data-Driven Analysis of Brain Connectivity during Emotion Regulation by EEG Neurofeedback. *Brain Connect* 2020; Epub ahead of print. PMID: 32458692. Request Article

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BACKGROUND: Emotion regulation by neurofeedback involves interactions among multiple brain regions, including prefrontal cortex and subcortical regions in the limbic system. Previous studies focused on connections of specific brain regions like amygdala with other brain regions. New method: EEG neurofeedback is used to upregulate positive emotion through induced happiness by retrieving positive autobiographical memories and fMRI data acquired simultaneously. A global data-driven approach, group independent component analysis (ICA), is applied to fMRI data and functional network connectivity is estimated. This study discovers all connections among independent components involved in emotion regulation. RESULTS: The proposed approach identified all functional networks engaged in positive autobiographical memories and evaluated effects of neurofeedback. The results revealed two pairs of networks with significantly different functional connectivity among emotion regulation blocks (relative to other blocks of experiment) and between experimental and control groups (FDR-corrected for multiple comparisons, q=0.05). Functional network connectivity distribution (FNCD) showed significant connectivity differences between neurofeedback blocks and other blocks, revealing more synchronized brain networks during neurofeedback. During emotion regulation, significant functional connectivity changes were found in and between prefrontal, parietal, temporal, occipital, and limbic networks. Comparison with existing methods: While the results are consistent with those of previous model based studies, some of the connections found in this study were not found previously. These connections are between a) occipital (fusiform, cuneus, middle occipital, and lingual gyrus) and other regions including limbic system/sub-lobar (thalamus, hippocampus, amygdala, caudate, putamen, insula, and ventral striatum), prefrontal/frontal cortex (DLPFC, VLPFC,

and OFC), inferior parietal, middle temporal gyrus and b) PCC and hippocampus. CONCLUSIONS: Using fMRI during EEG neurofeedback, this study provided a global insight to brain connectivity for emotion regulation. The brain networks interactions may be used to develop connectivity-based neurofeedback methods and alternative therapeutic approaches, which may be more effective than the traditional activity-based neurofeedback methods.

Research Administration
LaTourette PC, David EM, Pacharinsak C, Jampachaisri K, **Smith JC**, and Marx JO. Effects of Standard and Sustained-release Buprenorphine on the Minimum Alveolar Concentration of Isoflurane in C57BL/6 Mice. *J Am Assoc Lab Anim Sci* 2020; 59(3):298-304. PMID: 32268932. Request Article

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Both standard and sustained-release injectable formulations of buprenorphine (Bup and BupSR, respectively) are used as preemptive analgesics, potentially affecting gas anesthetic requirements. This study tested the effects of Bup and BupSR on isoflurane requirements and confirmed that buprenorphine could reduce isoflurane requirements during a laparotomy in mice. We hypothesized that both Bup and BupSR would significantly decrease the required minimum alveolar concentration (MAC) of isoflurane. C57BL/6 mice received either isotonic crystalloid fluid (control), Bup (0.1 mg/kg), or BupSR (1.2 mg/kg) subcutaneously 10 min prior to the induction of anesthesia. Each anesthetized mouse was tested at 2 isoflurane concentrations. A 300-g noxious stimulus was applied at each isoflurane concentration, alternating between hindfeet. In addition, a subset of mice underwent terminal laparotomy or 60 min of anesthesia after injection with Bup, BupSR, or saline to ensure an appropriate surgical plane of anesthesia. Mice were maintained at the lowest isoflurane concentration that resulted in 100% of mice at a surgical plane from the aforementioned MAC experiments (control, 2.0%; Bup and BupSR, 1.7%). Analysis showed that both Bup and BupSR significantly decreased isoflurane requirements by 25.5% and 14.4%, respectively. The isoflurane MAC for the control injection was 1.80% ± 0.09%; whereas Bup and BupSR decreased MAC to 1.34% ± 0.08% and 1.54% ± 0.09%, respectively. Sex was not a significantly different between the injection groups during MAC determination. All of the mice that underwent surgery achieved a surgical plane of anesthesia on the prescribed regimen and recovered normally after discontinuation of isoflurane. Lastly, heart and respiratory rates did not differ between mice that underwent surgery and those that were anesthetized only. Bup and BupSR are MAC-sparing in male and female C57BL/6 mice and can be used for effective multimodal anesthesia.

Research Administration
Reshef E, **Sabbah HN**, and Nussinovitch U. Effects of protective controlled coronary reperfusion on left ventricular remodeling in dogs with acute myocardial infarction: A pilot study. *Cardiovasc Revasc Med* 2020; Epub ahead of print. PMID: 32417208. Full Text

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BACKGROUND: Coronary artery obstruction causes ischemia of cardiac tissue, leading to acute myocardial infarction (AMI). The treatment of choice for reducing acute myocardial ischemic injury is early, effective vascular reperfusion using thrombolytic therapy or primary percutaneous coronary intervention. However, reperfusion can cause cardiomyocyte injury. Currently, there is no effective therapy to prevent cardiac reperfusion-related tissue damage. This study evaluated whether Protective Controlled Coronary Reperfusion (PCCR), selectively delivered to ischemic tissue, is associated with decreased myocardial scarring, contractile deterioration and reperfusion-associated myocardial edema. METHODS: Three hours of cardiac ischemia was induced in 10 mongrel dogs, and followed by either 30-minute PCCR or sham treatment. Cardiac performance was evaluated 2, 4 and 6 months later. Trichrome staining was used to distinguish collagen from viable myocardial tissue and to evaluate mean scar area. RESULTS: One hour following reperfusion, PCCR significantly attenuated the relative increase (edema) in left ventricular end diastolic posterior wall thickness compared with sham treatment. At 6 months follow-up, the PCCR group showed a modest corrected increase in left ventricular ejection fraction (cΔLVEF) in comparison to the sham group where it deteriorated (2.3 ± 10.5% vs. -16.4 ± 10.3%, respectively, p = 0.043). Histomorphometric assessments of the hearts showed the PCCR group had smaller area of scarring, as compared to sham-treated animals (9.0 ± 2.4% vs. 14.0 ± 3.3%, p = 0.047). CONCLUSIONS: In this pilot study, PCCR reduced myocardial edema,

modestly increased in cΔLVEF and resulted in a smaller scar area. Further studies are needed to fully ascertain the mechanisms that underlie the potential benefits of PCCR therapy prior to initiating clinical trials in human subjects with AMI.

Research Administration

Sisodiya SM, Whelan CD, Hatton SN, Huynh K, Altmann A, Ryten M, Vezzani A, Caligiuri ME, Labate A, Gambardella A, Ives-Deliperi V, Meletti S, Munsell BC, Bonilha L, Tondelli M, Rebsamen M, Rummel C, Vaudano AE, Wiest R, Balachandra AR, Bargalló N, Bartolini E, Bernasconi A, Bernasconi N, Bernhardt B, Caldairou B, Carr SJA, Cavalleri GL, Cendes F, Concha L, Desmond PM, Domin M, Duncan JS, Focke NK, Guerrini R, Hamandi K, Jackson GD, Jahanshad N, Kälviäinen R, Keller SS, Kochunov P, Kowalczyk MA, Kreilkamp BAK, Kwan P, Lariviere S, Lenge M, Lopez SM, Martin P, Mascalchi M, Moreira JCV, Morita-Sherman ME, Pardoe HR, Pariente JC, Raviteja K, Rocha CS, Rodríguez-Cruces R, Seeck M, Semmelroch M, Sinclair B, **Soltanian-Zadeh H**, Stein DJ, Striano P, Taylor PN, Thomas RH, Thomopoulos SI, Velakoulis D, Vivash L, Weber B, Yasuda CL, Zhang J, Thompson PM, and McDonald CR. The ENIGMA-Epilepsy working group: Mapping disease from large data sets. *Hum Brain Mapp* 2020; Epub ahead of print. PMID: 32468614. Full Text

Epilepsy is a common and serious neurological disorder, with many different constituent conditions characterized by their electro clinical, imaging, and genetic features. MRI has been fundamental in advancing our understanding of brain processes in the epilepsies. Smaller-scale studies have identified many interesting imaging phenomena, with implications both for understanding pathophysiology and improving clinical care. Through the infrastructure and concepts now well-established by the ENIGMA Consortium, ENIGMA-Epilepsy was established to strengthen epilepsy neuroscience by greatly increasing sample sizes, leveraging ideas and methods established in other ENIGMA projects, and generating a body of collaborating scientists and clinicians to drive forward robust research. Here we review published, current, and future projects, that include structural MRI, diffusion tensor imaging (DTI), and resting state functional MRI (rsfMRI), and that employ advanced methods including structural covariance, and event-based modeling analysis. We explore age of onset- and duration-related features, as well as phenomena-specific work focusing on particular epilepsy syndromes or phenotypes, multimodal analyses focused on understanding the biology of disease progression, and deep learning approaches. We encourage groups who may be interested in participating to make contact to further grow and develop ENIGMA-Epilepsy.

