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HENRY FORD HEALTH

Henry Ford Health Publication List – July 2022

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 personnel. Searches were conducted in PubMed, Embase, and Web of Science during the month, and then imported into EndNote for formatting. There are 125 unique citations listed this month, with 116 articles, 8 conference abstracts, and 1 book chapter.

Articles are listed first, followed by conference abstracts and books and book chapters. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health authors.

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Articles

Conference Abstracts

Cardiology/Cardiovascular Research
Center for Health Policy and Health Services Research
Gastroenterology
Nephrology
Neurology
Surgery

Books and Book Chapters

Nephrology

Articles

Anesthesiology

Fayed M, **Patel N**, **Angappan S**, **Nowak K**, Vasconcelos Torres F, **Penning DH**, and **Chhina AK**. Sequential Organ Failure Assessment (SOFA) Score and Mortality Prediction in Patients With Severe Respiratory Distress Secondary to COVID-19. *Cureus* 2022; 14(7):e26911. PMID: 35865183. Full Text

Anesthesiology, Pain Management and Perioperative Medicine, Henry Ford Health System, Detroit, USA.
Anesthesia, Henry Ford Health System, Detroit, USA.
Research, Henry Ford Health System, Detroit, USA.
Anesthesiology and Perioperative Medicine, Duke University Health System, Durham, USA.
Anesthesiology, Henry Ford Health System, Detroit, USA.
Anesthesiology/Critical Care, Henry Ford Health System, Detroit, USA.

Background This study looks at the validity of the sequential organ failure assessment score (SOFA) in detecting mortality in patients with Coronavirus disease of 2019 (COVID-19) pneumonia. Also, it is looking to determine the optimal SOFA score that will discriminate between mortality and survival. Methods It is a retrospective chart review of the patients admitted to Henry Ford Hospital from March 2020 to December 2020 with COVID-19 pneumonia who developed severe respiratory distress. We collected the following information; patient demographics (age, sex, body mass index), co-morbidities (history of diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, or cancer), SOFA scores (the ratio of arterial oxygen tension (PaO(2)) to the fraction of inspired oxygen, Glasgow Coma Scale (GCS) score, mean arterial pressure, serum creatinine level, bilirubin level, and platelet count) as well as inpatient mortality. Results There were 320 patients; out of these, 111 were intubated. The receiver operating characteristic (ROC) curve for SOFA at the moment of inclusion in the study had an area under the curve of 0.883. The optimal point for discrimination between mortality and survival is SOFA of 5. A SOFA score of less than two is associated with 100% survival, while a score of more than 11 is associated with 100% mortality. Conclusions SOFA score in COVID-19 patients with severe respiratory distress strongly correlates with the initial SOFA score. It is a valuable tool for predicting mortality in COVID-19 patients.

Behavioral Health Services/Psychiatry/Neuropsychology

Ahmedani BK, **Cannella CE**, **Yeh HH**, **Westphal J**, Simon GE, Beck A, Rossom RC, Lynch FL, Lu CY, Owen-Smith AA, Sala-Hamrick KJ, **Frank C**, **Akinyemi E**, **Beebani G**, **Busuito C**, Boggs JM, Daida YG, Waring S, Gui H, and **Levin AM**. Detecting and distinguishing indicators of risk for suicide using clinical records. *Transl Psychiatry* 2022; 12(1):280. PMID: 35831289. Full Text

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Harvard Pilgrim Health Care Institute & Harvard Medical School, Department of Population Health, Boston, MA, USA.
Georgia State University & Kaiser Permanente Georgia, Atlanta, GA, USA.
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Essentia Institute of Rural Health, Duluth, MN, USA.

Health systems are essential for suicide risk detection. Most efforts target people with mental health (MH) diagnoses, but this only represents half of the people who die by suicide. This study seeks to discover and validate health indicators of suicide death among those with, and without, MH diagnoses. This case-control study used statistical modeling with health record data on diagnoses, procedures, and encounters. The study included 3,195 individuals who died by suicide from 2000 to 2015 and 249,092 randomly selected matched controls, who were age 18+ and affiliated with nine Mental Health Research Network affiliated health systems. Of the 202 indicators studied, 170 (84%) were associated with suicide in the discovery cohort, with 148 (86%) of those in the validation cohort. Malignant cancer diagnoses were risk factors for suicide in those without MH diagnoses, and multiple individual psychiatric-related indicators were unique to the MH subgroup. Protective effects across MH-stratified models included diagnoses of benign neoplasms, respiratory infections, and utilization of reproductive services. MH-stratified latent class models validated five subgroups with distinct patterns of indicators in both those with and without MH. The highest risk groups were characterized via high utilization with multiple healthcare concerns in both groups. The lowest risk groups were characterized as predominantly young, female, and high utilizers of preventive services. Healthcare data include many indicators of suicide risk for those with and without MH diagnoses, which may be used to support the identification and understanding of risk as well as targeting of prevention in health systems.

