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Henry Ford Health System Publication List – February 2021

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 **106 unique citations** listed this month, with **3 articles** and **1 conference abstract on COVID-19**. Articles are listed first, followed by conference abstracts, books and book chapters, 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

<u>Anesthesiology</u>
Fegley MW, Gupta RG, Elkassabany N, Augoustides JG, Werlhof H, Gutsche JT, Kornfield ZN, **Patel N**, **Sanders J**, Fernando RJ, and Morris BN. Elective Total Knee Replacement in a Patient With a Left Ventricular Assist Device-Navigating the Challenges With Spinal Anesthesia. *J Cardiothorac Vasc Anesth* 2021; 35(2):662-669. PMID: 33183934. Full Text

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Department of Anesthesiology, Wake Forest School of Medicine, Winston Salem, NC.

<u>Behavioral Health Services/Psychiatry</u>
Martens K, **Hamann A**, **Miller-Matero LR**, **Miller C**, Bonham AJ, Ghaferi AA, and **Carlin AM**. Relationship between depression, weight, and patient satisfaction 2 years after bariatric surgery. *Surg Obes Relat Dis* 2021; 17(2):366-371. PMID: 33127323. Full Text

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BACKGROUND: Findings regarding longer term symptoms of depression and the impact of depression on outcomes such as weight loss and patient satisfaction, are mixed or lacking. OBJECTIVES: This study sought to understand the relationship between depression, weight loss, and patient satisfaction in the two years after bariatric surgery. SETTING: This study used data from a multi-institutional, statewide quality improvement collaborative of 45 different bariatric surgery sites. METHODS: Participants included patients (N = 1991) who underwent Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2015-2018. Participants self-reported symptoms of depression (Patient Health Questionnaire-8 [PHQ-8]), satisfaction with surgery, and weight presurgery and 1 year and 2 years postsurgery. RESULTS: Compared to presurgery, fewer patients' PHQ-8 scores indicated clinically significant depression (PHQ-8≥10) at 1 year (P < .001; 14.3% versus 5.1%) and 2 years postsurgery (P < .0001; 8.7%). There was a significant increase in the prevalence of clinical depression from the first to second year postsurgery (P < .0001; 5.1% versus 8.7%). Higher PHQ-8 at baseline was related to less weight loss (%Total Weight Loss [%TWL] and %Excess Weight Loss [%EWL]) at 1 year postsurgery (P < .001), with a trend toward statistical significance at 2 years (P = .06). Postoperative depression was related to lower %TWL and %EWL, and less reduction in body mass index (BMI) at 1 year (P < .001) and 2 years (P < .0001). Baseline and postoperative depression were associated with lower patient satisfaction at both postoperative time points. CONCLUSIONS: This study suggests improvements in depression up to 2 years postbariatric surgery, although it appears that the prevalence of depression increases after the first year. Depression, both pre- and postbariatric surgery, may impact weight loss and patient satisfaction.

Behavioral Health Services/Psychiatry
Miller-Matero LR, **Hecht L**, **Patel S**, **Martens KM**, **Hamann A**, and **Carlin AM**. The Influence of Health Literacy and Health Numeracy on Weight Loss Outcomes Following Bariatric Surgery. *Surg Obes Relat Dis* 2021; 17(2):384-389. PMID: 33082073. [Full Text](#)

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BACKGROUND: Although cognitive functioning and health literacy are related to weight loss 1year following bariatric surgery, the influence of health numeracy (i.e., health-related mathematical abilities) is unknown. In addition, further research is needed to examine the impact of all these factors on longer-term weight loss outcomes to determine if they influence the ability to maintain weight loss. SETTING: Single bariatric center. METHODS: Patients (N = 567) who underwent bariatric surgery from 2014-2017 completed a brief survey including current weight. Retrospective chart reviews were conducted to gather information from the presurgical evaluation including weight, body mass index (BMI), health literacy, health numeracy and score on a cognitive screener. RESULTS: Among participants in the weight loss period (< 2 years postsurgery), health literacy, health numeracy and cognitive functioning were not related to change in BMI (ΔBMI), percent total weight loss (%TWL) or percent excess weight loss (%EWL). However, for participants in the weight maintenance period (2-4 years postsurgery), higher health literacy scores were related to greater change in ΔBMI, and higher health numeracy scores were related to greater ΔBMI, %TWL, and %EWL. DISCUSSION: Although health literacy and health numeracy did not predict weight loss outcomes for those in the initial weight loss period, they were related to weight outcomes for participants in the weight maintenance period. This suggests that health literacy and health numeracy may play a role in facilitating longer-term weight maintenance among patients who undergo bariatric surgery. Clinicians conducting presurgical psychosocial evaluations should consider routinely screening for health literacy and health numeracy.

Behavioral Health Services/Psychiatry

Miller-Matero LR, **Hecht LM**, **Miller MK**, **Autio K**, **Pester BD**, **Tobin ET**, **Patel S**, **Braciszewski JM**, **Maye M**, and **Ahmedani BK**. A Brief Psychological Intervention for Chronic Pain in Primary Care: A Pilot Randomized Controlled Trial. *Pain Med* 2021; Epub ahead of print. PMID: 33616190. <u>Full Text</u>

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OBJECTIVE: Although evidence-based psychological interventions improve chronic pain, many patients do not engage in behavioral health services. Offering a brief intervention in a medical setting may provide benefits to patients with chronic pain. The purpose of this study was to examine preliminary outcomes of a brief psychological intervention for chronic pain delivered in primary care. DESIGN: Pilot randomized controlled trial. SETTING: Primary care clinic. SUBJECTS: Sixty participants with chronic pain were randomized to a 5-session psychological intervention or treatment-as-usual control group. METHODS: Participants completed pre- and post-intervention measures assessing pain severity, pain interference, pain catastrophizing, depression, and anxiety. RESULTS: Most participants (76.7%) randomized to the intervention completed all sessions. Compared to the control group, those in the intervention had decreases in pain severity (P = .048), pain catastrophizing (P = .04), and depression (P = .01) from pre- to post-intervention. Within the intervention group, there was a significant improvement in pain interference scores (P = 0.02). Within the intervention group, effect sizes were medium to large for changes in pain severity, pain interference, pain catastrophizing, and depression scores. There were no significant changes in anxiety scores. CONCLUSION: Results suggest that delivery of a brief psychological intervention for chronic pain in primary care appears to offer improvements in pain severity, pain interference, pain catastrophizing, and depression. Findings suggest that shorter-term psychological interventions may offer similar benefits as longer-term ones. Furthermore, offering a brief intervention in primary care may increase access and engagement in behavioral pain management services. Future research should examine this through a fully-powered trial with longer-term outcomes.

Behavioral Health Services/Psychiatry

Tsui JI, Akosile MA, Lapham GT, Boudreau DM, Johnson EA, Bobb JF, Binswanger IA, Yarborough BJH, Glass JE, Rossom RC, Murphy MT, Cunningham CO, Arnsten JH, Thakral M, Saxon AJ, Merrill JO, Samet JH, Bart GB, Campbell CI, **Loree AM**, Silva A, Stotts AL, **Ahmedani B**, **Braciszewski JM**, Hechter RC, Northrup TF, Horigian VE, and Bradley KA. Prevalence and Medication Treatment of Opioid Use Disorder Among Primary Care Patients with Hepatitis C and HIV. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33569735. <u>Full Text</u>

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BACKGROUND: Hepatitis C and HIV are associated with opioid use disorders (OUD) and injection drug use. Medications for OUD can prevent the spread of HCV and HIV. OBJECTIVE: To describe the prevalence of documented OUD, as well as receipt of office-based medication treatment, among primary care patients with HCV or HIV. DESIGN: Retrospective observational cohort study using electronic health record and insurance data. PARTICIPANTS: Adults ≥ 18 years with ≥ 2 visits to primary care during the study (2014-2016) at 6 healthcare systems across five states (CO, CA, OR, WA, and MN). MAIN MEASURES: The primary outcome was the diagnosis of OUD; the secondary outcome was OUD treatment with buprenorphine or oral/injectable naltrexone. Prevalence of OUD and OUD treatment was calculated across four groups: HCV only; HIV only; HCV and HIV; and neither HCV nor HIV. In addition, adjusted odds ratios (AOR) of OUD treatment associated with HCV and HIV (separately) were estimated, adjusting for age, gender, race/ethnicity, and site. KEY RESULTS: The sample included 1,368,604 persons, of whom 10,042 had HCV, 5821 HIV, and 422 both. The prevalence of diagnosed OUD varied across groups: 11.9% (95% CI: 11.3%, 12.5%) for those with HCV; 1.6% (1.3%, 2.0%) for those with HIV; 8.8% (6.2%, 11.9%) for those with both; and 0.92% (0.91%, 0.94%) among those with neither. Among those with diagnosed OUD, the prevalence of OUD medication treatment was 20.9%, 16.0%, 10.8%, and 22.3%, for those with HCV, HIV, both, and neither, respectively. HCV was not associated with OUD treatment (AOR = 1.03; 0.88, 1.21), whereas patients with HIV had a lower probability of OUD treatment (AOR = 0.43; 0.26, 0.72). CONCLUSIONS: Among patients receiving primary care, those diagnosed with HCV and HIV were more likely to have documented OUD than those without. Patients with HIV were less likely to have documented medication treatment for OUD.

Cardiology/Cardiovascular Research

Altawil M, **Greenberg J**, and **Ananthasubramaniam K**. Gated SPECT left ventricular shape and prediction of super responders to cardiac resynchronization therapy: Not so easy as it (LV) looks. *J Nucl Cardiol* 2021; Epub ahead of print. PMID: 33608854. Full Text

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Cardiology/Cardiovascular Research

Eng MH, and Verma DR. Mitral valve-in-ring: Simply complicated. *Catheter Cardiovasc Interv* 2021; 97(2):359-360. PMID: 33587799. Full Text

Center for Structural Heart Disease, Henry Ford Hospital, Detroit, Michigan.
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Cardiology/Cardiovascular Research

Estévez-Loureiro R, Shuvy M, Taramasso M, Benito-Gonzalez T, Denti P, Arzamendi D, Adamo M, Freixa X, **Villablanca P**, Krivoshei L, Fam N, Spargias K, Czarnecki A, Haberman D, Agmon Y, Sudarsky D, Pascual I, Ninios V, Scianna S, Moaraf I, Schiavi D, Chrissoheris M, Beeri R, Kerner A, Fernández-Peregrina E, Di Pasquale M, Regueiro A, Poles L, Iñiguez-Romo A, Fernández-Vázquez F, and Maisano F. Use of MitraClip for mitral valve repair in patients with acute mitral regurgitation following acute myocardial infarction: Effect of cardiogenic shock on outcomes (IREMMI Registry). *Catheter Cardiovasc Interv* 2021; Epub ahead of print. PMID: 33600072. Full Text

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OBJECTIVES: To assess outcomes in patients with acute mitral regurgitation (MR) following acute myocardial infarction (AMI) who received percutaneous mitral valve repair (PMVR) with the MitraClip device and to compare outcomes of patients who developed cardiogenic shock (CS) to those who did not (non-CS). BACKGROUND: Acute MR after AMI may lead to CS and is associated with high mortality. METHODS: This registry analyzed patients with MR after AMI who were treated with MitraClip at 18 centers within eight countries between January 2016 and February 2020. Patients were stratified into CS and non-CS groups. Primary outcomes were mortality and rehospitalization due to heart failure. Secondary outcomes were acute procedural success, functional improvement, and MR reduction. Multivariable Cox regression analysis evaluated association of CS with clinical outcomes. RESULTS: Among 93 patients analyzed (age 70.3 ± 10.2 years), 50 patients (53.8%) experienced CS before PMVR. Mortality at 30 days (10% CS vs. 2.3% non-CS; p = .212) did not differ between groups. After median follow-up of 7 months (IQR 2.5-17 months), the combined event mortality/re-hospitalization was similar (28% CS vs. 25.6% non-CS; p = .793). Likewise, immediate procedural success (90% CS vs. 93% non-CS; p = .793) and need for reintervention (CS 6% vs. non-CS 2.3%, p = .621) or re-admission due to HF (CS 13% vs. NCS 23%, p = .253) at 3 months did not differ. CS was not independently associated with the combined end-point (hazard ratio 1.1; 95% CI, 0.3-4.6; p = .889). CONCLUSIONS: Patients found to have significant MR during their index hospitalization for AMI had similar clinical outcomes with PMVR whether they presented in or out of cardiogenic shock, provided initial hemodynamic stabilization was first achieved before PMVR.

Cardiology/Cardiovascular Research
Giannitsis E, Blankenberg S, Christenson RH, Frey N, von Haehling S, Hamm CW, Inoue K, Katus HA, Lee CC, **McCord J**, Möckel M, Chieh JTW, Tubaro M, Wollert KC, and Huber K. Critical appraisal of the 2020 ESC guideline recommendations on diagnosis and risk assessment in patients with suspected non-ST-segment elevation acute coronary syndrome. *Clin Res Cardiol* 2021; Epub ahead of print. PMID: 33635437. Full Text

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Multiple new recommendations have been introduced in the 2020 ESC guidelines for the management of acute coronary syndromes with a focus on diagnosis, prognosis, and management of patients presenting without persistent ST-segment elevation. Most recommendations are supported by high-quality scientific evidence. The guidelines provide solutions to overcome obstacles presumed to complicate a convenient interpretation of troponin results such as age-, or sex-specific cutoffs, and to give practical advice to overcome delays of laboratory reporting. However, in some areas, scientific support is less well documented or even missing, and other areas are covered rather by expert opinion or subjective recommendations. We aim to provide a critical appraisal on several recommendations, mainly related to the diagnostic and prognostic assessment, highlighting the discrepancies between Guideline recommendations and the existing scientific evidence.

Cardiology/Cardiovascular Research

Lala A, Shah KB, **Lanfear DE**, Thibodeau JT, Palardy M, Ambardekar AV, McNamara DM, Taddei-Peters WC, Baldwin JT, Jeffries N, Khalatbari S, Spino C, Richards B, Mann DL, Stewart GC, Aaronson KD, and Mancini DM. Predictive Value of Cardiopulmonary Exercise Testing Parameters in Ambulatory Advanced Heart Failure. *JACC Heart Fail* 2021; 9(3):226-236. PMID: 33549559. Full Text

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OBJECTIVES: This study sought to determine cardiopulmonary exercise (CPX) predictors of the combined outcome of durable mechanical circulatory support (MCS), transplantation, or death at 1 year

among patients with ambulatory advanced heart failure (HF). BACKGROUND: Optimal CPX predictors of outcomes in contemporary ambulatory advanced HF patients are unclear. METHODS: REVIVAL (Registry Evaluation of Vital Information for ventricular assist devices [VADs] in Ambulatory Life) enrolled 400 systolic HF patients, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profiles 4-7. CPX was performed by 273 subjects 2 ± 1 months after study enrollment. Discriminative power of maximal (peak oxygen consumption [peak VO_2]; VO_2 pulse, circulatory power [CP]; peak systolic blood pressure • peak VO_2], peak end-tidal pressure CO_2 [$PEtCO_2$], and peak Borg scale score) and submaximal CPX parameters (ventilatory efficiency [VE/VCO_2 slope]; VO_2 at anaerobic threshold [VO_2AT]; and oxygen uptake efficiency slope [OUES]) to predict the composite outcome were assessed by univariate and multivariate Cox regression and Harrell's concordance statistic. RESULTS: At 1 year, there were 39 events (6 transplants, 15 deaths, 18 MCS implantations). Peak VO_2, VO_2AT, OUES, peak $PEtCO_2$, and CP were higher in the no-event group (all $p < 0.001$), whereas VE/VCO_2 slope was lower ($p < 0.0001$); respiratory exchange ratio was not different. CP (hazard ratio [HR]: 0.89; $p = 0.001$), VE/VCO_2 slope (HR: 1.05; $p = 0.001$), and peak Borg scale score (HR: 1.20; $p = 0.005$) were significant predictors on multivariate analysis (model C-statistic: 0.80). CONCLUSIONS: Among patients with ambulatory advanced HF, the strongest maximal and submaximal CPX predictor of MCS implantation, transplantation, or death at 1 year were CP and VE/VCO_2, respectively. The patient-reported measure of exercise effort (Borg scale score) contributed substantially to the prediction of outcomes, a surprising and novel finding that warrants further investigation. (Registry Evaluation of Vital Information for VADs in Ambulatory Life [REVIVAL]; NCT01369407).

Cardiology/Cardiovascular Research
Lemor A, **Basir MB**, **Gorgis S**, Todd J, Marso S, Gelormini J, Akhtar Y, Baker J, Chahin J, Abdul-Waheed M, Thukral N, and **O'Neill W**. Impact of Age in Acute Myocardial Infarction Cardiogenic Shock. Insights from the National Cardiogenic Shock Initiative. *Crit Pathw Cardiol* 2021; Epub ahead of print. PMID: 33606413. Full Text

Henry Ford Hospital, Detroit, Michigan Fort Sanders Medical Center, Knoxville, Tennessee Overland Park Regional Medical Center, Overland Park, Kansas Mercy Hospital of Buffalo, Buffalo, New York North Knoxville Medical Center, Knox County, Tennessee Jackson/Madison Co. General Hospital, Jackson, Tennessee Excela Health Westmoreland, Greensburg, Pennsylvania Medical Center of Bowling Green, Bowling Green, Kentucky Methodist Heart Hospital, San Antonio, Texas.

Acute myocardial infarction complicated by cardiogenic shock (AMICS) is associated with high mortality. Patients ≥75 years old represent an increasing proportion of those who present with AMICS and are at high risk for adverse outcomes. The National Cardiogenic Shock Initiative includes patients with AMICS treated using a standard shock protocol with early invasive hemodynamic monitoring, mechanical circulatory support (MCS), and percutaneous coronary intervention (PCI). We evaluated the outcomes of patients based on their age group, dividing them into <75 and ≥75 years old. We included 300 patients; 238 were <75 years old (79.3%) and 62 patients ≥75 years old. There were significant differences in survival; patients <75 years old had a 75.6% survival, while those ≥75 years old had a 50% survival (aOR:10.4, p=0.001). SCAI shock classification impacted survival as well; those <75 years old with class C or D shock had a survival of 84%, compared to 57% in those ≥75 years old. Patients ≥75 years old requiring 1 or 2 vasopressors had significantly lower survival rates (36% and 25%, respectively) when compared with patients <75 years old (76.7% with 1 and 60.5% with >1 vasopressor). In conclusion, age is inversely proportional with survival; patients <75 years old have high rates of survival if treated using best practices with RHC, early MCS and PCI. However, using a standardized protocol can improve survival in the elderly, therefore, age on its own should not be a reason to withhold PCI or MCS use.

Cardiology/Cardiovascular Research
Nona P, **Altawil M**, **Khan E**, and **Maskoun W**. Dual-chamber pacing using a hybrid transvenous and leadless pacing approach. *Pacing Clin Electrophysiol* 2021; Epub ahead of print. PMID: 33559285. Full Text

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An elderly gentleman with a dual-chamber pacemaker presented to our institution with symptoms of symptomatic bradycardia and high-grade atrioventricular (AV) block. Device interrogation revealed failure to capture in the right ventricle (RV) lead with bipolar pacing, high RV pacing threshold with unipolar pacing, and high impedance suggesting lead fracture. The atrial lead function was normal. Given his advanced age, gait instability, and dementia, the decision was made to proceed with Micra AV pacemaker implantation, while programming his dual-chamber pacemaker to AAIR mode, thus maintaining AV synchrony by tracking paced atrial impulses and providing ventricular pacing.

Cardiology/Cardiovascular Research
Nona P, **Coriasso N**, **Khan A**, **Singh G**, **Eng MH**, **Frisoli T**, **O'Neill BP**, **Villablanca PA**, **Lee JC**, **Jacobsen G**, **O'Neill WW**, and **Wang DD**. Pacemaker following transcatheter aortic valve replacement and tricuspid regurgitation: A single-center experience. *J Card Surg* 2021; Epub ahead of print. PMID: 33533038. Full Text

Division of Cardiology, Henry Ford Health System, Henry Ford Hospital, Detroit, Michigan, USA. Department of Public Health Sciences, Henry Ford Health System, Henry Ford Hospital, Detroit, Michigan, USA.

BACKGROUND: As transcatheter aortic valve replacement (TAVR) procedures increase, more data is available on the development of conduction abnormalities requiring permanent pacemaker (PPM) implantation post-TAVR. Mechanistically, new pacemaker implantation and incidence of associated tricuspid regurgitation (TR) post-TAVR is not well understood. Studies have evaluated the predictability of patient anatomy towards risk for needing permanent pacemaker (PPM) post-TAVR; however, little has been reported on new PPM and TR in patients post-TAVR. METHODS: This retrospective study identified patients at our health system who underwent PPM following TAVR from January 2014 to June 2018. Data from both TAVR and PPM procedures as well as patient demographics were collected. Echocardiographic data before TAVR, between TAVR and PPM placement, and the most recent echocardiogram at the time of chart review were analyzed. RESULTS: Of 796 patients who underwent TAVR between January 2014 and June 2018, 89 patients (11%) subsequently required PPM. Out of the 89 patients who required PPM implantation, 82 patients had pre-TAVR and 2-year post-TAVR echocardiographic imaging data. At baseline, 22% (18/82) of patients had at least moderate TR. At 2-year post-TAVR echocardiographic imaging follow-up; 27% (22/82) of patients had at least moderate TR. Subgroup analysis was performed according to the TAVR valve size implanted. In patients who received a TAVR device < 29 mm in diameter in size, 25% (11/44) had worsening TR. In patients who received a TAVR device ≥ 29 mm in diameter, 37% (14/38) had worsening TR. CONCLUSION: We have demonstrated a patient population that may be predisposed to developing worsening TR and right heart function after TAVR and Pacemaker implantation.

Cardiology/Cardiovascular Research
Parikh MJ, Schuleri KH, Chakrabarti AK, **O'Neill WW**, Kapur NK, and Wohns DH. Door-to-unload: left ventricular unloading before reperfusion in ST-elevation myocardial infarction. *Future Cardiol* 2021; Epub ahead of print. PMID: 33599135. Full Text

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ST-elevation myocardial infarction treatment in the modern era has focused on minimizing time of ischemia by reducing door-to-balloon time to limit infarct size and improve survival. Although there have been significant improvements in minimizing time to coronary reperfusion, the incidence of heart failure following a myocardial infarction has remained high. Preclinical studies have shown that unloading the left

ventricle for 30 min prior to coronary reperfusion can reduce infarct size and promote myocardial recovery. The DTU-STEMI randomized prospective trial will test the hypothesis that left ventricular unloading for at least 30 min prior to coronary reperfusion will improve infarct size and heart failure-related events as compared with the current standard of care.

Cardiology/Cardiovascular Research
Reiter-Brennan C, Dzaye O, Al-Mallah MH, Dardari Z, **Brawner CA**, **Lamerato LE**, **Keteyian SJ**, **Ehrman JK**, Blaha MJ, Visvanathan K, and Marshall CH. Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. *Cancer* 2021; Epub ahead of print. PMID: 33561293. Full Text

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BACKGROUND: The relation between cardiorespiratory fitness (CRF) and prostate cancer is not well established. The objective of this study was to determine whether CRF is associated with prostate cancer screening, incidence, or mortality. METHODS: The Henry Ford Exercise Testing Project is a retrospective cohort study of men aged 40 to 70 years without cancer who underwent physician-referred exercise stress testing from 1995 to 2009. CRF was quantified in metabolic equivalents of task (METs) (<6 [reference], 6-9, 10-11, and ≥12 METs), estimated from the peak workload achieved during a symptom-limited, maximal exercise stress test. Prostate-specific antigen (PSA) testing, incident prostate cancer, and all-cause mortality were analyzed with multivariable adjusted Poisson regression and Cox proportional hazard models. RESULTS: In total, 22,827 men were included, of whom 739 developed prostate cancer, with a median follow-up of 7.5 years. Men who had high fitness (≥12 METs) had an 28% higher risk of PSA screening (95% CI, 1.2-1.3) compared with those who had low fitness (<6 METs. After adjusting for PSA screening, fitness was associated with higher prostate cancer incidence (men aged <55 years, P = .02; men aged >55 years, P ≤ .01), but not with advanced prostate cancer. Among the men who were diagnosed with prostate cancer, high fitness was associated with a 60% lower risk of all-cause mortality (95% CI, 0.2-0.9). CONCLUSIONS: Although men with high fitness are more likely to undergo PSA screening, this does not fully account for the increased incidence of prostate cancer seen among these individuals. However, men with high fitness have a lower risk of death after a prostate cancer diagnosis, suggesting that the cancers identified may be low-risk with little impact on long-term outcomes.

Cardiology/Cardiovascular Research
Sadat B, Tirunagari D, **Karthikeyan V**, **Patel A**, **Van Harn M**, **Saleem MM**, and **Ananthasubramaniam K**. Clinical impact of pre-kidney transplant pulmonary hypertension on post-transplant outcomes. *Int J Cardiovasc Imaging* 2021; Epub ahead of print. PMID: 33616784. Full Text

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Outcomes of kidney transplant (KT) patients with pre-transplant pulmonary hypertension (PH) are poorly understood. PH patients are often considered high risk and excluded from KT. We investigated the association of pre-transplant PH with KT recipient's outcomes. A single-center, retrospective study that

reviewed all patients transplanted from 2010 to 2016, who had a transthoracic echocardiogram (TTE) before KT and at least one TTE post-KT. The TTE closest to the KT was used for analyses. PH is defined as pulmonary artery systolic pressure (PASP) ≥ 40 mm Hg. Of 204 patients, 61 had PASP ≥ 40 mm Hg (with PH) and 143 had PASP < 40 mm Hg (without PH) prior to KT. No statistically significant differences existed between the two groups in baseline demographics, renal failure etiologies, dialysis access type, and cardiovascular risk factors. The mean difference in pre-KT PASP was 18.1 ± 7 mm Hg (P < 0.001). Patients with PH had a statistically significant decrease in PASP post-KT compared to the patients without PH with a mean change of -7.03 ± 12.28 mm Hg vs. + 3.96 ± 11.98 mm Hg (p < 0.001), respectively. Moderate mitral and moderate-severe tricuspid regurgitation were the only factors found to be independently associated with PH (p = 0.001) on multivariable analysis. No statistically significant difference was notable in patient survival, graft function, and creatinine post-KT in both groups. PH pre-KT particularly mild-moderate PH did not adversely affect intermediate (90-day) and long-term allograft and patient survival. Patients with mild-moderate PH should not be excluded from KT.

Cardiology/Cardiovascular Research
So CY, **Kang G**, **Villablanca PA**, Nuñez-Gil IJ, and Ramakrishna H. Chasing the Cardiogenic Shock Unicorn. *J Cardiothorac Vasc Anesth* 2021; 35(2):366-367. PMID: 32950346. Full Text

Division of Cardiology, Henry Ford Hospital, Detroit, MI; Division of Cardiology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong.
Division of Cardiology, Henry Ford Hospital, Detroit, MI; Division of Cardiovascular Medicine, Department of Medicine, Veterans Affairs (VA) Palo Alto Health Care System, Palo Alto, CA.
Division of Cardiology, Henry Ford Hospital, Detroit, MI.
Interventional Cardiology, Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain.
Division of Cardiovascular and Thoracic Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic Rochester, MN.

Cardiology/Cardiovascular Research
Thompson MP, Yaser JM, Hou H, Syrjamaki JD, DeLucia A, 3rd, Likosky DS, **Keteyian SJ**, Prager RL, Gurm HS, and Sukul D. Determinants of Hospital Variation in Cardiac Rehabilitation Enrollment During Coronary Artery Disease Episodes of Care. *Circ Cardiovasc Qual Outcomes* 2021; 14(2):e007144. PMID: 33541107. Full Text

Department of Cardiac Surgery (M.P.T., H.H., D.S.L., R.L.P.), Michigan Medicine, Ann Arbor MI.
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BACKGROUND: Cardiac rehabilitation (CR) is associated with improved outcomes for patients with coronary artery disease (CAD). However, CR enrollment remains low and there is a dearth of real-world data on hospital-level variation in CR enrollment. We sought to explore determinants of hospital variability in CR enrollment during CAD episodes of care: medical management of acute myocardial infarction (AMI-MM), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). METHODS: A cohort of 71 703 CAD episodes of care were identified from 33 hospitals in the Michigan Value Collaborative statewide multipayer registry (2015 to 2018). CR enrollment was defined using professional and facility claims and compared across treatment strategies: AMI-MM (n=18 678), PCI (n=41 986), and CABG (n=11 039). Hierarchical logistic regression was used to estimate effects of predictors and hospital risk-adjusted rates of CR enrollment. RESULTS: Overall, 20 613 (28.8%) patients enrolled in CR, with significant differences by treatment strategy: AMI-MM=13.4%, PCI=29.0%, CABG=53.8% (P<0.001). There were significant differences in CR enrollment across age groups, comorbidity status, and payer status. At the hospital-level, there was over 5-fold variation in hospital risk-adjusted CR enrollment rates

(9.8%-51.6%). Hospital-level CR enrollment rates were highly correlated across treatment strategy, with the strongest correlation between AMI-MM versus PCI (R(2)=0.72), followed by PCI versus CABG (R(2)=0.51) and AMI-MM versus CABG (R(2)=0.46, all P<0.001). CONCLUSIONS: Substantial variation exists in CR enrollment during CAD episodes of care across hospitals. However, within-hospital CR enrollment rates were significantly correlated across all treatment strategies. These findings suggest that CR enrollment during CAD episodes of care is the product of hospital-specific rather than treatment-specific practice patterns.

Cardiology/Cardiovascular Research
Vemmou E, **Alaswad K**, Patel M, Mahmud E, Choi JW, Jaffer FA, Doing AH, Dattilo P, Karmpaliotis D, Krestyaninov O, Khelimskii D, Nikolakopoulos I, Karacsonyi J, Xenogiannis I, Garcia S, Burke MN, Abi Rafeh N, ElGuindy A, Goktekin O, Abdo A, Rangan BV, Abdullah S, and Brilakis ES. Chronic total occlusion percutaneous coronary intervention in octogenarians and nonagenarians. *J Am Geriatr Soc* 2021; Epub ahead of print. PMID: 33591578. Full Text

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Massachusetts General Hospital, Boston, Massachusetts, USA.
UC Health Medical Center of the Rockies, Loveland, Colorado, USA.
Columbia University Irving Medical Center, New York, New York, USA.
Meshalkin Novosibirsk Research Institute, Novosibirsk, Russian Federation.
Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, Minnesota, USA.
North Oaks Health System, Hammond, LA, USA.
Aswan Heart Centre, Magdi Yacoub Foundation, Egypt.
Memorial Bahcelievler Hospital, Istanbul, Turkey.
American University of Beirut Medical Center, Lebanon.
VA North Texas Healthcare System and UT Southewestern Medical Center, Dallas, Texas, USA.

OBJECTIVE: The outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) in octogenarians and nonagenarians have received limited study. METHODS: We compared in-hospital outcomes of CTO PCI between patients ≥80 vs. <80-years-old in 6233 CTO PCIs performed between 2012 and 2020 at 33 U.S. and international centers. RESULTS: There were 415 octogenarians and nonagenarians in our study (7% of the total population). Compared with younger patients, octo- and nonagenarians were less likely to be men (73% vs. 83.2%, p < 0.0001) and more likely to have atrial fibrillation (27% vs. 12%, p < 0.0001) and prior coronary artery bypass graft surgery (CABG) (43% vs. 29%, p < 0.0001). They were more likely to have CTOs with moderate/severe calcification (71% vs. 46%, p < 0.0001), but had similar mean J-CTO scores (2.5 ± 1.3 vs. 2.4 ± 1.3, p = 0.08). They had lower technical and procedural success (82.2% vs. 86.3%, p = 0.0201; 80.3% vs. 84.8%, p = 0.016, respectively) and higher incidence of in-hospital major adverse cardiovascular events (3.4% vs. 1.8%, p = 0.021). On multivariable analysis PCI in octo- and nonagenarians was not independently associated with technical and procedural success or with in-hospital MACE. CONCLUSION: CTO PCI is feasible in octo- and nonagenarians, although success rates are lower, and the risk of complications is higher compared with younger patients, likely related to more comorbidities and higher coronary lesion complexity.

Cardiology/Cardiovascular Research
Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Division of Cardiovascular Disease, Center for Structural Heart, Henry Ford Hospital, Detroit, Michigan, USA (Wang, O'Neill); Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA (Zervos, McKinnon, Alangaden, Suleyman); Family Medicine, Henry Ford Hospital, Detroit, Michigan, USA (Allard);

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OBJECTIVE: Examine the effect of a universal facemask policy for healthcare workers(HCW) and incidence of SARS-CoV-2 positivity. METHODS: Daily number of symptomatic HCW tested, SARS-CoV-2 positivity rates, and HCW job-descriptions were collected pre and post Universal HCW facemask policy(March 26). Multiple change point regression was used to model positive-test-rate data. SARS-CoV-2 testing and positivity rates were compared for pre-intervention, transition, post-intervention, and follow-up periods. RESULTS: Between March 12-August 10, 2020, 19.2% of HCW were symptomatic for COVID-19 and underwent SARS-CoV-2 testing. A single change point was identified ~March 28-30(95% probability). Before the change point, the odds of a tested HCW having a positive result doubled every 4.5-7.5 days. Post-change-point, the odds of a tested HCW having a positive result halved every 10.5-13.5 days. CONCLUSIONS: Universal facemasks was associated with reducing HCW's risk of acquiring COVID-19.