Sleep Medicine

Cheng P, **Kalmbach DA**, **Castelan AC**, **Murugan N**, and **Drake CL**. Depression prevention in digital cognitive behavioral therapy for insomnia: Is rumination a mediator? *Journal of Affective Disorders* 2020; 273:434-441. PMID: Not assigned. Full Text

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Background There has been growing support for digital Cognitive Behavioral Therapy (dCBT-I) as a scalable intervention that both reduces insomnia and prevents depression. However, the mechanisms by which dCBT-I reduces and prevents depression is less clear. Methods This was a randomized controlled trial with two parallel arms: dCBT-I (N=358), or online sleep education as the control condition (N=300). Outcome variables were measured at pre-treatment, post-treatment, and one-year follow-up, and included the Insomnia Severity Index (ISI), the Quick Inventory of Depressive Symptomatology (QIDS-SR16), and the Perseverative Thinking Questionnaire (PTQ). The analyses tested change in PTQ scores as a mediator for post-treatment insomnia, post-treatment depression, and incident depression at one-year follow-up. Results Reductions in rumination (PTQ) were significantly larger in the dCBT-I condition compared to control. Results also showed that reductions in rumination significantly mediated the improvement in post-treatment insomnia severity (proportional effect = 11%) and post-treatment depression severity (proportional effect = 19%) associated with the dCBT-I condition. Finally, reductions in rumination also significantly mediated the prevention of clinically significant depression via dCBT-I (proportional effect = 42%). Limitations Depression was measured with a validated self-report instrument instead of clinical interviews. Durability of results beyond one-year follow-up should also be tested in future research. Conclusions Results provide evidence that rumination is an important mechanism in how dCBT-I reduces and prevents depression.

Surgery

Clark-Sienkiewicz SM, **Hecht LM**, **Pester B**, **Martens K**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Racial Differences in Psychological Symptoms and Eating Behaviors Among Bariatric Surgery Candidates. *J Racial Ethn Health Disparities* 2020; Epub ahead of print. PMID: 32367444. Request Article

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BACKGROUND: Black patients typically lose less weight than White patients following bariatric surgery; however, the reasons for this racial disparity are unclear. The purpose of the current study was to evaluate whether there are differences in psychiatric symptoms and problematic eating behaviors between White and Black patients pursuing bariatric surgery as this may aid in understanding postsurgical weight loss disparities and inform psychosocial assessment of bariatric candidates. METHODS: A retrospective chart review was conducted of participants (N = 284) who completed a psychological evaluation prior to surgery. Information collected included history of binge eating and purging as well as data from measures administered (i.e., the Hospital Anxiety and Depression Scale, the Emotional Eating Scale, and the Yale Food Addiction Scale 2.0). RESULTS: White patients reported higher levels of eating in response to anger/frustration (p = .03) and eating in response to depression (p = .01) than Black patients. White patients also reported more symptoms of food addiction, a difference that was trending toward significance (p = .05). No significant differences were found on measures of anxiety or depression. CONCLUSION: White patients appear to have higher levels of presurgical problematic eating as compared with Black patients pursuing bariatric surgery; thus, these measurements of problematic eating may not explain the racial disparity in outcomes. However, future research should determine whether measures are valid among diverse populations and identify additional factors that may contribute to racial disparities in bariatric outcomes.

Surgery

Davis FM, Albright J, Battaglia M, Eliason J, Coleman D, Mouawad N, **Knepper J**, Mansour MA, Corriere M, Osborne NH, and Henke PK. Fenestrated Repair Improves Perioperative Outcomes but Lacks a Hospital Volume Association for Complex Abdominal Aortic Aneurysms. *J Vasc Surg* 2020; Epub ahead of print. PMID: 32473343. Full Text

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BACKGROUND: Complex abdominal aortic aneurysms (cAAAs) have traditionally been treated with an open surgical repair (OSR). Over the past decade, fenestrated endovascular graft repair (FEVAR) has emerged as a viable option. Hospital procedural volume to outcome relationship for OSR of cAAAs has been well established but the impact of procedural volume on FEVAR outcomes remains undefined. This study investigates the outcomes of OSR and FEVAR for the treatment of cAAAs and examines the hospital volume-outcome relationship for these procedures. METHODS: A retrospective review of a statewide vascular surgery registry was queried for all patients between 2012-2018 who underwent elective repair of a juxtarenal/pararenal abdominal aortic aneurysm with FEVAR or OSR. The primary outcomes were 30-day mortality, myocardial infarction, or new dialysis. Secondary endpoints included post-operative pneumonia, renal dysfunction (creatine concentration increase of >2 mg/dl from preoperative baseline), major bleeding, early procedural complications, length of stay, and need for reintervention. To evaluate procedural volume-outcomes relationship, hospitals were stratified into low and high-volume aortic centers based on a FEVAR annual procedural volume. To account for baseline differences, we calculated propensity scores and employed inverse probability of treatment weighting when comparing outcomes between treatment groups. RESULTS: A total of 589 patients underwent FEVAR (n=186) or OSR (n=403) for a cAAAs. After adjustment, OSR was associated with higher rates of 30-day mortality (10.7% vs. 2.9%, p<0.001) and need for dialysis (11.3% vs. 1.8; p<0.001). Postoperative pneumonia (6.8% vs. 0.3%; p<0.001) and need for transfusion (39.4% vs. 10.4%; p<0.001) were also significant higher in the OSR cohort. The median length of stay for OSR and FEVAR was 9 days and 3 days; respectively. For those who underwent FEVAR, endoleaks were present in 12.1% of patients at 30 days and 6.1% of patients at 1-year, with the majority being Type II. One percent of FEVAR patients required a secondary procedure with a median follow-up period of 331 days [229, 378], and there were no FEVAR conversions to an open aortic repair. Hospitals were divided into low and high-volume aortic centers based on their annual FEVAR cAAA volume. After adjustment, hospital FEVAR procedural volume was not associated with 30-day mortality or myocardial infarction. CONCLUSIONS: FEVAR was associated with lower perioperative morbidity and mortality compared to OSR for the management of complex AAAs. Procedural FEVAR volume outcome analysis suggests limited differences in 30-day morbidity although long-term durability warrants further research.

Surgery

Draxler MS, **Al-Adas Z**, **Abbas D**, **Kavousi Y**, **Kabbani LS**, **Lin JC**, **Weaver MR**, **Shepard AD**, and **Nypaver TJ**. Outcome Benefit of Arterial Duplex Stent Imaging After Superficial Femoral Artery Stent Implantation. *J Vasc Surg* 2020. PMID: 32437951. Full Text

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INTRODUCTION: In-stent stenosis is a frequent complication of superficial femoral artery (SFA) endovascular intervention and can lead to stent occlusion and/or symptom recurrence. Arterial duplex stent imaging can be used in the surveillance for recurrent stenosis, however, its uniform application is controversial. In this study, we aim to determine, in patients undergoing SFA stent implantation, whether surveillance with arterial duplex stent imaging yielded a better outcome than those with only ankle-brachial index (ABI) follow-up. METHODS: We performed a retrospective analysis of all patients undergoing SFA stent implantation for occlusive disease at a tertiary care referral center between 2009 and 2016. The patients were divided into those with arterial duplex stent imaging (ADSI group) and those with ankle brachial index follow-up only (ABI group). Life table analysis was performed, comparing stent patency, major adverse limb event, limb salvage, and mortality between groups. RESULTS: Two hundred forty-eight patients with SFA stent implantation were included: 160 into ADSI; 88 into ABI. Groups were homogenous regarding clinical indication (claudication/critical limb ischemia ADSI 39/61% vs ABI 38/62%; P = 0.982) and TASC classification (TASC A/B/C/D for ADSI 17/45/16/22% and ABI 21/43/16/20%; P = 0.874). Primary patency was similar between groups at 12/36/56 months: ADSI (65/43/32%) vs ABI (69/34/34%) (P = 0.770), whereas ADSI patients showed an improved assisted primary patency (84/68/54%) vs ABI (76/38/38%; P = 0.008) and secondary patency. There was a greater freedom from major adverse limb event in the ADSI group (91/76/64%) vs the ABI group (79/46/46%) (P < 0.001) at 12/36/56 months follow-up. Arterial duplex stent imaging patients were more likely to undergo an endovascular procedure as their initial post-SFA stent implantation intervention (P = 0.001) whereas ABI patients were more likely to undergo an amputation (P < 0.001). CONCLUSIONS: In SFA stent implantation, patients with arterial duplex stent imaging follow-up demonstrate an advantage in assisted-primary patency and secondary patency and are more likely to undergo an endovascular re-intervention. These factors likely effected a decrease in major adverse limb events, indicating the benefit of a more universal adoption of post-SFA stent implantation follow-up arterial duplex stent imaging.