Behavioral Health Services/Psychiatry/Neuropsychology

Damiani G, Tacastacas JD, **Wuerz T**, **Miller L**, **Fastenau P**, **Bailey C**, Chawa MS, Argenas A, Fiore M, Cooper KD, and **Lerner AJ**. Cognition/Psychological Burden and Resilience in Cutaneous T-Cell Lymphoma and Psoriasis Patients: Real-Life Data and Implications for the Treatment. *Biomed Res Int* 2022; 2022:8802469. PMID: 35937394. Full Text

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BACKGROUND: Psoriasis and cutaneous T-cell lymphoma (CTCL) expose patients to chronic inflammation as well as physical and psychological disabilities, but the impact of such alterations on cognitive function is unknown. OBJECTIVE: This study is aimed at determining if CTCL and psoriasis impact cognitive functioning in relation to psychological and health-related quality of life (HR-QOL) status. METHODS: A cross-sectional study was performed in an outpatient dermatology clinic of a university teaching hospital. Thirty-nine subjects with CTCL (N = 20) or psoriasis (N = 19) who met eligibility criteria were included. The cognitive domains of memory, attention and processing speed, and executive function were assessed with standard neuropsychological tests. Subjects were assessed for depression, anxiety, and HR-QOL (using the SKINDEX-29 questionnaire). RESULTS: Study participants were CTCL and psoriasis subjects; cognitive impairment was found in the domain of memory in 17.9% subjects with CTCL or psoriasis. Lower scores on executive function tests were predicted by higher (worse HR-QOL) SKINDEX-29 functioning scores ($p = 0.01$). A higher estimated baseline intellectual functioning predicted lower scores (better HR-QOL) on the symptoms and functioning domains of SKINDEX-29 ($p = 0.01$ and 0.02, respectively) and a statistical trend ($p = 0.07$) for the emotion domain. Memory and acute anxiety were adversely impacted by shorter disease duration ($p = 0.01$ for both). CONCLUSIONS: Memory impairment may be associated comorbidity in CTCL and psoriasis. Subjects with stronger cognitive resources appear to cope better with health-related quality of life (HR-QOL) challenges.

Behavioral Health Services/Psychiatry/Neuropsychology

Gautam M, **Sivananthan M**, Cotes R, and Beach S. Catatonia and Schizophrenia in a Young Man with Autism Spectrum Disorder and Clozapine-Induced Myocarditis. *Harv Rev Psychiatry* 2022; 30(4):261-269. PMID: 35849743. Full Text

From the Department of Psychiatry, Henry Ford Hospital, Detroit, MI (Drs. Gautam and Sivananthan); Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine (Dr. Cotes); Harvard Medical School (Dr. Beach); Department of Psychiatry, Massachusetts General Hospital, Boston, MA (Dr. Beach).

Behavioral Health Services/Psychiatry/Neuropsychology

Glanz JM, Binswanger IA, Clarke CL, Nguyen AP, Ford MA, Ray GT, Xu S, Hechter RC, Yarborough BJH, Roblin DW, **Ahmedani B**, Boscarino JA, Andrade SE, Rosa CL, and Campbell CI. The association between buprenorphine treatment duration and mortality: a multi-site cohort study of people who discontinued treatment. *Addiction* 2022; Epub ahead of print. PMID: 35815386. Full Text