Center for Health Policy and Health Services Research

Martens K, **Hamann A**, **Miller-Matero LR**, **Miller C**, Bonham AJ, Ghaferi AA, and **Carlin AM**. Relationship between depression, weight, and patient satisfaction 2 years after bariatric surgery. *Surg Obes Relat Dis* 2021; 17(2):366-371. PMID: 33127323. Full Text

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BACKGROUND: Findings regarding longer term symptoms of depression and the impact of depression on outcomes such as weight loss and patient satisfaction, are mixed or lacking. OBJECTIVES: This study sought to understand the relationship between depression, weight loss, and patient satisfaction in the two years after bariatric surgery. SETTING: This study used data from a multi-institutional, statewide quality improvement collaborative of 45 different bariatric surgery sites. METHODS: Participants included patients (N = 1991) who underwent Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2015-2018. Participants self-reported symptoms of depression (Patient Health Questionnaire-8 [PHQ-8]), satisfaction with surgery, and weight presurgery and 1 year and 2 years postsurgery. RESULTS: Compared to presurgery, fewer patients' PHQ-8 scores indicated clinically significant depression (PHQ-8≥10) at 1 year (P < .001; 14.3% versus 5.1%) and 2 years postsurgery (P < .0001; 8.7%). There was a significant increase in the prevalence of clinical depression from the first to second year postsurgery (P < .0001; 5.1% versus 8.7%). Higher PHQ-8 at baseline was related to less weight loss (%Total Weight Loss [%TWL] and %Excess Weight Loss [%EWL]) at 1 year postsurgery (P < .001), with a trend toward statistical significance at 2 years (P = .06). Postoperative depression was related to lower %TWL and %EWL, and less reduction in body mass index (BMI) at 1 year (P < .001) and 2 years (P < .0001). Baseline and postoperative depression were associated with lower patient satisfaction at both postoperative time points. CONCLUSIONS: This study suggests improvements in depression up to 2 years postbariatric surgery, although it appears that the prevalence of depression increases after the first year. Depression, both pre- and postbariatric surgery, may impact weight loss and patient satisfaction.

Center for Health Policy and Health Services Research

Miller-Matero LR, **Hecht L**, **Patel S**, **Martens KM**, **Hamann A**, and **Carlin AM**. The Influence of Health Literacy and Health Numeracy on Weight Loss Outcomes Following Bariatric Surgery. *Surg Obes Relat Dis* 2021; 17(2):384-389. PMID: 33082073. Full Text

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BACKGROUND: Although cognitive functioning and health literacy are related to weight loss 1year following bariatric surgery, the influence of health numeracy (i.e., health-related mathematical abilities) is unknown. In addition, further research is needed to examine the impact of all these factors on longer-term weight loss outcomes to determine if they influence the ability to maintain weight loss. SETTING: Single bariatric center. METHODS: Patients (N = 567) who underwent bariatric surgery from 2014-2017 completed a brief survey including current weight. Retrospective chart reviews were conducted to gather information from the presurgical evaluation including weight, body mass index (BMI), health literacy, health numeracy and score on a cognitive screener. RESULTS: Among participants in the weight loss period (< 2 years postsurgery), health literacy, health numeracy and cognitive functioning were not related to change in BMI (ΔBMI), percent total weight loss (%TWL) or percent excess weight loss (%EWL). However, for participants in the weight maintenance period (2-4 years postsurgery), higher health literacy scores were related to greater change in ΔBMI, and higher health numeracy scores were related to greater ΔBMI, %TWL, and %EWL. DISCUSSION: Although health literacy and health numeracy did not predict weight loss outcomes for those in the initial weight loss period, they were related to weight outcomes for participants in the weight maintenance period. This suggests that health literacy and health numeracy may play a role in facilitating longer-term weight maintenance among patients who undergo bariatric surgery. Clinicians conducting presurgical psychosocial evaluations should consider routinely screening for health literacy and health numeracy.

Center for Health Policy and Health Services Research

Miller-Matero LR, **Hecht LM**, **Miller MK**, **Autio K**, **Pester BD**, **Tobin ET**, **Patel S**, **Braciszewski JM**, **Maye M**, and **Ahmedani BK**. A Brief Psychological Intervention for Chronic Pain in Primary Care: A Pilot Randomized Controlled Trial. *Pain Med* 2021; Epub ahead of print. PMID: 33616190. Full Text

Behavioral Health, Henry Ford Health System, Detroit, Michigan, USA.
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OBJECTIVE: Although evidence-based psychological interventions improve chronic pain, many patients do not engage in behavioral health services. Offering a brief intervention in a medical setting may provide benefits to patients with chronic pain. The purpose of this study was to examine preliminary outcomes of a brief psychological intervention for chronic pain delivered in primary care. DESIGN: Pilot randomized controlled trial. SETTING: Primary care clinic. SUBJECTS: Sixty participants with chronic pain were randomized to a 5-session psychological intervention or treatment-as-usual control group. METHODS: Participants completed pre- and post-intervention measures assessing pain severity, pain interference, pain catastrophizing, depression, and anxiety. RESULTS: Most participants (76.7%) randomized to the intervention completed all sessions. Compared to the control group, those in the intervention had decreases in pain severity (P = .048), pain catastrophizing (P = .04), and depression (P = .01) from pre- to post-intervention. Within the intervention group, there was a significant improvement in pain interference scores (P = 0.02). Within the intervention group, effect sizes were medium to large for changes in pain severity, pain interference, pain catastrophizing, and depression scores. There were no significant changes in anxiety scores. CONCLUSION: Results suggest that delivery of a brief psychological intervention for chronic pain in primary care appears to offer improvements in pain severity, pain interference, pain catastrophizing, and depression. Findings suggest that shorter-term psychological interventions may offer similar benefits as longer-term ones. Furthermore, offering a brief intervention in

primary care may increase access and engagement in behavioral pain management services. Future research should examine this through a fully-powered trial with longer-term outcomes.

<u>Center for Health Policy and Health Services Research</u>
Spradling PR, Zhong Y, Moorman AC, **Rupp LB**, **Lu M**, Teshale EH, Schmidt MA, Daida YG, Boscarino JA, and **Gordon SC**. The persistence of underreporting of hepatitis C as an underlying or contributing cause of death, 2011-2017. *Clin Infect Dis* 2021; Epub ahead of print. PMID: 33561187. Full Text

Division of Viral Hepatitis, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.
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Using electronic health records, we found that hepatitis C reporting on death certificates of 2,901 HCV-infected decedents from four U.S. healthcare organizations during 2011-2017 was documented in only 50% of decedents with hepatocellular carcinoma and less than half with decompensated cirrhosis. National figures likely underestimate the U.S. HCV mortality burden.

<u>Center for Health Policy and Health Services Research</u>
Tsui JI, Akosile MA, Lapham GT, Boudreau DM, Johnson EA, Bobb JF, Binswanger IA, Yarborough BJH, Glass JE, Rossom RC, Murphy MT, Cunningham CO, Arnsten JH, Thakral M, Saxon AJ, Merrill JO, Samet JH, Bart GB, Campbell CI, **Loree AM**, Silva A, Stotts AL, **Ahmedani B**, **Braciszewski JM**, Hechter RC, Northrup TF, Horigian VE, and Bradley KA. Prevalence and Medication Treatment of Opioid Use Disorder Among Primary Care Patients with Hepatitis C and HIV. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33569735. Full Text

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BACKGROUND: Hepatitis C and HIV are associated with opioid use disorders (OUD) and injection drug use. Medications for OUD can prevent the spread of HCV and HIV. OBJECTIVE: To describe the prevalence of documented OUD, as well as receipt of office-based medication treatment, among primary care patients with HCV or HIV. DESIGN: Retrospective observational cohort study using electronic health

record and insurance data. PARTICIPANTS: Adults ≥ 18 years with ≥ 2 visits to primary care during the study (2014-2016) at 6 healthcare systems across five states (CO, CA, OR, WA, and MN). MAIN MEASURES: The primary outcome was the diagnosis of OUD; the secondary outcome was OUD treatment with buprenorphine or oral/injectable naltrexone. Prevalence of OUD and OUD treatment was calculated across four groups: HCV only; HIV only; HCV and HIV; and neither HCV nor HIV. In addition, adjusted odds ratios (AOR) of OUD treatment associated with HCV and HIV (separately) were estimated, adjusting for age, gender, race/ethnicity, and site. KEY RESULTS: The sample included 1,368,604 persons, of whom 10,042 had HCV, 5821 HIV, and 422 both. The prevalence of diagnosed OUD varied across groups: 11.9% (95% CI: 11.3%, 12.5%) for those with HCV; 1.6% (1.3%, 2.0%) for those with HIV; 8.8% (6.2%, 11.9%) for those with both; and 0.92% (0.91%, 0.94%) among those with neither. Among those with diagnosed OUD, the prevalence of OUD medication treatment was 20.9%, 16.0%, 10.8%, and 22.3%, for those with HCV, HIV, both, and neither, respectively. HCV was not associated with OUD treatment (AOR = 1.03; 0.88, 1.21), whereas patients with HIV had a lower probability of OUD treatment (AOR = 0.43; 0.26, 0.72). CONCLUSIONS: Among patients receiving primary care, those diagnosed with HCV and HIV were more likely to have documented OUD than those without. Patients with HIV were less likely to have documented medication treatment for OUD.

Clinical Quality and Safety

Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Division of Cardiovascular Disease, Center for Structural Heart, Henry Ford Hospital, Detroit, Michigan, USA (Wang, O'Neill); Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA (Zervos, McKinnon, Alangaden, Suleyman); Family Medicine, Henry Ford Hospital, Detroit, Michigan, USA (Allard); Public Health Sciences, Henry Ford Hospital, Detroit, Michigan, USA (Schultz, Poisson); Office of Clinical Quality and Safety, Henry Ford Health System, Detroit, Michigan, USA (Chu); Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA (Kalkanis).

OBJECTIVE: Examine the effect of a universal facemask policy for healthcare workers(HCW) and incidence of SARS-CoV-2 positivity. METHODS: Daily number of symptomatic HCW tested, SARS-CoV-2 positivity rates, and HCW job-descriptions were collected pre and post Universal HCW facemask policy(March 26). Multiple change point regression was used to model positive-test-rate data. SARS-CoV-2 testing and positivity rates were compared for pre-intervention, transition, post-intervention, and follow-up periods. RESULTS: Between March 12-August 10, 2020, 19.2% of HCW were symptomatic for COVID-19 and underwent SARS-CoV-2 testing. A single change point was identified ~March 28-30(95% probability). Before the change point, the odds of a tested HCW having a positive result doubled every 4.5-7.5 days. Post-change-point, the odds of a tested HCW having a positive result halved every 10.5-13.5 days. CONCLUSIONS: Universal facemasks was associated with reducing HCW's risk of acquiring COVID-19.

Dermatology

Austin E, Geisler AN, Nguyen J, **Kohli I**, **Hamzavi I**, **Lim HW**, and Jagdeo J. Visible Light Part I. Properties and Cutaneous Effects of Visible Light. *J Am Acad Dermatol* 2021; Epub ahead of print. PMID: 33640508. Full Text

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Approximately fifty percent of sunlight reaching the Earth's surface is visible light (400-700 nm). Other sources of visible light include lasers, light-emitting diodes (LEDs), and flash lamps. Photons from visible light are absorbed by photoreceptive chromophores (e.g., melanin, heme, and opsins), altering skin function by activating and imparting energy to chromophores. Additionally, visible light can penetrate the full thickness of the skin and induce pigmentation and erythema. Clinically, lasers and light devices are used to treat skin conditions by utilizing specific wavelengths and treatment parameters. Red and blue light from LEDs and intense pulsed light (IPL) have been studied as anti-microbial and anti-inflammatory treatments for acne. Pulsed dye lasers are used to treat vascular lesions in adults and infants. Further research is necessary to determine the functional significance of visible light on skin health and wellness without confounding the influence of ultraviolet and infrared wavelengths.

Dermatology
Bi X, **Zhou L**, Liu Y, Gu J, and **Mi Q**. MicroRNA-146a deficiency delays wound healing in normal and diabetic mice. *Adv Wound Care (New Rochelle)* 2021; Epub ahead of print. PMID: 33554730. [Request Article](#)

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OBJECTIVE: MiRNAs are important regulators of inflammation and wound healing. However, the mechanisms through which miRNAs regulate wound healing under normal and diabetic conditions are poorly understood. We aimed to determine the effects of miR-146a on the pathogenesis of wound healing in normal and streptozotocin (STZ)-induced diabetic mice. APPROACH: Wild-type (WT) and miR-146a knockout (KO) mice were induced to develop diabetes with STZ. Next, skin and corneal wounds were produced and measured. Percent wound closure and histology were evaluated. Inflammation at wound sites was analyzed using flow cytometry, RT-PCR, and Western blot. RESULTS: Healing of wounded skin was significantly delayed in miR-146a KO compared to WT mice. However, corneal epithelial wound healing did not differ significantly in the mice with normal blood glucose, whereas corneal and skin wound healing was significantly delayed in KO mice with diabetes. Neutrophil infiltration increased in skin wounds of KO compared with normal mice. The potential mechanisms were associated with dysregulated IL-1β, TNF-α, IRAK1, TRAF6, and NF-κB signaling induced by miR-146a KO. INNOVATION: Skin wound healing was delayed in miR-146a KO mice and enhanced inflammatory responses were mediated by the NF-κB signaling pathway. CONCLUSIONS: Deficiency in miR-146a delayed skin wound healing by enhancing inflammatory responses in normal and diabetic mice. Therefore, miR-146a may be a potential target for modulation to accelerate skin wound healing.

Dermatology
Geisler AN, Austin E, Nguyen J, **Hamzavi I**, Jagdeo J, and **Lim HW**. Visible Light Part II. Photoprotection against visible and ultraviolet light. *J Am Acad Dermatol* 2021; Epub ahead of print. PMID: 33640513. [Full Text](#)

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Cutaneous photobiology studies have focused primarily on the UV portion of the solar spectrum. However, VL comprises 50% of EMR that reaches the earth's surface, and, as discussed in Part I of this

CME, VL has cutaneous biologic effects such as pigment darkening and erythema. Photoprotection against VL includes sun avoidance, seeking shade, and the use of photoprotective clothing. Organic and inorganic UV filters used in sunscreens do not protect against VL; only tinted sunscreens do. In the US, these filters are regulated by the FDA as an over-the-counter drug and are subjected to more stringent regulations than in Europe, Asia, and Australia. There are no established guidelines regarding VL photoprotection. Alternative measures to confer VL photoprotection are being explored. These novel methods include topical, oral, and subcutaneous agents. Further development should focus on better protection in the range of UVA1 (340-400nm) and VL while enhancing the cosmesis of the final products.

Dermatology
Ju HJ, Bae JM, Lee RW, Kim SH, Parsad D, **Pourang A**, **Hamzavi I**, Shourick J, and Ezzedine K. Surgical Interventions for Patients With Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2021; Epub ahead of print. PMID: 33595599. Full Text

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IMPORTANCE: Surgical interventions are a key part of the therapeutic arsenal, especially in refractory and stable vitiligo. Comparison of treatment outcomes between the different surgical procedures and their respective adverse effects has not been adequately studied. OBJECTIVE: To investigate the reported treatment response following different surgical modalities in patients with vitiligo. DATA SOURCES: A comprehensive search of the MEDLINE, Embase, Web of Science, and Cochrane Library databases from the date of database inception to April 18, 2020, was conducted. The key search terms used were vitiligo, surgery, autologous, transplantation, punch, suction blister, and graft. STUDY SELECTION: Of 1365 studies initially identified, the full texts of 358 articles were assessed for eligibility. A total of 117 studies were identified in which punch grafting (n = 19), thin skin grafting (n = 10), suction blister grafting (n = 29), noncultured epidermal cell suspension (n = 45), follicular cell suspension (n = 9), and cultured epidermal cell suspension (n = 17) were used. DATA EXTRACTION AND SYNTHESIS: Three reviewers independently extracted data on study design, patients, intervention characteristics, and outcomes. Random effects meta-analyses using generic inverse-variance weighting were performed. MAIN OUTCOMES AND MEASURES: The primary outcomes were the rates of greater than 90%, 75%, and 50% repigmentation response. These rates were calculated by dividing the number of participants in an individual study who showed the corresponding repigmentation by the total number of participants who completed the study. The secondary outcomes were the factors associated with treatment response to the surgical intervention. RESULTS: Among the 117 unique studies and 8776 unique patients included in the analysis, rate of repigmentation of greater than 90% for surgical interventions was 52.69% (95% CI, 46.87%-58.50%) and 45.76% (95% CI, 30.67%-60.85%) for punch grafting, 72.08% (95% CI, 54.26%-89.89%) for thin skin grafting, 61.68% (95% CI, 47.44%-75.92%) for suction blister grafting, 47.51% (95% CI, 37.00%-58.03%) for noncultured epidermal cell suspension, 36.24% (95% CI, 18.92%-53.57%) for noncultured follicular cell suspension, and 56.82% (95% CI, 48.93%-64.71%) for cultured epidermal cell suspension. The rate of repigmentation of greater than 50% after any surgical intervention was 81.01% (95% CI, 78.18%-83.84%). In meta-regression analyses, the treatment response was associated with patient age (estimated slope, -1.1418), subtype of vitiligo (estimated slope, 0.3047), and anatomical sites (estimated slope, -0.4050). CONCLUSIONS AND RELEVANCE: The findings of this systematic review and meta-analysis suggest that surgical intervention can be an effective option for refractory stable vitiligo. An appropriate procedure should be recommended based on patient age, site and size of the lesion, and costs.

Dermatology
Kashlan R, **Lyons AB**, **Narla S**, and **Hamzavi IH**. Infusion reaction to infliximab biosimilar after transitioning from infliximab. *JAAD Case Rep* 2021; 8:77-79. PMID: 33532531. [Full Text](#)

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Dermatology
Price KN, Collier EK, Grogan T, Fernandez JM, Alhusayen R, Alavi A, **Hamzavi IH**, Lowes MA, Porter MJ, Hsiao JL, and Shi VY. Physician perspectives on complementary and alternative medicine in hidradenitis suppurativa. *Dermatol Ther* 2021; Epub ahead of print. PMID: 33547869. [Full Text](#)

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Hidradenitis suppurativa (HS) is a chronic and often debilitating inflammatory condition characterized by frequent nodules, abscesses, sinus tracts, and scars impacting the intertriginous areas. Many patients with HS often report limited treatment success and symptom coverage with conventional therapies. Recent studies have reported the widespread use of complementary and alternative medicine (CAM) among patients with HS. In this study, our aim was to examine current physician practice patterns, opinions, and comfort with recommending CAM. Our results indicate that provider comfort and opinions on CAM varied based on the provider's experiences, demographics, and the CAM modality itself. Overall, nearly two-thirds (n = 30, 61.2%) of respondents agreed that CAM and conventional medicine were more effective together than either alone. Meanwhile, 44.9% (n = 22) of respondents routinely recommend CAM while 64.6% (n = 31) of respondents reported that they are routinely asked about CAM. The majority (n = 41, 83.7%) of respondents indicated a lack of scientific evidence in the medical literature as a barrier to recommending CAM along with efficacy concerns (n = 34, 69.4%) and ability to recommend reputable CAM products (n = 32, 65.3%) and practitioners (n = 32, 65.3%). Future investigations are warranted to establish a better understanding of the efficacy and benefit of CAM methods in conjunction with conventional methods.

Dermatology
Stein Gold L, Paul C, and Romiti R. Efficacy and safety of fixed-dose combination calcipotriol/betamethasone dipropionate foam for the treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2021; 35 Suppl 1:10-19. PMID: 33619777. [Full Text](#)

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The fixed-dose combination calcipotriol (Cal; 50 μg/g) plus betamethasone dipropionate (BD; 0.5 mg/g) ointment and gel formulations have well-established efficacy profiles in the treatment of psoriasis vulgaris (chronic plaque psoriasis); this combination has been shown to produce favourable outcomes versus either monotherapy. To improve upon the efficacy and cosmetic acceptability of these treatments Cal/BD

foam was developed, demonstrating superior efficacy in Phase II/III studies compared with either of its monocomponents, Cal/BD ointment, Cal/BD gel and various other therapies for the treatment of psoriasis. Multiple outcome measures were evaluated in the clinical studies, including physician's global assessment of disease severity and modified psoriasis area and severity index. Of note, 38-55% of patients across studies achieved a physician's global assessment of 'clear' or 'almost clear' after 4 weeks of Cal/BD treatment. This superior efficacy was not associated with an increased frequency or severity of adverse events, and there was no evidence for dysregulation of the hypothalamic-pituitary-adrenal axis or calcium homeostasis. Overall, Cal/BD foam was efficacious, with a good tolerability profile consistent with established Cal/BD formulations.

Dermatology

Umeh ON, **Beekman R**, **D'sa H**, and **Friedman BJ**. An Elderly Male With Progressive Nail Atrophy: Answer. *Am J Dermatopathol* 2021; 43(2):152-153. PMID: 33492842. Full Text

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Diagnostic Radiology

Marcum ZA, Gold LS, James KT, Meier EN, Turner JA, Kallmes DF, Cherkin DC, Deyo RA, Sherman KJ, Luetmer PH, Avins AL, **Griffith B**, Friedly JL, Suri P, Heagerty PJ, and Jarvik JG. Effects of Including Epidemiologic Data in Lumbar Spine Imaging Reports on Prescribing Non-Opioid Medications for Pain. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33559061. Full Text

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Rehabilitation Care Services, VA Puget Sound Health Care System, Seattle, WA, USA.

BACKGROUND: Information on the prevalence of common imaging findings among patients without back pain in spine imaging reports might affect pain medication prescribing for patients with back pain. Prior research on inserting this text suggested a small reduction in opioid prescribing. OBJECTIVE: To evaluate the effect of epidemiologic information in spine imaging reports on non-opioid pain medication prescribing for primary care patients with back pain. DESIGN: Post hoc analysis of the Lumbar Imaging with Reporting of Epidemiology cluster-randomized trial. PARTICIPANTS: A total of 170,680 patients aged ≥ 18 years from four healthcare systems who received thoracolumbar, lumbar, or lumbosacral spine imaging from 2013 to 2016 and had not received a prescription for non-opioid pain medication in the preceding 120 days. INTERVENTION: Text of age- and modality-specific epidemiologic benchmarks indicating the prevalence of common findings in people without back pain inserted into thoracolumbar, lumbar, or lumbosacral spine imaging reports at intervention clinics. MAIN MEASURES: Primary outcomes: any non-opioid prescription within 90 days after index imaging, overall, and by sub-class (skeletal muscle relaxants, NSAIDs, gabapentinoids, tricyclic antidepressants, benzodiazepines, duloxetine). SECONDARY OUTCOMES: count of non-opioid prescriptions within 90 days, overall, and by sub-class. KEY RESULTS: The intervention was not associated with the likelihood of patients receiving at

least one prescription for new non-opioid pain-related medications, overall (adjusted OR, 1.02; 95% CI, 0.97-1.08) or by sub-class. The intervention was not associated with the number of prescriptions for any non-opioid medication (adjusted incidence rate ratio [IRR], 1.02; 95% CI, 0.99-1.04). However, the intervention was associated with more new prescriptions for NSAIDs (IRR, 1.12) and tricyclic antidepressants (IRR, 1.11). CONCLUSIONS: Inserting epidemiologic text in spine imaging reports had no effect on whether new non-opioid pain-related medications were prescribed but was associated with the number of new prescriptions for certain non-opioid sub-classes. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02015455.

<u>Diagnostic Radiology</u>
Mosella MS, **Sabedot TS**, Silva TC, **Malta TM**, Segato FD, **Asmaro KP**, **Wells M**, **Mukherjee A**, **Poisson LM**, **Snyder J**, **deCarvalho AC**, **Walbert T**, **Aho T**, **Kalkanis S**, Elias PC, Antonini SR, **Rock J**, **Noushmehr H**, Castro M, and **Castro AV**. DNA Methylation-based Signatures Classify Sporadic Pituitary Tumors According to Clinicopathological Features. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33631002. Full Text

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BACKGROUND: Distinct genome-wide methylation patterns cluster pituitary neuroendocrine tumors (PitNETs) into molecular groups associated with specific clinicopathological features. Here we aim to identify, characterize and validate methylation signatures that objectively classify PitNET into clinicopathological groups. METHODS: Combining in-house and publicly available data, we conducted an analysis of the methylome profile of a comprehensive cohort of 177 tumors (Panpit cohort) and 20 nontumor specimens from the pituitary gland. We also retrieved methylome data from an independent PitNET cohort (N=86) to validate our findings. RESULTS: We identified three methylation clusters associated with adenohypophyseal cell lineages and functional status using an unsupervised approach. Differentially methylated CpG probes (DMP) significantly distinguished the Panpit clusters and accurately assigned the samples of the validation cohort to their corresponding lineage and functional subtypes memberships. The DMPs were annotated in regulatory regions enriched of enhancer elements, associated with pathways and genes involved in pituitary cell identity, function, tumorigenesis, invasiveness. Some DMPs correlated with genes with prognostic and therapeutic values in other intra or extracranial tumors. CONCLUSIONS: We identified and validated methylation signatures, mainly annotated in enhancer regions that distinguished PitNETs by distinct adenohypophyseal cell lineages and functional status. These signatures provide the groundwork to develop an unbiased approach to classifying PitNETs according to the most recent classification recommended by the 2017 WHO and to explore their biological and clinical relevance in these tumors.

<u>Diagnostic Radiology</u>
Suri P, Meier EN, Gold LS, Marcum ZA, Johnston SK, James KT, Bresnahan BW, O'Reilly M, Turner JA, Kallmes DF, Sherman KJ, Deyo RA, Luetmer PH, Avins AL, **Griffith B**, Heagerty PJ, Rundell SD, Jarvik JG, and Friedly JL. Providing Epidemiologic Data in Lumbar Spine Imaging Reports Did Not Affect Subsequent Utilization of Spine Procedures: Secondary Outcomes from a Stepped-Wedge Randomized Controlled Trial. *Pain Med* 2021; Epub ahead of print. PMID: 33595635. Full Text

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Kaiser Permanente Washington.
Departments of Family Medicine and Internal Medicine, Oregon Health & Science University, Portland, OR, USA.
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OBJECTIVE: To evaluate the effect of inserting epidemiologic information into lumbar spine imaging reports on subsequent non-surgical and surgical procedures involving the thoracolumbosacral spine and sacroiliac (SI) joints. DESIGN: Analysis of secondary outcomes from the Lumbar Imaging with Reporting of Epidemiology (LIRE) pragmatic stepped-wedge randomized trial. SETTING: Primary care clinics within four integrated healthcare systems in the United States. SUBJECTS: 238,886 patients aged ≥18 years who received lumbar diagnostic imaging between 2013-2016. METHODS: Clinics were randomized to receive text containing age- and modality-specific epidemiologic benchmarks indicating the prevalence of common spine imaging findings in people without low back pain, inserted into lumbar spine imaging reports (the "LIRE intervention"). The study outcomes were receiving (1) any non-surgical lumbosacral or sacroiliac spine procedure (lumbosacral epidural steroid injection, facet joint injection, or facet joint radiofrequency ablation; or sacroiliac joint injection) or (2) any surgical procedure involving the lumbar, sacral, or thoracic spine (decompression surgery or spinal fusion or other spine surgery). RESULTS: The LIRE intervention was not significantly associated with subsequent utilization of non-surgical lumbosacral or sacroiliac spine procedures (odds ratio [OR]=1.01, 95% confidence interval [CI] 0.93-1.09; p = 0.79) or any surgical procedure (OR = 0.99, 95 CI 0.91-1.07; p = 0.74) involving the lumbar, sacral, or thoracic spine. The intervention was also not significantly associated with any individual spine procedure. CONCLUSIONS: Inserting epidemiologic text into spine imaging reports had no effect on non-surgical or surgical procedure utilization among patients receiving lumbar diagnostic imaging.

Emergency Medicine
Daxon BT, **Lark E**, Matzek LJ, Fields AR, and Haselton KJ. Nebulized Nitroglycerin for Coronavirus Disease 2019-Associated Acute Respiratory Distress Syndrome: A Case Report. *A A Pract* 2021; 15(2):e01376. PMID: 33560642. Full Text

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We present a case where nitroglycerin tablets dissolved in saline and intravenous nitroglycerin solution were nebulized as surrogates for inhaled nitric oxide (iNO) after our iNO supply was depleted during the coronavirus disease 2019 (COVID-19) surge in New York. We gave this treatment to a COVID-19 patient with severe acute respiratory distress syndrome (ARDS) and hypercarbia. In response, the patient had immediate and clinically meaningful improvement in multiple organ systems despite no other interventions or ventilator changes.

Emergency Medicine
Dean D, **Passalacqua KD**, Oh SM, Aaron C, **Van Harn MG**, and King A. Pediatric Cannabis Single-Substance Exposures Reported to the Michigan Poison Center From 2008-2019 After Medical Marijuana Legalization. *J Emerg Med* 2021; Epub ahead of print. PMID: 33541760. Full Text

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BACKGROUND: Legalization of medical and recreational cannabis is a major contributor to pediatric cannabis exposures. The trends and magnitude of pediatric cannabis exposures in Michigan after medical cannabis legalization in 2008 have not been assessed. OBJECTIVE: To describe the temporal trends of pediatric cannabis exposures reported to the Michigan Poison Center (MiPC) after medical cannabis was legalized in 2008 and 1 year after legalization of recreational cannabis in 2018. METHODS: Retrospective electronic chart review of pediatric (<18 years old) single-substance cannabis exposures reported to the MiPC from January 1, 2008 to December 31, 2019. Routes of cannabis exposure were reported as ingestion, inhalation, and unknown. Types of ingested cannabis products were also documented. RESULTS: Between 2008 and 2019, 426 pediatric cannabis single exposures were reported. The median patient age was 6.0 years (interquartile range 2-15 years). Age distribution was bimodal. A total of 327 (76.8%) exposures were from cannabis ingestion, 79 (18.5%) from inhalation, 2 (0.5%) from both ingestion and inhalation, and 18 (4.2%) from unknown route. The doubling time for number of cases was 2.1 years, and the total number of annual reported cases increased after 2016. Teenagers (13-17 years) had the highest number of inhalational exposures, whereas young children (0-5 years) had the highest number of ingestions. CONCLUSION: Single-substance pediatric cannabis exposures reported to the Michigan Poison Center increased after medical cannabis was legalized in 2008 through recreational legalization in 2018.

Emergency Medicine
Hamera JA, Bryant NB, **Shievitz MS**, and Berger DA. Systemic thrombolysis for refractory cardiac arrest due to presumed myocardial infarction. *Am J Emerg Med* 2021; 40:226.e223-226.e225. PMID: 32747160.
[Full Text](#)

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The empiric usage of systemic thrombolysis for refractory out of hospital cardiac arrest (OHCA) is considered for pulmonary embolism (PE), but not for undifferentiated cardiac etiology [1, 2]. We report a case of successful resuscitation after protracted OHCA with suspected non-PE cardiac etiology, with favorable neurological outcome after empiric administration of systemic thrombolysis. A 47-year-old male presented to the emergency department (ED) after a witnessed OHCA with no bystander cardiopulmonary resuscitation (CPR). His initial rhythm was ventricular fibrillation (VF) which had degenerated into pulseless electrical activity (PEA) by ED arrival. Fifty-seven minutes into his arrest, we gave systemic thrombolysis which obtained return of spontaneous circulation (ROSC). He was transferred to the coronary care unit (CCU) and underwent therapeutic hypothermia. On hospital day (HD) 4 he began following commands and was extubated on HD 5. Subsequent percutaneous coronary intervention (PCI) revealed non-obstructive stenosis in distal LAD. He was discharged home directly from the hospital, with one-month cerebral performance category (CPC) score of one. He was back to work three months post-arrest. Emergency physicians (EP) should be aware of this topic since we are front-line health care professionals for OHCA. Thrombolytics have the advantage of being widely available in ED and therefore offer an option on a case-by-case basis when intra-arrest PCI and ECPR are not available. This case report adds to the existing literature on systemic thrombolysis as salvage therapy for cardiac arrest from an undifferentiated cardiac etiology. The time is now for this treatment to be reevaluated.

Emergency Medicine

Horiuchi Y, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, **Nowak R**, Hogan C, Kontos MC, Cannon CM, Müeller GA, Birkhahn R, Taub P, Vilke GM, Barnett O, McDonald K, Mahon N, Nuñez J, Briguori C, Passino C, Maisel A, and Murray PT. Relation of Decongestion and Time to Diuretics to Biomarker Changes and Outcomes in Acute Heart Failure. *Am J Cardiol* 2021; Epub ahead of print. PMID: 33617811. Full Text

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Prompt treatment may mitigate the adverse effects of congestion in the early phase of heart failure (HF) hospitalization, which may lead to improved outcomes. We analyzed 814 acute HF patients for the relationships between time to first intravenous loop diuretics, changes in biomarkers of congestion and multi-organ dysfunction, and 1-year composite endpoint of death or HF hospitalization. B-type natriuretic peptide (BNP), high sensitivity cardiac troponin I (hscTnI), urine and serum neutrophil gelatinase-associated lipocalin (NGAL), and galectin 3 were measured at hospital admission, hospital day 1, 2, 3 and discharge. Time to diuretics was not correlated with the timing of decongestion defined as BNP decrease ≥ 30% compared to admission. Earlier BNP decreases but not time to diuretics were associated with earlier and greater decreases in hscTnI and urine NGAL, and lower incidence of the composite endpoint. After adjustment for confounders, only no BNP decrease at discharge was significantly associated with mortality but not the composite endpoint (p = 0.006 and p = 0.062, respectively). In conclusion, earlier time to decongestion but not the time to diuretics was associated with better biomarker trajectories. Residual congestion at discharge rather than the timing of decongestion predicted a worse prognosis.

Endocrinology and Metabolism

Athimulam S, Grebe S, and Bancos I. Steroid profiling in the diagnosis of mild and overt Cushing's syndrome. *Best Pract Res Clin Endocrinol Metab* 2021; Epub ahead of print. PMID: 33589355. Request Article

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In this review, we provide a comprehensive overview of the utility of steroid profiling for diagnosis of management of overt Cushing syndrome and mild autonomous cortisol secretion. A diagnosis of Cushing syndrome is made through a multistep process that includes confirmation of endogenous hypercortisolism, followed by determination of its cause. Steroid metabolomic testing applied to serum or urine steroids and their metabolites can provide additional and novel insights into alterations of steroid biosynthesis and metabolism and its causes. In particular, increased availability and advances in mass spectrometry-based steroid analysis, coupled with machine learning-based algorithms, have facilitated the development of tailored diagnostic and subtyping approaches for autonomous cortisol secretion and might be useful for detecting low grade autonomous glucocorticoid secretion and in predicting and monitoring of disease severity and associated comorbidities.