Surgery
Kassam AF, Cortez AR, Winer LK, Conzen KD, El-Hinnawi A, Jones CM, Matsuoka L, Watkins AC, **Collins KM**, Bhati C, Selzner M, Sonnenday CJ, Englesbe MJ, Diwan TS, Dick AAS, and Cutler Quillin R, 3rd. Extinguishing burnout: National analysis of predictors and effects of burnout in abdominal transplant surgery fellows. *Am J Transplant* 2020; Epub ahead of print. PMID: 32463950. Full Text

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Virginia Commonwealth University, Department of Surgery, Richmond, Virginia, USA.
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Burnout among surgeons has been attributed to increased workload and decreased autonomy. Although prior studies have examined burnout among transplant surgeons, no studies have evaluated burnout in abdominal transplant surgery fellows. The objective of our study was to identify predictors of burnout and understand its impact on personal and patient care during fellowship. A survey was sent to all abdominal transplant surgery fellows in an American Society of Transplant Surgeons-accredited fellowship. The response rate was 59.2% (n=77) and 22.7% (n=17) of fellows met criteria for burnout. Fellows with lower grit scores were more likely to exhibit burnout compared to fellows with higher scores (3.6 vs 4.0, p=0.026). Those with burnout were more likely to work over 100 hours per week (58.8% vs 27.6%, p=0.023), have severe work-related stress (58.8% vs 22.4%, p=0.010), consider quitting fellowship (94.1% vs 20.7%, p<0.001), or make a medical error (35.3% vs 5.2%, p=0.003). This national analysis of abdominal transplant fellows found that burnout rates are relatively low, but few fellows engage in self-care. Personal and program-related factors attribute to burnout and it has unacceptable effects on patient care. Transplant societies and fellowship programs should develop interventions to give fellows tools to prevent and combat burnout.

Surgery
Kitajima T, and **Nagai S**. ASO Author Reflections: It Is Not a Low-Hanging Fruit: Center Experience Plays an Important Role in Improving Outcomes in Liver Transplantation for Hilar Cholangiocarcinoma. *Ann Surg Oncol* 2020; Epub ahead of print. PMID: 32458323. Full Text

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Surgery

Lin JC, **Kavousi Y**, **Sullivan B**, and **Stevens C**. Analysis of Outpatient Telemedicine Reimbursement in an Integrated Healthcare System. *Ann Vasc Surg* 2020; 65:100-106. PMID: 31678131. Full Text

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BACKGROUND: Current reimbursement policy surrounding telemedicine has been cited as a barrier for the adaptation of this care model. The objective of this study is to analyze the reimbursement figures for outpatient telemedicine consultation in vascular surgery. METHODS: Patients first underwent synchronous telemedicine visits after receiving point-of-care ultrasound at one of 3 satellite locations of Henry Ford Health System in Michigan. Visit types included new, return, and postoperative patients. Reimbursement information related to payor, adjustment, denial, paid and outstanding balances were recorded for each telemedicine visit. Then, using an enterprise data warehouse, a retrospective analysis was performed for the aforementioned telemedicine visits. The data were analyzed to determine the outcome of total billed charges, number of denied claims, reimbursement per payor, reimbursement per patient, and out-of-pocket costs to the patients. RESULTS: Among 184 virtual clinical encounters, the payors included Aetna US Healthcare, Blue Advantage, Blue Cross Blue Shield, Cofinity Plan, Health Alliance Plan, HAP Medicare Advantage, Humana Medicare Advantage, Medicaid, Medicare, Molina Medicaid HMO, United Healthcare, Blue Care Network, Aetna Better Health of Michigan, Priority Health, and self-pay. Among the 15 payors, reimbursement ranged from 0% to 67% of the total charges billed. Among the 184 virtual visits, a grand total of $22,145 was collected or an average of $120.35 per virtual encounter. The breakdown of charges billed was 40% adjusted, 41% paid by insurance, 10% paid by patient, and 13% denied. There were 27 total denials (15%). Denial of payment included telehealth and nontelehealth reasons, citing noncovered charges, payment included for other prior services, new patient quality not met, and not covered by payor. The average out-of-pocket cost to patients was $12.59 per visit. CONCLUSIONS: These reimbursement data validate the economic potential within this new platform of healthcare delivery. As our experience with the business model grows, we expect to see an increase in reimbursement from private payors and acceptance from patients. Within a tertiary care system, telemedicine for chronic vascular disease has proven to be a viable means to reach a broader population base, and without significant cost to the patients.

Urology

Kovacevic L, Lu H, **Kovacevic N**, and Lakshmanan Y. Effect of bisphosphonates on the crystallization of stone-forming salts in synthetic urine. *Investig Clin Urol* 2020; 61(3):310-315. PMID: 32377608. Full Text

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PURPOSE: We investigated the inhibitory effect of bisphosphonates (BPs) on the crystallization of calcium oxalate monohydrate (COM), calcium phosphate (CaP), and magnesium ammonium phosphate (MAP) in synthetic urine, aiming to see 1) which specific BPs work best on a particular type of crystal and 2) what is the lowest concentration of BPs that inhibits crystal formation. MATERIALS AND METHODS: Crystals from synthetic urine were exposed to different concentrations of BPs. Urinary turbidity was used as a marker of crystallization and was measured by spectrophotometry by use of a validated method in our laboratory. The percent inhibitory activity (IA) was calculated by using the formula: (a-b)/a×100, where a is baseline maximal turbidity and b is maximal turbidity with various concentrations of medication. Potassium citrate and magnesium citrate were used as positive controls. RESULTS: At the lowest dose of 0.001 mg/mL, risedronate induced the highest IA of 37% on CaP, whereas ibandronate had the strongest IA on COM (24%). To initiate the inhibition of MAP crystallization, risedronate required a two-fold higher concentration (0.002 mg/mL) to reach 30% IA, whereas etidronate required a four-fold higher concentration (0.004 mg/mL) to reach 42% IA. CONCLUSIONS: BPs are good inhibitors of crystallization in synthetic urine, with risedronate and ibandronate being the most potent. At a low clinically acceptable dose, their highest inhibitory action was on CaP and COM crystals. Higher doses were needed to prevent MAP crystallization. Further investigation of the use of BPs in kidney stone prevention is warranted.

Urology

Kovacevic N, Lopes NN, **Raffee S**, and **Atiemo HO**. Predicting Upper Urinary Tract Risk in the Neurogenic Bladder Patient. *Current Bladder Dysfunction Reports* 2020; Epub ahead of print. PMID: Not assigned. Full Text

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Purpose of Review: In this review, we explore if risk factors for developing renal deterioration can be identified in a timely fashion, thereby preventing or delaying the progression of renal injury in the neurogenic bladder patient. Recent Findings: Historically detrusor leak point pressure (DLPP) > 40 cm H2O has been used to identify risk of upper urinary tract dysfunction (UUTD). Recent studies suggest that DLPP should not be the only decision-making parameter to predict the risk of UUTD and that patients with DLPP > 20 cm H2O should be followed closely for upper tract assessment. Furthermore, a variety of urinary

biomarkers can be used markers of UUTD to guide management of neurogenic patients. Summary: Urodynamic studies represent a valuable tool in the evaluation and monitoring of urinary tract function. Multiple sources have emphasized the early identification and regular follow-up of these patients to not only have a baseline urinary tract function but also to monitor renal function and evaluate for upper tract damage.

Conference Abstracts

Emergency Medicine
Baltarowich L, **Dean D**, **Fontana J**, **Akram A**, **Shayya S**, and **Miller J**. Heroin overdose trends in a high volume urban emergency department over a 4-year period: 2014-2017. *Journal of Medical Toxicology* 2020; 16(2):142.

L. Baltarowich, Henry Ford Hospital, Detroit, MI, United States

Background: Urban emergency departments (ED) have experienced increasing visits for heroin overdoses since 2014, with noted federal reports that most involve heroin adulteratedwith fentanyl. Our study objectivewas to characterize this evolving trend in an urban trauma center ED from 2014 to 2017. Methods: This is a retrospective observational study of ED patients from 2014 to 2017 with a diagnosis of heroin overdose. Patients in cardiac arrest were excluded. Trained abstractors collected standardized data on clinical information, substance use, and ED disposition. We assessed changes in overdose patterns over time and compared characteristics of admitted and discharged patients. Analysis included descriptive statistics and generalized linear or mixed models where appropriate. Results: A total of 900 patients were included. The incidence of heroin overdose visits increased twofold between 2015 and 2016 and threefold between 2014 and 2017. During the overall period, 73% of patients were discharged from ED, 11% left AMA, and 16% were admitted. Mean LOS in ED was 6.6 hours. The mean age increased from 47.7 years in 2014 to 50 in 2017 ($p < 0.01$). Gender, race, and ED disposition did not change significantly. Concomitant drugs on urine screens were opiates 87%, cocaine 46%, benzos 35%, THC 31%, and ethanol 23%. Comparison of admitted and discharged patients showed similar age, gender, and race. Admitted patients were more likely to have concomitant amphetamine use ($p = 0.037$) and less likely THC ($p = 0.006$); 14% of admitted patients required ICU care. Respiratory compromise was the most common complication; 66% of patients with an abnormal chest X-ray had pneumonia or pulmonary edema. Conclusion: This study shows a significant increase in ED patient visits for heroin overdose from 2014 to 2017 with increasing mean age over time. Most patients were discharged from the ED, and of those admitted, the majority went to non-ICU beds.

Emergency Medicine
Barton CE, Mauck MC, Linnstaedt SD, Kurz MC, Hendry PL, Pearson C, O'Neil BJ, **Lewandowski C**, Datner E, Liberzon I, Domeier RM, and McLean SA. Immune Profile in the Immediate Aftermath of MVC and its Prediction of APNS. *Biological Psychiatry* 2020; 87(9):S296.

Background: African Americans (AAs) experience an increased burden of motor vehicle collision (MVC) and rates of adverse posttraumatic neuropsychiatric sequelae (APNS) after MVC, versus non-Hispanic whites. Accumulating evidence suggests that immune cells play an important role in APNS development. Methods: AAs presenting to the Emergency Department (ED) within 24 hours of MVC were enrolled. ED assessment included measurement of pain symptoms (0-10 scale), severity of life threat (0-10 scale) and blood RNA sample (PAXgene) collection. Post-traumatic depressive (CES-D), stress (IES-R), and pain symptoms were assessed at six weeks, six months, and one year. Repeated measures linear regression analyses were performed evaluating whether circulating peritraumatic immune cell subtypes (i.e., neutrophils, monocytes, B-cells, CD4+ T-cells, estimated via application of CIBERSORT method to ED blood sample total RNA sequencing data) predicted APNS outcomes. False discovery rate threshold was set at 5%. Results: After adjustment for sociodemographic characteristics and perceived life threat within this study sample (n=183), the peritraumatic CD4+ T immune cell proportion predicted depressive ($\beta = 19.5$, $p = 0.031$), stress ($\beta = 51.7$, $p = 0.008$), and pain ($\beta = 6.3$, $p = 0.002$) symptom severity, and peritraumatic neutrophil proportion predicted pain ($\beta = -2.9$, $p = 0.047$). Conclusions: Among AAs experiencing MVC, an increased proportion of peritraumatic CD4+ T immune cells predicted more severe depressive, stress, and pain symptoms over time. Studies examining associations between peritraumatic immune phenotypes and APNS may provide pathogenic insights. Supported By: NIAMS R01AR060852, UNC BIRCWH K12HD001441 Keywords: Psychoneuroimmunology, Posttraumatic Stress Symptoms, Depressive Symptoms, Motor Vehicle Collision, African Americans

Emergency Medicine
Dean DJ, Jacobs E, King AM, **Malone E**, and Aaron CK. Characteristics of pediatric lead admissions seen by medical toxicology service. *Journal of Medical Toxicology* 2020; 16(2):124-125.

D.J. Dean, Michigan Poison Center at Wayne State University, Detroit, MI, United States

Background: Pediatric lead poisoning is a frequent consultation to our toxicology service. In partnership with pediatric hematology, the toxicology service developed a unique protocol that includes admission and chelation for patients with blood

lead levels (BLL) > 40 mcg/dL. Chelation is performed with DMSA and IV CaNa2EDTA infusion for 120 hours. Admission removes the child from further exposure and allows the health department to identify and mitigate the source. Further, admission facilitates family education and nutritional counseling, arranges close follow-up with our lead clinic, and provides expeditious access to ancillary services to optimize health outcomes. Methods: This is a retrospective review of pediatric medical toxicology consultations with the diagnosis of lead intoxication, plumbism, and lead exposures. Results: Of the 101 consultations completed between July 2013 and August 10, 2019, there were 77 unique patients with 24 (23.8%) having > 2 hospitalizations and 4 with > 3 hospitalizations. The average LOS was 6 days and average presenting BLL was 41.5 mcg/dL; 38% of patients had radiopaque foreign bodies presumed to be lead and were administered whole bowel irrigation; 74/101 consultations were chelated. There were infrequent minor reported adverse effects and no moderate or major effects of chelation. Discussion: Compliance with less-aggressive and prolonged outpatient succimer protocols can be problematic due to availability of succimer and lack of knowledgeable providers. Further, a large proportion requires acute gut decontamination. This protocol is intensive and comprehensive. A subset of patients had repeat admissions for persistently elevated BLL likely from re-exposure or redistribution. Conclusion: We find that hospitalization at a specialty center, utilizing this protocol, efficiently coordinates medical and governmental social support services: it is safe and comprehensive.

Emergency Medicine
Dean DJ, **Sabagha N**, **Rose K**, **Weiss A**, **Asmar T**, **Rammal JA**, **Beyer M**, **Bussa R**, Smoot T, and **Miller J**. A pilot trial of topical capsaicin cream for treatment of cannabinoid hyperemesis. *Journal of Medical Toxicology* 2020; 16(2):145-146.

D.J. Dean, Michigan Poison Center at Wayne State University, Detroit, MI, United States

Background: Patients with cannabinoid hyperemesis syndrome (CHS) frequently present to the emergency department. Previous case studies suggest dramatic symptomatic improvement with topical capsaicin treatment. Research Question: This exploratory study examines the safety and potential efficacy of topical capsaicin in patients with vomiting due to a suspected CHS exacerbation. Methods: This is a double-blind, randomized placebo-controlled pilot trial. Adults who presented with vomiting suspected to be from CHS were eligible for enrollment. We excluded pregnant females and those with resolution of nausea. Following randomization, topical 0.1% capsaicin or placebo cream was applied to the anterior abdomen in a uniform manner. Primary outcome was the severity of nausea on a visual analog scale (VAS) of 0-10 assessed at 30 minutes. Secondary outcomes were occurrence of post-treatment vomiting, nausea by VAS at 60minutes, and hospital admission. Results: This pilot trial enrolled 30 patients: 17 in the capsaicin arm and 13 in the placebo arm. One patient in the capsaicin arm did not tolerate treatment due to skin irritation. Nausea severity at 30 minutes was 4.1 (95%CI 2.8-5.4) in the capsaicin arm and 6.1 (95% CI 4.1-8.1) in the placebo arm. At 60 minutes, nausea severity was 3.2 (95%CI 1.6-4.8) vs. 6.4 (4.7-8.1). The percent reduction in nausea at 60 minutes from baseline was 46.0% (95% CI 25.5-66.5%) in the capsaicin arm and 24.9% (95% CI 7.8-41.9%) in the placebo arm. Hospital admission was necessary for four patients in the capsaicin arm (23.5%) vs. five (38.5%) in the placebo arm (RR 0.61, 95% CI 0.20-1.84). Conclusion: In this pilot trial of topical capsaicin for CHS, capsaicin was well-tolerated and demonstrated signs of efficacy. Further trials are warranted.

Emergency Medicine
Dean DJ, and Schoenling A. Prolonged and severe CNS depression and truncal ataxia in an accidental pediatric perampanel ingestion. *Journal of Medical Toxicology* 2020; 16(2):124.

D.J. Dean, Michigan Poison Center at Wayne State University, Detroit, MI, United States

Background: Perampanel exerts antiepileptic effects by reducing neuronal excitation via noncompetitive antagonism of the postsynaptic ionotropic-AMPA-glutamate receptors. Clinical effects in overdose are limited and only mild effects have been reported in adults. Methods: This is a single patient chart review. Results: A previously healthy 2-year-old 15-kg female presented after witnessed ingestion of 30mg of perampanel (2mg/kg).Within 10 minutes of ingestion, the child became ataxic and was unable to walk. She presented to the ED, 30 minutes post-ingestion and had normal VS but was minimally responsive. She was emergently intubated due to profound CNS depression. After transfer to a tertiary care facility, vitals were as follows: 36.5 °C, HR 117, BP 113/73, RR 20(vent), and 100% on 40% FiO2. She required no sedation and ABG showed 7.24/56/65. Serum laboratory results were otherwise unremarkable. UDS immunoassay and GC-MS were both negative. She remained hemodynamically stable and remained intubated for 72 hours with gradual improvement in mental status. After extubation, patient still exhibited truncal ataxia and did not return to her neurologic baseline until 96 hours post-ingestion. Serum perampanel level was 870 ng/mL (ref < 20 ng/mL). Discussion: To date, there are no reported pediatric ingestions of perampanel. Adult toxicity describes mild neurologic symptoms. In this case, our patient exhibited profound CNS depression requiring mechanical ventilation for a prolonged period. At this time, we suggest all pediatric exposures be referred to the ED. Conclusion: This is the first reported confirmed case of perampanel overdose in a child. Pediatric toxicity may result in profound CNS depression requiring prolonged mechanical ventilatory support.

Emergency Medicine
Jacobs ET, **Dean DJ**, Aaron CK, King AM, and **Malone ER**. The caterpillars are coming! *Journal of Medical Toxicology* 2020; 16(2):161.