Endocrinology and Metabolism
Gubitosi-Klug RA, Braffett BH, Hitt S, Arends V, Uschner D, **Jones K**, Diminick L, Karger AB, Paterson AD, Roshandel D, Marcovina S, Lachin JM, Steffes M, and Palmer JP. Residual β cell function in long-term type 1 diabetes associates with reduced incidence of hypoglycemia. *J Clin Invest* 2021; 131(3). PMID: 33529168. Full Text

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BACKGROUND: We investigated residual β cell function in Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study participants with an average 35-year duration of type 1 diabetes mellitus (T1DM). METHODS: Serum C-peptide was measured during a 4-hour mixed-meal tolerance test. Associations with metabolic outcomes and complications were explored among nonresponders (all C-peptide values after meal <0.003 nmol/L) and 3 categories of responders, classified by peak C-peptide concentration (nmol/L) as high (>0.2), intermediate (>0.03 to ≤0.2), and low (≥ 0.003 to ≤0.03). RESULTS: Of the 944 participants, 117 (12.4%) were classified as responders. Residual C-peptide concentrations were associated with higher DCCT baseline concentrations of stimulated C-peptide (P value for trend = 0.0001). Residual C-peptide secretion was not associated with current or mean HbA1c, HLA high-risk haplotypes for T1DM, or the current presence of T1DM autoantibodies. The proportion of subjects with a history of severe hypoglycemia was lower with high (27%) and intermediate (48%) residual C-peptide concentrations than with low (74%) and no (70%) residual C-peptide concentrations (P value for trend = 0.0001). Responders and nonresponders demonstrated similar rates of advanced microvascular complications. CONCLUSION: β Cell function can persist in long-duration T1DM. With a peak C-peptide concentration of >0.03 nmol/L, we observed clinically meaningful reductions in the prevalence of severe hypoglycemia. TRIAL REGISTRATION: ClinicalTrials.gov NCT00360815 and NCT00360893.FUNDINGDivision of Diabetes Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (DP3-DK104438, U01 DK094176, and U01 DK094157).

Family Medicine

Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Division of Cardiovascular Disease, Center for Structural Heart, Henry Ford Hospital, Detroit, Michigan, USA (Wang, O'Neill); Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA (Zervos, McKinnon, Alangaden, Suleyman); Family Medicine, Henry Ford Hospital, Detroit, Michigan, USA (Allard); Public Health Sciences, Henry Ford Hospital, Detroit, Michigan, USA (Schultz, Poisson); Office of Clinical Quality and Safety, Henry Ford Health System, Detroit, Michigan, USA (Chu); Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA (Kalkanis).

OBJECTIVE: Examine the effect of a universal facemask policy for healthcare workers(HCW) and incidence of SARS-CoV-2 positivity. METHODS: Daily number of symptomatic HCW tested, SARS-CoV-2 positivity rates, and HCW job-descriptions were collected pre and post Universal HCW facemask policy(March 26). Multiple change point regression was used to model positive-test-rate data. SARS-CoV-2 testing and positivity rates were compared for pre-intervention, transition, post-intervention, and follow-up periods. RESULTS: Between March 12-August 10, 2020, 19.2% of HCW were symptomatic for COVID-19 and underwent SARS-CoV-2 testing. A single change point was identified ~March 28-30(95% probability). Before the change point, the odds of a tested HCW having a positive result doubled every 4.5-7.5 days. Post-change-point, the odds of a tested HCW having a positive result halved every 10.5-13.5 days. CONCLUSIONS: Universal facemasks was associated with reducing HCW's risk of acquiring COVID-19.

Gastroenterology

Jou J, **Watson A**, and **Zuchelli T**. The use of a rescue stent in the management of lumen-apposing metal stent migration during EUS-directed transgastric ERCP with stent-in-stent technique to remove a forgotten metal biliary stent. *VideoGIE* 2021; 6(2):84-86. PMID: Not assigned. Full Text

Gastroenterology

Semaan L, **Zeng Q**, **Lu Y**, **Zhang Y**, **Zreik MM**, **Chamseddine MB**, **Chopp M**, **Zhang ZG**, and **Moonka D**. MicroRNA-214 enriched exosomes from human cerebral endothelial cells (hCEC) sensitize hepatocellular carcinoma to anti-cancer drugs. *Oncotarget* 2021; 12(3):185-198. PMID: 33613846. Full Text

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor worldwide. Current medical therapy for HCC has limited efficacy. The present study tests the hypothesis that human cerebral endothelial cell-derived exosomes carrying elevated miR-214 (hCEC-Exo-214) can amplify the efficacy of anti-cancer drugs on HCC cells. Treatment of HepG2 and Hep3B cells with hCEC-Exo-214 in combination with anti-cancer agents, oxaliplatin or sorafenib, significantly reduced cancer cell viability and invasion compared with monotherapy with either drug. Additionally, the therapeutic effect of the combination therapy was detected in primary tumor cells derived from patients with HCC. The ability of hCEC-Exo-214 in sensitizing HCC cells to anti-cancer drugs was specific, in that combination therapy did not affect the viability and invasion of human liver epithelial cells and non-cancer primary cells. Furthermore, compared to monotherapy with oxaliplatin and sorafenib, hCEC-Exo-214 in combination with either drug substantially reduced protein levels of P-glycoprotein (P-gp) and splicing factor 3B subunit 3 (SF3B3) in HCC cells. P-gp and SF3B3 are among miR-214 target genes and are known to

mediate drug resistance and cancer cell proliferation, respectively. In conclusion, the present in vitro study provides evidence that hCEC-Exo-214 significantly enhances the anti-tumor efficacy of oxaliplatin and sorafenib on HCC cells.

Gastroenterology
Spradling PR, Zhong Y, Moorman AC, **Rupp LB**, **Lu M**, Teshale EH, Schmidt MA, Daida YG, Boscarino JA, and **Gordon SC**. The persistence of underreporting of hepatitis C as an underlying or contributing cause of death, 2011-2017. *Clin Infect Dis* 2021; Epub ahead of print. PMID: 33561187. Full Text

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Using electronic health records, we found that hepatitis C reporting on death certificates of 2,901 HCV-infected decedents from four U.S. healthcare organizations during 2011-2017 was documented in only 50% of decedents with hepatocellular carcinoma and less than half with decompensated cirrhosis. National figures likely underestimate the U.S. HCV mortality burden.

Global Health Initiative
Acharya Y, Nepal P, Yang D, Karki K, Bajracharya D, **Prentis T**, **Davis SL**, and **Kaljee L**. Economic and Social Drivers of Antibiotic Dispensing Practices among Community Pharmacies in Nepal. *Trop Med Int Health* 2021; Epub ahead of print. PMID: 33524230. Full Text

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OBJECTIVE: To assess economic and social drivers of dispensing antibiotics without prescription by community pharmacies in Nepal. METHOD: A survey was conducted among 111 pharmacy owners and managers in five districts. Information on demographic and economic characteristics of the pharmacies (e.g., revenue and profits from antibiotics), and their inclination to sell antibiotics without a physician's prescription under various scenarios (e.g., diarrhea in a child), was collected. Univariate analysis was conducted to assess the demographic and economic characteristics. Bivariate analysis was conducted to examine the relationship between dispensing antibiotics without prescription and economic and social factors. RESULTS: Azithromycin and amoxicillin were the most commonly dispensed antibiotics. The proportions of pharmacies reporting that they would 'most likely' or 'likely' dispense antibiotics without prescription to adult patients ranged from 36.9% (sore throat) to 67.6% (cough). The proportions for pediatric patients ranged from 62.2% (sore throat) to 80.2% (cough or diarrhea). There was no consistent relationship between the likelihood of dispensing antibiotics and revenues, profits, or the number of patients. Instead, dispensing behavior was influenced by the pressure from the patient; the respondents were more likely to dispense antibiotics when the patient specifically asked for "an antibiotic" rather than for "a medicine", and 68.5% respondents ranked 'customer satisfaction' as the most important factor motivating their work. CONCLUSIONS: In Nepal, inappropriate sale of antibiotics by community pharmacists is high, particularly for pediatric patients. Additional research is needed to establish key drivers of this behavior and to help design effective approaches to reducing AMR.

Hematology/Oncology
Abdel Rahman ZH, Miller KC, **Jabbour H**, **Alkhatib Y**, and **Donthireddy V**. Outcomes of patients with thrombocytopenia evaluated at hematology subspecialty clinics. *Hematol Oncol Stem Cell Ther* 2021; Epub ahead of print. PMID: 33607100. Full Text

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BACKGROUND: Thrombocytopenia is a frequently encountered laboratory abnormality and a common reason for hematology referrals. Workup for thrombocytopenia is not standardized and frequently does not follow an evidence-based algorithm. We conducted a systematic analysis to evaluate the laboratory testing and outcomes of patients evaluated for thrombocytopenia at hematology clinics in a tertiary referral center between 2013 and 2016. PATIENT AND METHODS: We performed a comprehensive chart review for patients evaluated for thrombocytopenia during the study period. Patients were followed for 1 year from the initial hematology evaluation and assessed for the development of a hematologic malignancy, rheumatologic, or infectious diseases among other clinical outcomes. RESULTS: We evaluated 472 patients with a median (range) age of 61 (17-94) years. The majority (63.8%) had mild thrombocytopenia. Within 1 year of follow-up, 14 patients (3.0%) were diagnosed with a hematologic malignancy. A higher likelihood of developing a hematologic malignancy was noted in patients with concurrent leukopenia (hazard ratio [HR] 9.97, 95% confidence interval [CI] 3.28-30.32, p < .01) and increasing age (HR per 10-year deciles 1.52, 95% CI 1.03-2.25, p = .03). In patients with asymptomatic isolated mild thrombocytopenia, laboratory testing did not reveal any significant positive findings and patients did not receive any new major diagnosis during the follow-up period. CONCLUSION: Our findings provide basis and call for development of an evidence-based algorithmic approach for evaluation of patients with thrombocytopenia, testing, and referrals. It also supports a conservative approach mainly driven by physical exam signs, symptoms, and other laboratory findings for patients with isolated mild thrombocytopenia.

Hematology/Oncology
Balanchivadze N, **Purtell JP**, Anderson J, **Guo Y**, and Dobrosotskaya I. A Case of Chronic Eosinophilic Leukemia in a Patient With Recurrent Cough, Dyspnea, and Eosinophilia. *Cureus* 2021; 13(1):e12654. PMID: 33585139. Full Text

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We report the case of a 40-year-old man with no significant past medical history who had been hospitalized multiple times over the course of one year with recurring cough, dyspnea, pruritic rash, and variable degrees of eosinophilia. He was variably diagnosed with asthma and pneumonia. After his last hospitalization with severe symptoms, the patient was referred for pulmonary evaluation where hypereosinophilia (HE) led to a hematologic workup. Fluorescence in situ hybridization revealed the FIP1L1-PDGFRA gene fusion and bone marrow analysis confirmed a diagnosis of chronic eosinophilic leukemia. The patient was treated with daily imatinib and prednisone and he was symptom-free at a four-week follow-up examination.

Hematology/Oncology
Jiagge EM, Ulintz PJ, Wong S, McDermott SP, **Fossi SI**, Suhan TK, Hoenerhoff MJ, **Bensenhaver JM**, Salem B, Dziubinski M, Oppong JK, Aitpillah F, Ishmael K, Osei-Bonsu E, Adjei E, Baffour A, Aldrich J, Kurdoglu A, **Fernando K**, Craig DW, Trent JM, Li J, **Chitale D**, Newman LA, Carpten JD, Wicha MS, and Merajver SD. Multiethnic PDX models predict a possible immune signature associated with TNBC of African ancestry. *Breast Cancer Res Treat* 2021; Epub ahead of print. PMID: 33576900. Full Text

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PURPOSE: Triple-negative breast cancer (TNBC) is an aggressive subtype most prevalent among women of Western Sub-Saharan African ancestry. It accounts for 15-25% of African American (AA) breast cancers (BC) and up to 80% of Ghanaian breast cancers, thus contributing to outcome disparities in BC for black women. The aggressive biology of TNBC has been shown to be regulated partially by breast cancer stem cells (BCSC) which mediate tumor recurrence and metastasis and are more abundant in African breast tumors. METHODS: We studied the biological differences between TNBC in women with African ancestry and those of Caucasian women by comparing the gene expression of the BCSC. From low-passage patient derived xenografts (PDX) from Ghanaian (GH), AA, and Caucasian American (CA) TNBCs, we sorted for and sequenced the stem cell populations and analyzed for differential gene enrichment. RESULTS: In our cohort of TNBC tumors, we observed that the ALDH expressing stem cells display distinct ethnic specific gene expression patterns, with the largest difference existing between the GH and AA ALDH+ cells. Furthermore, the tumors from the women of African ancestry [GH/AA] had ALDH stem cell (SC) enrichment for expression of immune related genes and processes. Among the significantly upregulated genes were CD274 (PD-L1), CXCR9, CXCR10 and IFI27, which could serve as potential drug targets. CONCLUSIONS: Further exploration of the role of immune regulated genes and biological processes in BCSC may offer insight into developing novel approaches to treating TNBC to help ameliorate survival disparities in women with African ancestry.

Hematology/Oncology

Mok T, Peters S, Camidge DR, Noé J, **Gadgeel S**, Ou SI, Kim DW, Konopa K, Pozzi E, Liu T, Loftin IR, Williams C, and Shaw AT. Outcomes According to ALK Status Determined by Central Immunohistochemistry or Fluorescence In Situ Hybridization in Patients With ALK-Positive NSCLC Enrolled in the Phase 3 ALEX Study. *J Thorac Oncol* 2021; 16(2):259-268. PMID: 33334571. Full Text

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INTRODUCTION: We retrospectively examined progression-free survival (PFS) and response by ALK fluorescence in situ hybridization (FISH) status in patients with advanced ALK immunohistochemistry (IHC)-positive NSCLC in the ALEX study. METHODS: A total of 303 treatment-naive patients were randomized to receive twice-daily alectinib 600 mg or crizotinib 250 mg. ALK status was assessed centrally using Ventana ALK (D5F3) CDx IHC and Vysis ALK Break Apart FISH Probe Kit. Primary end point is investigator-assessed PFS. Secondary end points of interest are objective response rate and duration. RESULTS: Investigator-assessed PFS was significantly prolonged with alectinib versus crizotinib in ALK IHC-positive and FISH-positive tumors (n = 203, 67%) (hazard ratio [HR] = 0.37, 95% confidence interval [CI]: 0.25-0.56; p < 0.0001) and ALK IHC-positive and FISH-uninformative tumors (n = 61, 20%) (HR = 0.39, 95% CI: 0.20-0.78) but not in ALK IHC-positive and FISH-negative tumors (n = 39, 13%) (HR = 1.33, 95% CI: 0.6-3.2). Objective response rates were higher with alectinib versus crizotinib in ALK IHC-positive and FISH-positive tumors (90.6% versus 81.4%; stratified OR = 2.22, 95% CI: 0.97-5.07) and ALK IHC-positive and FISH-uninformative tumors (96.0% versus 75.0%; OR = 9.29, 95% CI: 1.05-81.88) but not in ALK IHC-positive and FISH-negative tumors (28.6% versus 44.4%; OR = 0.45, 95% CI: 0.12-1.74). Next-generation sequencing was performed in 35 of 39 patients with ALK IHC-positive and FISH-negative tumors; no ALK fusion was identified in 20 of 35 patients (57.1%) by next-generation sequencing, but 10 of 20 (50.0%) had partial response or stable disease. CONCLUSIONS: Outcomes of patients with ALK IHC-positive and FISH-positive and ALK IHC-positive and FISH-uninformative NSCLC were similar to those of the overall ALEX population. These results suggest that Ventana ALK IHC is a standard testing method for selecting patients for treatment with alectinib.

Hematology/Oncology
Riely GJ, Neal JW, Camidge DR, Spira AI, Piotrowska Z, Costa DB, Tsao AS, Patel JD, **Gadgeel SM**, Bazhenova L, Zhu VW, West HL, Mekhail T, Gentzler RD, Nguyen D, Vincent S, Zhang S, Lin J, Bunn V, Jin S, Li S, and Janne PA. Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non-Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations From a Phase 1/2 Trial. *Cancer Discov* 2021; Epub ahead of print. PMID: 33632775. [Full Text]

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Mobocertinib, an oral epidermal growth factor receptor (EGFR) inhibitor targeting EGFR gene mutations including exon 20 insertions (EGFRex20ins) in non-small cell lung cancer, was evaluated in a phase 1/2 dose-escalation/expansion trial (ClinicalTrials.gov NCT02716116). Dose escalation identified 160 mg daily as the recommended phase 2 dose and maximum tolerated dose. Among 136 patients treated with 160 mg daily, the most common any grade treatment-related adverse events (TRAEs; >25%) were diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%), with diarrhea (21%) the only grade {greater than or equal to}3 TRAE >5%. Among 28 EGFRex20ins patients treated at 160 mg daily, the investigator-assessed confirmed response rate was 43% (12/28; 95% confidence interval (CI): 24-63%) with median duration of response of 14 months (5.0-not reached), and median progression-free survival of 7.3 months (4.4-15.6). Mobocertinib demonstrated antitumor activity in patients with diverse EGFRex20ins variants with a safety profile consistent with other EGFR inhibitors.

Hospital Medicine

Sadat B, Tirunagari D, **Karthikeyan V**, **Patel A**, **Van Harn M**, **Saleem MM**, and **Ananthasubramaniam K**. Clinical impact of pre-kidney transplant pulmonary hypertension on post-transplant outcomes. *Int J Cardiovasc Imaging* 2021; Epub ahead of print. PMID: 33616784. Full Text

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Outcomes of kidney transplant (KT) patients with pre-transplant pulmonary hypertension (PH) are poorly understood. PH patients are often considered high risk and excluded from KT. We investigated the association of pre-transplant PH with KT recipient's outcomes. A single-center, retrospective study that reviewed all patients transplanted from 2010 to 2016, who had a transthoracic echocardiogram (TTE) before KT and at least one TTE post-KT. The TTE closest to the KT was used for analyses. PH is defined as pulmonary artery systolic pressure (PASP) ≥ 40 mm Hg. Of 204 patients, 61 had PASP ≥ 40 mm Hg (with PH) and 143 had PASP < 40 mm Hg (without PH) prior to KT. No statistically significant differences existed between the two groups in baseline demographics, renal failure etiologies, dialysis access type, and cardiovascular risk factors. The mean difference in pre-KT PASP was 18.1 ± 7 mm Hg (P < 0.001). Patients with PH had a statistically significant decrease in PASP post-KT compared to the patients without PH with a mean change of -7.03 ± 12.28 mm Hg vs. + 3.96 ± 11.98 mm Hg (p < 0.001), respectively. Moderate mitral and moderate-severe tricuspid regurgitation were the only factors found to be independently associated with PH (p = 0.001) on multivariable analysis. No statistically significant difference was notable in patient survival, graft function, and creatinine post-KT in both groups. PH pre-KT particularly mild-moderate PH did not adversely affect intermediate (90-day) and long-term allograft and patient survival. Patients with mild-moderate PH should not be excluded from KT.

Hypertension and Vascular Research

Kim H, Wei J, Song Z, **Mottillo E**, Samavati L, Zhang R, Li L, Chen X, Jena BP, Lin JD, Fang D, and Zhang K. Regulation of Hepatic Circadian Metabolism by the E3 ubiquitin ligase HRD1-controlled CREBH/PPARα Transcriptional Program. *Mol Metab* 2021; Epub ahead of print.:101192. PMID: 33592335. Full Text

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OBJECTIVE: The Endoplasmic Reticulum (ER)-resident E3 ligase HRD1 and its co-activator Sel1L are major components of ER-Associated Degradation (ERAD) machinery. Here, we investigated the molecular mechanism and functional significance underlying the circadian regulation of HRD1/Sel1L-mediated protein degradation program in hepatic energy metabolism. METHODS: Genetically engineered animal models as well as gain- and loss-of function studies were employed to address the circadian regulatory mechanism and functional significance. Gene expression, transcriptional activation, protein-protein interaction, and animal metabolic phenotyping analyses were performed to dissect the molecular network and metabolic pathways. RESULTS: Hepatic HRD1 and Sel1L expression exhibits circadian rhythmicity that is controlled by the ER-tethered transcriptional activator CREBH, the nuclear receptor PPARα, and the core clock oscillator BMAL1 in mouse livers. HRD1/Sel1L mediates polyubiquitination and degradation of the CREBH protein across the circadian cycle to modulate rhythmic expression of the genes encoding the rate-limiting enzymes or regulators in fatty acid (FA) oxidation, triglycerides (TG) lipolysis, lipophagy, and gluconeogenesis. HRD1 liver-specific knockout (LKO) mice displayed increased expression of the genes involved in lipid and glucose metabolism and impaired circadian profiles of circulating TG, FA, and glucose due to over-production of CREBH. The circadian metabolic activities of HRD1 LKO mice were inversely correlated with those of CREBH KO mice. Suppressing CREBH over-production in the livers of HRD1 LKO mice restored the diurnal levels of circulating TG and FA of HRD1 LKO mice. CONCLUSION: Our work revealed a key circadian-regulated molecular network through which the E3 ubiquitin ligase HRD1 and its co-activator Sel1L regulate hepatic circadian metabolism.

Infectious Diseases

Taimur S, Pouch SM, Zubizarreta N, Mazumdar M, Rana M, Patel G, Freire MP, Pellett Madan R, Kwak EJ, Blumberg E, Satlin MJ, Pisney L, Clemente WT, **Zervos MJ**, La Hoz RM, and Huprikar S. Impact of pre-transplant carbapenem-resistant Enterobacterales colonization and/or infection on solid organ transplant outcomes. *Clin Transplant* 2021; Epub ahead of print. PMID: 33527453. Full Text

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The impact of pre-transplant (SOT) carbapenem-resistant Enterobacterales (CRE) colonization or infection on post-SOT outcomes is unclear. We conducted a multi-center, international, cohort study of SOT recipients, with microbiologically diagnosed CRE colonization and/or infection pre-SOT. Sixty adult SOT recipients were included (liver n = 30, hearts n = 17). Klebsiella pneumoniae (n = 47, 78%) was the most common pre-SOT CRE species. Median time from CRE detection to SOT was 2.32 months (IQR 0.33-10.13). Post-SOT CRE infection occurred in 40% (n = 24/60), at a median of 9 days (IQR 7-17), and most commonly due to K pneumoniae (n = 20/24, 83%). Of those infected, 62% had a surgical site infection, and 46% had bloodstream infection. Patients with post-SOT CRE infection more commonly had a liver transplant (16, 67% vs. 14, 39%; p =.0350) or pre-SOT CRE BSI (11, 46% vs. 7, 19%; p =.03).

One-year post-SOT survival was 77%, and those with post-SOT CRE infection had a 50% less chance of survival vs. uninfected (0.86, 95% CI, 0.76-0.97 vs. 0.34, 95% CI 0.08-1.0, p =.0204). Pre-SOT CRE infection or colonization is not an absolute contraindication to SOT and is more common among abdominal SOT recipients, those with pre-SOT CRE BSI, and those with early post-SOT medical and surgical complications.

Internal Medicine
Balanchivadze N, **Purtell JP**, Anderson J, **Guo Y**, and Dobrosotskaya I. A Case of Chronic Eosinophilic Leukemia in a Patient With Recurrent Cough, Dyspnea, and Eosinophilia. *Cureus* 2021; 13(1):e12654. PMID: 33585139. Full Text

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We report the case of a 40-year-old man with no significant past medical history who had been hospitalized multiple times over the course of one year with recurring cough, dyspnea, pruritic rash, and variable degrees of eosinophilia. He was variably diagnosed with asthma and pneumonia. After his last hospitalization with severe symptoms, the patient was referred for pulmonary evaluation where hypereosinophilia (HE) led to a hematologic workup. Fluorescence in situ hybridization revealed the FIP1L1-PDGFRA gene fusion and bone marrow analysis confirmed a diagnosis of chronic eosinophilic leukemia. The patient was treated with daily imatinib and prednisone and he was symptom-free at a four-week follow-up examination.

Internal Medicine
Bhatia K, Jain V, **Gupta K**, Bansal A, Fox A, Qamar A, Damman K, and Vaduganathan M. Prevention of Heart Failure Events with SGLT-2 Inhibitors Across a Spectrum of Cardio-Renal-Metabolic Risk. *Eur J Heart Fail* 2021; Epub ahead of print. PMID: 33609071. Full Text

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INTRODUCTION: Trials have tested the safety and efficacy of sodium-glucose-cotransporter-2 inhibitors (SGLT2i) across various disease states. We performed a meta-analysis of randomized controlled trials (RCTs) to estimate the relative and absolute effects of SGLT2i in prevention of heart failure (HF) events across different risk groups. METHODS: We conducted a systematic review and meta-analysis of large, placebo-controlled RCTs with >1000 participants evaluating HF hospitalization and the composite of CV death or HF hospitalization. Due to varying durations of therapeutic exposure and follow-up, absolute risk reductions and number needed to treat (NNT) were calculated based on incidence rates (per 100 patient-years). RESULTS: Across 71 553 patients enrolled in 10 late-phase RCTs, SGLT2i reduced the risk of HF hospitalization by 31% (HR 0.69, 95% CI 0.64-0.74; I(2) = 0%) and the composite outcome of CV death or HF hospitalization by 24% (HR 0.76, 95% CI 0.72-0.80; I(2) = 1.4%) compared with placebo. The number of patient-years of treatment exposure needed to prevent 1 CV death or HF hospitalization ranged from 19-26 (established HF) to 72-125 (chronic kidney disease) to 96-400 (high-risk type 2 diabetes). In mixed-effects meta-regression analyses, the benefits of SGLT2i on HF hospitalizations or the composite outcome (CV death or HF hospitalization) were not influenced by age, sex, or change in intermediate markers (glycated hemoglobin, systolic blood pressure, and body weight) (all P ≥ 0.10). CONCLUSION: Despite wide variation in baseline risks and disease states evaluated, SGLT2i

demonstrated comparable relative risk reductions in preventing HF events. Patients at highest baseline risk derived the greatest absolute benefits in preventing HF events. These composite estimates may help guide targeted implementation of SGLT2i for the prevention of HF events in type 2 diabetes and chronic kidney disease and in the treatment of HF.

Medical Education
Dean D, **Passalacqua KD**, Oh SM, Aaron C, **Van Harn MG**, and King A. Pediatric Cannabis Single-Substance Exposures Reported to the Michigan Poison Center From 2008-2019 After Medical Marijuana Legalization. *J Emerg Med* 2021; Epub ahead of print. PMID: 33541760. Full Text

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BACKGROUND: Legalization of medical and recreational cannabis is a major contributor to pediatric cannabis exposures. The trends and magnitude of pediatric cannabis exposures in Michigan after medical cannabis legalization in 2008 have not been assessed. OBJECTIVE: To describe the temporal trends of pediatric cannabis exposures reported to the Michigan Poison Center (MiPC) after medical cannabis was legalized in 2008 and 1 year after legalization of recreational cannabis in 2018. METHODS: Retrospective electronic chart review of pediatric (<18 years old) single-substance cannabis exposures reported to the MiPC from January 1, 2008 to December 31, 2019. Routes of cannabis exposure were reported as ingestion, inhalation, and unknown. Types of ingested cannabis products were also documented. RESULTS: Between 2008 and 2019, 426 pediatric cannabis single exposures were reported. The median patient age was 6.0 years (interquartile range 2-15 years). Age distribution was bimodal. A total of 327 (76.8%) exposures were from cannabis ingestion, 79 (18.5%) from inhalation, 2 (0.5%) from both ingestion and inhalation, and 18 (4.2%) from unknown route. The doubling time for number of cases was 2.1 years, and the total number of annual reported cases increased after 2016. Teenagers (13-17 years) had the highest number of inhalational exposures, whereas young children (0-5 years) had the highest number of ingestions. CONCLUSION: Single-substance pediatric cannabis exposures reported to the Michigan Poison Center increased after medical cannabis was legalized in 2008 through recreational legalization in 2018.

Medical Education
Owusu IA, Quaye O, **Passalacqua KD**, and Wobus CE. Egress of non-enveloped enteric RNA viruses. *J Gen Virol* 2021; Epub ahead of print. PMID: 33560198. Full Text

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A long-standing paradigm in virology was that non-enveloped viruses induce cell lysis to release progeny virions. However, emerging evidence indicates that some non-enveloped viruses exit cells without inducing cell lysis, while others engage both lytic and non-lytic egress mechanisms. Enteric viruses are transmitted via the faecal-oral route and are important causes of a wide range of human infections, both gastrointestinal and extra-intestinal. Virus cellular egress, when fully understood, may be a relevant target for antiviral therapies, which could minimize the public health impact of these infections. In this review, we outline lytic and non-lytic cell egress mechanisms of non-enveloped enteric RNA viruses belonging to five families: Picornaviridae, Reoviridae, Caliciviridae, Astroviridae and Hepeviridae. We discuss factors that contribute to egress mechanisms and the relevance of these mechanisms to virion stability, infectivity and

transmission. Since most data were obtained in traditional two-dimensional cell cultures, we will further attempt to place them into the context of polarized cultures and in vivo pathogenesis. Throughout the review, we highlight numerous knowledge gaps to stimulate future research into the egress mechanisms of these highly prevalent but largely understudied viruses.

Nephrology

Sadat B, Tirunagari D, **Karthikeyan V**, **Patel A**, **Van Harn M**, **Saleem MM**, and **Ananthasubramaniam K**. Clinical impact of pre-kidney transplant pulmonary hypertension on post-transplant outcomes. *Int J Cardiovasc Imaging* 2021; Epub ahead of print. PMID: 33616784. Full Text

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Outcomes of kidney transplant (KT) patients with pre-transplant pulmonary hypertension (PH) are poorly understood. PH patients are often considered high risk and excluded from KT. We investigated the association of pre-transplant PH with KT recipient's outcomes. A single-center, retrospective study that reviewed all patients transplanted from 2010 to 2016, who had a transthoracic echocardiogram (TTE) before KT and at least one TTE post-KT. The TTE closest to the KT was used for analyses. PH is defined as pulmonary artery systolic pressure (PASP) ≥ 40 mm Hg. Of 204 patients, 61 had PASP ≥ 40 mm Hg (with PH) and 143 had PASP < 40 mm Hg (without PH) prior to KT. No statistically significant differences existed between the two groups in baseline demographics, renal failure etiologies, dialysis access type, and cardiovascular risk factors. The mean difference in pre-KT PASP was 18.1 ± 7 mm Hg (P < 0.001). Patients with PH had a statistically significant decrease in PASP post-KT compared to the patients without PH with a mean change of -7.03 ± 12.28 mm Hg vs. + 3.96 ± 11.98 mm Hg (p < 0.001), respectively. Moderate mitral and moderate-severe tricuspid regurgitation were the only factors found to be independently associated with PH (p = 0.001) on multivariable analysis. No statistically significant difference was notable in patient survival, graft function, and creatinine post-KT in both groups. PH pre-KT particularly mild-moderate PH did not adversely affect intermediate (90-day) and long-term allograft and patient survival. Patients with mild-moderate PH should not be excluded from KT.

Nephrology

Wright CB, Auchus AP, Lerner A, Ambrosius WT, Ay H, Bates JT, Chen J, Meschia JF, Pancholi S, Papademetriou V, Rastogi A, Sweeney M, Willard JJ, **Yee J**, and Oparil S. Effect of Intensive Versus Standard Blood Pressure Control on Stroke Subtypes. *Hypertension* 2021; Epub ahead of print. PMID: 33583199. Full Text

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In the SPRINT (Systolic Blood Pressure Intervention Trial), the number of strokes did not differ significantly by treatment group. However, stroke subtypes have heterogeneous causes that could respond differently to intensive blood pressure control. SPRINT participants (N=9361) were randomized to target systolic blood pressures of <120 mm Hg (intensive treatment) compared with <140 mm Hg (standard treatment). We compared incident hemorrhage, cardiac embolism, large- and small-vessel infarctions across treatment arms. Participants randomized to the intensive arm had mean systolic blood pressures of 121.4 mm Hg in the intensive arm (N=4678) and 136.2 mm Hg in the standard arm (N=4683) at one year. Sixty-nine strokes occurred in the intensive arm and 78 in the standard arm when SPRINT was stopped. The breakdown of stroke subtypes across treatment arms included hemorrhagic (intensive treatment, n=6, standard treatment, n=7) and ischemic stroke subtypes (large artery atherosclerosis: intensive treatment n=11, standard treatment, n=13; cardiac embolism: intensive treatment n=11, standard treatment n=15; small artery occlusion: intensive treatment n=8, standard treatment n=8; other ischemic stroke: intensive treatment n=3, standard treatment n=1). Fewer strokes occurred among participants without prior cardiovascular disease in the intensive (n=43) than the standard arm (n=61), but the difference did not reach predefined statistical significance level of 0.05 (P=0.09). The interaction between baseline cardiovascular risk factor status and treatment arm on stroke risk did not reach significance (P=0.05). Similar numbers of stroke subtypes occurred in the intensive BP control and standard control arms of SPRINT.

Neurology
Acosta JN, Leasure AC, Kuohn LR, Both CP, Petersen NH, Sansing LH, Matouk CC, Testai F, Langefeld CD, Woo D, Kamel H, Murthy SB, Qureshi A, **Mayer SA**, Sheth KN, and Falcone GJ. Admission Hemoglobin Levels Are Associated With Functional Outcome in Spontaneous Intracerebral Hemorrhage. *Crit Care Med* 2021; Epub ahead of print. PMID: 33591003. Full Text

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OBJECTIVES: To test the hypothesis that admission hemoglobin levels are associated with outcome in primary, nontraumatic intracerebral hemorrhage. DESIGN: Individual patient data meta-analysis of three studies of intracerebral hemorrhage. SETTING: Two randomized clinical trials and one multiethnic observational study. PATIENTS: Patients with spontaneous, nontraumatic intracerebral hemorrhage. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Our exposure of interest was admission hemoglobin levels and the primary outcome was 3-month postintracerebral hemorrhage-dichotomized modified Rankin Scale (0-3 vs 4-6). Intermediate outcomes were admission hematoma volume and hematoma expansion defined as 6 mL or 33% increase in hemorrhage size on repeat CT. A total of 4,172 intracerebral hemorrhage patients were included in the study (mean age 63 [SD = 14]; female sex 1,668 [40%]). Each additional g/dL of admission hemoglobin was associated with 14% (odds ratio, 0.86; 95% CI, 0.82-0.91) and 7% (odds ratio, 0.93; 95% CI, 0.88-0.98) reductions in the risk of poor outcome in unadjusted and adjusted analyses, respectively. Dose-response analyses indicated a linear relationship between admission hemoglobin levels and poor outcome across the entire evaluated range (test-for-trend p < 0.001). No consistent associations were found between the admission hemoglobin levels and hematoma volume or hematoma expansion. CONCLUSIONS: Higher hemoglobin levels are associated with better outcome in intracerebral hemorrhage. Further research is needed to evaluate admission hemoglobin levels as both a therapeutic target and predictor of outcome.