E.T. Jacobs, Michigan Poison Center, Detroit, MI, United States

Background: Every year, caterpillars come out in droves to feast and prepare for the transformation into butterflies and moths. This occurs from spring to autumn. Caterpillars appear defenseless but that is not the case. There are thousands of different species in Michigan alone. A few species have urticating hair and a few have venom-containing hairs similar to hypodermic needles. The result of contact with these defense mechanisms includes local itching, erythema, and edema. Absolute numbers of caterpillars depend on environmental factors such as food source and predators. The Michigan Poison Center has seen an increase in the calls related to caterpillar exposures over the past 14 years. Methods: This is a retrospective chart review of the Michigan Poison Center data on calls for caterpillar exposure from 2005 to 2019. Yearly totals were tabulated. Results: Over the 14 years through 2019, there has been an increase in the calls related to caterpillar exposure with 2019 being the highest at 55 calls. Year 2005 had 13 calls followed by a 7-year lull with call volume ranging from 3 to 8 per year. Call volume began increasing yearly starting in 2014. Though most calls do not contain adequate descriptors to speciate, they report minor, local effects on the hands or arms consistent with caterpillar dermatitis. Serious cases included those that had generalized urticaria as well as those who had oral contact with edema involving the upper airway. Conclusion: As climate changes and human encroachment of habitats continue, wildlife exposure frequency changes as well.

Emergency Medicine
Jacobs ET, **Dean DJ**, Aaron CK, Tilford BD, Schneider JS, Clark JA, and King AM. First double lung transplant secondary to suspected ecigarette vaping-associated lung injury. *Journal of Medical Toxicology* 2020; 16(2):147-148.

E.T. Jacobs, Michigan Poison Center, Detroit, MI, United States

Background: As of November 13, 2019, the CDC has confirmed 2172 cases of E-cigarette vaping-associated lung injury (EVALI): 70% in males, 86% involving THC, and 64% involving nicotine. Although there have been 42 deaths, this is the first reported lung transplant in an EVALI patient. Methods: This is a single case review. Results: A 16-year-old white male presented to the ED for dyspnea and cough with history of vaping. He was admitted to "hospital #1" and treated with antibiotics for suspected pneumonia. Additional history revealed use of self-created THC products containing vitamin E. On hospital day 4, he was transferred to the pediatric ICU for worsening hypoxemia and placed on steroids for suspected EVALI. On hospital day 6, he was intubated due to persistent hypoxia and worsening respiratory status. An extensive infectious and inflammatory evaluation was negative. Lung cytology from BAL did not reveal lipid-laden macrophages or other pathology. Due to worsening respiratory status, he was transferred to "hospital #2" for veno-venous ECMO on hospital day 11. The remainder of organ function was normal. Despite multiple attempts to wean from ECMO, lung function showed no signs of improvement, and he was referred to "hospital #3" for lung transplant. After 27 days on ECMO (hospital day 39,) he received a double lung transplant for irreversible lung damage and accumulating barotrauma. The patient is now off EMCO, has a tracheostomy, and is neurologically intact. He is able to speak and is undergoing intensive rehabilitation. Conclusion: Although most cases of EVALI survive and most often show improvement temporally related to steroid administration, EVALI can be relentless and lead to severe lung injury and death. This patient suffered irreparable lung damage despite early presentation, steroids, and early ECMO. Lung transplant can be considered a viable option for severe and refractory cases.

Emergency Medicine
Kim R, Pan Y, Kurz M, Hendry P, Pearson C, O'Neil B, **Lewandowski C**, Datner E, Liu Y, McLean SA, and Linnstaedt S. Prediction of Co-Morbid Chronic Pain and Posttraumatic Stress: Results of a Pilot Analysis of Clinical and MicroRNA Data From a Longitudinal Cohort of African American Trauma Survivors. *Biological Psychiatry* 2020; 87(9):S212.

Background: Co-morbid chronic musculoskeletal pain and posttraumatic stress (CMSP/PTS) is a common outcome of trauma exposure and is associated with greater disability than either outcome alone. Identification of CMSP/PTS vulnerable individuals would aid in preventative treatment decisions. In the current study, we performed analyses to identify significant predictors and build a prediction tool for CMSP/PTS based on clinical and biological data. Methods: African American men/women presenting to the emergency department (ED) within 24 hours of motor vehicle collision were enrolled. Sociodemographic and psychological/cognitive characteristics, and blood (PAXgeneRNA) for microRNA-seq were collected in the ED. Six-month surveys identified individuals with CMSP (≥4, 0-10 Numeric Rating Scale)/PTS (≥33, Impact of Events Scale-Revised). The prediction tool was built using regularized logistic regression with feature selection, where significant predictors were identified via 1,000x repetitions of Monte Carlo cross-validation. Results: 30% (n=222/741) of the full cohort reported CMSP/PTS and 27% (n=198/741) reported neither outcome. Clinical and demographic variables were identified using a subset of individuals without miRNA data (n=332); selected variables showed good reliability in predicting CMSP/PTS (AUC=0.76+/-0.008). miRNA data alone (n=88) yielded weak reliability (AUC=0.64+/-0.009). Combining clinical, demographic, and miRNA variables (n=88) improved prediction versus either subset alone (AUC=0.79+/-0.008). Top predictors included initial pain severity, fear of pain getting worse, feeling frustrated or angry, socioeconomic status and microRNAs miR-199a, miR-339, let-7d, miR-192, and miR-29. Conclusions: These analyses suggest that supplementing clinical prediction with microRNA moderately improves accuracy of identifying vulnerable individuals. Future studies should aim to replicate these

findings in additional trauma cohorts. Supported By: K01AR071504, R01AR060852, The Mayday Fund Keywords: PTSD, Chronic Pain, Machine Learning, Cross-Validation, microRNA

Emergency Medicine
Son E, Tungate AS, Mauck MC, Pan Y, Witkemper K, Kurz MC, Hendry PL, Pearson C, **Lewandowski C**, Datner E, Cairns BA, McLean SA, and Linnstaedt SD. Peritraumatic Circulating 17β-Estradiol as a Resiliency Factor for Chronic Pain Outcomes in Women Following Trauma. *Biological Psychiatry* 2020; 87(9):S320.

Background: Musculoskeletal pain is common following traumatic/stressful life events and is more common in women than men. However, resiliency factors that predict improved chronic posttraumatic musculoskeletal pain (CPMP) in women are poorly understood. In the current study, we examined whether peritraumatic circulating 17β-estradiol (E2) levels influence CPMP trajectories in women. Methods: Peritraumatic E2 levels were measured via ELISA in plasma samples (n=167) derived from three multiethnic longitudinal cohort studies of trauma survivors. These cohorts enrolled individuals experiencing motor vehicle collision (MVC, n=89), sexual assault (n=64), and major thermal burn injury (n=14). CPMP (0-10 numeric rating scale) was assessed 6-weeks, 6-months, and 1-year following traumatic stress exposure. Repeated measures mixed models were used to test the relationship between log-transformed E2 levels and CPMP. Secondary analyses of MVC cohort gene expression data (n=37) evaluated mediating transcripts and associated biological pathways (Ingenuity, IPA). Results: An inverse relationship between peritraumatic E2 and the development of CPMP was observed (β= -0.353, p=0.033) such that women with high E2 at the time of trauma had less CPMP over the following year. Secondary analyses identified 250 mRNA that mediated the relationship between E2 and CPMP; initial enrichment analyses identified eIF2 signaling as a top pathway through which E2 might influence CPMP development. Conclusions: Increased peritraumatic E2 levels predict improved CPMP outcomes in women. Supported By: K01AR071504; R01AR064700; R01AR060852; UNC BIRCWH K12HD001441 Keywords: Chronic Pain, Trauma, Estrogen, Women, Sex Differences

Emergency Medicine
Taheri C, Ziemba N, Jones C, Agala C, Soward A, House S, Beaudoin F, **Lewandowski C**, Hendry PL, Musey P, Kessler RC, Koenen KC, Ressler K, and McLean SA. Short-Term Mental Health Outcomes Among Individuals Enrolled at the Emergency Department After Physical Assault. *Biological Psychiatry* 2020; 87(9):S222-S223.