Neurology

Alsrouji O, and **Memon AB**. Encéphalite auto-immune séronégative. *CMAJ* 2021; 193(8):E300-e301. PMID: 33619075. [Full Text]

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Neurology

Junker J, Berman BD, Hall J, Wahba DW, Brandt V, Perlmutter JS, Jankovic J, Malaty IA, Wagle Shukla A, Reich SG, Espay AJ, Duque KR, **Patel N**, Roze E, Vidailhet M, Jinnah HA, and Brüggemann N. Quality of life in isolated dystonia: non-motor manifestations matter. *J Neurol Neurosurg Psychiatry* 2021; Epub ahead of print. PMID: 33563813. [Full Text]

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OBJECTIVE: To evaluate the relationship between health-related quality of life (HR-QoL) and both physical and psychiatric factors in a large, international, multicentre cohort of patients with isolated dystonia, the Dystonia Coalition. METHODS: Natural history data from 603 patients with isolated dystonia (median age 57 years (IQR: 48 to 64 years), 67.0% women) were prospectively acquired and analysed. HR-QoL (RAND 36-Item Health Survey), severity of depressive symptoms, generalised anxiety (Hospital Anxiety and Depression Scale) and social anxiety (Liebowitz Social Anxiety Scale) were assessed. Dystonia severity (Burke-Fahn-Marsden Dystonia Rating Scale) and dystonic tremor were examined. Statistical predictors of HR-QoL were calculated using saturated path analysis. RESULTS: Reduced HR-QoL was strongly associated with the degree of depressive symptoms and generalised and social anxiety (8/8 RAND 36 subscales, p≤0.001). Increased dystonia severity was associated with worse physical functioning, physical and emotional role functioning and social functioning (all p≤0.001). The presence of tremor correlated with worse physical functioning and pain (all p≤0.006). Younger age was associated with reduced emotional well-being and vitality (all p≤0.006). There were no HR-QoL differences between sexes. CONCLUSION: HR-QoL in isolated dystonia is strongly associated with psychiatric and physical features. While current standard of care focus on motor aspects of dystonia, comprehensive care should address both physical and mental aspects of health.

Neurology

Li C, **Wang C**, **Zhang Y**, **Alsrouji OK**, **Chebl AB**, **Ding G**, **Jiang Q**, Mayer SA, **Lu M**, **Kole MK**, Marin HL, **Zhang L**, **Chopp M**, and **Zhang ZG**. Cerebral endothelial cell-derived small extracellular vesicles enhance neurovascular function and neurological recovery in rat acute ischemic stroke models of mechanical thrombectomy and embolic stroke treatment with tPA. *J Cereb Blood Flow Metab* 2021; Epub ahead of print. PMID: 33557693. [Full Text]

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Treatment of patients with cerebral large vessel occlusion with thrombectomy and tissue plasminogen activator (tPA) leads to incomplete reperfusion. Using rat models of embolic and transient middle cerebral artery occlusion (eMCAO and tMCAO), we investigated the effect on stroke outcomes of small extracellular vesicles (sEVs) derived from rat cerebral endothelial cells (CEC-sEVs) in combination with tPA (CEC-sEVs/tPA) as a treatment of eMCAO and tMCAO in rat. The effect of sEVs derived from clots acquired from patients who had undergone mechanical thrombectomy on healthy human CEC permeability was also evaluated. CEC-sEVs/tPA administered 4 h after eMCAO reduced infarct volume by ~36%, increased recanalization of the occluded MCA, enhanced cerebral blood flow (CBF), and reduced blood-brain barrier (BBB) leakage. Treatment with CEC-sEVs given upon reperfusion after 2 h tMCAO significantly reduced infarct volume by ~43%, and neurological outcomes were improved in both CEC-sEVs treated models. CEC-sEVs/tPA reduced a network of microRNAs (miRs) and proteins that mediate thrombosis, coagulation, and inflammation. Patient-clot derived sEVs increased CEC permeability, which was reduced by CEC-sEVs. CEC-sEV mediated suppression of a network of pro-thrombotic, -coagulant, and -inflammatory miRs and proteins likely contribute to therapeutic effects. Thus, CEC-sEVs have a therapeutic effect on acute ischemic stroke by reducing neurovascular damage.

Neurology

Semaan L, **Zeng Q**, **Lu Y**, **Zhang Y**, **Zreik MM**, **Chamseddine MB**, **Chopp M**, **Zhang ZG**, and **Moonka D**. MicroRNA-214 enriched exosomes from human cerebral endothelial cells (hCEC) sensitize hepatocellular carcinoma to anti-cancer drugs. *Oncotarget* 2021; 12(3):185-198. PMID: 33613846. [Full Text]

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor worldwide. Current medical therapy for HCC has limited efficacy. The present study tests the hypothesis that human cerebral endothelial cell-derived exosomes carrying elevated miR-214 (hCEC-Exo-214) can amplify the efficacy of anti-cancer drugs on HCC cells. Treatment of HepG2 and Hep3B cells with hCEC-Exo-214 in combination with anti-cancer agents, oxaliplatin or sorafenib, significantly reduced cancer cell viability and invasion compared with monotherapy with either drug. Additionally, the therapeutic effect of the combination therapy was detected in primary tumor cells derived from patients with HCC. The ability of hCEC-Exo-214 in sensitizing HCC cells to anti-cancer drugs was specific, in that combination therapy did not affect the viability and invasion of human liver epithelial cells and non-cancer primary cells. Furthermore, compared to monotherapy with oxaliplatin and sorafenib, hCEC-Exo-214 in combination with either drug substantially reduced protein levels of P-glycoprotein (P-gp) and splicing factor 3B

subunit 3 (SF3B3) in HCC cells. P-gp and SF3B3 are among miR-214 target genes and are known to mediate drug resistance and cancer cell proliferation, respectively. In conclusion, the present in vitro study provides evidence that hCEC-Exo-214 significantly enhances the anti-tumor efficacy of oxaliplatin and sorafenib on HCC cells.

Neurosurgery
Chen C, **Lee I**, Tatsui C, Elder T, and Sloan AE. Laser interstitial thermotherapy (LITT) for the treatment of tumors of the brain and spine: a brief review. *J Neurooncol* 2021; 151(3):429-442. PMID: 33611709. [Full Text](#)

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INTRODUCTION: Laser Interstitial Thermotherapy (LITT; also known as Stereotactic Laser Ablation or SLA), is a minimally invasive treatment modality that has recently gained prominence in the treatment of malignant primary and metastatic brain tumors and radiation necrosis and studies for treatment of spinal metastasis has recently been reported. METHODS: Here we provide a brief literature review of the various contemporary uses for LITT and their reported outcomes. RESULTS: Historically, the primary indication for LITT has been for the treatment of recurrent glioblastoma (GBM). However, indications have continued to expand and now include gliomas of different grades, brain metastasis (BM), radiation necrosis (RN), other types of brain tumors as well as spine metastasis. LITT is emerging as a safe, reliable, minimally invasive clinical approach, particularly for deep seated, focal malignant brain tumors and radiation necrosis. The role of LITT for treatment of other types of tumors of the brain and for spine tumors appears to be evolving at a small number of centers. While the technology appears to be safe and increasingly utilized, there have been few prospective clinical trials and most published studies combine different pathologies in the same report. CONCLUSION: Well-designed prospective trials will be required to firmly establish the role of LITT in the treatment of lesions of the brain and spine.

Neurosurgery
Hamilton T, **Macki M**, **Zervos TM**, and **Chang V**. Minimally Invasive Techniques for Iliac Bolt Placement: 2-Dimensional Operative Video. *Oper Neurosurg (Hagerstown)* 2021; Epub ahead of print. PMID: 33556166. [Full Text](#)

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As the popularity of minimally invasive surgery (MIS) continues to grow, novel techniques are needed to meet the demands of multisegment fixation for advanced spinal diseases. In one such example, iliac bolts are often required to anchor large fusion constructs, but MIS technical notes are missing from the literature. A 67-yr-old female presented with a symptomatic coronal deformity: preoperative pelvic incidence = 47°, pelvic tilt = 19°, and lumbar lordosis = 29°, sagittal vertical axis = +5.4 cm with 30° of scoliosis. The operative plan included T10-ilium fusion with transforaminal interbody grafts at L2-3, L3-4, L4-5, and L5-S1. The intraoperative video is of minimally invasive placement of iliac bolts using the O-Arm Surgical Imaging System (Medtronic®). The patient consented to the procedure.   A mini-open exposure that remains above the fascial planes allows for multilevel instrumentation with appropriate decompression at the interbody segments. After the placement of the pedicle screws under image-guidance, the direction is turned to the minimally invasive iliac bolts. Following the trajectory described in the standard open approach,1 the posterior superior iliac spine (PSIS) is identified with the navigation probe, which will guide the Bovie cautery through the fascia. This opening assists in the trajectory of the navigated-awl tap toward the anterior superior iliac spine (ASIS). Next, 8.5 mm x 90 mm iliac screws were placed in the cannulated bone under navigation. After intraoperative image confirmation of screw placement, the contoured rods are threaded under the fascia. The setscrews lock the rod in position. MIS

approaches obviate cross-linking the rods, rendering pelvic fixation more facile. This technique allows for minimal dissection of the posterior pelvic soft tissue while maintaining adequate fixation.

Neurosurgery
Li C, **Wang C**, **Zhang Y**, **Alsrouji OK**, **Chebl AB**, **Ding G**, **Jiang Q**, Mayer SA, **Lu M**, **Kole MK**, Marin HL, **Zhang L**, **Chopp M**, and **Zhang ZG**. Cerebral endothelial cell-derived small extracellular vesicles enhance neurovascular function and neurological recovery in rat acute ischemic stroke models of mechanical thrombectomy and embolic stroke treatment with tPA. *J Cereb Blood Flow Metab* 2021; Epub ahead of print. PMID: 33557693. Full Text

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Treatment of patients with cerebral large vessel occlusion with thrombectomy and tissue plasminogen activator (tPA) leads to incomplete reperfusion. Using rat models of embolic and transient middle cerebral artery occlusion (eMCAO and tMCAO), we investigated the effect on stroke outcomes of small extracellular vesicles (sEVs) derived from rat cerebral endothelial cells (CEC-sEVs) in combination with tPA (CEC-sEVs/tPA) as a treatment of eMCAO and tMCAO in rat. The effect of sEVs derived from clots acquired from patients who had undergone mechanical thrombectomy on healthy human CEC permeability was also evaluated. CEC-sEVs/tPA administered 4 h after eMCAO reduced infarct volume by ∼36%, increased recanalization of the occluded MCA, enhanced cerebral blood flow (CBF), and reduced blood-brain barrier (BBB) leakage. Treatment with CEC-sEVs given upon reperfusion after 2 h tMCAO significantly reduced infarct volume by ∼43%, and neurological outcomes were improved in both CEC-sEVs treated models. CEC-sEVs/tPA reduced a network of microRNAs (miRs) and proteins that mediate thrombosis, coagulation, and inflammation. Patient-clot derived sEVs increased CEC permeability, which was reduced by CEC-sEVs. CEC-sEV mediated suppression of a network of pro-thrombotic, -coagulant, and -inflammatory miRs and proteins likely contribute to therapeutic effects. Thus, CEC-sEVs have a therapeutic effect on acute ischemic stroke by reducing neurovascular damage.

Neurosurgery
Macki M, **Pawloski J**, **Fadel H**, **Hamilton T**, **Haider S**, **Elmenini J**, **Fakih M**, **Johnson JL**, and **Rock J**. The Effect of Antithrombotics on Hematoma Expansion in Small- to Moderate-Sized Traumatic Intraparenchymal Hemorrhages. *World Neurosurg* 2021; Epub ahead of print. PMID: 33640526. Full Text

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BACKGROUND: Although pre-injury antithrombotic agents, including antiplatelets and anticoagulants, are historically associated with expansion of traumatic intraparenchymal hemorrhage (tIPH), the literature has poorly elucidated the actual risk of hematoma expansion on repeat computed tomography (CT). The objective is to determine the effect of antithrombotic agents on hematoma expansion in tIPH by comparing patients with and without pre-injury antithrombotic medication. METHODS: The volume of all tIPHs over a 5-year period at an academic Level 1 Trauma Center was measured retrospectively. The initial tIPH was divided into three equally-sized quantiles. The third tertile, representing the largest subset of tIPH, was then removed from the study population because these patients reflect a different pathophysiological mechanism that may require a more acute and aggressive level of care with reversal agents and/or operative management. Per institutional policy, all patients with small- to moderate-sized hemorrhages received a 24-hour stability CT scan. Patients who received reversal agents were excluded.

RESULTS: Of the 105 patients with a tIPH on the initial head CT scan, small- to moderate-size hemorrhages were <5 cm(3). The size of tIPH on initial imaging did not statistically significantly differ between the antithrombotic cohort (0.7±0.1 cm(3)) and the non-antithrombotic cohort (0.5±0.1 cm(3)) (P=0.091). Similarly, the volume of tIPH failed to differ on 24-hour repeat imaging (1.0±0.2 cm(3) vs. 0.6±0.1 cm(3), respectively, P=0.172). Following a multiple linear regression, only history of stroke, not antithrombotic medications, predicted increased tIPH on 24-hour repeat imaging. CONCLUSION: In small- to moderate-sized tIPH, withholding antithrombotic agents without reversal may be sufficient.

Neurosurgery
Mosella MS, **Sabedot TS**, Silva TC, **Malta TM**, Segato FD, **Asmaro KP**, **Wells M**, **Mukherjee A**, **Poisson LM**, **Snyder J**, **deCarvalho AC**, **Walbert T**, **Aho T**, **Kalkanis S**, Elias PC, Antonini SR, **Rock J**, **Noushmehr H**, Castro M, and **Castro AV**. DNA Methylation-based Signatures Classify Sporadic Pituitary Tumors According to Clinicopathological Features. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33631002. Full Text

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Department of Biostatistics, Henry Ford Health System, Detroit, MI, USA.
Department of Radiology, Henry Ford Health System, Detroit, MI, USA.
Internal Medicine Department, Ribeirao Preto Medical School, University of São Paulo, Ribeirao Preto, Brazil.
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BACKGROUND: Distinct genome-wide methylation patterns cluster pituitary neuroendocrine tumors (PitNETs) into molecular groups associated with specific clinicopathological features. Here we aim to identify, characterize and validate methylation signatures that objectively classify PitNET into clinicopathological groups. METHODS: Combining in-house and publicly available data, we conducted an analysis of the methylome profile of a comprehensive cohort of 177 tumors (Panpit cohort) and 20 nontumor specimens from the pituitary gland. We also retrieved methylome data from an independent PitNET cohort (N=86) to validate our findings. RESULTS: We identified three methylation clusters associated with adenohypophyseal cell lineages and functional status using an unsupervised approach. Differentially methylated CpG probes (DMP) significantly distinguished the Panpit clusters and accurately assigned the samples of the validation cohort to their corresponding lineage and functional subtypes memberships. The DMPs were annotated in regulatory regions enriched of enhancer elements, associated with pathways and genes involved in pituitary cell identity, function, tumorigenesis, invasiveness. Some DMPs correlated with genes with prognostic and therapeutic values in other intra or extracranial tumors. CONCLUSIONS: We identified and validated methylation signatures, mainly annotated in enhancer regions that distinguished PitNETs by distinct adenohypophyseal cell lineages and functional status. These signatures provide the groundwork to develop an unbiased approach to classifying PitNETs according to the most recent classification recommended by the 2017 WHO and to explore their biological and clinical relevance in these tumors.

Neurosurgery
Sabedot T, **Malta T**, **Snyder J**, **Nelson K**, **Wells M**, **deCarvalho A**, **Mukherjee A**, **Chitale D**, **Mosella M**, Sokolov A, **Asmaro K**, **Robin A**, **Rosenblum M**, **Mikkelsen T**, **Rock J**, **Poisson L**, **Lee I**, **Walbert T**, **Kalkanis S**, Iavarone A, **Castro AV**, and **Noushmehr H**. A serum-based DNA methylation assay provides accurate detection of glioma. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33560371. Full Text

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BACKGROUND: The detection of somatic mutations in cell-free DNA (cfDNA) from liquid biopsy has emerged as a non-invasive tool to monitor the follow-up of cancer patients. However, the significance of cfDNA clinical utility remains uncertain in patients with brain tumors, primarily because of the limited sensitivity cfDNA has to detect real tumor-specific somatic mutations. This unresolved challenge has prevented accurate follow-up of glioma patients with non-invasive approaches. METHODS: Genome-wide DNA methylation profiling of tumor tissue and serum cell-free DNA of glioma patients. RESULTS: Here, we developed a non-invasive approach to profile the DNA methylation status in the serum of patients with gliomas and identified a cfDNA-derived methylation signature that is associated with the presence of gliomas and related immune features. By testing the signature in an independent discovery and validation cohorts, we developed and verified a score metric (the "glioma epigenetic liquid biopsy score" or GeLB) that optimally distinguished patients with or without glioma (sensitivity: 100%, specificity: 97.78%). Furthermore, we found that changes in GeLB score reflected clinicopathological changes during surveillance (e.g., progression, pseudoprogression or response to standard or experimental treatment). CONCLUSIONS: Our results suggest that the GeLB score can be used as a complementary approach to diagnose and follow up patients with glioma.

Neurosurgery
Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Division of Cardiovascular Disease, Center for Structural Heart, Henry Ford Hospital, Detroit, Michigan, USA (Wang, O'Neill); Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA (Zervos, McKinnon, Alangaden, Suleyman); Family Medicine, Henry Ford Hospital, Detroit, Michigan, USA (Allard); Public Health Sciences, Henry Ford Hospital, Detroit, Michigan, USA (Schultz, Poisson); Office of Clinical Quality and Safety, Henry Ford Health System, Detroit, Michigan, USA (Chu); Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA (Kalkanis).

OBJECTIVE: Examine the effect of a universal facemask policy for healthcare workers(HCW) and incidence of SARS-CoV-2 positivity. METHODS: Daily number of symptomatic HCW tested, SARS-CoV-2 positivity rates, and HCW job-descriptions were collected pre and post Universal HCW facemask policy(March 26). Multiple change point regression was used to model positive-test-rate data. SARS-CoV-2 testing and positivity rates were compared for pre-intervention, transition, post-intervention, and follow-up periods. RESULTS: Between March 12-August 10, 2020, 19.2% of HCW were symptomatic for COVID-19 and underwent SARS-CoV-2 testing. A single change point was identified ~March 28-30(95% probability). Before the change point, the odds of a tested HCW having a positive result doubled every 4.5-7.5 days. Post-change-point, the odds of a tested HCW having a positive result halved every 10.5-13.5 days. CONCLUSIONS: Universal facemasks was associated with reducing HCW's risk of acquiring COVID-19.

Orthopaedics/Bone and Joint Center
Cross AG, **Tramer JS**, **Guo EW**, **Muh SJ**, and **Makhni EC**. Arthroscopic Repair of Humeral Avulsion of the Glenohumeral Ligament Lesion With Capsular Plication in the Lateral Decubitus Position. *Arthrosc Tech* 2021; 10(2):e569-e574. PMID: Not assigned. Full Text

E.C. Makhni, Henry Ford Health System, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI, United States

Humeral avulsion of the glenohumeral ligament (HAGL) lesions can lead to persistent shoulder instability. While rare, HAGL lesions may present as a concomitant injury following shoulder dislocation events. Traditionally, an open approach has been used to repair the inferior glenohumeral ligament and restore

shoulder stability. Modern arthroscopic techniques and instrumentation have permitted a minimally invasive approach for treating HAGL lesions. While technically demanding, arthroscopic repair of HAGL lesions has demonstrated favorable outcomes with less soft-tissue disruption. The following Technical Note describes a safe and effective method for the arthroscopic repair of HAGL lesions. Our technique highlights the use of the lateral decubitus position, a 70° arthroscope, a curved anchor device, and a 90° SutureLasso device.

Orthopaedics/Bone and Joint Center
Jildeh TR, **Meta F**, Young J, Page B, Nwachukwu B, Westermann RW, and **Okoroha KR**. Concussion Is Associated With Increased Odds of Acute Lower-Extremity Musculoskeletal Injury Among National Basketball Association Players. *Arthrosc Sports Med Rehabil* 2021; 3(1):e219-e225. PMID: 33615268. Full Text

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PURPOSE: To determine the odds of sustaining an acute lower-extremity (LE) musculoskeletal injury during the 90-day period after return-to-play (RTP) from concussion in National Basketball Association (NBA) athletes. METHODS: Concussion data for NBA players were collected from the 1999-2000 to 2017-2018 seasons, from publicly available sources. Age, position, injury, time to RTP, and demographic factors were collected. The 90-day period after each case of concussion was reviewed for acute noncontact LE musculoskeletal injury. Control athletes without a documented history of concussion were matched to concussed athletes by age, body mass index, position, and experience. Conditional logistic regression with a calculated odds ratio and a 95% confidence interval were used to assess the association between concussion and subsequent risk of LE injury. RESULTS: In total, 189 concussions were documented in 153 athletes. Of these, 140 cases were the first recorded instance of concussion in players with publicly available data. Thirty-six (25.7%) athletes sustained a LE injury within 90 days of concussion; 26 (20.2%) were non-season-ending and included in RTP analysis. The odds of sustaining an acute LE musculoskeletal injury within the 90-day period after concussion was 4.69 times greater in concussed players compared with controls (95% confidence interval 1.96-11.23, P < .001). There was no significant difference in games (4.2 ± 5.0 vs 4.7 ± 4.7 games, P = .566) or days (18.5 ± 39.1 days vs 10.9 ± 10.6 days, P = .912) missed between concussed players with LE injury and nonconcussed controls. The most common LE injuries in concussed athletes were ligament sprains/tears (65%). CONCLUSIONS: Concussed NBA athletes have increased odds for sustaining an acute LE musculoskeletal injury within 90 days of RTP compared with nonconcussed controls. The most common injuries were ligament strains or tears. Changes in neuromotor control and proprioception following a concussion should be evaluated in high-level basketball players returning to sport. LEVEL OF EVIDENCE: Level III, Case-Control Study.

Orthopaedics/Bone and Joint Center
Koolmees D, Ramkumar PN, **Hessburg L**, **Guo E**, Bernstein DN, and **Makhni EC**. Time-Driven Activity-based Costing for Anterior Cruciate Ligament Reconstruction: A Comparison to Traditional Accounting Methods. *Arthrosc Sports Med Rehabil* 2021; 3(1):e39-e45. PMID: 33615246. Full Text

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PURPOSE: The primary purpose of this study was to compare the cost of care of one of the most common sports medicine surgical procedures, anterior cruciate ligament reconstruction (ACLR), using the time-driven activity-based costing (TDABC) method to traditional accounting methods such as activity-based costing (ABC). Our secondary purpose was to identify the main drivers of the cost of ACLR using both of these techniques. METHODS: A process map of ACLR was constructed through direct observation in the clinical setting according to established techniques to identify drivers of fixed, direct variable, and indirect costs. An episode of care consisted of each step in the surgical process from

admission to discharge. Personnel costs were combined with the process map to determine the cost drivers and overall cost of the procedure. The cost generated from the TDABC method was compared with the cost from our institution's internal accounting system, which used an ABC method. RESULTS: The total cost of ACLR was $5,242.25 when using TDABC versus $10,318 when using the traditional ABC method. The largest difference between the 2 methods was within the domain of direct variable costs. CONCLUSIONS: When compared with TDABC, the hospital's traditional cost-accounting estimate for ACLR is nearly twice as costly. These findings highlight the variability of cost calculation for the same clinical episode between the 2 accounting methods. For the traditional accounting method, the direct variable cost was the main cost driver, whereas for the TDABC method, the direct fixed cost was the main cost driver. CLINICAL RELEVANCE: This study is important because it elucidates important cost drivers for one of the most common sports medicine orthopaedic surgical procedures and attempts to identify the true overall cost of the procedure.

Orthopaedics/Bone and Joint Center
Umeh ON, **Beekman R**, **D'sa H**, and **Friedman BJ**. An Elderly Male With Progressive Nail Atrophy: Answer. *Am J Dermatopathol* 2021; 43(2):152-153. PMID: 33492842. Full Text

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Otolaryngology – Head & Neck Surgery
Craig JR, Poetker DM, Aksoy U, Allevi F, Biglioli F, Cha BY, Chiapasco M, Lechien JR, Safadi A, Simuntis R, Tataryn R, Testori T, Troeltzsch M, Vaitkus S, Yokoi H, Felisati G, and Saibene AM. Diagnosing odontogenic sinusitis: An international multidisciplinary consensus statement. *Int Forum Allergy Rhinol* 2021; Epub ahead of print. PMID: 33583151. Full Text

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BACKGROUND: Odontogenic sinusitis (ODS) is distinct from non-odontogenic rhinosinusitis, and often requires multidisciplinary collaboration between otolaryngologists and dental providers to make the diagnosis. The purpose of this study was to develop international multidisciplinary consensus on diagnosing ODS. METHODS: A modified Delphi method was used to assess for expert consensus on diagnosing bacterial ODS. A multidisciplinary panel of 17 authors with ODS expertise from 8 countries (8 otolaryngologists, 9 dental specialists) was assembled. Each author completed 2 of 3 surveys (2 specialty-specific, and 1 for all authors). Thirty-seven clinical statements were created, focusing on 4 important diagnostic components: suspecting ODS; confirming sinusitis in ODS; confirming different dental pathologies causing ODS; and multidisciplinary collaborative aspects of diagnosing ODS. Target audiences were all otolaryngologists and dental providers. RESULTS: Of the 37 clinical statements, 36 reached consensus or strong consensus, and 1 reached no consensus. Strong consensus was reached that certain clinical and microbiologic features should arouse suspicion for ODS, and that multidisciplinary collaboration between otolaryngologists and dental providers is generally required to diagnose ODS. To diagnose ODS, otolaryngologists should confirm sinusitis mainly based on nasal endoscopic findings of middle meatal purulence, edema, or polyps, and dental providers should confirm dental pathology based on clinical examination and dental imaging. CONCLUSION: Based on multidisciplinary international consensus, diagnosing ODS generally requires otolaryngologists to confirm sinusitis, and dental providers to confirm maxillary odontogenic pathology. Importantly, both dental providers and otolaryngologists should suspect ODS based on certain clinical features, and refer patients to appropriate providers for disease confirmation.

Otolaryngology – Head & Neck Surgery

Goyal VK, Spillinger A, **Peterson EI**, and **Craig JR**. Odontogenic sinusitis publication trends from 1990 to 2019: a systematic review. *Eur Arch Otorhinolaryngol* 2021; Epub ahead of print. PMID: 33609178. Full Text

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PURPOSE: Odontogenic sinusitis (ODS) is underrepresented in the literature compared to other forms of rhinosinusitis, specifically in sinusitis guidelines and position statements. ODS publication characteristics could help explain why ODS has received less attention in sinusitis guidelines and position statements. The purpose of this study was to explore trends in the quantity and quality of ODS studies over 3 decades from 1990 to 2019. METHODS: A systematic review was performed to identify all ODS studies from 1990 to 2019. The following variables from all ODS studies were compared between and across the 3 decades: authors' specialties, journal specialties, authors' geographic origins (continents), study topics, study designs, and evidence levels. RESULTS: From 1990 to 2019, there were 254 ODS studies that met inclusion criteria. Numbers of publications increased each decade, with 161 being published from 2010 to 2019. Otolaryngologists and dental authors published over 75% of ODS studies each decade, with 60-75% of ODS articles being published in otolaryngology or dental journals. European and Asian authors published the most ODS studies each decade. Overall, 92-100% of ODS publications per decade were level 4 and 5 evidence, with no significant changes between or across decades. CONCLUSION: While numbers of ODS publications increased each decade from 1990 to 2019, evidence levels remained low without significant changes over time. Otolaryngologists and dental authors published the majority of ODS studies each decade, with a minority of these studies being multidisciplinary. More ODS studies are needed across all aspects of the condition, and future projects would benefit from improved study designs and multidisciplinary collaboration.

Otolaryngology – Head & Neck Surgery

Tam S, Gajera M, Luo X, Glisson BS, Ferrarotto R, Johnson FM, Mott FE, Gillison ML, Lu C, Le X, Blumenschein GR, Wong MK, Rosenthal DI, Nagarajan P, El-Naggar AK, Midgen MR, Weber RS, Myers JN, and Gross ND. Cytotoxic and targeted systemic therapy in patients with advanced cutaneous squamous cell carcinoma in the head and neck. *Head Neck* 2021; Epub ahead of print. PMID: 33522021. [Full Text]

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Division of Radiation Oncology, Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA.
Division of Pathology/Lab Medicine, Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA.
Division of Internal Medicine, Department of Dermatology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA.

BACKGROUND: The outcomes of patients treated with cytotoxic or targeted systemic therapy is not well defined for cutaneous squamous cell carcinoma of the head and neck (cSCCHN). METHODS: Patients with cSCCHN treated with cytotoxic or targeted systemic therapy were included. Patients were divided into two groups based on the presence of distant metastasis (M1 vs. M0) at presentation. A proportional hazards model was used to assess for independent predictors of overall survival. RESULTS: Of 129 patients with cSCCHN, 20 (16%) were M1 and 109 (84%) were M0. Independent predictors of improved survival were M0 status, treatment of locally advanced disease with radiotherapy, and lower Eastern Cooperative Oncology Group (ECOG) score. CONCLUSIONS: Survival was worse in M1 patients treated with cytotoxic or targeted systemic therapy and poor baseline performance status but improved in those receiving radiotherapy. These data can serve as historical controls for future systemic therapy trials, including immunotherapy.

Pathology and Laboratory Medicine

Abou Shaar R, Eby CS, van Dorp S, de Witte T, and **Otrock ZK**. Increasing ferritin predicts early death in adult hemophagocytic lymphohistiocytosis. *Int J Lab Hematol* 2021; Epub ahead of print. PMID: 33595184. [Full Text]

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INTRODUCTION: Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of pathologic immune activation. Most studies on adult HLH have evaluated prognostic factors for overall survival; factors predicting early mortality have not been sufficiently investigated. METHODS: This was a collaborative study between Henry Ford Hospital and Barnes-Jewish Hospital. We identified all adult HLH patients with at least 2 ferritin levels within 30 days from admission. RESULTS: One-hundred twenty-four patients were identified. There were 77 males and 47 females; the median age at diagnosis was 48 years. Multivariate analysis showed that age (OR = 11.41; 95% CI:2.71-48.04; P = .001), hepatomegaly (OR = 15.68; 95% CI:3.24-75.96; P = .001), hyponatremia (OR = 5.94; 95% CI:1.76-20.1; P = .004), hypoalbuminemia (OR = 7.47; 95% CI:2.08-26.85; P = .002), and increasing ferritin levels (OR = 19.46; 95% CI:4.69-80.71; P < .001) were significant predictors of 30-day mortality. Patients with declining ferritin by more than 35% from the ferritin peak were more likely to survive the first 30 days of admission (OR = 4.33; 95% CI:1.04-

18.1; P = .033). By risk stratifying our cohort, we identified changes in ferritin levels to be the most significant prognostic factor of 30-day mortality among other risk factors. Further investigating the prognostic utility of ferritin showed that increasing ferritin during the 1st week of admission (data available for 44 patients) was the only significant predictor of 30-day mortality. CONCLUSIONS: To the best of our knowledge, this is the first study reporting changes in ferritin to be a predictor for early death in adult HLH. Changes in ferritin might be a useful indicator of adult HLH disease activity and early prognosis.

Pathology and Laboratory Medicine

Jiagge EM, Ulintz PJ, Wong S, McDermott SP, **Fossi SI**, Suhan TK, Hoenerhoff MJ, **Bensenhaver JM**, Salem B, Dziubinski M, Oppong JK, Aitpillah F, Ishmael K, Osei-Bonsu E, Adjei E, Baffour A, Aldrich J, Kurdoglu A, **Fernando K**, Craig DW, Trent JM, Li J, **Chitale D**, Newman LA, Carpten JD, Wicha MS, and Merajver SD. Multiethnic PDX models predict a possible immune signature associated with TNBC of African ancestry. *Breast Cancer Res Treat* 2021; Epub ahead of print. PMID: 33576900. Full Text

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PURPOSE: Triple-negative breast cancer (TNBC) is an aggressive subtype most prevalent among women of Western Sub-Saharan African ancestry. It accounts for 15-25% of African American (AA) breast cancers (BC) and up to 80% of Ghanaian breast cancers, thus contributing to outcome disparities in BC for black women. The aggressive biology of TNBC has been shown to be regulated partially by breast cancer stem cells (BCSC) which mediate tumor recurrence and metastasis and are more abundant in African breast tumors. METHODS: We studied the biological differences between TNBC in women with African ancestry and those of Caucasian women by comparing the gene expression of the BCSC. From low-passage patient derived xenografts (PDX) from Ghanaian (GH), AA, and Caucasian American (CA) TNBCs, we sorted for and sequenced the stem cell populations and analyzed for differential gene enrichment. RESULTS: In our cohort of TNBC tumors, we observed that the ALDH expressing stem cells display distinct ethnic specific gene expression patterns, with the largest difference existing between the GH and AA ALDH+ cells. Furthermore, the tumors from the women of African ancestry [GH/AA] had ALDH stem cell (SC) enrichment for expression of immune related genes and processes. Among the significantly upregulated genes were CD274 (PD-L1), CXCR9, CXCR10 and IFI27, which could serve as potential drug targets. CONCLUSIONS: Further exploration of the role of immune regulated genes and biological processes in BCSC may offer insight into developing novel approaches to treating TNBC to help ameliorate survival disparities in women with African ancestry.

Pathology and Laboratory Medicine

Mosella MS, **Sabedot TS**, Silva TC, **Malta TM**, Segato FD, **Asmaro KP**, **Wells M**, **Mukherjee A**, **Poisson LM**, **Snyder J**, **deCarvalho AC**, **Walbert T**, **Aho T**, **Kalkanis S**, Elias PC, Antonini SR, **Rock J**, **Noushmehr H**, Castro M, and **Castro AV**. DNA Methylation-based Signatures Classify Sporadic Pituitary

Tumors According to Clinicopathological Features. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33631002. [Full Text](#)

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BACKGROUND: Distinct genome-wide methylation patterns cluster pituitary neuroendocrine tumors (PitNETs) into molecular groups associated with specific clinicopathological features. Here we aim to identify, characterize and validate methylation signatures that objectively classify PitNET into clinicopathological groups. METHODS: Combining in-house and publicly available data, we conducted an analysis of the methylome profile of a comprehensive cohort of 177 tumors (Panpit cohort) and 20 nontumor specimens from the pituitary gland. We also retrieved methylome data from an independent PitNET cohort (N=86) to validate our findings. RESULTS: We identified three methylation clusters associated with adenohypophyseal cell lineages and functional status using an unsupervised approach. Differentially methylated CpG probes (DMP) significantly distinguished the Panpit clusters and accurately assigned the samples of the validation cohort to their corresponding lineage and functional subtypes memberships. The DMPs were annotated in regulatory regions enriched of enhancer elements, associated with pathways and genes involved in pituitary cell identity, function, tumorigenesis, invasiveness. Some DMPs correlated with genes with prognostic and therapeutic values in other intra or extracranial tumors. CONCLUSIONS: We identified and validated methylation signatures, mainly annotated in enhancer regions that distinguished PitNETs by distinct adenohypophyseal cell lineages and functional status. These signatures provide the groundwork to develop an unbiased approach to classifying PitNETs according to the most recent classification recommended by the 2017 WHO and to explore their biological and clinical relevance in these tumors.

Pathology and Laboratory Medicine

Sabedot T, **Malta T**, **Snyder J**, **Nelson K**, **Wells M**, **deCarvalho A**, **Mukherjee A**, **Chitale D**, **Mosella M**, Sokolov A, **Asmaro K**, **Robin A**, **Rosenblum M**, **Mikkelsen T**, **Rock J**, **Poisson L**, **Lee I**, **Walbert T**, **Kalkanis S**, lavarone A, **Castro AV**, and **Noushmehr H**. A serum-based DNA methylation assay provides accurate detection of glioma. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33560371. [Full Text](#)

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BACKGROUND: The detection of somatic mutations in cell-free DNA (cfDNA) from liquid biopsy has emerged as a non-invasive tool to monitor the follow-up of cancer patients. However, the significance of cfDNA clinical utility remains uncertain in patients with brain tumors, primarily because of the limited sensitivity cfDNA has to detect real tumor-specific somatic mutations. This unresolved challenge has prevented accurate follow-up of glioma patients with non-invasive approaches. METHODS: Genome-wide DNA methylation profiling of tumor tissue and serum cell-free DNA of glioma patients. RESULTS: Here, we developed a non-invasive approach to profile the DNA methylation status in the serum of patients with gliomas and identified a cfDNA-derived methylation signature that is associated with the presence of

gliomas and related immune features. By testing the signature in an independent discovery and validation cohorts, we developed and verified a score metric (the "glioma epigenetic liquid biopsy score" or GeLB) that optimally distinguished patients with or without glioma (sensitivity: 100%, specificity: 97.78%). Furthermore, we found that changes in GeLB score reflected clinicopathological changes during surveillance (e.g., progression, pseudoprogression or response to standard or experimental treatment). CONCLUSIONS: Our results suggest that the GeLB score can be used as a complementary approach to diagnose and follow up patients with glioma.

Pathology and Laboratory Medicine
Samuel LP, Hansen GT, Kraft CS, and Pritt BS. The Need for Dedicated Microbiology Leadership in the Clinical Microbiology Laboratory. *J Clin Microbiol* 2021; Epub ahead of print. PMID: 33597258. Full Text

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Clinical microbiology laboratories play a crucial role in patient care using traditional and innovative diagnostics. Challenges faced by laboratories include emerging pathogens, rapidly evolving technologies, healthcare-acquired infections, antibiotic-resistant organisms and diverse patient populations. Despite these challenges, many clinical microbiology laboratories in the United States are not directed by doctoral level microbiology-trained individuals with sufficient time dedicated to laboratory leadership. This manuscript highlights the need for medical microbiology laboratory directors with appropriate training and qualifications.

Pharmacy
Acharya Y, Nepal P, Yang D, Karki K, Bajracharya D, **Prentis T**, **Davis SL**, and **Kaljee L**. Economic and Social Drivers of Antibiotic Dispensing Practices among Community Pharmacies in Nepal. *Trop Med Int Health* 2021; Epub ahead of print. PMID: 33524230. Full Text

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OBJECTIVE: To assess economic and social drivers of dispensing antibiotics without prescription by community pharmacies in Nepal. METHOD: A survey was conducted among 111 pharmacy owners and managers in five districts. Information on demographic and economic characteristics of the pharmacies (e.g., revenue and profits from antibiotics), and their inclination to sell antibiotics without a physician's prescription under various scenarios (e.g., diarrhea in a child), was collected. Univariate analysis was conducted to assess the demographic and economic characteristics. Bivariate analysis was conducted to examine the relationship between dispensing antibiotics without prescription and economic and social factors. RESULTS: Azithromycin and amoxicillin were the most commonly dispensed antibiotics. The proportions of pharmacies reporting that they would 'most likely' or 'likely' dispense antibiotics without prescription to adult patients ranged from 36.9% (sore throat) to 67.6% (cough). The proportions for pediatric patients ranged from 62.2% (sore throat) to 80.2% (cough or diarrhea). There was no consistent relationship between the likelihood of dispensing antibiotics and revenues, profits, or the number of patients. Instead, dispensing behavior was influenced by the pressure from the patient; the respondents were more likely to dispense antibiotics when the patient specifically asked for "an antibiotic" rather than for "a medicine", and 68.5% respondents ranked 'customer satisfaction' as the most important factor motivating their work. CONCLUSIONS: In Nepal, inappropriate sale of antibiotics by community pharmacists is high, particularly for pediatric patients. Additional research is needed to establish key drivers of this behavior and to help design effective approaches to reducing AMR.

Pharmacy
Griebe K, **Jiang C**, **To L**, **Peters M**, and **MacDonald NC**. Pharmacy emergency preparedness training as a PGY2 longitudinal rotation. *Am J Health Syst Pharm* 2021; Epub ahead of print. PMID: 33594437. Full Text

Department of Pharmacy Services, Henry Ford Hospital, Detroit, MI.

Plastic Surgery
Chamogeorgakis T, **Moquin K**, **Simoff M**, and **Nemeh H**. Repair of Bronchial Anastomosis Following Lung Transplantation. *Thorac Cardiovasc Surg* 2021; Epub ahead of print. PMID: 33580492. Request Article

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BACKGROUND: Bronchial anastomotic complications are reported in 2 to 18% of patients after lung transplantation. The majority of complications can be managed with bronchoscopic intervention. When extensive dehiscence is present, surgical intervention can be entertained. MATERIALS AND METHODS: Between March 1, 2006, and December 31, 2019, our program performed 244 lung transplantations. We conducted a retrospective review of our patient cohort and identified patients who suffered from significant anastomotic complications that required surgical interventions. RESULTS: Twenty-eight and 216 patients underwent single and bilateral lung transplantations, respectively. Eighteen patients developed airway complications (7.4%). The incidence of anastomotic complications was 5.2% (24 complications for a total of 460 bronchial anastomoses). Four patients were managed conservatively. The majority of the bronchial anastomotic complications were managed endoscopically (eight patients). Four patients with associated massive air leak underwent repair of the bronchial anastomosis and two patients were retransplanted because they developed severe distal airway stenosis. CONCLUSION: Bronchial anastomotic complications are a major cause of morbidity in lung transplantation. The majority of cases can be managed bronchoscopically. In more severe cases associated with massive air leak or imminent massive hemoptysis from bronchopulmonary arterial fistula, surgical intervention is necessary. Aortic homograft interposition along with vascularized pedicle wrapping may be a viable option to re-establish airway continuity when tension-free bronchial anastomotic revision is not possible. In cases with smaller bronchial defects, primary repair with utilization of a vascularized flap can be effective as treatment option.

Public Health Sciences
Dean D, **Passalacqua KD**, Oh SM, Aaron C, **Van Harn MG**, and King A. Pediatric Cannabis Single-Substance Exposures Reported to the Michigan Poison Center From 2008-2019 After Medical Marijuana Legalization. *J Emerg Med* 2021; Epub ahead of print. PMID: 33541760. Full Text

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BACKGROUND: Legalization of medical and recreational cannabis is a major contributor to pediatric cannabis exposures. The trends and magnitude of pediatric cannabis exposures in Michigan after

medical cannabis legalization in 2008 have not been assessed. OBJECTIVE: To describe the temporal trends of pediatric cannabis exposures reported to the Michigan Poison Center (MiPC) after medical cannabis was legalized in 2008 and 1 year after legalization of recreational cannabis in 2018. METHODS: Retrospective electronic chart review of pediatric (<18 years old) single-substance cannabis exposures reported to the MiPC from January 1, 2008 to December 31, 2019. Routes of cannabis exposure were reported as ingestion, inhalation, and unknown. Types of ingested cannabis products were also documented. RESULTS: Between 2008 and 2019, 426 pediatric cannabis single exposures were reported. The median patient age was 6.0 years (interquartile range 2-15 years). Age distribution was bimodal. A total of 327 (76.8%) exposures were from cannabis ingestion, 79 (18.5%) from inhalation, 2 (0.5%) from both ingestion and inhalation, and 18 (4.2%) from unknown route. The doubling time for number of cases was 2.1 years, and the total number of annual reported cases increased after 2016. Teenagers (13-17 years) had the highest number of inhalational exposures, whereas young children (0-5 years) had the highest number of ingestions. CONCLUSION: Single-substance pediatric cannabis exposures reported to the Michigan Poison Center increased after medical cannabis was legalized in 2008 through recreational legalization in 2018.

Public Health Sciences
Goyal VK, Spillinger A, **Peterson EI**, and **Craig JR**. Odontogenic sinusitis publication trends from 1990 to 2019: a systematic review. *Eur Arch Otorhinolaryngol* 2021; Epub ahead of print. PMID: 33609178. Full Text

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PURPOSE: Odontogenic sinusitis (ODS) is underrepresented in the literature compared to other forms of rhinosinusitis, specifically in sinusitis guidelines and position statements. ODS publication characteristics could help explain why ODS has received less attention in sinusitis guidelines and position statements. The purpose of this study was to explore trends in the quantity and quality of ODS studies over 3 decades from 1990 to 2019. METHODS: A systematic review was performed to identify all ODS studies from 1990 to 2019. The following variables from all ODS studies were compared between and across the 3 decades: authors' specialties, journal specialties, authors' geographic origins (continents), study topics, study designs, and evidence levels. RESULTS: From 1990 to 2019, there were 254 ODS studies that met inclusion criteria. Numbers of publications increased each decade, with 161 being published from 2010 to 2019. Otolaryngologists and dental authors published over 75% of ODS studies each decade, with 60-75% of ODS articles being published in otolaryngology or dental journals. European and Asian authors published the most ODS studies each decade. Overall, 92-100% of ODS publications per decade were level 4 and 5 evidence, with no significant changes between or across decades. CONCLUSION: While numbers of ODS publications increased each decade from 1990 to 2019, evidence levels remained low without significant changes over time. Otolaryngologists and dental authors published the majority of ODS studies each decade, with a minority of these studies being multidisciplinary. More ODS studies are needed across all aspects of the condition, and future projects would benefit from improved study designs and multidisciplinary collaboration.

Public Health Sciences
Hallmark B, **Wegienka G**, **Havstad S**, Billheimer D, Ownby D, Mendonca EA, Gress L, Stern DA, Myers JB, Khurana Hershey GK, Hoepner L, Miller RL, Lemanske RF, Jackson DJ, Gold DR, O'Connor GT, Nicolae DL, Gern JE, Ober C, Wright AL, and Martinez FD. Chromosome 17q12-21 Variants are Associated with Multiple Wheezing Phenotypes in Childhood. *Am J Respir Crit Care Med* 2021; Epub ahead of print. PMID: 33535024. Full Text

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RATIONALE: Birth cohort studies have identified several temporal patterns of wheezing, only some of which are associated with asthma. Whether 17q12-21 genetic variants, which are closely associated with asthma, are also associated with childhood wheezing phenotypes remains poorly explored. OBJECTIVES: Our goal was to determine whether wheezing phenotypes, defined by latent class analysis (LCA), are associated with nine 17q12-21 single nucleotide polymorphisms (SNPs) and if so, whether these relationships differ by race/ancestry. METHODS: Data from seven US birth cohorts (n=3786) from the Children's Respiratory Research and Environment Workgroup (CREW) were harmonized to represent whether subjects wheezed in each year of life from birth until age 11 years. LCA was then performed to identify wheeze phenotypes. Genetic associations between SNPs and wheeze phenotypes were assessed separately in European American (EA, n=1308), and for the first time, in African American (AA, n=620) children. RESULTS: The LCA best supported four latent classes of wheeze: Infrequent, Transient, Late-onset, and Persistent. Odds of belonging to any of the three wheezing classes (vs Infrequent) increased with the risk alleles for multiple SNPs in EA children. Only one SNP, rs2305480, showed increased odds of belonging to any wheezing class in both AA and EA children. CONCLUSIONS: These results indicate that 17q12-21 is a "wheezing locus" and this association may reflect an early life susceptibility to respiratory viruses common to all wheezing children. Which children will have their symptoms remit or reoccur during childhood may be independent of the influence of rs2305480.

Public Health Sciences
Li C, **Wang C**, **Zhang Y**, **Alsrouji OK**, **Chebl AB**, **Ding G**, **Jiang Q**, Mayer SA, **Lu M**, **Kole MK**, Marin HL, **Zhang L**, **Chopp M**, and **Zhang ZG**. Cerebral endothelial cell-derived small extracellular vesicles enhance neurovascular function and neurological recovery in rat acute ischemic stroke models of mechanical thrombectomy and embolic stroke treatment with tPA. *J Cereb Blood Flow Metab* 2021; Epub ahead of print. PMID: 33557693. Full Text

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Treatment of patients with cerebral large vessel occlusion with thrombectomy and tissue plasminogen activator (tPA) leads to incomplete reperfusion. Using rat models of embolic and transient middle cerebral artery occlusion (eMCAO and tMCAO), we investigated the effect on stroke outcomes of small extracellular vesicles (sEVs) derived from rat cerebral endothelial cells (CEC-sEVs) in combination with tPA (CEC-sEVs/tPA) as a treatment of eMCAO and tMCAO in rat. The effect of sEVs derived from clots acquired from patients who had undergone mechanical thrombectomy on healthy human CEC permeability was also evaluated. CEC-sEVs/tPA administered 4 h after eMCAO reduced infarct volume by ∼36%, increased recanalization of the occluded MCA, enhanced cerebral blood flow (CBF), and reduced blood-brain barrier (BBB) leakage. Treatment with CEC-sEVs given upon reperfusion after 2 h tMCAO significantly reduced infarct volume by ∼43%, and neurological outcomes were improved in both CEC-sEVs treated models. CEC-sEVs/tPA reduced a network of microRNAs (miRs) and proteins that mediate thrombosis, coagulation, and inflammation. Patient-clot derived sEVs increased CEC permeability, which was reduced by CEC-sEVs. CEC-sEV mediated suppression of a network of pro-thrombotic, -coagulant, and -inflammatory miRs and proteins likely contribute to therapeutic effects. Thus, CEC-sEVs have a therapeutic effect on acute ischemic stroke by reducing neurovascular damage.

Public Health Sciences
Mosella MS, **Sabedot TS**, Silva TC, **Malta TM**, Segato FD, **Asmaro KP**, **Wells M**, **Mukherjee A**, **Poisson LM**, **Snyder J**, **deCarvalho AC**, **Walbert T**, **Aho T**, **Kalkanis S**, Elias PC, Antonini SR, **Rock J**, **Noushmehr H**, Castro M, and **Castro AV**. DNA Methylation-based Signatures Classify Sporadic Pituitary Tumors According to Clinicopathological Features. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33631002. Full Text

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BACKGROUND: Distinct genome-wide methylation patterns cluster pituitary neuroendocrine tumors (PitNETs) into molecular groups associated with specific clinicopathological features. Here we aim to identify, characterize and validate methylation signatures that objectively classify PitNET into clinicopathological groups. METHODS: Combining in-house and publicly available data, we conducted an analysis of the methylome profile of a comprehensive cohort of 177 tumors (Panpit cohort) and 20 nontumor specimens from the pituitary gland. We also retrieved methylome data from an independent PitNET cohort (N=86) to validate our findings. RESULTS: We identified three methylation clusters associated with adenohypophyseal cell lineages and functional status using an unsupervised approach. Differentially methylated CpG probes (DMP) significantly distinguished the Panpit clusters and accurately assigned the samples of the validation cohort to their corresponding lineage and functional subtypes memberships. The DMPs were annotated in regulatory regions enriched of enhancer elements, associated with pathways and genes involved in pituitary cell identity, function, tumorigenesis, invasiveness. Some DMPs correlated with genes with prognostic and therapeutic values in other intra or extracranial tumors. CONCLUSIONS: We identified and validated methylation signatures, mainly annotated in enhancer regions that distinguished PitNETs by distinct adenohypophyseal cell lineages and functional status. These signatures provide the groundwork to develop an unbiased approach to classifying PitNETs according to the most recent classification recommended by the 2017 WHO and to explore their biological and clinical relevance in these tumors.

Public Health Sciences

Nona P, **Coriasso N**, **Khan A**, **Singh G**, **Eng MH**, **Frisoli T**, **O'Neill BP**, **Villablanca PA**, **Lee JC**, **Jacobsen G**, **O'Neill WW**, and **Wang DD**. Pacemaker following transcatheter aortic valve replacement and tricuspid regurgitation: A single-center experience. *J Card Surg* 2021; Epub ahead of print. PMID: 33533038. Full Text

Division of Cardiology, Henry Ford Health System, Henry Ford Hospital, Detroit, Michigan, USA. Department of Public Health Sciences, Henry Ford Health System, Henry Ford Hospital, Detroit, Michigan, USA.

BACKGROUND: As transcatheter aortic valve replacement (TAVR) procedures increase, more data is available on the development of conduction abnormalities requiring permanent pacemaker (PPM) implantation post-TAVR. Mechanistically, new pacemaker implantation and incidence of associated tricuspid regurgitation (TR) post-TAVR is not well understood. Studies have evaluated the predictability of patient anatomy towards risk for needing permanent pacemaker (PPM) post-TAVR; however, little has been reported on new PPM and TR in patients post-TAVR. METHODS: This retrospective study identified patients at our health system who underwent PPM following TAVR from January 2014 to June 2018. Data from both TAVR and PPM procedures as well as patient demographics were collected. Echocardiographic data before TAVR, between TAVR and PPM placement, and the most recent echocardiogram at the time of chart review were analyzed. RESULTS: Of 796 patients who underwent TAVR between January 2014 and June 2018, 89 patients (11%) subsequently required PPM. Out of the 89 patients who required PPM implantation, 82 patients had pre-TAVR and 2-year post-TAVR echocardiographic imaging data. At baseline, 22% (18/82) of patients had at least moderate TR. At 2-year post-TAVR echocardiographic imaging follow-up; 27% (22/82) of patients had at least moderate TR. Subgroup analysis was performed according to the TAVR valve size implanted. In patients who received a TAVR device < 29 mm in diameter in size, 25% (11/44) had worsening TR. In patients who received a TAVR device ≥ 29 mm in diameter, 37% (14/38) had worsening TR. CONCLUSION: We have demonstrated a patient population that may be predisposed to developing worsening TR and right heart function after TAVR and Pacemaker implantation.

Public Health Sciences

Olufade T, **Lamerato L**, Sánchez JJG, Jiang L, Huang J, Nolan S, and Rangaswami J. Clinical Outcomes and Healthcare Resource Utilization in a Real-World Population Reflecting the DAPA-CKD Trial Participants. *Adv Ther* 2021; 38(2):1352-1363. PMID: 33474707. Full Text

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INTRODUCTION: The DAPA-CKD trial assessed dapagliflozin in patients with chronic kidney disease (CKD) with or without type 2 diabetes (T2D). To aid interpretation of results, renal and cardiovascular outcomes plus healthcare resource utilization (HCRU) and costs were assessed in a real-world population similar to that of DAPA-CKD. METHODS: Henry Ford Health System (2006-2016) data were used to identify patients with CKD stages 2-4 [estimated glomerular filtration rate (eGFR) 25-75 ml/min/1.73 m(2) at index and urine albumin-to-creatinine ratio (UACR) 0-5000 mg/g; n = 22,251]. Included patients had confirmatory eGFR ≥ 90 days post-index and no kidney transplant or progression to end-stage kidney disease during 12 months pre-index. The final population (n = 6557) was stratified by UACR (0-29, 30-199 and 200-5000 mg/g; the last comprising the DAPA-CKD-like cohort). Patients were followed for 5 years post-index. RESULTS: Adverse clinical outcomes incidence increased with UACR and was highest for the DAPA-CKD-like cohort (UACR 200-5000 mg/g) versus lower UACR categories (0-29 mg/g and 30-199 mg/g): renal composite outcome (progression to CKD stage 5, dialysis, transplant, ≥ 50% sustained eGFR decline): 26.0% versus 2.2% and 5.8%; heart failure (HF): 36.1% versus 13.9% and 24.6%; myocardial infarction: 11.3% versus 4.7% and 7.4%; stroke: 8.9% versus 4.0% and 5.7%; and mortality: 18.5% versus 6.0% and 11.7%, respectively. Within the DAPA-CKD-like cohort,

patients with versus without T2D or HF had a higher frequency of adverse outcomes. The DAPA-CKD-like cohort also had significantly higher annualized per-patient healthcare costs ($39,222/year versus $19,547/year), hospital admission rate (0.55/year versus 0.20/year) and outpatient specialist visit rate (7.55/year versus 6.74/year) versus the lowest UACR category. CONCLUSION: The significant adverse renal and cardiovascular outcomes observed, particularly in the DAPA-CKD-like cohort, represent a substantial burden resulting in increased mortality, HCRU and costs, demonstrating the need for additional treatment options.

Public Health Sciences
Reiter-Brennan C, Dzaye O, Al-Mallah MH, Dardari Z, **Brawner CA**, **Lamerato LE**, **Keteyian SJ**, **Ehrman JK**, Blaha MJ, Visvanathan K, and Marshall CH. Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. *Cancer* 2021; Epub ahead of print. PMID: 33561293. Full Text

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BACKGROUND: The relation between cardiorespiratory fitness (CRF) and prostate cancer is not well established. The objective of this study was to determine whether CRF is associated with prostate cancer screening, incidence, or mortality. METHODS: The Henry Ford Exercise Testing Project is a retrospective cohort study of men aged 40 to 70 years without cancer who underwent physician-referred exercise stress testing from 1995 to 2009. CRF was quantified in metabolic equivalents of task (METs) (<6 [reference], 6-9, 10-11, and ≥12 METs), estimated from the peak workload achieved during a symptom-limited, maximal exercise stress test. Prostate-specific antigen (PSA) testing, incident prostate cancer, and all-cause mortality were analyzed with multivariable adjusted Poisson regression and Cox proportional hazard models. RESULTS: In total, 22,827 men were included, of whom 739 developed prostate cancer, with a median follow-up of 7.5 years. Men who had high fitness (≥12 METs) had an 28% higher risk of PSA screening (95% CI, 1.2-1.3) compared with those who had low fitness (<6 METs. After adjusting for PSA screening, fitness was associated with higher prostate cancer incidence (men aged <55 years, P = .02; men aged >55 years, P ≤ .01), but not with advanced prostate cancer. Among the men who were diagnosed with prostate cancer, high fitness was associated with a 60% lower risk of all-cause mortality (95% CI, 0.2-0.9). CONCLUSIONS: Although men with high fitness are more likely to undergo PSA screening, this does not fully account for the increased incidence of prostate cancer seen among these individuals. However, men with high fitness have a lower risk of death after a prostate cancer diagnosis, suggesting that the cancers identified may be low-risk with little impact on long-term outcomes.

Public Health Sciences
Sabedot T, **Malta T**, **Snyder J**, **Nelson K**, **Wells M**, **deCarvalho A**, **Mukherjee A**, **Chitale D**, **Mosella M**, Sokolov A, **Asmaro K**, **Robin A**, **Rosenblum M**, **Mikkelsen T**, **Rock J**, **Poisson L**, **Lee I**, **Walbert T**, **Kalkanis S**, Iavarone A, **Castro AV**, and **Noushmehr H**. A serum-based DNA methylation assay provides accurate detection of glioma. *Neuro Oncol* 2021; Epub ahead of print. PMID: 33560371. Full Text

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BACKGROUND: The detection of somatic mutations in cell-free DNA (cfDNA) from liquid biopsy has emerged as a non-invasive tool to monitor the follow-up of cancer patients. However, the significance of cfDNA clinical utility remains uncertain in patients with brain tumors, primarily because of the limited sensitivity cfDNA has to detect real tumor-specific somatic mutations. This unresolved challenge has prevented accurate follow-up of glioma patients with non-invasive approaches. METHODS: Genome-wide DNA methylation profiling of tumor tissue and serum cell-free DNA of glioma patients. RESULTS: Here, we developed a non-invasive approach to profile the DNA methylation status in the serum of patients with gliomas and identified a cfDNA-derived methylation signature that is associated with the presence of gliomas and related immune features. By testing the signature in an independent discovery and validation cohorts, we developed and verified a score metric (the "glioma epigenetic liquid biopsy score" or GeLB) that optimally distinguished patients with or without glioma (sensitivity: 100%, specificity: 97.78%). Furthermore, we found that changes in GeLB score reflected clinicopathological changes during surveillance (e.g., progression, pseudoprogression or response to standard or experimental treatment). CONCLUSIONS: Our results suggest that the GeLB score can be used as a complementary approach to diagnose and follow up patients with glioma.

Public Health Sciences
Sadat B, Tirunagari D, **Karthikeyan V**, **Patel A**, **Van Harn M**, **Saleem MM**, and **Ananthasubramaniam K**. Clinical impact of pre-kidney transplant pulmonary hypertension on post-transplant outcomes. *Int J Cardiovasc Imaging* 2021; Epub ahead of print. PMID: 33616784. Full Text

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Outcomes of kidney transplant (KT) patients with pre-transplant pulmonary hypertension (PH) are poorly understood. PH patients are often considered high risk and excluded from KT. We investigated the association of pre-transplant PH with KT recipient's outcomes. A single-center, retrospective study that reviewed all patients transplanted from 2010 to 2016, who had a transthoracic echocardiogram (TTE) before KT and at least one TTE post-KT. The TTE closest to the KT was used for analyses. PH is defined as pulmonary artery systolic pressure (PASP) ≥ 40 mm Hg. Of 204 patients, 61 had PASP ≥ 40 mm Hg (with PH) and 143 had PASP < 40 mm Hg (without PH) prior to KT. No statistically significant differences existed between the two groups in baseline demographics, renal failure etiologies, dialysis access type, and cardiovascular risk factors. The mean difference in pre-KT PASP was 18.1 ± 7 mm Hg (P < 0.001). Patients with PH had a statistically significant decrease in PASP post-KT compared to the patients without PH with a mean change of -7.03 ± 12.28 mm Hg vs. + 3.96 ± 11.98 mm Hg (p < 0.001), respectively. Moderate mitral and moderate-severe tricuspid regurgitation were the only factors found to be independently associated with PH (p = 0.001) on multivariable analysis. No statistically significant difference was notable in patient survival, graft function, and creatinine post-KT in both groups. PH pre-KT particularly mild-moderate PH did not adversely affect intermediate (90-day) and long-term allograft and patient survival. Patients with mild-moderate PH should not be excluded from KT.

Public Health Sciences
Spradling PR, Zhong Y, Moorman AC, **Rupp LB**, **Lu M**, Teshale EH, Schmidt MA, Daida YG, Boscarino JA, and **Gordon SC**. The persistence of underreporting of hepatitis C as an underlying or contributing cause of death, 2011-2017. *Clin Infect Dis* 2021; Epub ahead of print. PMID: 33561187. Full Text

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Using electronic health records, we found that hepatitis C reporting on death certificates of 2,901 HCV-infected decedents from four U.S. healthcare organizations during 2011-2017 was documented in only 50% of decedents with hepatocellular carcinoma and less than half with decompensated cirrhosis. National figures likely underestimate the U.S. HCV mortality burden.

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Section of Inflammation, Repair and Development, National Heart and Lung Institute, Imperial College London, London, United Kingdom.
The ORIGINS Project, Telethon Kids Institute, Perth Childrens Hospital, University of Western Australia, Crawley, WA, Australia.
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Introduction: The functional role of milk for the developing neonate is an area of great interest, and a significant amount of research has been done. However, a lot of work remains to fully understand the complexities of milk, and the variations imposed through genetics. It has previously been shown that both secretor (Se) and Lewis blood type (Le) status impacts the human milk oligosaccharide (HMO) content of human milk. While some studies have compared the non-HMO milk metabolome of Se+ and Se- women, none have reported on the non-HMO milk metabolome of Se- and Le- mothers. Method and Results: To determine the differences in the non-HMO milk metabolome between Se-Le- mothers and other HMO phenotypes (Se+Le+, Se+Le-, and Se-Le+), 10 milk samples from 10 lactating mothers were analyzed using nuclear magnetic resonance (NMR) spectroscopy. Se or Le HMO phenotypes were assigned based on the presence and absence of 6 HMOs generated by the Se and Le genes. After classification, 58 milk metabolites were compared among the HMO phenotypes. Principal component analysis (PCA) identified clear separation between Se-Le- milk and the other milks. Fold change analysis demonstrated that the Se-Le- milk had major differences in free fatty acids, free amino acids, and metabolites related to energy metabolism. Conclusion: The results of this brief research report suggest that the milk metabolome of mothers with the Se-Le- phenotype differs in its non-HMO metabolite composition from mothers with other HMO phenotypes.

Public Health Sciences
Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Division of Cardiovascular Disease, Center for Structural Heart, Henry Ford Hospital, Detroit, Michigan, USA (Wang, O'Neill); Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA (Zervos, McKinnon, Alangaden, Suleyman); Family Medicine, Henry Ford Hospital, Detroit, Michigan, USA (Allard); Public Health Sciences, Henry Ford Hospital, Detroit, Michigan, USA (Schultz, Poisson); Office of Clinical Quality and Safety, Henry Ford Health System, Detroit, Michigan, USA (Chu); Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA (Kalkanis).

OBJECTIVE: Examine the effect of a universal facemask policy for healthcare workers(HCW) and incidence of SARS-CoV-2 positivity. METHODS: Daily number of symptomatic HCW tested, SARS-CoV-2 positivity rates, and HCW job-descriptions were collected pre and post Universal HCW facemask policy(March 26). Multiple change point regression was used to model positive-test-rate data. SARS-CoV-2 testing and positivity rates were compared for pre-intervention, transition, post-intervention, and follow-up periods. RESULTS: Between March 12-August 10, 2020, 19.2% of HCW were symptomatic for COVID-19 and underwent SARS-CoV-2 testing. A single change point was identified ~March 28-30(95% probability). Before the change point, the odds of a tested HCW having a positive result doubled every 4.5-7.5 days. Post-change-point, the odds of a tested HCW having a positive result halved every 10.5-13.5 days. CONCLUSIONS: Universal facemasks was associated with reducing HCW's risk of acquiring COVID-19.

Public Health Sciences
Wegienka G, Stewart EA, Nicholson WK, Zhang S, Li F, Thomas L, Spies JB, Venable S, Laughlin-Tommaso S, Diamond MP, Anchan RM, Maxwell GL, Marsh EE, Myers ER, Vines AI, Wise LA, Wallace K, and Jacoby VL. Black Women Are More Likely Than White Women to Schedule a Uterine-Sparing Treatment for Leiomyomas. *J Womens Health (Larchmt)* 2021; Epub ahead of print. PMID: 33524308. Full Text

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Background: To evaluate differences in the proportion of uterine fibroid (UF) treatments that are uterine-sparing between Black women and White women and identify factors that could explain disparities. Methods: Women at age 18-54 years who were enrolled from 10 clinical sites in the United States into the Comparing Options for Management: Patient-Centered Results for UFs (COMPARE-UF) treatment registry completed questionnaires before their UF procedure. UF symptoms and quality of life were assessed by questionnaires. Details on UF imaging and treatment (hysterectomy, myomectomy, or uterine artery embolization [UAE]) were collected from each patient's medical record. Random-effects logistic regression was used to assess the association between race and the odds of having a uterine-sparing procedure versus hysterectomy. Subgroup analyses compared each uterine-sparing procedure with hysterectomy. Results: In this cohort of 1141 White women and 1196 Black women, Black women tended to be younger (median 41.0 vs. 42.0 years) and report worse symptoms, pain, and function on every scale compared with White women. Black women were more likely to have had a prior UF treatment compared with White women (22.8% vs. 14.6%). White women had more hysterectomies (43.6% vs. 32.2%) and myomectomies (50.9% vs. 50.2%) versus Black women. Black women had more UAEs (15.1% vs. 4.7%) than White women. After adjusting for clinical site and other variables, Black women had greater odds than White women of having a myomectomy (odds ratio [OR] = 2.41, 95% confidence interval [CI] = 1.63-3.56) or a UAE versus hysterectomy (OR = 4.24, 95% CI = 2.41-7.46). Conclusion: In these participants, Black women were more likely to schedule a uterine-sparing UF treatment and a nonsurgical UF treatment than their White counterparts; this may not be true for all women. Longer comparative effectiveness studies are needed to inform women about the durability of UF treatments. Greater understanding of factors influencing treatment selection is needed as are studies that include women without access to tertiary care centers. Clinical Trial Registration: Clinicaltrials.gov, NCT02260752 (enrollment start: November 2015).