Background: Physical assault (PA) survivors commonly present to the emergency department (ED) for care. The prevalence and outcome trajectories of posttraumatic stress (PTS), depressive, and pain symptoms in this common trauma population have not previously been clearly defined. Methods: Individuals presenting to an AURORA Network ED within 72 hours of PA were enrolled. Baseline demographic information was obtained in the ED; patient outcome assessments included three month survey. Substantial PTS, depressive, and pain symptoms were defined via PTSD Checklist (PCL-5) ≥28, PROMIS-8b depression scale ≥60, and Numeric Pain Rating scale ≥4, respectively. Results: Individuals experiencing PA (n=173, 89/173(51%) men) were enrolled, including individuals who had intentionally started or joined a fight/brawl (n=26, 15%), been attacked or jumped (n=133, 77%) or had experienced another type of PA (n=14, 8%). High rates of substantial depressive (52/173(34%)), PTS (74/173, 43%), and pain (75/173, 43%) symptoms were reported three months after PA. After adjusting for age and sex, individuals who had been attacked or jumped had not significantly different depressive (OR=0.12, p=0.49), PTS (OR=0.15, p=0.47), and pain symptoms (OR=0.25, p=0.34) at three months as individuals who had intentionally started or joined a fight or brawl. Women had higher rates of pain (OR=3.47, p=0.001) than men, and individuals experiencing PA between ages 18-29 had lower rates of pain (OR=2.14, p=0.014) and PTS (OR=1.98, p=0.015) symptoms than individuals age 50 or older Conclusions: PA survivors frequently experience substantial depressive, PTS, and pain symptoms after assault. Further studies are needed to compare risk factors after PA vs. other types of trauma. Supported By: R01AR0664700 Keywords: AURORA Study, Trauma, Physical Assault, Adverse Neuropsychiatric Sequelae

Internal Medicine
Khan BSA, **Reddy S**, **Zakhour S**, **Sallam O**, and **Shaban H**. Clostridium difficile peritonitis in PD: Transmural migration or intestinal perforation? *Am J Kidney Dis* 2020; 75(4):595-596.

Clostridium difficile (C.diff) causes colitis of varying severity and extra colonic infections are rarely seen. We present a case of C. diff peritonitis in a patient on peritoneal dialysis (PD) and sigmoid colonic perforation. An 85-year-old female with end stage renal disease on PD for 1 year presented with 1 day duration of abdominal pain. Upon presentation she was noted to be hypotensive with a BP 93/48mm Hg and a diffusely tender abdomen on exam. Labs revealed WBC 10.6 K/uL, Hgb 10.2g/dl, lactate 2.8 mmol/L. Computed tomography (CT) of the abdomen showed diverticulosis, mild colitis and free intraperitoneal air. PD fluid cell count was WBC 6310/ cu mm with a neutrophilic predominanace. Intraperitoneal vancomycin and cefepime were empirically initiated to treat PD associated peritonitis. Fluid cultures grew C.diff, Klebsiella oxytoca and Escherichia coli. Subsequently, she underwent an exploratory laparotomy which showed a full thickness ulcer in the sigmoid colon adjacent to the PD catheter. A wedge resection of the sigmoid colon and primary closure was performed and she was transitioned to hemodialysis. Dialysis patients have impaired immune responses and are frequently treated with antibiotics for infectious complications which increases their risk of nosocomial infections with C. diff. PD patients are inherently at risk of peritonitis due to the peritoneal cavity being accessible to the external environment as well as transmural migration of intestinal bacteria

causing contamination. Diagnosing perforation could be delayed as CT findings of peritoneal air could be an expected finding in these patients. C.diff causing peritonitis as part of a polymicrobial isolate from PD fluid should alert the nephrologist to a possibility of a perforated viscus.

Internal Medicine
Shah V, **Lamerato L**, Abraham L, Cappelleri J, DeLor B, **Ellsworth S**, Hegeman-Dingle R, and Park PW. PNS19 Design of study to assess impact of electronic chronic pain questions on patient-reported outcomes and healthcare utilization in a United States general practice setting. *Value in Health* 2020; 23:S287.

Gaps exist in capturing real world data for chronic pain, making it difficult for physicians to assess and monitor patients, and for healthcare organizations to understand prevalence, utilization trends, and the impact of diagnosis and treatment decisions for chronic pain patients. The Electronic Chronic Pain Questions (eCPQ) is a 14-item questionnaire developed and psychometrically validated to help providers capture relevant chronic pain data from the electronic health record (EHR). A prospective, randomized pragmatic study is underway to determine if utilizing the eCPQ within a primary care practice setting results in improved patient-reported function and overall improvement. The eCPQ is being self-administered immediately prior to patient visits to those in the intervention group. Answers are then reviewed by their physician during the visit. Other questionnaires, including the Brief Pain Inventory-Short Form (BPI-sf), Patient Global Assessment (PGA) and the Patient Health Questionnaire for Depression and Anxiety (PHQ-2 and PHQ-9) are being administered following the appointment in order not to influence the standard of care (SOC). Patients in both the intervention and control groups will be evaluated at baseline, 6 and 12 months for their chronic pain condition as per SOC. The main outcome is the BPI-sf interference score change from baseline to 6 months comparing the control and intervention groups, with the PGA scores at 6 months a co-primary endpoint. After both their 6 and 12-month visits the intervention group will be invited to complete a survey to assess ease of use, utility, feasibility, and satisfaction with the eCPQ and their perception of its impact on their care. Providers will also complete a similar survey towards the end of the study. A subset in the intervention arm will also be randomly assigned to participate in a qualitative interview to further explore patients' perception of the eCPQ. Providers will also be interviewed.

Nephrology
Khan BSA, **Reddy S**, **Zakhour S**, **Sallam O**, and **Shaban H**. Clostridium difficile peritonitis in PD: Transmural migration or intestinal perforation? *Am J Kidney Dis* 2020; 75(4):595-596.

Clostridium difficile (C.diff) causes colitis of varying severity and extra colonic infections are rarely seen. We present a case of C. diff peritonitis in a patient on peritoneal dialysis (PD) and sigmoid colonic perforation. An 85-year-old female with end stage renal disease on PD for 1 year presented with 1 day duration of abdominal pain. Upon presentation she was noted to be hypotensive with a BP 93/48mm Hg and a diffusely tender abdomen on exam. Labs revealed WBC 10.6 K/uL, Hgb 10.2g/dl, lactate 2.8 mmol/L. Computed tomography (CT) of the abdomen showed diverticulosis, mild colitis and free intraperitoneal air. PD fluid cell count was WBC 6310/ cu mm with a neutrophilic predominanace. Intraperitoneal vancomycin and cefepime were empirically initiated to treat PD associated peritonitis. Fluid cultures grew C.diff, Klebsiella oxytoca and Escherichia coli. Subsequently, she underwent an exploratory laparotomy which showed a full thickness ulcer in the sigmoid colon adjacent to the PD catheter. A wedge resection of the sigmoid colon and primary closure was performed and she was transitioned to hemodialysis. Dialysis patients have impaired immune responses and are frequently treated with antibiotics for infectious complications which increases their risk of nosocomial infections with C. diff. PD patients are inherently at risk of peritonitis due to the peritoneal cavity being accessible to the external environment as well as transmural migration of intestinal bacteria causing contamination. Diagnosing perforation could be delayed as CT findings of peritoneal air could be an expected finding in these patients. C.diff causing peritonitis as part of a polymicrobial isolate from PD fluid should alert the nephrologist to a possibility of a perforated viscus.

Nephrology
Srour K, **Khan BSA**, and **Novak J**. Starvation ketoacidosis in patient with muscular dystrophy. *Am J Kidney Dis* 2020; 75(4):640.

Patients with Muscular Dystrophy have small muscle mass; thus, they have less glycogen stores, and therefore they are more prone to develop ketoacidosis with minimal stress or decreased oral intake. In our case we are presenting a rare presentation of ketoacidosis in a patient with muscular dystrophy, who was treated successfully with Lactated Ringer and Dextrose solution due to her concurrent hyperchloremic non-anion gap metabolic acidosis. Our Patient is forty-eight-year-old female with history of Muscular Dystrophy and Chronic Respiratory Failure dependent on Ventilator, she was referred to our hospital for evaluation of a granulation tissue in her Trachea. She was admitted and found to have non-AG metabolic Acidosis, VBG showed Ph of 7.23 Bicarbonate of 12, BMP showed Cr <0.1, Chloride 114 (high), BMI 18, in addition to leukocytosis with WBC>16000. Next day her labs showed Bicarbonate of 8, Ph of 7.29 and AG of 16 (Na 137, Cl 113), Albumin 4.2. We checked her Beta Hydroxybutyrate (BHB) which came back 6.6 (High). Due to her underlying Muscular Dystrophy and decrease oral intake, she was diagnosed with Starvation Ketoacidosis. Since she had a non-anion gap metabolic acidosis at the time of admission which was most likely secondary to Renal Tubular Acidosis, (Patient labs showed Hypokalemia, Urine AG of 30), we decided to start her on ringer lactate and dextrose solution. After 24 hours, her labs showed significant

improvement and her BHB trended down and after 48 hours her labs have been normalized. Few cases have been reported regarding ketoacidosis in patients with muscular dystrophy, all reported cases were treated directly with dextrose and normal saline. In our case we used LR and D5% due to concurrent non anion gap metabolic acidosis which we believe it was due to RTA, in which giving normal saline (hgih Chloride content) will worsen the acidosis. HAGMA in patient with no diabetes and Muscular dystrophy should raise suspicion for Ketoacidosis. Treatment is with Dextrose and normal saline ususally. Using LR solurion sometime is better option in cases with concurrent hyperchloremic acidosis.