Pulmonary and Critical Care Medicine
Chamogeorgakis T, **Moquin K**, **Simoff M**, and **Nemeh H**. Repair of Bronchial Anastomosis Following Lung Transplantation. *Thorac Cardiovasc Surg* 2021; Epub ahead of print. PMID: 33580492. [Request Article]

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BACKGROUND: Bronchial anastomotic complications are reported in 2 to 18% of patients after lung transplantation. The majority of complications can be managed with bronchoscopic intervention. When extensive dehiscence is present, surgical intervention can be entertained. MATERIALS AND METHODS: Between March 1, 2006, and December 31, 2019, our program performed 244 lung transplantations. We conducted a retrospective review of our patient cohort and identified patients who suffered from significant anastomotic complications that required surgical interventions. RESULTS: Twenty-eight and 216 patients underwent single and bilateral lung transplantations, respectively. Eighteen patients developed airway complications (7.4%). The incidence of anastomotic complications was 5.2% (24 complications for a total of 460 bronchial anastomoses). Four patients were managed conservatively. The majority of the bronchial anastomotic complications were managed endoscopically (eight patients). Four patients with associated massive air leak underwent repair of the bronchial anastomosis and two patients were retransplanted because they developed severe distal airway stenosis. CONCLUSION: Bronchial anastomotic complications are a major cause of morbidity in lung transplantation. The majority of cases can be managed bronchoscopically. In more severe cases associated with massive air leak or imminent massive hemoptysis from bronchopulmonary arterial fistula, surgical intervention is necessary. Aortic homograft interposition along with vascularized pedicle wrapping may be a viable option to re-establish airway continuity when tension-free bronchial anastomotic revision is not possible. In cases with smaller

bronchial defects, primary repair with utilization of a vascularized flap can be effective as treatment option.

Pulmonary and Critical Care Medicine
Reaume M, **Noor Ul Husnain SM**, **Kapadia D**, and **Tatem G**. Recommended Reading from the Henry Ford Hospital Pulmonary and Critical Care Medicine Fellowship Program. *Am J Respir Crit Care Med* 2021; Epub ahead of print. PMID: 33631088. Full Text

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Radiation Oncology
Karim S, Benn R, Carlson LE, Fouladbakhsh J, Greenlee H, Harris R, Henry NL, Jolly S, Mayhew S, Spratke L, **Walker EM**, Zebrack B, and Zick SM. Integrative Oncology Education: An Emerging Competency for Oncology Providers. *Curr Oncol* 2021; 28(1):853-862. PMID: 33578660. Full Text

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A growing number of cancer patients use complementary and alternative therapies during and after conventional cancer treatment. Patients are often reluctant to discuss these therapies with their oncologist, and oncologists may have limited knowledge and confidence on how to advise patients on the appropriate use. Integrative oncology is a patient-centered, evidence-informed field that utilizes mind-body practices, lifestyle modifications and/or natural products interwoven with conventional cancer treatment. It prioritizes safety and best available evidence to offer appropriate interventions alongside conventional care. There are few opportunities for oncologists to learn about integrative oncology. In this commentary, we highlight the Integrative Oncology Scholars (IOS) program as a means to increase competency in this growing field. We provide an overview of several integrative oncology modalities that are taught through this program, including lifestyle modifications, physical activity, and mind-body interventions. We conclude that as more evidence is generated in this field, it will be essential that oncology healthcare providers are aware of the prevalent use of these modalities by their patients and cancer centers include Integrative Oncology trained physicians and other healthcare professionals in their team to discuss and recommend evidence-based integrative oncology therapies alongside conventional cancer treatments to their patients.

Radiation Oncology
Liu HY, Tam L, Woody NM, Caudell J, Reddy CA, **Ghanem A**, **Schymick M**, Joshi N, Geiger J, Lamarre E, Burkey B, Adelstein D, Dunlap N, **Siddiqui F**, Koyfman S, and Porceddu SV. Failure rate in the untreated contralateral node negative neck of small lateralized oral cavity cancers: A multi-institutional collaborative study. *Oral Oncol* 2021; 115:105190. PMID: 33581503. Full Text

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OBJECTIVES: The importance of treating the bilateral neck in lateralized small oral cavity squamous cell carcinoma (OCC) is unclear. We sought to define the incidence and predictors of contralateral neck failure (CLF) in patients who underwent unilateral treatment. MATERIALS AND METHODS: We performed a multi-institutional retrospective study of patients with pathologic T1-T2 (AJCC 7th edition) OCC with clinically node negative contralateral neck who underwent unilateral treatment with primary surgical resection ± adjuvant radiotherapy between 2005 and 2015. Incidence of CLF was estimated using the cumulative incidence method. Clinicopathological factors were analyzed by univariate (UVA) and multivariate analysis (MVA) for possible association with CLF. Kaplan-Meier analysis was used to estimate overall survival (OS). RESULTS: 176 patients were evaluated with a median of 65.9 months of follow-up. Predominant pathologic T-stage was T1 (68%), 8.5% of patients were N1, 2.8% were N2b. Adjuvant radiotherapy was delivered to 17% of patients. 5-year incidence of CLF was 4.3% (95% CI 1.2-7.4%). Depth of invasion (DOI) > 10 mm and positive ipsilateral neck node were significant predictors for CLF on UVA. DOI > 10 mm remained significant on MVA (HR = 6.7, 95% CI 1.4-32.3, p = 0.02). The 2- and 5-year OS was 90.6% (95% CI 86.2-95.0%) and 80.6% (95% CI 74.5-86.8%), respectively. CONCLUSION: Observation of the clinically node negative contralateral neck in small lateralized OCC can be a suitable management approach in well selected patients, however caution should be applied when DOI upstages small but deeply invasive tumors to T3 on 8th edition AJCC staging.

Research Administration
Jiagge EM, Ulintz PJ, Wong S, McDermott SP, **Fossi SI**, Suhan TK, Hoenerhoff MJ, **Bensenhaver JM**, Salem B, Dziubinski M, Oppong JK, Aitpillah F, Ishmael K, Osei-Bonsu E, Adjei E, Baffour A, Aldrich J, Kurdoglu A, **Fernando K**, Craig DW, Trent JM, Li J, **Chitale D**, Newman LA, Carpten JD, Wicha MS, and Merajver SD. Multiethnic PDX models predict a possible immune signature associated with TNBC of African ancestry. *Breast Cancer Res Treat* 2021; Epub ahead of print. PMID: 33576900. Full Text

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PURPOSE: Triple-negative breast cancer (TNBC) is an aggressive subtype most prevalent among women of Western Sub-Saharan African ancestry. It accounts for 15-25% of African American (AA) breast cancers (BC) and up to 80% of Ghanaian breast cancers, thus contributing to outcome disparities in BC for black women. The aggressive biology of TNBC has been shown to be regulated partially by breast cancer stem cells (BCSC) which mediate tumor recurrence and metastasis and are more abundant in African breast tumors. METHODS: We studied the biological differences between TNBC in women with African ancestry and those of Caucasian women by comparing the gene expression of the BCSC. From low-passage patient derived xenografts (PDX) from Ghanaian (GH), AA, and Caucasian American (CA) TNBCs, we sorted for and sequenced the stem cell populations and analyzed for differential gene enrichment. RESULTS: In our cohort of TNBC tumors, we observed that the ALDH expressing stem cells display distinct ethnic specific gene expression patterns, with the largest difference existing between the GH and AA ALDH+ cells. Furthermore, the tumors from the women of African ancestry [GH/AA] had ALDH stem cell (SC) enrichment for expression of immune related genes and processes. Among the significantly upregulated genes were CD274 (PD-L1), CXCR9, CXCR10 and IFI27, which could serve as potential drug targets. CONCLUSIONS: Further exploration of the role of immune regulated genes and biological processes in BCSC may offer insight into developing novel approaches to treating TNBC to help ameliorate survival disparities in women with African ancestry.

Research Administration
Salmanpour MR, Shamsaei M, Saberi A, Hajianfar G, **Soltanian-Zadeh H**, and Rahmim A. Robust identification of Parkinson's disease subtypes using radiomics and hybrid machine learning. *Comput Biol Med* 2021; 129:104142. PMID: 33260101. Full Text

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OBJECTIVES: It is important to subdivide Parkinson's disease (PD) into subtypes, enabling potentially earlier disease recognition and tailored treatment strategies. We aimed to identify reproducible PD subtypes robust to variations in the number of patients and features. METHODS: We applied multiple feature-reduction and cluster-analysis methods to cross-sectional and timeless data, extracted from longitudinal datasets (years 0, 1, 2 & 4; Parkinson's Progressive Marker Initiative; 885 PD/163 healthy-control visits; 35 datasets with combinations of non-imaging, conventional-imaging, and radiomics features from DAT-SPECT images). Hybrid machine-learning systems were constructed invoking 16

feature-reduction algorithms, 8 clustering algorithms, and 16 classifiers (C-index clustering evaluation used on each trajectory). We subsequently performed: i) identification of optimal subtypes, ii) multiple independent tests to assess reproducibility, iii) further confirmation by a statistical approach, iv) test of reproducibility to the size of the samples. RESULTS: When using no radiomics features, the clusters were not robust to variations in features, whereas, utilizing radiomics information enabled consistent generation of clusters through ensemble analysis of trajectories. We arrived at 3 distinct subtypes, confirmed using the training and testing process of k-means, as well as Hotelling's T2 test. The 3 identified PD subtypes were 1) mild; 2) intermediate; and 3) severe, especially in terms of dopaminergic deficit (imaging), with some escalating motor and non-motor manifestations. CONCLUSION: Appropriate hybrid systems and independent statistical tests enable robust identification of 3 distinct PD subtypes. This was assisted by utilizing radiomics features from SPECT images (segmented using MRI). The PD subtypes provided were robust to the number of the subjects, and features.

Rheumatology
Sheikh SZ, Scheinberg MA, Wei JCC, Tegzova D, Stohl W, de Toledo RA, Mucenic T, Banfi MRA, **Maksimowicz-McKinnon K**, Abud-Mendoza C, Navarra S, Garcia M, Garcia-De La Torre I, Ros JO, Levy RA, Bass DL, Terrés JR, Punwaney R, Harris J, Nami A, Pierce A, Thorneloe KS, Ji B, and Roth DA. Mortality and adverse events of special interest with intravenous belimumab for adults with active, autoantibody-positive systemic lupus erythematosus (BASE): a multicentre, double-blind, randomised, placebo-controlled, phase 4 trial. *Lancet Rheumatol* 2021; 3(2):e122-e130. PMID: Not assigned. Request Article

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Background: Belimumab is approved for the treatment of active systemic lupus erythematosus (SLE). Although clinical trials showed a favourable benefit–risk profile, numerical differences in the incidence of mortality and adverse events of special interest (AESIs) have been reported. We assessed the frequency of these events in patients with SLE receiving belimumab or placebo plus standard therapy. Methods: BASE was a double-blind, randomised, placebo-controlled, phase 4 trial done in 33 countries. Adults with active SLE were randomly assigned (1:1) to receive intravenous belimumab (10 mg/kg) or placebo, plus standard therapy, for 48 weeks. The primary endpoints were incidences of all-cause mortality and AESIs during the on-treatment period (first-to-last study drug dose + 28 days). Safety analyses were done in the as-treated population (patients grouped by actual treatment received >50% of the time). This study was registered with ClinicalTrials.gov (NCT01705977). Findings: Between Nov 27, 2012, and July 28, 2017, we randomly assigned 4018 patients. The as-treated population included 2002 patients in the belimumab group versus 2001 in the placebo group. Ten (0·50%) patients in the belimumab group died versus eight (0·40%) in the placebo group (difference 0·10%, 95% CI −0·31 to 0·51). Incidences were similar in the belimumab and placebo groups for serious infections (75 [3·75%] of 2002 vs 82 [4·10%] of 2001; difference −0·35%, 95% CI −1·55 to 0·85), opportunistic infections and other infections of interest (36 [1·80%] vs 50 [2·50%]; −0·70%, −1·60 to 0·20), non-melanoma skin cancers (4 [0·20%] vs 3 [0·15%]; 0·05%, −0·21 to 0·31) and other malignancies (5 [0·25%] vs 5 [0·25%]; 0·00%, −0·31 to 0·31). A higher proportion of patients in the belimumab group than in the placebo group had infusion and hypersensitivity reactions (8 [0·40%] vs 2 [0·10%]; 0·30%, −0·01 to 0·61), serious depression (7 [0·35%] vs 1 [0·05%]; 0·30%, 0·02 to 0·58), treatment-emergent suicidality (28 [1·42%] of 1972 patients vs 23 [1·16%] of 1986; 0·26%, −0·44 to 0·96), and sponsor-adjudicated serious suicide or self-injury (15 [0·75%] of 1972 patients vs 5 [0·25%] of 1986; post hoc difference 0·50%, 0·06 to 0·94). Interpretation: In line with previously published data, incidences of all-cause mortality and AESIs were similar in patients given belimumab and placebo, except for serious infusion or hypersensitivity reactions, serious depression, treatment-emergent suicidality, and sponsor-adjudicated serious suicide or self-injury events. Funding: GSK.

Sleep Medicine
Roehrs T, **Sibai M**, and **Roth T**. Sleep and alertness disturbance and substance use disorders: A bi-directional relation. *Pharmacol Biochem Behav* 2021; 203:173153. PMID: 33582097. [Request Article](#)

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The majority of the literature describing the relation of sleep/alertness disturbance and substance use disorders (SUD) has focused on the disruptive effects of substances with abuse liability on sleep and alertness. Rarely have studies or literature reviews assessed or discussed how sleep/alertness disturbance affects substance use. This paper focuses on the sleep/alertness disturbance side of the relation. We argue that the relation is bi-directional and review evidence showing that sleep/alertness disturbance affects all phases of the addiction cycle, including the initiation, maintenance and relapse of SUD. We review a variety of substances across all phases of the addiction cycle and conclude sleep/alertness disturbance is a critical factor in both understanding and treating SUD.

Sleep Medicine
Singh M, Bird SP, Charest J, Huyghe T, and Calleja-Gonzalez J. From the NBA to the NHL: a parallel problem exists. *J Clin Sleep Med* 2021; Epub ahead of print. PMID: 33538689. [Full Text](#)

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Sleep Medicine
Zamani E, Akbari M, Mohammadkhani S, Riskind JH, **Drake CL**, and Palagini L. The Relationship of Neuroticism with Sleep Quality: The Mediating Role of Emotional, Cognitive and Metacognitive Factors. *Behav Sleep Med* 2021; Epub ahead of print.:1-16. PMID: 33618569. [Request Article](#)

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Background: Poor sleep quality is associated with a broad range of psychopathology and is a common problem among college students. This study aimed to investigate the mediating role of metacognitive beliefs related to sleep, emotion regulation and a negative cognitive style related to anxiety (looming cognitive style) in the relation between neuroticism and reported sleep quality. Participants: Participants were 343 undergraduates from three universities in Tehran (56.3% females, Mean age = 22.01 ± 2.74 years). Method: Data were gathered with a questionnaire packet that included the Pittsburgh Sleep Quality Index (PSQI), Metacognitions Questionnaire-Insomnia (MCQ-I), Emotion Regulation Questionnaire (ERQ), Looming Maladaptive Style Questionnaire (LMSQ) and Neuroticism subscale of NEO-PI-R. Results: Structural equation modeling analyses supported a proposed model (R(2) = 37%) which proposed that neuroticism both directly and indirectly linked to reported sleep quality

through metacognitions related to sleep, cognitive reappraisal and looming cognitive style ($\chi2 = 1194.87$, $p < .001$; CFI = 0.93, NFI = 0.90, RMSEA = 0.065, GFI = 0.92, SRMR = 0.069, IFI = 0.93). Conclusions: The results provide evidence for the impact of neuroticism on reported sleep quality through metacognitive, cognitive and emotional factors. The result suggest that special attention should be paid to these factors in the treatment and psychopathology of sleep quality.

Surgery
Chamogeorgakis T, **Moquin K**, **Simoff M**, and **Nemeh H**. Repair of Bronchial Anastomosis Following Lung Transplantation. *Thorac Cardiovasc Surg* 2021; Epub ahead of print. PMID: 33580492. [Request Article](#)

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BACKGROUND: Bronchial anastomotic complications are reported in 2 to 18% of patients after lung transplantation. The majority of complications can be managed with bronchoscopic intervention. When extensive dehiscence is present, surgical intervention can be entertained. MATERIALS AND METHODS: Between March 1, 2006, and December 31, 2019, our program performed 244 lung transplantations. We conducted a retrospective review of our patient cohort and identified patients who suffered from significant anastomotic complications that required surgical interventions. RESULTS: Twenty-eight and 216 patients underwent single and bilateral lung transplantations, respectively. Eighteen patients developed airway complications (7.4%). The incidence of anastomotic complications was 5.2% (24 complications for a total of 460 bronchial anastomoses). Four patients were managed conservatively. The majority of the bronchial anastomotic complications were managed endoscopically (eight patients). Four patients with associated massive air leak underwent repair of the bronchial anastomosis and two patients were retransplanted because they developed severe distal airway stenosis. CONCLUSION: Bronchial anastomotic complications are a major cause of morbidity in lung transplantation. The majority of cases can be managed bronchoscopically. In more severe cases associated with massive air leak or imminent massive hemoptysis from bronchopulmonary arterial fistula, surgical intervention is necessary. Aortic homograft interposition along with vascularized pedicle wrapping may be a viable option to re-establish airway continuity when tension-free bronchial anastomotic revision is not possible. In cases with smaller bronchial defects, primary repair with utilization of a vascularized flap can be effective as treatment option.

Surgery
Kandagatla P, **Ghandour AH**, **Amro A**, **Popoff A**, and **Hammoud Z**. Long-term outcomes after robotic-assisted Ivor Lewis esophagectomy. *J Robot Surg* 2021; Epub ahead of print. PMID: 33638759. [Full Text](#)

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Robotic assistance has gained acceptance in thoracic procedures, including esophagectomy. There is a paucity of data regarding long-term outcomes for robotic esophagectomy. We previously reported our initial series of robot-assisted Ivor Lewis (RAIL) esophagectomy. We report long-term outcomes to assess the efficacy of the procedure. We performed a retrospective review of 112 consecutive patients who underwent a RAIL. Patient demographics, diagnosis, pathology, operative characteristics, post-operative complications, and long-term outcomes were documented. Descriptive statistical analysis was performed for all the variables. Primary endpoints were mortality and disease-free survival. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method. Of the 112 patients, 106 had a diagnosis of cancer, with adenocarcinoma the dominant histology (87.5%). Of these 106 patients, 81

(76.4%) received neo-adjuvant chemoradiation. The 30-, 60-, and 90-day mortality was 1 (0.9%), 3 (2.7%), and 4 (3.6%), respectively. There were 9 anastomotic leaks (8%) and 18 (16.1%) patients had a stricture requiring dilation. All-patient OS at 1, 3, and 5 years was 81.4%, 60.5%, and 51.0%, respectively. For cancer patients, the 1-, 3-, and 5-year OS was 81.3%, 59.2%, and 49.4%, respectively, and the DFS was 75.3%, 42.3%, and 44.0%. We have shown that long-term outcomes after RAIL esophagectomy are similar to other non-robotic esophagectomies. Given the potential advantages of robotic assistance, our results are crucial to demonstrate that RAIL does not result in inferior outcomes.

Surgery
Macki M, **Pawloski J**, **Fadel H**, **Hamilton T**, **Haider S**, **Elmenini J**, **Fakih M**, **Johnson JL**, and **Rock J**. The Effect of Antithrombotics on Hematoma Expansion in Small- to Moderate-Sized Traumatic Intraparenchymal Hemorrhages. *World Neurosurg* 2021; Epub ahead of print. PMID: 33640526. <u>Full Text</u>

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BACKGROUND: Although pre-injury antithrombotic agents, including antiplatelets and anticoagulants, are historically associated with expansion of traumatic intraparenchymal hemorrhage (tIPH), the literature has poorly elucidated the actual risk of hematoma expansion on repeat computed tomography (CT). The objective is to determine the effect of antithrombotic agents on hematoma expansion in tIPH by comparing patients with and without pre-injury antithrombotic medication. METHODS: The volume of all tIPHs over a 5-year period at an academic Level 1 Trauma Center was measured retrospectively. The initial tIPH was divided into three equally-sized quantiles. The third tertile, representing the largest subset of tIPH, was then removed from the study population because these patients reflect a different pathophysiological mechanism that may require a more acute and aggressive level of care with reversal agents and/or operative management. Per institutional policy, all patients with small- to moderate-sized hemorrhages received a 24-hour stability CT scan. Patients who received reversal agents were excluded. RESULTS: Of the 105 patients with a tIPH on the initial head CT scan, small- to moderate-size hemorrhages were <5 cm(3). The size of tIPH on initial imaging did not statistically significantly differ between the antithrombotic cohort (0.7±0.1 cm(3)) and the non-antithrombotic cohort (0.5±0.1 cm(3)) (P=0.091). Similarly, the volume of tIPH failed to differ on 24-hour repeat imaging (1.0±0.2 cm(3) vs. 0.6±0.1 cm(3), respectively, P=0.172). Following a multiple linear regression, only history of stroke, not antithrombotic medications, predicted increased tIPH on 24-hour repeat imaging. CONCLUSION: In small- to moderate-sized tIPH, withholding antithrombotic agents without reversal may be sufficient.

Surgery
Martens K, **Hamann A**, **Miller-Matero LR**, **Miller C**, Bonham AJ, Ghaferi AA, and **Carlin AM**. Relationship between depression, weight, and patient satisfaction 2 years after bariatric surgery. *Surg Obes Relat Dis* 2021; 17(2):366-371. PMID: 33127323. <u>Full Text</u>

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BACKGROUND: Findings regarding longer term symptoms of depression and the impact of depression on outcomes such as weight loss and patient satisfaction, are mixed or lacking. OBJECTIVES: This study sought to understand the relationship between depression, weight loss, and patient satisfaction in the two years after bariatric surgery. SETTING: This study used data from a multi-institutional, statewide quality

improvement collaborative of 45 different bariatric surgery sites. METHODS: Participants included patients (N = 1991) who underwent Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2015-2018. Participants self-reported symptoms of depression (Patient Health Questionnaire-8 [PHQ-8]), satisfaction with surgery, and weight presurgery and 1 year and 2 years postsurgery. RESULTS: Compared to presurgery, fewer patients' PHQ-8 scores indicated clinically significant depression (PHQ-8≥10) at 1 year (P < .001; 14.3% versus 5.1%) and 2 years postsurgery (P < .0001; 8.7%). There was a significant increase in the prevalence of clinical depression from the first to second year postsurgery (P < .0001; 5.1% versus 8.7%). Higher PHQ-8 at baseline was related to less weight loss (%Total Weight Loss [%TWL] and %Excess Weight Loss [%EWL]) at 1 year postsurgery (P < .001), with a trend toward statistical significance at 2 years (P = .06). Postoperative depression was related to lower %TWL and %EWL, and less reduction in body mass index (BMI) at 1 year (P < .001) and 2 years (P < .0001). Baseline and postoperative depression were associated with lower patient satisfaction at both postoperative time points. CONCLUSIONS: This study suggests improvements in depression up to 2 years postbariatric surgery, although it appears that the prevalence of depression increases after the first year. Depression, both pre- and postbariatric surgery, may impact weight loss and patient satisfaction.

Surgery
Miller-Matero LR, **Hecht L**, **Patel S**, **Martens KM**, **Hamann A**, and **Carlin AM**. The Influence of Health Literacy and Health Numeracy on Weight Loss Outcomes Following Bariatric Surgery. *Surg Obes Relat Dis* 2021; 17(2):384-389. PMID: 33082073. Full Text

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BACKGROUND: Although cognitive functioning and health literacy are related to weight loss 1year following bariatric surgery, the influence of health numeracy (i.e., health-related mathematical abilities) is unknown. In addition, further research is needed to examine the impact of all these factors on longer-term weight loss outcomes to determine if they influence the ability to maintain weight loss. SETTING: Single bariatric center. METHODS: Patients (N = 567) who underwent bariatric surgery from 2014-2017 completed a brief survey including current weight. Retrospective chart reviews were conducted to gather information from the presurgical evaluation including weight, body mass index (BMI), health literacy, health numeracy and score on a cognitive screener. RESULTS: Among participants in the weight loss period (< 2 years postsurgery), health literacy, health numeracy and cognitive functioning were not related to change in BMI (ΔBMI), percent total weight loss (%TWL) or percent excess weight loss (%EWL). However, for participants in the weight maintenance period (2-4 years postsurgery), higher health literacy scores were related to greater change in ΔBMI, and higher health numeracy scores were related to greater ΔBMI, %TWL, and %EWL. DISCUSSION: Although health literacy and health numeracy did not predict weight loss outcomes for those in the initial weight loss period, they were related to weight outcomes for participants in the weight maintenance period. This suggests that health literacy and health numeracy may play a role in facilitating longer-term weight maintenance among patients who undergo bariatric surgery. Clinicians conducting presurgical psychosocial evaluations should consider routinely screening for health literacy and health numeracy.

Surgery
Rizzari MD, **Safwan M**, **Sobolic M**, **Kitajima T**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. The Impact of Portal Vein Thrombosis on Liver Transplant Outcomes: Does Grade or Flow Rate Matter? *Transplantation* 2021; 105(2):363-371. PMID: 32217946. Full Text

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BACKGROUND: Portal vein thrombosis (PVT) makes the technical aspect of liver transplantation challenging and also affects outcomes. Our aim was to study impact of PVT grade and postreperfusion portal flow on posttransplant outcomes. METHODS: Patients who underwent transplantation with PVT between January 2007 and May 2017 were selected (n = 126). Data on grade of PVT and portal vein flow were collected. Patients were classified into 2 groups; low grade (Yerdel Grade I, n = 73) and high grade (Yerdel Grade II or III, n = 53). Using portal flow rate, patients were divided into high flow (≥1000 mL/min, n = 95) and low flow (<1000 mL/min, n = 31). Additional analyses of flow by graft weight and complications were performed. RESULTS: Postoperatively, incidence of biliary strictures were significantly greater in high-grade PVT compared with low grade (P = 0.02). Incidence of postoperative portal vein thrombosis was higher in low flow after reperfusion compared with high flow (P = 0.02), as was bile leak (P = 0.02). On identifying factors associated with graft loss, moderate to severe ascites preoperatively, high PVT grade and bile leak were associated with worse graft survival. Subanalysis performed combining grade and flow showed that low grade, high flow had the highest graft survival while high grade, low flow had the lowest (P = 0.006). High-grade PVT with low flow also appeared to be an independent risk factor for biliary complications (P = 0.01). CONCLUSIONS: In conclusion, biliary complications, especially strictures are more common in high-grade PVT and graft survival is worse in high-grade PVT and low portal flow.

Surgery

Shah R, and **Hammoud Z**. Comments on: Lower Incidence of Postoperative Pulmonary Complications Following Robot-Assisted Minimally Invasive Esophagectomy for Esophageal Cancer: Propensity Score-Matched Comparison to Conventional Minimally Invasive Esophagectomy. *Ann Surg Oncol* 2021; 28(2):594-595. PMID: 32996019. Full Text

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Undergraduate Medical Education

Koolmees D, Ramkumar PN, **Hessburg L**, **Guo E**, Bernstein DN, and **Makhni EC**. Time-Driven Activity-based Costing for Anterior Cruciate Ligament Reconstruction: A Comparison to Traditional Accounting Methods. *Arthrosc Sports Med Rehabil* 2021; 3(1):e39-e45. PMID: 33615246. Full Text

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PURPOSE: The primary purpose of this study was to compare the cost of care of one of the most common sports medicine surgical procedures, anterior cruciate ligament reconstruction (ACLR), using the time-driven activity-based costing (TDABC) method to traditional accounting methods such as activity-based costing (ABC). Our secondary purpose was to identify the main drivers of the cost of ACLR using both of these techniques. METHODS: A process map of ACLR was constructed through direct observation in the clinical setting according to established techniques to identify drivers of fixed, direct variable, and indirect costs. An episode of care consisted of each step in the surgical process from admission to discharge. Personnel costs were combined with the process map to determine the cost drivers and overall cost of the procedure. The cost generated from the TDABC method was compared with the cost from our institution's internal accounting system, which used an ABC method. RESULTS: The total cost of ACLR was $5,242.25 when using TDABC versus $10,318 when using the traditional ABC method. The largest difference between the 2 methods was within the domain of direct variable costs. CONCLUSIONS: When compared with TDABC, the hospital's traditional cost-accounting estimate for ACLR is nearly twice as costly. These findings highlight the variability of cost calculation for the same clinical episode between the 2 accounting methods. For the traditional accounting method, the direct variable cost was the main cost driver, whereas for the TDABC method, the direct fixed cost was the main cost driver. CLINICAL RELEVANCE: This study is important because it elucidates important cost drivers for one of the most common sports medicine orthopaedic surgical procedures and attempts to identify the true overall cost of the procedure.

Urology

Dalela D, **Arora S**, **Peabody J**, and **Rogers C**. Letter to the editor Re: Wilson et al. Outpatient Extraperitoneal Single-Port Robotic Radical Prostatectomy. Urology 2020; 144: 142-146. *Urology* 2021; Epub ahead of print. PMID: 33600837. Full Text

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Urology

Harms K, Zhao L, Johnson B, Wang X, **Carskadon S**, **Palanisamy N**, Rhodes DR, Mannan R, Vo J, Choi JE, Chan MP, Fullen DR, Patel RM, Siddiqui J, Ma VT, Hrycaj S, McLean SA, Hughes TM, Bichakjian CK, Tomlins SA, and Harms PW. Virus-positive Merkel cell carcinoma is an independent prognostic group with distinct predictive biomarkers. *Clin Cancer Res* 2021; Epub ahead of print. PMID: 33547200. Full Text

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PURPOSE: Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine carcinoma that can be divided into two classes: virus-positive (VP) MCC, associated with oncogenic Merkel cell polyomavirus (MCPyV); and virus-negative (VN) MCC, associated with photodamage. EXPERIMENTAL DESIGN: We classified 346 MCC tumors from 300 patients for MCPyV using a combination of immunohistochemistry, in situ hybridization, and quantitative PCR assays. In a subset of tumors, we profiled mutation status and expression of cancer-relevant genes. MCPyV and molecular profiling results were correlated with disease-specific outcomes. Potential prognostic biomarkers were further validated by immunohistochemistry. RESULTS: 177 tumors were classified as VP-MCC, 151 tumors were VN-MCC, and 17 tumors were indeterminate. MCPyV positivity in primary tumors was associated with longer disease-specific and recurrence-free survival in univariate analysis, and in multivariate analysis incorporating age, sex, immune status, and stage at presentation. Prioritized oncogene or tumor suppressor mutations were frequent in VN-MCC but rare in VP-MCC. TP53 mutation developed with recurrence in one VP-MCC case. Importantly, for the first time we find that VP-MCC and VN-MCC display distinct sets of prognostic molecular biomarkers. For VP-MCC, shorter survival was associated with decreased expression of immune markers including granzyme and IDO1. For VN-MCC, shorter survival correlated with high expression of several genes including UBE2C Conclusions: MCPyV status is an independent prognostic factor for MCC. Features of the tumor genome, transcriptome, and microenvironment may modify prognosis in a manner specific to viral status. MCPyV status has clinicopathologic significance and allows for identification of additional prognostic subgroups.

Urology

Rakic N, **Jamil M**, **Keeley J**, **Sood A**, Vetterlein M, **Dalela D**, **Arora S**, Modonutti D, **Bronkema C**, Novara G, **Peabody J**, **Rogers C**, **Menon M**, and **Abdollah F**. Evaluation of lymphovascular invasion as a prognostic predictor of overall survival after radical prostatectomy. *Urol Oncol* 2021; Epub ahead of print. PMID: 33602620. Full Text

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OBJECTIVE: To assess the prognostic ability of lymphovascular invasion (LVI) as a predictor of overall survival (OS). MATERIALS AND METHODS: We included 126,682 prostate cancer (CaP) cM0 patients who underwent radical prostatectomy with lymph node dissection between 2010 and 2015, within the National Cancer Database. Patients who received androgen deprivation therapy were included. Patients were divided into four sub-cohorts based on LVI and lymph node invasion (LNI) status: pL(0)N(0), pL(1)N(0), pL(0)N(1), and pL(1)N(1). Kaplan-Meier curves estimated OS and Cox-regression analysis tested the relationship between LVI and OS. RESULTS: Median (IQR) age and PSA at diagnosis were 62 (57-66) years and 5.7 (4.5-8.9) ng/ml, respectively. Most patients had pT2 stage (68.5%), and pathological Gleason 3+4 (46.7%). 10.0% and 4.0% patients had LVI and LNI, respectively. Median follow-up was 42 months (27-58). At 5-years, OS was 96.5% in pL(0)N(0) patients vs 93.1% pL(1)N(0) patients vs 93.3% in pL(0)N(1) patients vs 86.6% pL(1)N(1) patients. LVI was an independent predictor of OS (hazard ratio [HR]:1.28). LVI showed interaction with LNI, as LVI was associated with a higher overall-mortality in patients with LNI (HR:1.66), than in patients without LNI (HR:1.22). (all P<0.0001) CONCLUSIONS: Our report highlights the detrimental impact of LVI on OS. Patients with LVI alone fared similarly to patients with LNI alone. Patients with both LVI and LNI had worse OS than those with only LVI or LNI, implying a synergetic detrimental interaction. Our findings demonstrate an important utility that LVI can provide in deciding patients' prognoses.