Nephrology
Srour K, **Lakshmikanth J**, **Chitturi C**, and **Faber M**. C3 glomerulonephritis; a rare complication of CLL. *American Journal of Kidney Diseases* 2020; 75(4):640.

Kidney disease develops in chronic lymphocytic leukemia (CLL) patients via multiple mechanisms including infiltration, obstruction, tumor lysis syndrome, and glomerular disease. We present a rare case of C3 glomerulonephritis (C3GN) associated with pulmonary renal syndrome that we believe was an autoimmune manifestation of CLL. A 76-year-old male with a 15-year history of SLL/CLL, DVT, HTN, DM and Stage 3 CKD developed SOB and dry cough. At ED presentation he was in respiratory distress with BIPAP-resistant hypoxia requiring intubation. Labs included Cr 7.1 mg/dL, K 5.7 mEq/L and uric acid 12.2 mg/dL CXR showed vascular congestion. Prior to developing anuria urine sediment showed RBC casts. Bronchoscopy DAH, consistent with a pulmonary renal syndrome. Patient was started on plasmapheresis, high-dose steroids and CRRT. Autoimmune workup including ANA, anti-GBM and ANCA was negative. Kidney biopsy showed diffuse proliferative and sclerosing glomerulonephritis with lymphocytic infiltrates consistent with involvement by patient's known CD5+, CD23+ B-cell lymphoproliferative disorder. IF showed diffuse C3 staining. Steroids and plasmapheresis were continued. Renal function improved and dialysis discontinued, with Cr at last follow up 1.9. Chemotherapy for CLL has been ordered. We present a case of C3GN and DAH secondary to CLL autoimmune etiology, a rare complication of CLL which usually affects the kidney by infiltration and by toxicity of the CLL treatment. Due to the rarity of the disease, there is no standard of care treatment but this patient initially responded well to steroids and plasmapheresis. Recent case reports suggest improved outcomes of CLL-associated C3GN when CLL is treated. CLL is a rare cause of C3GN. A high suspicion of the disease and early intervention with immunosuppression is the key in treating such condition. Chemotherapy for CLL is expected to improve the patient's long-term renal outcome.

Nephrology
Zasuwa G, **Frinak S**, **Uduman J**, and **Yee J**. Automated alert of sustained low-efficiency dialysis (sled) machines. *American Journal of Kidney Diseases* 2020; 75(4):661.

SLED machines are used to treat critically ill patients with kidney failure for prolonged intervals. Technicians surveil machines every 2 hours. If alarms occur during therapy, nursing staff mute the alarm and notify dedicated technicians. However, alarms may be ignored, thereby permitting machines to remain in “error” mode for hours, potentially compromising patient care. Targeted alarm-based surveillance of SLED machines would optimize therapy. In 2017, SLED machines were linked by WIFI to the hospital private phone network (ASCOM) to develop an automated alarm system. When an alarm occurred, the machine computer sent an email to a dedicated Outlook SLED email account for subsequent transmission to ASCOM MailGate. This system next created an “alarm” text message on ASCOM phones provided to technicians. Response times to machine alarms by technicians decreased significantly after system implementation. No additional training was required to implement the protocol. Enhanced safety using an automated SLED alarm-based system is feasible with WIFI- and ASCOM-based architectures. Figure presented

Nephrology
Zasuwa G, **Frinak S**, and **Yee J**. Improving detection of symptomatic, asymptomatic intradialytic hypotension (AIDH), during hemodialysis (HD) with guided automated blood pressure (BP). *American Journal of Kidney Diseases* 2020; 75(4):661.

IDH is an HD complication associated with patient morbidity and mortality. IDH detection enables early intervention that may reduce complications. We explored the hypothesis that that continuous intra-access pressure (IAP) measurements using the Vasc-Alert™ algorithm1 (VA) can detect IDH.during HD and initiate a blood pressure (BP) measurement. Undetected A/IDH was defined as a systolic BP (SBP) decline of 40 mmHg from the predialysis SBP and an intradialytic SBP <100 mmHg. Fresenius™ T2 dialysis machines (n=24) with CLiC™ devices that assess blood volume changes had software (LabVIEW) installed to calculate IAP at 20-sec intervals from DM data. IAP was determined by hematocrit (default value, 0.34) and venous pressure (VP) by VA from 3470 treatments among 291 patients over 36 days. Electronic health records and dialysis machine data were merged. IAP curves and slopes were correlated with A/IDH. Figure 1 displays an IDH event after 130 min of treatment. SBP declined from 143/77 to 74/44 mmHg, and goal ultrafiltration was reduced from 2.4 L to 1.9 L, blood flow rate from 385 to 350 ml/min. IAP differences during IDH were significant p<.0001. Inset shows an IAP drop that triggers an alarm. The IAP slope and IAP declines of 30 mm Hg or more correlate with IDH during HD. In Figure 1, episodes of A/IDH revealed by IAP slopes and delta-IAP prior to the event can trigger the BP module. A drop in IAP or IAP slope would enable staff to intercede in a timely fashion to mitigate more severe IDH episodes. Combined analysis of blood volume, IAP, and slope of IAP

in an AI algorithm has potential to trigger an IDH alarm. Further research much include larger datasets for validation. Figure presented

Pharmacy

Dean DJ, **Sabagha N**, **Rose K**, **Weiss A**, **Asmar T**, **Rammal JA**, **Beyer M**, **Bussa R**, Smoot T, and **Miller J**. A pilot trial of topical capsaicin cream for treatment of cannabinoid hyperemesis. *Journal of Medical Toxicology* 2020; 16(2):145-146.

D.J. Dean, Michigan Poison Center at Wayne State University, Detroit, MI, United States

Background: Patients with cannabinoid hyperemesis syndrome (CHS) frequently present to the emergency department. Previous case studies suggest dramatic symptomatic improvement with topical capsaicin treatment. Research Question: This exploratory study examines the safety and potential efficacy of topical capsaicin in patients with vomiting due to a suspected CHS exacerbation. Methods: This is a double-blind, randomized placebo-controlled pilot trial. Adults who presented with vomiting suspected to be from CHS were eligible for enrollment. We excluded pregnant females and those with resolution of nausea. Following randomization, topical 0.1% capsaicin or placebo cream was applied to the anterior abdomen in a uniform manner. Primary outcome was the severity of nausea on a visual analog scale (VAS) of 0-10 assessed at 30 minutes. Secondary outcomes were occurrence of post-treatment vomiting, nausea by VAS at 60minutes, and hospital admission. Results: This pilot trial enrolled 30 patients: 17 in the capsaicin arm and 13 in the placebo arm. One patient in the capsaicin arm did not tolerate treatment due to skin irritation. Nausea severity at 30 minutes was 4.1 (95%CI 2.8-5.4) in the capsaicin arm and 6.1 (95% CI 4.1-8.1) in the placebo arm. At 60 minutes, nausea severity was 3.2 (95%CI 1.6-4.8) vs. 6.4 (4.7-8.1). The percent reduction in nausea at 60 minutes from baseline was 46.0% (95% CI 25.5-66.5%) in the capsaicin arm and 24.9% (95% CI 7.8-41.9%) in the placebo arm. Hospital admission was necessary for four patients in the capsaicin arm (23.5%) vs. five (38.5%) in the placebo arm (RR 0.61, 95% CI 0.20-1.84). Conclusion: In this pilot trial of topical capsaicin for CHS, capsaicin was well-tolerated and demonstrated signs of efficacy. Further trials are warranted.

Public Health Sciences

Shah V, **Lamerato L**, Abraham L, Cappelleri J, DeLor B, **Ellsworth S**, Hegeman-Dingle R, and Park PW. PNS19 Design of study to assess impact of electronic chronic pain questions on patient-reported outcomes and healthcare utilization in a United States general practice setting. *Value in Health* 2020; 23:S287.

Gaps exist in capturing real world data for chronic pain, making it difficult for physicians to assess and monitor patients, and for healthcare organizations to understand prevalence, utilization trends, and the impact of diagnosis and treatment decisions for chronic pain patients. The Electronic Chronic Pain Questions (eCPQ) is a 14-item questionnaire developed and psychometrically validated to help providers capture relevant chronic pain data from the electronic health record (EHR). A prospective, randomized pragmatic study is underway to determine if utilizing the eCPQ within a primary care practice setting results in improved patient-reported function and overall improvement. The eCPQ is being self-administered immediately prior to patient visits to those in the intervention group. Answers are then reviewed by their physician during the visit. Other questionnaires, including the Brief Pain Inventory-Short Form (BPI-sf), Patient Global Assessment (PGA) and the Patient Health Questionnaire for Depression and Anxiety (PHQ-2 and PHQ-9) are being administered following the appointment in order not to influence the standard of care (SOC). Patients in both the intervention and control groups will be evaluated at baseline, 6 and 12 months for their chronic pain condition as per SOC. The main outcome is the BPI-sf interference score change from baseline to 6 months comparing the control and intervention groups, with the PGA scores at 6 months a co-primary endpoint. After both their 6 and 12-month visits the intervention group will be invited to complete a survey to assess ease of use, utility, feasibility, and satisfaction with the eCPQ and their perception of its impact on their care. Providers will also complete a similar survey towards the end of the study. A subset in the intervention arm will also be randomly assigned to participate in a qualitative interview to further explore patients' perception of the eCPQ. Providers will also be interviewed.