Urology

Wu Z, Chen Q, Djaladat H, Minervini A, Uzzo RG, Sundaram CP, Rha KH, Gonzalgo ML, Mehrazin R, Mazzone E, **Marcus J**, **Danno A**, Porter J, Asghar A, Ghali F, Guruli G, Douglawi A, Cacciamani G, Ghoreifi A, Simone G, Margulis V, Ferro M, Tellini R, Mari A, Srivastava A, Steward J, Al-Qathani A, Al-Mujalhem A, Bhattu AS, Mottrie A, **Abdollah F**, Eun DD, Derweesh I, Veccia A, Autorino R, and Wang L. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). *Eur Urol Focus* 2021; Epub ahead of print. PMID: 33549537. Full Text

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BACKGROUND: Postoperative renal function impairment represents a main limitation for delivering adjuvant chemotherapy after radical nephroureterectomy (RNU). OBJECTIVE: To create a model predicting renal function decline after minimally invasive RNU. DESIGN, SETTING, AND PARTICIPANTS: A total of 490 patients with nonmetastatic UTUC who underwent minimally invasive RNU were identified from a collaborative database including 17 institutions worldwide (February 2006 to March 2020). Renal function insufficiency for cisplatin-based regimen was defined as estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m(2) at 3 mo after RNU. Patients with baseline eGFR >50 ml/min/1.73 m(2) (n = 361) were geographically divided into a training set (n = 226) and an independent external validation set (n = 135) for further analysis. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Using transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines, a nomogram to predict postoperative eGFR <50 ml/min/1.73 m(2) was built based on the coefficients of the least absolute shrinkage and selection operation (LASSO) logistic regression. The discrimination, calibration, and clinical use of the nomogram were investigated. RESULTS AND LIMITATIONS: The model that incorporated age, body mass index, preoperative eGFR, and hydroureteronephrosis was developed with an area under the curve of 0.771, which was confirmed to be 0.773 in the external validation set. The calibration curve demonstrated good agreement. Besides, the model was converted into a risk score with a cutoff value of 0.583, and the difference between the low- and high-risk groups both in overall death risk (hazard ratio [HR]: 4.59, p < 0.001) and cancer-specific death risk (HR: 5.19, p < 0.001) was statistically significant. The limitation mainly lies in its retrospective design. CONCLUSIONS: A nomogram incorporating immediately available clinical variables can accurately predict renal insufficiency for cisplatin-based adjuvant chemotherapy after minimally invasive RNU and may serve as a tool facilitating patient selection. PATIENT SUMMARY: We have developed a model for the prediction of renal function loss after radical nephroureterectomy to facilitate patient selection for perioperative chemotherapy.

Conference Abstracts

Administration

Cho J, Mak A, Hu D, Oh S, Hunstman S, Eng C, Farber H, Rodriguez-Cintron W, Serebrisky D, Thyne S, Borrell L, Rodriguez-Santana J, **Williams LK**, Seibold M, Burchard E, and Kumar R. (1) Associations of PAI-1 Promoter Polymorphism and African Ancestry with Asthma in the GALA2 cohort. *J Allergy Clin Immunol* 2021; 147(2):AB55.

Rationale: Plasminogen activator inhibitor-1 (PAI-1) promoter variants and African ancestry both are associated with asthma. We evaluated the independent and joint effects of a gain of function (GOF) PAI-1 promoter variant and African ancestry on asthma odds. Methods: Latinx subjects aged 8-21 years (1736 with asthma and 1747 healthy controls) from the GALA2 study were classified using African ancestry dichotomized at the 5th quintile. The variant (rs1799768) was dichotomized as wild type (GG) or risk allele (either heterozygous AG or homozygous AA). Using logistic regression, we evaluated the independent and joint effects of a PAI-1 GOF polymorphism and African ancestry proportion on asthma odds, controlling for confounding variables Results: Subjects were 50% male, 13.2 (SD 3.5) years old, and had mean African ancestry proportion of 0.14 (SD 0.12). Compared to those with the wild type and African ancestry at the 1st-4th quintile, subjects at the top 5th quintile of African ancestry and the risk genotype had an increased odds of asthma (OR: 1.47, p = 0.003). Neither subjects with the risk genotype and at the lower quintiles (OR=1.07, P=0.39) nor those with the highest quintile of African ancestry and wild type genotype (OR 1.11, p=0.50) had an increased odds of asthma. In subgroup analysis, Puerto Rican subjects with the risk genotype and elevated ancestry retained this association (OR: 1.43, p = 0.035) but Mexican subjects with lower mean African ancestry did not. Conclusions: A GOF promoter variant in PAI-1 and higher African ancestry proportion was synergistically associated with an increased odds of asthma.

Allergy & Immunology

Altman M, **Zoratti E**, Liu A, Pongracic J, Gereige J, Wood R, Hershey GK, Kercsmar C, Gruchalla R, Kattan M, Teach S, Ylescupidez A, Sigelman S, Gergen P, Togias A, Visness C, Presnell S, Gern J, Busse W, and Jackson D. Airway Epithelial Gene Expression Differs Across Urban Childhood Asthma Phenotypes. *J Allergy Clin Immunol* 2021; 147(2):AB37.

Rationale: Children living in low-income urban environments experience high asthma morbidity. Prior phenotyping of these children has identified a subgroup with low levels of allergy (T2-low) but highly symptomatic asthma. Assessment of the airway epithelium in these children can provide important mechanistic insights into disease pathogenesis. Methods: We performed RNA-sequencing of nasal brush samples from 123 children in the Asthma Phenotypes in the Inner City (APIC) cohort. These children were previously clustered into 5 phenotypes according to metrics of T2 biomarkers, lung function, rhinitis and asthma symptoms, and asthma severity. Differential gene expression was assessed by modular analysis. Results: The cluster of children characterized by T2-low highly-symptomatic asthma and rhinitis had significantly increased expression of a module of 875 genes. This module was highly enriched for Neuroactive ligand-receptor interaction genes (KEGG; FDR=2.3E-5), Olfactory transduction genes (KEGG; FDR=2.6E-4) and Extracellular matrix genes (UniProtKB; FDR=8.6E-12), the latter of which included multiple collagen and ADAM (a disintegrin and metalloproteinase) genes. This expression module also included a small number of cytokine/receptor pathway genes notable for IL23R, IL26, and IL2 and an absence of canonical T2 genes. This pathway was upregulated 1.5-fold over the cluster of children with T2-low mild asthma, and 2.4-fold over the cluster of children with highly symptomatic T2-high asthma (FDRs <0.05). Conclusions: Our results demonstrate a unique nasal gene expression profile characteristic of urban children with highly symptomatic asthma and rhinitis but with minimal allergy, most notable for numerous genes related to neuronal signaling and components of Th17 signaling, suggesting unique molecular mechanisms of disease.

Allergy & Immunology

Elisa A, **Chatfield A**, **Havstad S**, **Sitarik A**, **Kim H**, **Jones K**, **Wegienka G**, **Joseph C**, Lukacs N, **Johnson C**, Ownby D, Lynch S, and **Zoratti E**. Association Of Dog Exposure and Early-Life IgE Production In The Microbes, Asthma, Allergy and Pets (MAAP) Birth Cohort. *J Allergy Clin Immunol* 2021; 147(2):AB162.

Rationale: Early-life dog exposure has been associated with decreased IgE levels. Methods: Pregnant women living with indoor dog(s) (n=81) and those with no pets (n=60) were recruited. Total IgE trajectories were constructed using serum samples collected at cord, 6 months and 18 months of age. Using mixed effects models, the trajectories were compared between infants from pet-free and dog-keeping households, and between dog-free, 1 dog only, and 2 or more dog households. Demographic variables were assessed as potential effect modifiers. Results: Prenatal indoor dog exposure and the number of dogs was not associated with early life IgE (p=0.12 and 0.71, respectively). Infant sex was a significant modifier for both the binary dog and number of dogs outcomes (p=0.013 and p=0.024, respectively). For males, total IgE trajectory was 44.3% lower with prenatal indoor dog exposure (p=0.013), versus 39.3% higher for females (p=0.206). Compared to males without prenatal indoor dog exposure, total IgE trajectory was 34.7% lower when exposed to one dog (p=0.084), and 60.6% lower when exposed to 2 or more dogs (p=0.003). This effect was not observed in females (p=0.205). Conclusions: Infant sex was a significant modifier in the relationship between prenatal dog exposure and early life IgE. Specifically, males with prenatal indoor dog exposure have lower early life total IgE trajectories than males without indoor pet exposure.

Allergy & Immunology

Horbal A, **Modi S**, **Sitarik A**, **Liu B**, **Kim H**, and **Zoratti E**. A Retrospective Study of Risk Factors for Redocumentation of Penicillin Allergy. *J Allergy Clin Immunol* 2021; 147(2):AB119.

Rationale: Electronic Medical Record (EMR) documentation of allergies is critical for patient safety and efficacious for appropriate treatment. Inaccuracies in documentation can cause serious problems and lead to increase in mortality and morbidity. Studies have addressed the detrimental effects of redocumentation of penicillin (PCN) though few have expanded on risk factors. Methods: Patients who underwent inpatient or outpatient PCN skin testing between 3/1/13 and 10/31/19 at Henry Ford Health System were identified using EMR data. Existence and potential removal of PCN allergy in the EMR was extracted. Risk factors such as age, race, ethnicity, language, testing location, insurance, deprivation index, and dementia diagnosis were tested for association with PCN redocumentation using ANOVA, chi-squared tests, and Fisher's exact tests. Results: A total of 456 patients had a negative PCN skin test and had PCN allergy deleted from their EMR. Eleven of these patients were excluded because a reaction to PCN following skin testing was documented and PCN was therefore added back to their chart. Of the remaining 445, 81 (18.2%) had PCN redocumented without further explanation. Significant of reentry was recorded by 17 MDs, 30 RNs, 18 MAs, 4 CNPs. No statistically significant associations were identified with the examined risk factors, though patients who had an inpatient PCN skin test were slightly more likely to have PCN redocumentation (23.5% vs. 15.9%, p=0.072). Conclusion: None of the examined risk factors were significantly associated with PCN redocumentation, though redocumentation was more likely to occur after inpatient PCN skin testing, and was primarily recorded by non-physicians.

Endocrinology and Metabolism

Minisola S, Colangelo L, Pepe J, Diacinti D, Cipriani C, and **Rao SD**. Osteomalacia and Vitamin D Status: A Clinical Update 2020. *JBMR Plus* 2021; 5(1).

S. Minisola, Department of Clinical, Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

Historically, rickets and osteomalacia have been synonymous with vitamin D deficiency dating back to the 17th century. The term osteomalacia, which literally means soft bone, was traditionally applied to characteristic radiologically or histologically documented skeletal disease and not just to clinical or biochemical abnormalities. Osteomalacia results from impaired mineralization of bone that can manifest in several types, which differ from one another by the relationships of osteoid (ie, unmineralized bone

matrix) thickness both with osteoid surface and mineral apposition rate. Osteomalacia related to vitamin D deficiency evolves in three stages. The initial stage is characterized by normal serum levels of calcium and phosphate and elevated alkaline phosphatase, PTH, and 1,25-dihydroxyvitamin D [1,25(OH)2D]—the latter a consequence of increased PTH. In the second stage, serum calcium and often phosphate levels usually decline, and both serum PTH and alkaline phosphatase values increase further. However, serum 1,25(OH)2D returns to normal or low values depending on the concentration of its substrate, 25-hydroxyvitamin D (25OHD; the best available index of vitamin D nutrition) and the degree of PTH elevation. In the final stage, hypocalcemia and hypophosphatemia are invariably low with further exacerbation of secondary hyperparathyroidism. The exact,or even an approximate, prevalence of osteomalacia caused by vitamin D deficiency is difficult to estimate, most likely it is underrecognized or misdiagnosed as osteoporosis. Signs and symptoms include diffuse bone, muscle weakness, and characteristic fracture pattern, often referred to as pseudofractures, involving ribs, scapulae, pubic rami, proximal femurs, and codfish-type vertebrae. The goal of therapy of vitamin D-deficiency osteomalacia is to alleviate symptoms, promote fracture healing, restore bone strength, and improve quality of life while correcting biochemical abnormalities. There is a need for better understanding of the epidemiology of osteomalacia. Simplified tools validated by concurrent bone histology should be developed to help clinicians promptly diagnose osteomalacia. © 2020 The Authors. JBMR Plus published by Wiley Periodicals LLC. on behalf of American Society for Bone and Mineral Research.

Gastroenterology

Ivanics T, **Leonard-Murali S**, **Mouzaihem H**, **Moonka D**, **Kitajima T**, **Yeddula S**, **Shamaa T**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Extreme Hyponatremia as a Risk Factor for Early Mortality after Liver Transplantation in the MELD-Sodium Era. *Am J Transplant* 2021; 21(SUPPL 1):29-30.

T. Ivanics, Henry Ford Hospital, Detroit, MI, United States

BackgroundThe impact of hyponatremia on waitlist and post-transplant outcomes following the implementation of MELD-Na based liver allocation remains unclear. We sought to evaluate waitlist and post-liver transplant (LT) outcomes in patients with hyponatremia before and after implementation of MELD-Na based allocation. MethodsAdult primary LT candidates between 2009 and 2019 were identifi ed in the OPTN/UNOS database. Multi-organ transplants and re-LT were excluded. Two eras were defi ned: before and after implementation of MELD-Na based allocation. Patients were categorized into the following groups: extreme hyponatremia (≤120 mEq/L), severe hyponatremia (121-124), moderate hyponatremia (125-129), mild hyponatremia (130-134), normal sodium (135-145), and hypernatremia (>145). 90-day waitlist outcomes and post-LT survival were compared according to era and sodium concentration using Fine-Gray and Cox proportional hazard models. Results87,845 patients were included in waitlist outcome analyses (N=64,911[pre- MELD-Na], N=22,934[post-MELD-Na]). In the pre-MELD-Na era, extreme hyponatremia at listing was associated with increased risk of 90-day waitlist mortality (HR:2.08,p<0.001) and lower likelihood of transplant within 90- days (HR:0.63,p<0.001). In the post-MELD-Na era, patients with extreme hyponatremia had a similar risk of waitlist mortality (HR:1.02,p=0.95) and likelihood of transplant (HR:0.90,p=0.48) as patients with normal serum sodium. Post-LT outcome analyses included 30,639 and 12,585 patients in pre and post- MELD-Na eras. While extreme hyponatremia was not associated with post-LT mortality in the pre-MELD-Na era, it was an independent risk factor for 90-day post-LT mortality in the post-MELD-Na era. (HR:5.20,p<0.001). ConclusionsWith the introduction of MELD-Na based allocation, waitlist outcomes have improved in patients with extreme hyponatremia but paradoxically been associated with worse short-term post-LT survival.

Hematology/Oncology

Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier P, Lopes G, Tan DSW, Garralda E, Paz-Ares L, Cho BC, **Gadgeel SM**, Thomas M, Liu SV, Clifford C, Zhang H, Turner CD, and Subbiah V. MO01.38 Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small-Cell Lung Cancer (NSCLC). *J Thorac Oncol* 2021; 16(1):S31-S32.

Background: Pralsetinib is an investigational, highly potent, selective RET inhibitor. We provide the registrational dataset for patients with RET fusion+ NSCLC with and without prior treatment from ARROW. Methods: ARROW (75 sites/11 countries; NCT03037385) consists of phase 1 dose escalation to establish recommended phase 2 dose (400 mg once daily [QD] orally) and phase 2 expansion cohorts defined by tumor type and/or RET alteration. Primary objectives were overall response rate (ORR; blinded independent central review per RECIST v1.1) and safety. Efficacy is shown for response-evaluable patients (REP) with RET fusion+ NSCLC who initiated 400 mg QD pralsetinib by July 11, 2019 and safety for all patients (all diagnoses) who initiated 400 mg QD. Results: As of November 18, 2019, 354 patients with advanced solid tumors had initiated 400 mg QD pralsetinib (median follow-up 8.8 months). Efficacy outcomes are shown (Table) for patients with metastatic RET fusion+ NSCLC (n=116; 72% KIF5B; 16% CCDC6; 12% other/fusion present but type unknown) with prior platinum treatment (n=80) or without prior systemic treatment (n=26). ORR was similar regardless of RET fusion partner, prior therapies, or central nervous system involvement. Overall there were 7 (6%) complete responses, 4 (5%) in prior platinum patients and 3 (12%) in treatment-naïve patients; median time to response overall was 1.8 months and median duration of response (DOR) was not reached (95% CI, 11.3–not reached). In the safety population (n=354; all tumor types), most treatment-related adverse events (TRAEs) were grade 1–2, and included increased aspartate aminotransferase (31%), anemia (22%), increased alanine aminotransferase (21%), constipation (21%) and hypertension (20%). 4% of patients in the safety population discontinued due to TRAEs. Conclusions: Pralsetinib has rapid, potent, and durable clinical activity in patients with advanced RET fusion+ NSCLC regardless of RET fusion genotype or prior therapies, and QD oral dosing is well-tolerated. [Formula presented]

Hematology/Oncology

Spigel D, Waqar SN, Burkard ME, Lin JJ, Chae YK, Socinski MA, **Gadgeel S**, Reckamp KL, Leland SM, Plessinger D, Kunkel L, Bauman JR, Otterson G, Halmos B, Ignatius Ou SH, Patil T, Elamin YY, and Kim ES. MO01.33 CRESTONE – Clinical Study of REsponse to Seribantumab in Tumors with NEuregulin-1 (NRG1) Fusions – A Phase 2 Study of the anti-HER3 mAb for Advanced or Metastatic Solid Tumors (NCT04383210). *J Thorac Oncol* 2021; 16(1):S29-S30.

Background: NRG1 (Neuregulin-1) gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including lung, pancreatic, gallbladder, breast, ovarian, colorectal, neuroendocrine, and sarcomas. NRG1 is the predominant ligand of HER3 and to a lesser extent HER4. NRG1 fusion proteins retaining an active EGF-like domain drive tumorigenesis and proliferation through aberrant HER3 activation. Importantly, NRG1 fusions are often mutually exclusive with other known driver alterations. NRG1 fusions have been correlated with worse overall and disease-free survival and poor response to treatment with standard therapies including chemotherapy, PD-(L)1 checkpoint inhibitors and combinations of these agents. Inhibition of HER3 and its dimerization partners represents a rational and novel therapeutic approach for tumors harboring an NRG1 fusion supported by case studies of clinical responses to anti-HER3 antibodies or pan-ERBB (tyrosine kinase inhibitors) TKIs like afatinib. Seribantumab is a fully human IgG2 mAb against HER3 uniquely able to inhibit NRG1-dependent activation of HER3, HER3-HER2 dimerization, and downstream signaling through the PI3K/AKT and MAPK pathways. The clinical safety profile of seribantumab has been well characterized through prior monotherapy and combination studies in over 800 patients. Methods: CRESTONE is an open label, multicenter Phase 2 basket trial of seribantumab in adult patients with NRG1 fusion-positive locally advanced or metastatic solid tumors who have progressed on or are nonresponsive to available therapies. The trial will enroll at least 75 previously treated patients across three cohorts. Cohort 1 (N=55) will include patients who have not received prior treatment with any ERBB targeted therapy. Cohort 2 (up to N=10) will include patients who have progressed after prior treatment which includes ERBB targeted therapy. Cohort 3 (up to N=10) will include patients harboring NRG1 fusions without an EGF-like binding domain. NRG1 fusion status for enrollment will be determined through a local CLIA or similarly accredited molecular assay. NRG1 fusion status for patients in Cohort 1 will be centrally confirmed using an RNA-based NGS assay. This study will evaluate a novel dosing regimen of weekly induction, biweekly consolidation, and Q3W maintenance designed to rapidly achieve steady state levels, optimize exposure, and deliver maximal NRG1 inhibition. The primary endpoint is ORR per RECIST v1.1 by independent radiologic review. Secondary endpoints include duration of response (DoR), safety, PFS, OS, and overall clinical benefit rate. An interim analysis is

planned following enrollment of 20 patients in Cohort 1. CRESTONE is open and accruing patients in the United States. Clinical trial information: NCT04383210.

Infectious Diseases
Mohamed A, **Prashar R**, **Alangaden G**, **Malinzak L**, **Denny J**, **Delvecchio K**, and **Kim D**. Persistence of SARS-CoV-2 Virus in a Kidney Transplant Recipient. *Am J Transplant* 2021; 21(SUPPL 1):46.

A. Mohamed, Henry Ford Health System, Detroit, MI, United States

Background: We are now discovering the sequelae of the novel coronavirus disease (COVID-19) as they relate to the transplant population. Questions regarding duration of viral shedding, infectivity, and reinfection remain. We present the case of a kidney transplant recipient who had COVID-19 prior to transplantation. The patient had presumably cleared the infection, but subsequently tested positive after transplantation. Case: A 30-year-old female with chronic kidney disease secondary to IgA nephropathy was found to be suitable for a living related kidney transplant. Shortly after her evaluation, before her surgery, she developed symptoms of SARS-CoV-2 virus, and was found to be positive via PCR. She presumably cleared her infection as evidenced by negative PCR testing, two weeks after cessation of symptoms. She underwent robotic-assisted living-related kidney transplantation with basiliximab induction. She developed a postoperative hematoma that required operative evacuation. Thus, she was tested for the virus prior to reoperation, and found to be positive-83 days following symptom onset. She remained asymptomatic by this point. She also tested positive for SARS-CoV-2 IgG antibodies. Conclusion: This case illustrates the persistence of SARS-CoV-2 virus and highlights the potential for viral replication after initiation of immunosuppression. It also highlights the possibility of prolonged viral shedding, beyond the maximum reported timeframe. Depletion of T cells from immunosuppression may explain the persistent viral replication and shedding. The clinical significance of prolonged viral shedding in transplant patients remains undefined. The timing of clearance for transplantation, role of retesting after transplantation, and management of immunosuppression are questions that need to be investigated.

Internal Medicine
Horbal A, **Modi S**, **Sitarik A**, **Liu B**, **Kim H**, and **Zoratti E**. A Retrospective Study of Risk Factors for Redocumentation of Penicillin Allergy. *J Allergy Clin Immunol* 2021; 147(2):AB119.

Rationale: Electronic Medical Record (EMR) documentation of allergies is critical for patient safety and efficacious for appropriate treatment. Inaccuracies in documentation can cause serious problems and lead to increase in mortality and morbidity. Studies have addressed the detrimental effects of redocumentation of penicillin (PCN) though few have expanded on risk factors. Methods: Patients who underwent inpatient or outpatient PCN skin testing between 3/1/13 and 10/31/19 at Henry Ford Health System were identified using EMR data. Existence and potential removal of PCN allergy in the EMR was extracted. Risk factors such as age, race, ethnicity, language, testing location, insurance, deprivation index, and dementia diagnosis were tested for association with PCN redocumentation using ANOVA, chi-squared tests, and Fisher's exact tests. Results: A total of 456 patients had a negative PCN skin test and had PCN allergy deleted from their EMR. Eleven of these patients were excluded because a reaction to PCN following skin testing was documented and PCN was therefore added back to their chart. Of the remaining 445, 81 (18.2%) had PCN redocumented without further explanation. Significant of reentry was recorded by 17 MDs, 30 RNs, 18 MAs, 4 CNPs. No statistically significant associations were identified with the examined risk factors, though patients who had an inpatient PCN skin test were slightly more likely to have PCN redocumentation (23.5% vs. 15.9%, p=0.072). Conclusion: None of the examined risk factors were significantly associated with PCN redocumentation, though redocumentation was more likely to occur after inpatient PCN skin testing, and was primarily recorded by non-physicians.

Internal Medicine
Konel J, **Shamaa MT**, **Shamaa O**, **Elsabbagh A**, **Kitajima T**, **Ivanics T**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Collins K**, **Yoshida A**, **Abouljoud M**, **Nagai S**, and **Rizzari M**. Combined liver and lung transplantation with extended normothermic liver preservation using TransmedicsOrgan Care System (OCS)™ liver: A single center experience. *Am J Transplant* 2021; 21(SUPPL 1):59.

J. Konel, Wayne State University School of Medicine, Detroit, MI, United States

Combined liver-lung transplantation (CLLT) is indicated in patients who cannot survive single-organ transplantation alone. Ex-situ normothermic machine perfusion (NMP) has been used to increase the pool of suboptimal donors and has been previously used for extended normothermic lung preservation in CLLT. We aim to describe our single-center experience using the 'Transmedics Organ Care System (OCS) ™ liver for extended normothermic liver preservation in CLLT. Results [Values shown as mean (standard deviation)]: Four CLLTs were performed from 2015 to 2020 including 3 male and 1 female recipients, age 50 (±13.7) years (Table 1). Indications for lung transplantation: (1) cystic fi brosis (CF), (1) severe bronchiectasis, and (2) interstitial pulmonary fi brosis. Indications for liver transplantation: (1) biliary cirrhosis secondary to CF, (1) autoimmune hepatitis, (1) alcoholic cirrhosis, and (1) cryptogenic cirrhosis. The lung was transplanted fi rst for all patients. Recipient characteristics at transplant: Mean forced expiratory volume in 1 second (FEV1) was 51% (±22), and Model for End- Stage Liver Disease was 12 (±3.7). The livers were donated after brain death with donor age of 34 (±9.4) years and cold ischemia time 566 (±38) minutes. Ex-vivo pump time for the livers was 411 (±38) minutes (Table 2). Mean hospital stay was 34 days (±18). Over a median follow-up of 201 days, all patients were alive and doing well, while 50% had biopsy-proven acute cellular rejection of the liver. Conclusion: Normothermic extended liver preservation is a safe method to prolong perfusion time and preserve the liver during combined organ transplantation.

Nephrology
Mohamed A, **Prashar R**, **Alangaden G**, **Malinzak L**, **Denny J**, **Delvecchio K**, and **Kim D**. Persistence of SARS-CoV-2 Virus in a Kidney Transplant Recipient. *Am J Transplant* 2021; 21(SUPPL 1):46.

A. Mohamed, Henry Ford Health System, Detroit, MI, United States

Background: We are now discovering the sequelae of the novel coronavirus disease (COVID-19) as they relate to the transplant population. Questions regarding duration of viral shedding, infectivity, and reinfection remain. We present the case of a kidney transplant recipient who had COVID-19 prior to transplantation. The patient had presumably cleared the infection, but subsequently tested positive after transplantation. Case: A 30-year-old female with chronic kidney disease secondary to IgA nephropathy was found to be suitable for a living related kidney transplant. Shortly after her evaluation, before her surgery, she developed symptoms of SARS-CoV-2 virus, and was found to be positive via PCR. She presumably cleared her infection as evidenced by negative PCR testing, two weeks after cessation of symptoms. She underwent robotic-assisted living-related kidney transplantation with basiliximab induction. She developed a postoperative hematoma that required operative evacuation. Thus, she was tested for the virus prior to reoperation, and found to be positive-83 days following symptom onset. She remained asymptomatic by this point. She also tested positive for SARS-CoV-2 IgG antibodies. Conclusion: This case illustrates the persistence of SARS-CoV-2 virus and highlights the potential for viral replication after initiation of immunosuppression. It also highlights the possibility of prolonged viral shedding, beyond the maximum reported timeframe. Depletion of T cells from immunosuppression may explain the persistent viral replication and shedding. The clinical significance of prolonged viral shedding in transplant patients remains undefined. The timing of clearance for transplantation, role of retesting after transplantation, and management of immunosuppression are questions that need to be investigated.

Obstetrics, Gynecology, and Women's Health Services
Khangura RK, Torti S, Tesfay L, Torti F, Kuo C, Hammer E, Bakaysa S, and Campbell W. 38 Daily vs. Intermittent Iron Therapy in Moderate Iron Deficient Pregnant Patients: A Randomized Non-inferiority Trial. *Am J Obstet Gynecol* 2021; 224(2):S28.

Objective: Evaluate the hematological response of pregnant women to iron therapy in daily vs. intermittent treatment groups & evaluate gastrointestinal side effects & adherence to therapy. Study Design: A pragmatic non-blinded randomized controlled non-inferiority trial performed at two medical sites. Pregnant women undergoing routine prenatal labs at 26-29 weeks gestation were approached about the study. Exclusion criteria were: diagnosed iron deficiency anemia < 26 weeks, already on iron supplementation, had a condition known to affect iron metabolism. Enrolled patients were randomized to

supplemental iron daily or intermittently (every other day). The primary outcome was change in hemoglobin (Hgb) after treatment, with the non-inferiority margin set at 1 Standard Deviation (SD) (0.5 g/dL Hgb). Secondary outcomes were: differences in other hematological indices (hematocrit, mean corpuscular volume, serums transferrin receptor molecule, hepcidin, ferritin, calculated body iron store), gastrointestinal side effects & adherence. We assumed a mean increase of Hgb was 1 g/dL in the daily group. A 0.5 g/dL or more mean Hgb difference between groups was considered clinically significant. With a two sided, two-sample t-test, to achieve a power of 90%, α of 0.05, 23 patients per group were needed. Results: One hundred seventy-nine women were screened & 58 met study criteria, 29 were randomized to daily & 29 to intermittent iron groups. Twenty-two patients were analyzed in the daily group & 24 patients were analyzed in the intermittent group. Baseline characteristics were not different between groups (p >.05). Intermittent iron therapy was non-inferior to daily therapy, with a mean SD difference of 0.27 g/dL (95% CI: -0.33 to 0.89) (Figure). Changes in other hematological indices were not significant (Table). Women in the daily group had more nausea compared to intermittent group (p = 0.040). Women in the intermittent group were not more adherent with therapy (p=0.244). Conclusion: Intermittent iron therapy is non-inferior to daily iron therapy and is associated with less nausea but not increased adherence.

Obstetrics, Gynecology, and Women's Health Services
Pitts DS, **Smith N**, **Ayyash M**, and O'Brien L. 1156 Social determinants of sleep in black pregnant women. *Am J Obstet Gynecol* 2021; 224(2):S712.

Objective: Racial and socioeconomic disparities in adverse health outcomes across the lifespan are more pronounced in populations within the United States despite public health efforts to eliminate them. Black women are disproportionately affected with an increased risk for adverse perinatal outcomes. Poor sleep has emerged as a key variable linked to perinatal health. There are a lack of data on how social determinants of health impact sleep in Black pregnant women. The goal of this study was to examine whether key social determinants of health play a role in sleep. Study Design: Third trimester Black pregnant women were recruited into a cohort study at a large tertiary medical center. All women were screened for sleep complaints including poor sleep quality, poor daytime function, excessive daytime sleepiness (EDS), sleep duration, and habitual snoring. Short sleep duration was defined as 6 or fewer hours of sleep and long sleep duration was defined as at least 10 hours of sleep. The following were considered stressors: single women, receipt of Medicaid, no more than a high school education, and age less than 21 years. Results: A total of 289 Black women were recruited. Mean age was 27.4 +/- 6.2 years, BMI was 35.0 +/- 8.9kg/m2 and gestational age was 33.2 +/- 4.7 weeks. Overall 65% of women were single, 66% received Medicaid, 40% had no more than a high school education, and 15% were less than 21 years of age. Table 1 shows the sleep complaints by the stress indicators. Only 75 women (26%) had none of the identified stressors. Regardless of the presence and number of the stressors, EDS was present in approximately half of women, poor sleep quality and poor daytime function were present in the majority of women. Women without stressors were more likely to report short sleep than those with stressors (see Table 2) while long sleep was more common those with stressors. Conclusion: Regardless of which social determinant was present, a large proportion of women reported poor sleep. Of note, majority of women who endorsed all four stressors reported long sleep duration, which is known to be a marker of depression.

Obstetrics, Gynecology, and Women's Health Services
Smith N, **Floyd M**, **Sangha R**, **Cheng P**, **Osborne A**, **Pitts DS**, and **Bazan L**. 102 The efficacy of a pilot program for obstructive sleep apnea screening in pregnancy. *Am J Obstet Gynecol* 2021; 224(2):S71-S72.

Objective: Pregnant patients with Obstructive Sleep Apnea (OSA) are at higher risk for eclampsia, gestational diabetes, cardiomyopathy, congestive heart failure and higher in-hospital mortality than pregnant patients without OSA. Unfortunately, OSA in pregnancy is under-diagnosed and opportunities for interventions are missed. A screening pilot program was developed at an obstetrics clinic in an urban teaching facility to improve diagnosis of OSA among pregnant patients. Study Design: Every new obstetric patient was screened by a nurse for snoring/apneas, body mass index (BMI) > 35, essential hypertension, glucose disorders, neck size > 36 cm, and sleepiness. If a patient scored 2/6 or greater, a

home sleep apnea test (HSAT) was ordered to diagnose OSA after discussion of risks and benefits with an obstetrician. Results: In the 6 months prior to implementation of the screening program, zero patients were referred to the sleep medicine clinic. After the initiation of the screening program, 571 women were screened and 124 met criteria to be at high risk for OSA. The rate of tests ordered for patients who screened positive was 35%. Of the tests that were ordered 57% of patients performed the test. Out of the 26 patients who performed portable sleep testing, 16 were diagnosed with OSA with an apnea-hypopnea index (AHI) ≥ 5, which is 61% of those tested. Only 4 patients followed up in the sleep clinic after diagnosis, and only 3 patients met initial compliance with CPAP therapy as measured by percent usage over 30 days greater than 4 hours. Conclusion: A significant increase in screening for obstructive sleep apnea was achieved with implementation of screening protocol. High rate of diagnosis of OSA via HSAT does point to adequacy of six-question screening protocol. There were several patients who screened positive; however, few underwent testing for OSA, and even fewer still started CPAP and were compliant with therapy. This quality initiative program increased detection rates, however there is room for improvement in educating and maintaining patient compliance with therapy.

Public Health Sciences
Chau L, **Delvecchio K**, **Mohamed A**, **Kitajima T**, **Lu M**, **Yedulla S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Aboujoud M**, and **Nagai S**. Developing and validation of a liver transplantation donation after cardiac death risk index using the UNOS database. *Am J Transplant* 2021; 21(SUPPL 1):21.

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

Introduction: Donation after cardiac death (DCD) liver transplantation is an increasing form of organ donation. Shlegal et. al. identified seven factors predicting 1-year DCD graft survival based on the UK transplantation population. This project aims to validate the existing predictive model and to develop a novel DCD graft failure prediction model based on the UNOS database. Methods: We examined all adult DCD transplanted Jan 1 2014 to Mar 31 2020 in the UNOS registry. The population was divided into train (66%) and validation (34%) subsets. Variables of interest were selected from the train subset with backwards stepwise selection with criteria for entry P = 0.05 and exit P = 0.06. Logistic regression models were fitted based on selected variables to predict 1-year graft failure. Performance of the model was assessed in the validation population by computing the area under the receiver operating characteristic curve (AUROC) after 10-fold stratified cross-validation. The performance of the novel model was compared to the UK DCD prediction model. Results: 2738 DCD transplants were included in this study with 1835 in the train and 903 in the validation subsets. The model identified 12 factors predictive for 1-year graft failure among DCD recipients. The model AUROC was 0.741 (95% CI: 0.686, 0.796). When validating the UK DCD model in the UNOS database, the model achieved AUROC of 0.628 (0.564, 0.691). Conclusions: This model identified 12 predictive factors predictive of 1-year graft failure among DCD recipients from the UNOS database, which outperformed the existing model.