Pulmonary

Chiu YW, Kao YH, **Simoff MJ**, Ost D, Wagner O, Lavin J, Culbertson R, and Smith DG. PCN137 Costs of biopsy and complications in patients with lung cancer. *Value in Health* 2020; 23:S47.

Objectives: Diagnostic work up for lung cancer has high rates of repeat biopsies and associated complications causing increased economic burden. This research analyzed the costs associated with different diagnostic approaches and complications. Methods: Patient-level de-identified records of commercial and Medicare insurance claims from IBM MarketScan® included patients 18 years and older who had continuous health plan enrollment between July 1, 2013 and June 30, 2017, at least one biopsy and a primary diagnosis of lung cancer. Patients had lung cancer treatment, defined by Current Procedural Terminology (CPT), ICD-9-CM or ICD-10-CM procedure codes. Costs from payer and patient perspectives were included in the analyses. Costs of chest CT scans, biopsy, and post-procedural complications were estimated from total payments by payers and patient as reported in the claims data. Costs for capitated arrangements were estimated using payment proxies that were computed based on average paid claims. Costs of biopsy included both procedure and physician costs in outpatient setting. Biopsies performed in the inpatient setting included all costs during the entire hospital stay for that biopsy, inclusive of complications and were reported by care setting and by procedure. All costs were normalized to 2017 US

dollars using the Bureau of Labor Statistics' Consumer Price Index Medical Care Component. Results: Median costs were highest for surgical ($28,487.94; 95% CI: $1095.90 to $126,280.26) and lowest for percutaneous ($1,462.65; 95% CI: $111.21 to $61,481.79) procedures. Inpatient costs were 4-10 fold higher than outpatient costs for percutaneous and bronchoscopic procedures. Those receiving multiple percutaneous or bronchoscopic biopsies had costs 2-3 fold higher than those with only one biopsy. Conclusions: Median costs of lung cancer diagnosis ranged from $1024.21 to $48,332.88 and varied substantially by procedure and setting of care. Multiple diagnostic procedures increased median cost by as much as a factor of three.

Pulmonary
Zhang Y, **Simoff M**, Ost D, Wagner O, Lavin J, Nauman B, Hsieh MC, Wu XC, and Shi L. PCN237 Follow-up of patients with a SPN and no evidence of lung cancer: A data linkage study. *Value in Health* 2020; 23:S64.

Objectives: This research analyzed the clinical pathway among patients without lung cancer diagnosis from a diagnosis of solitary pulmonary nodule including demographics, and diagnostic procedures through data linkage. Methods: REACHnet is one of 9 clinical research networks (CRNs) in PCORnet®, the National Patient-Centered Clinical Research Network and includes electronic health record for over 8 million patients from multiple partner health systems. Data from Ochsner Health System and Tulane Medical Center were linked to Louisiana Tumor Registry (LTR), a statewide population-based cancer registry, for analysis of patient's clinical pathways. Index date was defined as diagnosis of solitary pulmonary nodule (SPN) between July 2013 and December 2017. Patients with a lung biopsy only or pleural biopsy as the first biopsy were excluded. Results: 24,141 patients with an SPN were identified in REACHnet. After one year of follow-up, 150 (0.6%) had lung cancer diagnosis in LTR but were not identified in the REACHnet database. 8,012 (33.2%) were lost to follow-up and 15,979 (66.2%) received follow-up care for the initial SPN diagnosis. For the 15,979 patients receiving follow up care, 14,610 (91.4%) received SPN procedures or encounters related to their SPN diagnosis. Of these, 94.6% received additional medical consultation, 92% had CT scans or X-ray of the chest and 5.9% had 1 or more biopsies. The distribution of biopsy type was 4.5% surgical, 74.3% bronchoscopy, and 21.2% CT guided. Conclusions: Follow-up for clinical outcomes in these information systems is hampered by a high rate of loss to follow-up. Patients with follow-up information are seeking consultation for their original SPN diagnosis. A small proportion of patients with SPN are diagnosed with lung cancer outside of the original healthcare system.

Pulmonary
Zhang Y, **Simoff M**, Ost D, Wagner O, Lavin J, Nauman E, Hsieh MC, Wu XC, and Shi L. PCN349 Data linkage between tumor registry and electronic medical records for patient journey study in lung cancer. *Value in Health* 2020; 23:S86.

Objective: Lung cancer is the leading cause of cancer death in the US, with most patients diagnosed at advanced stages. Patient pathways prior to cancer diagnosis remains unclear. This study linked tumor registry and electronic medical records data to analyze varying clinical pathways to lung cancer diagnosis. Methods: Research Action for Health Network (REACHnet) and Louisiana Tumor Registry (LTR) data from 2013 to 2017 were linked using a Privacy Preserving Record Linkage (PPRL) algorithm. REACHnet provides longitudinal clinical data extracted from electronic health records, including Ochsner Health system and Tulane Medical Center. LTR, a statewide population-based registry, collects information of demographics, tumor characteristics, cancer stage at diagnosis and initial treatment of cancer cases. ICD-9 and ICD-10 diagnosis codes were used to define patients with primary lung cancer from REACHnet. ICD-O-3 codes were used to select patients with primary lung cancer from LTR. Patients with solitary pulmonary nodule (SPN), low-dose computer tomography (LDCT) or chest computer tomography (CT) identified between July 2013 and December 2017 diagnosed with primary lung cancer were included in REACHnet sample. Patients excluded were 1) SPN with pleural biopsy as first biopsy, 2) lung cancer as secondary diagnosis, 3) non-LA residents, 4) diagnosed by Death Certificate and 5) diagnosis on autopsy. Results: From 2013 to 2017, 2,860 patients with primary lung cancer were identified in LTR. Among 30,561 patients obtained from REACHnet, 2,929 (9.58%) patients had a recorded diagnosis of primary lung cancer. Furthermore, 1,964 (67.05%) of 2,929 received primary lung cancer diagnosis by linkage to LTR records using the PPRL algorithm. The linked database had lung cancer characteristics (e.g., stages), and health resource utilization prior to diagnosis (e.g., patterns of clinical work-up). Conclusion: Data linkage between tumor registry and electronic medical records allows researchers to investigate clinical pathways and health outcomes in lung cancer.

Pulmonary
Zhang Y, **Simoff M**, Ost D, Wagner O, Lavin J, Nauman E, Hsieh MC, Wu XC, and Shi L. PCN226 Lung cancer patient characteristics from a data linkage study. *Value in Health* 2020; 23:S62.

Objectives: This research analyzed the clinical pathway of patients from a diagnosis of solitary pulmonary nodule including demographics, diagnostic procedures and lung cancer diagnosis through data linkage. Methods: REACHnet is one of 9 clinical research networks (CRNs) in PCORnet®, the National Patient-Centered Clinical Research Network and includes electronic health record for over 8 million patients from multiple partner health systems. Data from Ochsner Health System and Tulane Medical Center were linked to Louisiana Tumor Registry (LTR), a statewide population-based cancer registry, for analysis of patient's clinical pathways. Index date was diagnosis of solitary pulmonary nodule (SPN), low-dose computer tomography (LDCT) or chest computer tomography (CT) between July 2013 and 2017. Patients with lung biopsy and without SPN diagnosis, SPN with pleural biopsy as first biopsy, secondary lung cancer diagnosis, residence outside of Louisiana, Death

Certificate diagnosis, and diagnosis on autopsy were excluded. Results: A total of 30,561 patients with SPN, LDCT or qualifying biopsy were identified and 2,929 (9.58%) had primary lung cancer. 1,496 (51.1%) were documented in LTR. When linking REACHnet and LTR, 94% of 1,496 patients had diagnosis of SPN, 84% had CTs capturing portions of the lung and 89% had 1 or more biopsies. Biopsy distribution was 2.4% surgical, 50.1% bronchoscopy and 47.5% CT guided. Median interval and interquartile from index date to biopsy was 11 days and 28 days respectively. AJCC stage among these patients was Stage 0 (0.53%), Stage I (20.66%), Stage II (7.22%), Stage III (21.86%) Stage IV (47.26%), and Unknown (2.47%). Conclusions: Despite clinical workup, 70% of patients were diagnosed as having stage III or IV disease. Approximately half of lung cancer patients receiving care at Ochsner or Tulane healthcare systems do not appear in the LTR. Reasons for this are not clear but are presumed to be attributable to residence.

HFHS Publications on COVID-19

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