Public Health Sciences
Elisa A, **Chatfield A**, **Havstad S**, **Sitarik A**, **Kim H**, **Jones K**, **Wegienka G**, **Joseph C**, Lukacs N, **Johnson C**, Ownby D, Lynch S, and **Zoratti E**. Association Of Dog Exposure and Early-Life IgE Production In The Microbes, Asthma, Allergy and Pets (MAAP) Birth Cohort. *J Allergy Clin Immunol* 2021; 147(2):AB162.

Rationale: Early-life dog exposure has been associated with decreased IgE levels. Methods: Pregnant women living with indoor dog(s) (n=81) and those with no pets (n=60) were recruited. Total IgE trajectories were constructed using serum samples collected at cord, 6 months and 18 months of age. Using mixed effects models, the trajectories were compared between infants from pet-free and dog-keeping households, and between dog-free, 1 dog only, and 2 or more dog households. Demographic variables were assessed as potential effect modifiers. Results: Prenatal indoor dog exposure and the number of dogs was not associated with early life IgE (p=0.12 and 0.71, respectively). Infant sex was a significant modifier for both the binary dog and number of dogs outcomes (p=0.013 and p=0.024, respectively). For males, total IgE trajectory was 44.3% lower with prenatal indoor dog exposure (p=0.013), versus 39.3% higher for females (p=0.206). Compared to males without prenatal indoor dog exposure, total IgE trajectory was 34.7% lower when exposed to one dog (p=0.084), and 60.6% lower

when exposed to 2 or more dogs (p=0.003). This effect was not observed in females (p=0.205). Conclusions: Infant sex was a significant modifier in the relationship between prenatal dog exposure and early life IgE. Specifically, males with prenatal indoor dog exposure have lower early life total IgE trajectories than males without indoor pet exposure.

Public Health Sciences

Horbal A, **Modi S**, **Sitarik A**, **Liu B**, **Kim H**, and **Zoratti E**. A Retrospective Study of Risk Factors for Redocumentation of Penicillin Allergy. *J Allergy Clin Immunol* 2021; 147(2):AB119.

Rationale: Electronic Medical Record (EMR) documentation of allergies is critical for patient safety and efficacious for appropriate treatment. Inaccuracies in documentation can cause serious problems and lead to increase in mortality and morbidity. Studies have addressed the detrimental effects of redocumentation of penicillin (PCN) though few have expanded on risk factors. Methods: Patients who underwent inpatient or outpatient PCN skin testing between 3/1/13 and 10/31/19 at Henry Ford Health System were identified using EMR data. Existence and potential removal of PCN allergy in the EMR was extracted. Risk factors such as age, race, ethnicity, language, testing location, insurance, deprivation index, and dementia diagnosis were tested for association with PCN redocumentation using ANOVA, chi-squared tests, and Fisher's exact tests. Results: A total of 456 patients had a negative PCN skin test and had PCN allergy deleted from their EMR. Eleven of these patients were excluded because a reaction to PCN following skin testing was documented and PCN was therefore added back to their chart. Of the remaining 445, 81 (18.2%) had PCN redocumented without further explanation. Significant of reentry was recorded by 17 MDs, 30 RNs, 18 MAs, 4 CNPs. No statistically significant associations were identified with the examined risk factors, though patients who had an inpatient PCN skin test were slightly more likely to have PCN redocumentation (23.5% vs. 15.9%, p=0.072). Conclusion: None of the examined risk factors were significantly associated with PCN redocumentation, though redocumentation was more likely to occur after inpatient PCN skin testing, and was primarily recorded by non-physicians.

Public Health Sciences

Shamaa MT, **Kitajima T**, **Ivanics T**, **Elsabbagh A**, **Lu M**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Variations in transplant rates and post-transplant outcomes in liver transplantation based on season and climate regions in the United States. *Am J Transplant* 2021; 21(SUPPL 1):35.

M.T. Shamaa, Henry Ford Hospital, Detroit, MI, United States

Introduction: Cold climate is known to affect the frequency and attributable mortality of various illnesses. Whether similar trends exist in LT donors and recipients remains unknown. This study aims to evaluate the effect of different seasons and regions on the rates and outcomes of liver transplant (LT). Methods: We analyzed the data from United Network for Organ Sharing (UNOS) registry for 50,668 adult patients (≥18 years) who underwent single-organ LT between 2010 and 2019. Patients were categorized by seasons: Summer (n=15,614), Winter (n=18,252), and Spring/Fall (n=16,802). Secondary analysis was performed after stratifying states based on their mean winter temperature (Cold states, 0°-30° F; Intermediate states, 30°-40° F; Warm states, 40°-70° F; Figure 1). Post-LT outcomes were compared according to the season and states using Cox proportional hazard models. Results: Deceased donors during winter were more likely to be older (>50 years, p<0.001), had higher BMI (>25, p<0.001), and died from cerebrovascular disease (p<0.001). Daily LT rates were significantly lower during winter (13.43 transplants/day, p<0.001) and even more pronounced in colder states (Figure 2). The adjusted risk of post-transplant graft loss (HR 1.116, p=0.001) and mortality (HR 1.172, p<0.001) was higher at 1-year in colder states compared to warmer states. Worse post-transplant outcomes in colder states were observed regardless of the season (Winter HR 1.151, p=0.025; spring/fall HR 1.160, p=0.023; Summer HR 1.217, p=0.004). Conclusion: Our study showed significantly lower liver transplant activity during the winter. Colder states had worse post-LT outcomes regardless of the season.

Public Health Sciences

Shamaa MT, **Kitajima T**, **Ivanics T**, **Elsabbagh A**, **Lu M**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Variation of liver and kidney transplant practice and outcomes during public holidays in the United States. *Am J Transplant* 2021; 21(SUPPL 1):68-69.

M.T. Shamaa, Henry Ford Hospital, Detroit, MI, United States

Background: Possible effects of holidays on organ transplant practice/outcomes have not been fully investigated. This study aims to compare the rates of liver and kidney transplant (LT & KT) during different types of holidays and explore whether post-transplant outcomes differ. Methods: We assessed rates of singleorgan LT or KT from 2010 to 2018 for recipients age ≥18 years using the UNOS database. Holidays included Easter/Spring break, Memorial Day, July 4th, Labor Day, Thanksgiving, and Christmas/New-Years (winter holidays). Patients were stratified by transplant timing during holiday±3 d (LT: n=6701; KT: n=15,718) and non-holiday periods (LT: n=43,967, KT: n=102,359). Risk of graft loss and mortality were analyzed using multivariable Cox regression models. Results: KT deceased donors and recipient characteristics were similar between holidays and non-holidays. LT deceased donors during the holidays had shorter cold ischemia time (≤ 8hr, $p<0.001$) and were not marginal (DCD or >70 years, $p=0.001$). Compared to non-holidays, there were lower number of transplant during all holidays both in LT and KT (LT 15.5 vs. 15.2 transplants/day, $p=0.18$, Figure 1A; KT 32.4 vs. 32.1/day, $p<0.001$, Figure 1B). After risk adjustment, LT during holidays showed lower risk of overall mortality (HR 0.921, $p=0.013$; Figure 2), while KT showed a slightly higher risk of overall graft failure during holidays compared to non-holidays (HR 1.038, $p= 0.052$). Conclusion: While favorable donor characteristics were found, LT and KT activities were slower during holidays. Transplants during holidays were associated with significantly better LT outcomes but might lead to worse KT outcomes.

Sleep Medicine

Pitts DS, **Smith N**, **Ayyash M**, and O'Brien L. 1156 Social determinants of sleep in black pregnant women. *Am J Obstet Gynecol* 2021; 224(2):S712.

Objective: Racial and socioeconomic disparities in adverse health outcomes across the lifespan are more pronounced in populations within the United States despite public health efforts to eliminate them. Black women are disproportionately affected with an increased risk for adverse perinatal outcomes. Poor sleep has emerged as a key variable linked to perinatal health. There are a lack of data on how social determinants of health impact sleep in Black pregnant women. The goal of this study was to examine whether key social determinants of health play a role in sleep. Study Design: Third trimester Black pregnant women were recruited into a cohort study at a large tertiary medical center. All women were screened for sleep complaints including poor sleep quality, poor daytime function, excessive daytime sleepiness (EDS), sleep duration, and habitual snoring. Short sleep duration was defined as 6 or fewer hours of sleep and long sleep duration was defined as at least 10 hours of sleep. The following were considered stressors: single women, receipt of Medicaid, no more than a high school education, and age less than 21 years. Results: A total of 289 Black women were recruited. Mean age was 27.4 +/- 6.2 years, BMI was 35.0 +/- 8.9kg/m2 and gestational age was 33.2 +/- 4.7 weeks. Overall 65% of women were single, 66% received Medicaid, 40% had no more than a high school education, and 15% were less than 21 years of age. Table 1 shows the sleep complaints by the stress indicators. Only 75 women (26%) had none of the identified stressors. Regardless of the presence and number of the stressors, EDS was present in approximately half of women, poor sleep quality and poor daytime function were present in the majority of women. Women without stressors were more likely to report short sleep than those with stressors (see Table 2) while long sleep was more common those with stressors. Conclusion: Regardless of which social determinant was present, a large proportion of women reported poor sleep. Of note, majority of women who endorsed all four stressors reported long sleep duration, which is known to be a marker of depression.

Smith N, **Floyd M**, **Sangha R**, **Cheng P**, **Osborne A**, **Pitts DS**, and **Bazan L**. 102 The efficacy of a pilot program for obstructive sleep apnea screening in pregnancy. *Am J Obstet Gynecol* 2021; 224(2):S71-S72.

Objective: Pregnant patients with Obstructive Sleep Apnea (OSA) are at higher risk for eclampsia, gestational diabetes, cardiomyopathy, congestive heart failure and higher in-hospital mortality than pregnant patients without OSA. Unfortunately, OSA in pregnancy is under-diagnosed and opportunities for interventions are missed. A screening pilot program was developed at an obstetrics clinic in an urban teaching facility to improve diagnosis of OSA among pregnant patients. Study Design: Every new obstetric patient was screened by a nurse for snoring/apneas, body mass index (BMI) > 35, essential hypertension, glucose disorders, neck size > 36 cm, and sleepiness. If a patient scored 2/6 or greater, a home sleep apnea test (HSAT) was ordered to diagnose OSA after discussion of risks and benefits with an obstetrician. Results: In the 6 months prior to implementation of the screening program, zero patients were referred to the sleep medicine clinic. After the initiation of the screening program, 571 women were screened and 124 met criteria to be at high risk for OSA. The rate of tests ordered for patients who screened positive was 35%. Of the tests that were ordered 57% of patients performed the test. Out of the 26 patients who performed portable sleep testing, 16 were diagnosed with OSA with an apnea-hypopnea index (AHI) ≥ 5, which is 61% of those tested. Only 4 patients followed up in the sleep clinic after diagnosis, and only 3 patients met initial compliance with CPAP therapy as measured by percent usage over 30 days greater than 4 hours. Conclusion: A significant increase in screening for obstructive sleep apnea was achieved with implementation of screening protocol. High rate of diagnosis of OSA via HSAT does point to adequacy of six-question screening protocol. There were several patients who screened positive; however, few underwent testing for OSA, and even fewer still started CPAP and were compliant with therapy. This quality initiative program increased detection rates, however there is room for improvement in educating and maintaining patient compliance with therapy.

Chau L, **Delvecchio K**, **Mohamed A**, **Kitajima T**, **Lu M**, **Yedulla S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Aboulioud M**, and **Nagai S**. Developing and validation of a liver transplantation donation after cardiac death risk index using the UNOS database. *Am J Transplant* 2021; 21(SUPPL 1):21.

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

Introduction: Donation after cardiac death (DCD) liver transplantation is an increasing form of organ donation. Shlegal et. al. identified seven factors predicting 1-year DCD graft survival based on the UK transplantation population. This project aims to validate the existing predictive model and to develop a novel DCD graft failure prediction model based on the UNOS database. Methods: We examined all adult DCD transplanted Jan 1 2014 to Mar 31 2020 in the UNOS registry. The population was divided into train (66%) and validation (34%) subsets. Variables of interest were selected from the train subset with backwards stepwise selection with criteria for entry P = 0.05 and exit P = 0.06. Logistic regression models were fitted based on selected variables to predict 1-year graft failure. Performance of the model was assessed in the validation population by computing the area under the receiver operating characteristic curve (AUROC) after 10-fold stratified cross-validation. The performance of the novel model was compared to the UK DCD prediction model. Results: 2738 DCD transplants were included in this study with 1835 in the train and 903 in the validation subsets. The model identified 12 factors predictive for 1-year graft failure among DCD recipients. The model AUROC was 0.741 (95% CI: 0.686, 0.796). When validating the UK DCD model in the UNOS database, the model achieved AUROC of 0.628 (0.564, 0.691). Conclusions: This model identified 12 predictive factors predictive of 1-year graft failure among DCD recipients from the UNOS database, which outperformed the existing model.

Ivanics T, **Leonard-Murali S**, **Mouzaihem H**, **Moonka D**, **Kitajima T**, **Yeddula S**, **Shamaa T**, **Rizzari M**, **Collins K**, **Yoshida A**, **Aboulioud M**, and **Nagai S**. Extreme Hyponatremia as a Risk Factor for Early Mortality after Liver Transplantation in the MELD-Sodium Era. *Am J Transplant* 2021; 21(SUPPL 1):29-30.

T. Ivanics, Henry Ford Hospital, Detroit, MI, United States

Background: The impact of hyponatremia on waitlist and post-transplant outcomes following the implementation of MELD-Na based liver allocation remains unclear. We sought to evaluate waitlist and post-liver transplant (LT) outcomes in patients with hyponatremia before and after implementation of MELD-Na based allocation. Methods: Adult primary LT candidates between 2009 and 2019 were identifi ed in the OPTN/UNOS database. Multi-organ transplants and re-LT were excluded. Two eras were defi ned: before and after implementation of MELD-Na based allocation. Patients were categorized into the following groups: extreme hyponatremia (≤120 mEq/L), severe hyponatremia (121-124), moderate hyponatremia (125-129), mild hyponatremia (130-134), normal sodium (135-145), and hypernatremia (>145). 90-day waitlist outcomes and post-LT survival were compared according to era and sodium concentration using Fine-Gray and Cox proportional hazard models. Results: 87,845 patients were included in waitlist outcome analyses (N=64,911[pre- MELD-Na], N=22,934[post-MELD-Na]). In the pre-MELD-Na era, extreme hyponatremia at listing was associated with increased risk of 90-day waitlist mortality (HR:2.08,p<0.001) and lower likelihood of transplant within 90- days (HR:0.63,p<0.001). In the post-MELD-Na era, patients with extreme hyponatremia had a similar risk of waitlist mortality (HR:1.02,p=0.95) and likelihood of transplant (HR:0.90,p=0.48) as patients with normal serum sodium. Post-LT outcome analyses included 30,639 and 12,585 patients in pre and post- MELD-Na eras. While extreme hyponatremia was not associated with post-LT mortality in the pre-MELD-Na era, it was an independent risk factor for 90-day post-LT mortality in the post-MELD-Na era. (HR:5.20,p<0.001). Conclusions: With the introduction of MELD-Na based allocation, waitlist outcomes have improved in patients with extreme hyponatremia but paradoxically been associated with worse short-term post-LT survival.

<u>Surgery</u>
Kitajima T, **Kuno Y**, **Arevalo L**, **Murray N**, **Lisznyai E**, **Shamaa T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Aboujoud M**, and **Nagai S**. Careful donor selection is key to improving post-liver transplant graft survival in older patients with acute-on-chronic liver failure. *Am J Transplant* 2021; 21(SUPPL 1):37-38.

T. Kitajima, Henry Ford Hospital, Detroit, MI, United States

Background: Elderly liver transplant (LT) patients with acute-on-chronic liver failure (ACLF) may be at higher risk for adverse post-transplant outcomes. This study aims to determine appropriate donor selection for older ACLF patients. Methods: Using OPTN/UNOS data, we analyzed elderly LT recipients (>60 years) with ACLF between 2004 and 2019. ACLF were identified using the EASL-CLIF criteria. Risk factors were analyzed. Based on multivariable analysis, points corresponding to hazard ratios (HRs) were assigned to the significant donor factors. Total risk score was calculated by multiplying HRs. Patients were categorized into lower-, mid-, and higher-risk donor group based on cut-off scores determined by 25 and 75 percentile. One-year graft survival were compared in each ACLF grade. Results: A total of 8,146 older ACLF patients were eligible for this study. Multivariable model revealed national share (HR 1.52, p=0.007), DCD donors (HR 1.74, p<0.001), prolonged CIT (>6 hours, HR 1.18, p=0.021) and older donors (age>50, HR 1.34, p<0.001) had an increased risk of 1-year graft loss. Based on these donor factors, risk scores for the high, mid, and low-risk groups were >1.34, 1.01-1.34, and ≤1.00. The higher-risk group had higher adjusted risk of one-year graft loss than the lower-risk group in ACLF-1 and 3 (Figure). Use of higher-risk donors for patients with ACLF-3 was associated with worse one-year graft survival (68.0%). Conclusion: In older ACLF patients, prolonged CIT and the use of DCD, older donor, and national share organs were associated with worse post-transplant outcomes. Careful donor selection is key to ensure successful outcomes.

<u>Surgery</u>
Konel J, **Shamaa MT**, **Shamaa O**, **Elsabbagh A**, **Kitajima T**, **Ivanics T**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Collins K**, **Yoshida A**, **Aboujoud M**, **Nagai S**, and **Rizzari M**. Combined liver and lung transplantation with extended normothermic liver preservation using TransmedicsOrgan Care System (OCS)™ liver: A single center experience. *Am J Transplant* 2021; 21(SUPPL 1):59.

J. Konel, Wayne State University School of Medicine, Detroit, MI, United States

Combined liver-lung transplantation (CLLT) is indicated in patients who cannot survive single-organ transplantation alone. Ex-situ normothermic machine perfusion (NMP) has been used to increase the pool of suboptimal donors and has been previously used for extended normothermic lung preservation in CLLT. We aim to describe our single-center experience using the 'Transmedics Organ Care System (OCS) ™ liver for extended normothermic liver preservation in CLLT. Results [Values shown as mean (standard deviation)]: Four CLLTs were performed from 2015 to 2020 including 3 male and 1 female recipients, age 50 (±13.7) years (Table 1). Indications for lung transplantation: (1) cystic fi brosis (CF), (1) severe bronchiectasis, and (2) interstitial pulmonary fi brosis. Indications for liver transplantation: (1) biliary cirrhosis secondary to CF, (1) autoimmune hepatitis, (1) alcoholic cirrhosis, and (1) cryptogenic cirrhosis. The lung was transplanted fi rst for all patients. Recipient characteristics at transplant: Mean forced expiratory volume in 1 second (FEV1) was 51% (±22), and Model for End- Stage Liver Disease was 12 (±3.7). The livers were donated after brain death with donor age of 34 (±9.4) years and cold ischemia time 566 (±38) minutes. Ex-vivo pump time for the livers was 411 (±38) minutes (Table 2). Mean hospital stay was 34 days (±18). Over a median follow-up of 201 days, all patients were alive and doing well, while 50% had biopsy-proven acute cellular rejection of the liver. Conclusion: Normothermic extended liver preservation is a safe method to prolong perfusion time and preserve the liver during combined organ transplantation.

<u>Surgery</u>
Lisznyai E, **Kitajima T**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Shamaa T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Pre-Transplant Prognostic Nutritional Index Predicts Short-Term Outcomes after Liver Transplantation. *Am J Transplant* 2021; 21(SUPPL 1):13-14.

E. Lisznyai, Henry Ford Hospital, Detroit, MI, United States

The prognostic nutritional index (PNI) is a serum marker of nutrition and infl ammation. PNI previously predicted outcomes in liver transplant (LT) patients with recurrence of hepatocellular carcinoma. However, effi cacy of PNI to predict post-LT outcomes is unknown. We hypothesized pre-transplant PNI would predict short-term post-LT outcomes in deceased donor liver transplant (DDLT) patients. 451 patients underwent primary DDLT between 2013-2018 at our center. Re-transplants, multi-organ transplants and living donor liver transplants were excluded. Pre-transplant PNI = (10)∗[albumin (g/dL)] + (0.005)∗[Total Lymphocyte Count (/µL)]. PNI was analyzed as both a continuous and categorical variable. ROC curves yielded an optimal PNI cutoffof 35 to compare shortterm outcomes between PNI≥35 and PNI<35 cohorts. Risk factors for patient death within 1-year were analyzed using Cox regression models and adjusted by recipient factors at LT. Multivariable analysis associated PNI with 1-year survival as a continuous variable (HR=0.94; 95% CI=0.90-0.98; p=0.007). Of 451 patients, 215 (47.7%) had PNI<35. Pre-LT MELD score was higher in PNI<35 (22 vs. 19; p=0.028). Recipient age, gender, BMI, rates of diabetes mellitus, donor age and donors after cardiac death were equivocal. PNI<35 demonstrated lower 1-year survival (89.6% vs. 95.2%; p=0.026, Figure A). After risk adjustment, PNI<35 showed higher 6-month (HR=2.44; p=0.047) and 1-year death risk (HR=2.47; p=0.018). Multivariable analysis revealed PNI<35 at LT was an independent risk factor for patient death within 1 year (HR=2.37; p=0.023, Figure B). Lower pre-transplant PNI portended worse short-term survival in DDLT patients. PNI may be useful in evaluating pre-transplant nutritional status to optimize LT outcomes.

<u>Surgery</u>
Mohamed A, **Prashar R**, **Alangaden G**, **Malinzak L**, **Denny J**, **Delvecchio K**, and **Kim D**. Persistence of SARS-CoV-2 Virus in a Kidney Transplant Recipient. *Am J Transplant* 2021; 21(SUPPL 1):46.

A. Mohamed, Henry Ford Health System, Detroit, MI, United States

Background: We are now discovering the sequelae of the novel coronavirus disease (COVID-19) as they relate to the transplant population. Questions regarding duration of viral shedding, infectivity, and reinfection remain. We present the case of a kidney transplant recipient who had COVID-19 prior to

transplantation. The patient had presumably cleared the infection, but subsequently tested positive after transplantation. Case: A 30-year-old female with chronic kidney disease secondary to IgA nephropathy was found to be suitable for a living related kidney transplant. Shortly after her evaluation, before her surgery, she developed symptoms of SARS-CoV-2 virus, and was found to be positive via PCR. She presumably cleared her infection as evidenced by negative PCR testing, two weeks after cessation of symptoms. She underwent robotic-assisted living-related kidney transplantation with basiliximab induction. She developed a postoperative hematoma that required operative evacuation. Thus, she was tested for the virus prior to reoperation, and found to be positive-83 days following symptom onset. She remained asymptomatic by this point. She also tested positive for SARS-CoV-2 IgG antibodies. Conclusion: This case illustrates the persistence of SARS-CoV-2 virus and highlights the potential for viral replication after initiation of immunosuppression. It also highlights the possibility of prolonged viral shedding, beyond the maximum reported timeframe. Depletion of T cells from immunosuppression may explain the persistent viral replication and shedding. The clinical significance of prolonged viral shedding in transplant patients remains undefined. The timing of clearance for transplantation, role of retesting after transplantation, and management of immunosuppression are questions that need to be investigated.

Surgery

Shamaa MT, **Kitajima T**, **Ivanics T**, **Elsabbagh A**, **Lu M**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Variations in transplant rates and post-transplant outcomes in liver transplantation based on season and climate regions in the United States. *Am J Transplant* 2021; 21(SUPPL 1):35.

M.T. Shamaa, Henry Ford Hospital, Detroit, MI, United States

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Surgery

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Background: Possible effects of holidays on organ transplant practice/outcomes have not been fully investigated. This study aims to compare the rates of liver and kidney transplant (LT & KT) during different types of holidays and explore whether post-transplant outcomes differ. Methods: We assessed rates of singleorgan LT or KT from 2010 to 2018 for recipients age ≥18 years using the UNOS database. Holidays included Easter/Spring break, Memorial Day, July 4th, Labor Day, Thanksgiving, and Christmas/New-Years (winter holidays). Patients were stratified by transplant timing during holiday±3 d

(LT: n=6701; KT: n=15,718) and non-holiday periods (LT: n=43,967, KT: n=102,359). Risk of graft loss and mortality were analyzed using multivariable Cox regression models. Results: KT deceased donors and recipient characteristics were similar between holidays and non-holidays. LT deceased donors during the holidays had shorter cold ischemia time (≤ 8hr, p<0.001) and were not marginal (DCD or >70 years, p=0.001). Compared to non-holidays, there were lower number of transplant during all holidays both in LT and KT (LT 15.5 vs. 15.2 transplants/day, p=0.18, Figure 1A; KT 32.4 vs. 32.1/day, p<0.001, Figure 1B). After risk adjustment, LT during holidays showed lower risk of overall mortality (HR 0.921, p=0.013; Figure 2), while KT showed a slightly higher risk of overall graft failure during holidays compared to non-holidays (HR 1.038, p= 0.052). Conclusion: While favorable donor characteristics were found, LT and KT activities were slower during holidays. Transplants during holidays were associated with significantly better LT outcomes but might lead to worse KT outcomes.

Undergraduate Medical Education
Ivanics T, **Leonard-Murali S**, **Mouzaihem H**, **Moonka D**, **Kitajima T**, **Yeddula S**, **Shamaa T**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Extreme Hyponatremia as a Risk Factor for Early Mortality after Liver Transplantation in the MELD-Sodium Era. *Am J Transplant* 2021; 21(SUPPL 1):29-30.

T. Ivanics, Henry Ford Hospital, Detroit, MI, United States

Background: The impact of hyponatremia on waitlist and post-transplant outcomes following the implementation of MELD-Na based liver allocation remains unclear. We sought to evaluate waitlist and post-liver transplant (LT) outcomes in patients with hyponatremia before and after implementation of MELD-Na based allocation. Methods: Adult primary LT candidates between 2009 and 2019 were identified in the OPTN/UNOS database. Multi-organ transplants and re-LT were excluded. Two eras were defined: before and after implementation of MELD-Na based allocation. Patients were categorized into the following groups: extreme hyponatremia (≤120 mEq/L), severe hyponatremia (121-124), moderate hyponatremia (125-129), mild hyponatremia (130-134), normal sodium (135-145), and hypernatremia (>145). 90-day waitlist outcomes and post-LT survival were compared according to era and sodium concentration using Fine-Gray and Cox proportional hazard models. Results: 87,845 patients were included in waitlist outcome analyses (N=64,911[pre- MELD-Na], N=22,934[post-MELD-Na]). In the pre-MELD-Na era, extreme hyponatremia at listing was associated with increased risk of 90-day waitlist mortality (HR:2.08,p<0.001) and lower likelihood of transplant within 90- days (HR:0.63,p<0.001). In the post-MELD-Na era, patients with extreme hyponatremia had a similar risk of waitlist mortality (HR:1.02,p=0.95) and likelihood of transplant (HR:0.90,p=0.48) as patients with normal serum sodium. Post-LT outcome analyses included 30,639 and 12,585 patients in pre and post- MELD-Na eras. While extreme hyponatremia was not associated with post-LT mortality in the pre-MELD-Na era, it was an independent risk factor for 90-day post-LT mortality in the post-MELD-Na era. (HR:5.20,p<0.001). Conclusions: With the introduction of MELD-Na based allocation, waitlist outcomes have improved in patients with extreme hyponatremia but paradoxically been associated with worse short-term post-LT survival.

Undergraduate Medical Education
Kitajima T, **Kuno Y**, **Arevalo L**, **Murray N**, **Lisznyai E**, **Shamaa T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Careful donor selection is key to improving post-liver transplant graft survival in older patients with acute-on-chronic liver failure. *Am J Transplant* 2021; 21(SUPPL 1):37-38.

T. Kitajima, Henry Ford Hospital, Detroit, MI, United States

Background: Elderly liver transplant (LT) patients with acute-on-chronic liver failure (ACLF) may be at higher risk for adverse post-transplant outcomes. This study aims to determine appropriate donor selection for older ACLF patients. Methods: Using OPTN/UNOS data, we analyzed elderly LT recipients (>60 years) with ACLF between 2004 and 2019. ACLF were identified using the EASL-CLIF criteria. Risk factors were analyzed. Based on multivariable analysis, points corresponding to hazard ratios (HRs) were assigned to the significant donor factors. Total risk score was calculated by multiplying HRs. Patients

were categorized into lower-, mid-, and higher-risk donor group based on cut-offscores determined by 25 and 75 percentile. One-year graft survival were compared in each ACLF grade. Results: A total of 8,146 older ACLF patients were eligible for this study. Multivariable model revealed national share (HR 1.52, p=0.007), DCD donors (HR 1.74, p<0.001), prolonged CIT (>6 hours, HR 1.18, p=0.021) and older donors (age>50, HR 1.34, p<0.001) had an increased risk of 1-year graft loss. Based on these donor factors, risk scores for the high, mid, and low-risk groups were >1.34, 1.01-1.34, and ≤1.00. The higher-risk group had higher adjusted risk of one-year graft loss than the lower-risk group in ACLF-1 and 3 (Figure). Use of higher-risk donors for patients with ACLF-3 was associated with worse one-year graft survival (68.0%). Conclusion: In older ACLF patients, prolonged CIT and the use of DCD, older donor, and national share organs were associated with worse post-transplant outcomes. Careful donor selection is key to ensure successful outcomes.

<u>Undergraduate Medical Education</u>
Lisznyai E, **Kitajima T**, **Delvecchio K**, **Mohamed A**, **Yeddula S**, **Shamaa T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Pre-Transplant Prognostic Nutritional Index Predicts Short-Term Outcomes after Liver Transplantation. *Am J Transplant* 2021; 21(SUPPL 1):13-14.

E. Lisznyai, Henry Ford Hospital, Detroit, MI, United States

The prognostic nutritional index (PNI) is a serum marker of nutrition and infl ammation. PNI previously predicted outcomes in liver transplant (LT) patients with recurrence of hepatocellular carcinoma. However, effi cacy of PNI to predict post-LT outcomes is unknown. We hypothesized pre-transplant PNI would predict short-term post-LT outcomes in deceased donor liver transplant (DDLT) patients. 451 patients underwent primary DDLT between 2013-2018 at our center. Re-transplants, multi-organ transplants and living donor liver transplants were excluded. Pre-transplant PNI = $(10)*$[albumin (g/dL)] + $(0.005)*$[Total Lymphocyte Count (/µL)]. PNI was analyzed as both a continuous and categorical variable. ROC curves yielded an optimal PNI cutoffof 35 to compare shortterm outcomes between PNI≥35 and PNI<35 cohorts. Risk factors for patient death within 1-year were analyzed using Cox regression models and adjusted by recipient factors at LT. Multivariable analysis associated PNI with 1-year survival as a continuous variable (HR=0.94; 95% CI=0.90-0.98; p=0.007). Of 451 patients, 215 (47.7%) had PNI<35. Pre-LT MELD score was higher in PNI<35 (22 vs. 19; p=0.028). Recipient age, gender, BMI, rates of diabetes mellitus, donor age and donors after cardiac death were equivocal. PNI<35 demonstrated lower 1-year survival (89.6% vs. 95.2%; p=0.026, Figure A). After risk adjustment, PNI<35 showed higher 6-month (HR=2.44; p=0.047) and 1-year death risk (HR=2.47; p=0.018). Multivariable analysis revealed PNI<35 at LT was an independent risk factor for patient death within 1 year (HR=2.37; p=0.023, Figure B). Lower pre-transplant PNI portended worse short-term survival in DDLT patients. PNI may be useful in evaluating pre-transplant nutritional status to optimize LT outcomes.

HFHS Publications on COVID-19

Cardiology/Cardiovascular Research

Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Clinical Quality and Safety

Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Emergency Medicine

Daxon BT, **Lark E**, Matzek LJ, Fields AR, and Haselton KJ. Nebulized Nitroglycerin for Coronavirus Disease 2019-Associated Acute Respiratory Distress Syndrome: A Case Report. *A A Pract* 2021; 15(2):e01376. PMID: 33560642. Full Text

Family Medicine

Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Infectious Diseases

Mohamed A, **Prashar R**, **Alangaden G**, **Malinzak L**, **Denny J**, **Delvecchio K**, and **Kim D**. Persistence of SARS-CoV-2 Virus in a Kidney Transplant Recipient. *Am J Transplant* 2021; 21(SUPPL 1):46.

Neurosurgery

Wang DD, **O'Neill WW**, **Zervos MJ**, **McKinnon JE**, **Allard D**, **Alangaden GJ**, **Schultz LR**, **Poisson LM**, **Chu BS**, **Kalkanis SN**, and **Suleyman G**. Association between Implementation of a Universal Face Mask Policy for Healthcare Workers in a Health Care System & SARS-CoV-2 positivity testing rate in Healthcare Workers. *J Occup Environ Med* 2021; Epub ahead of print. PMID: 33596025. Full Text

Nephrology

Mohamed A, **Prashar R**, **Alangaden G**, **Malinzak L**, **Denny J**, **Delvecchio K**, and **Kim D**. Persistence of SARS-CoV-2 Virus in a Kidney Transplant Recipient. *Am J Transplant* 2021; 21(SUPPL 1):46.

Pharmacy

Griebe K, **Jiang C**, **To L**, **Peters M**, and **MacDonald NC**. Pharmacy emergency preparedness training as a PGY2 longitudinal rotation. *Am J Health Syst Pharm* 2021; Epub ahead of print. PMID: 33594437. Full Text

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Surgery

Mohamed A, **Prashar R**, **Alangaden G**, **Malinzak L**, **Denny J**, **Delvecchio K**, and **Kim D**. Persistence of SARS-CoV-2 Virus in a Kidney Transplant Recipient. *Am J Transplant* 2021; 21(SUPPL 1):46.