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Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, United States.
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BACKGROUND AND AIMS: Buprenorphine is an effective medication for opioid use disorder that reduces mortality; however, many patients are not retained in buprenorphine treatment, and an optimal length of treatment after which patients can safely discontinue treatment has not been identified. This study measured the association between buprenorphine treatment duration and all-cause mortality among patients who discontinued treatment. Secondary objectives were to measure the association between treatment duration and drug overdose and opioid-related overdoses. DESIGN: Multi-site cohort study. SETTING: Eight US health systems. PARTICIPANTS: Patients who initiated and discontinued buprenorphine treatment between 1 January 2012 and 31 December 2018 (n = 6550). Outcomes occurring after patients discontinued buprenorphine treatment were compared between patients who initiated and discontinued treatment after 8-30, 31-90, 91-180, 181-365 and > 365 days. MEASUREMENTS: Covariate data were obtained from electronic health records (EHRs). Mortality outcomes were derived from EHRs and state vital statistics. Non-fatal opioid and drug overdoses were obtained from diagnostic codes. Four sites provided cause-of-death data to identify fatal drug and opioid-related overdoses. Adjusted frailty regression was conducted on a propensity-weighted cohort to assess associations between duration of the final treatment episode and outcomes. FINDINGS: The mortality rate after buprenorphine treatment was 1.82 per 100 person-years (n = 191 deaths). In regression analyses with > 365 days as the reference group, treatment duration was not associated with all-cause mortality and drug overdose (P > 0.05 for both). However, compared with > 365 days of treatment, 91-180 days of treatment was associated with increased opioid overdose risk (hazard ratio = 2.94, 95% confidence interval = 1.11-7.79). CONCLUSIONS: Among patients who discontinue buprenorphine

treatment, there appears to be no treatment duration period associated with a reduced risk for all-cause mortality. Patients who discontinue buprenorphine treatment after 91-180 days appear to be at heightened risk for opioid overdose compared with patients who discontinue after > 365 days of treatment.

Behavioral Health Services/Psychiatry/Neuropsychology
Huang Y, Liu Y, Wu Y, Tang Y, Zhang M, Liu S, Xiao L, Tao S, Xie M, Dai M, Li M, **Gui H**, and Wang Q. Patterns of Convergence and Divergence Between Bipolar Disorder Type I and Type II: Evidence From Integrative Genomic Analyses. *Front Cell Dev Biol* 2022; 10:956265. PMID: 35912095. Full Text

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Aim: Genome-wide association studies (GWAS) analyses have revealed genetic evidence of bipolar disorder (BD), but little is known about the genetic structure of BD subtypes. We aimed to investigate the genetic overlap and distinction of bipolar type I (BD I) & type II (BD II) by conducting integrative post-GWAS analyses. Methods: We utilized single nucleotide polymorphism (SNP)-level approaches to uncover correlated and distinct genetic loci. Transcriptome-wide association analyses (TWAS) were then approached to pinpoint functional genes expressed in specific brain tissues and blood. Next, we performed cross-phenotype analysis, including exploring the potential causal associations between two BD subtypes and lithium responses and comparing the difference in genetic structures among four different psychiatric traits. Results: SNP-level evidence revealed three genomic loci, SLC25A17, ZNF184, and RPL10AP3, shared by BD I and II, and one locus (MAD1L1) and significant gene sets involved in calcium channel activity, neural and synapsed signals that distinguished two subtypes. TWAS data implicated different genes affecting BD I and II through expression in specific brain regions (nucleus accumbens for BD I). Cross-phenotype analyses indicated that BD I and II share continuous genetic structures with schizophrenia and major depressive disorder, which help fill the gaps left by the dichotomy of mental disorders. Conclusion: These combined evidences illustrate genetic convergence and divergence between BD I and II and provide an underlying biological and trans-diagnostic insight into major psychiatric disorders.

Behavioral Health Services/Psychiatry/Neuropsychology
Mahr G, and **Drake CL**. Singing in tune: Carl Jung and The Red Book. *Sleep Health* 2022; Epub ahead of print. PMID: 35831228. Full Text

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Behavioral Health Services/Psychiatry/Neuropsychology
Tobin ET, **Hadwiger A**, **DiChiara A**, **Entz A**, and **Miller-Matero LR**. Demographic Predictors of Telehealth Use for Integrated Psychological Services in Primary Care During the COVID-19 Pandemic. *J Racial Ethn Health Disparities* 2022; Epub ahead of print. PMID: 35794514. Request Article

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OBJECTIVE: Prior to the COVID-19 pandemic, growing mental health needs were well documented, particularly those of diverse patient populations. The current study aims to better understand racial and psychosocial factors associated with patient utilization of integrated psychological services via telehealth during the COVID-19 pandemic within a diverse primary care clinic. METHODS: Retrospective chart reviews were completed for patients seen by an integrated psychology team within a general internal medicine clinic at a large urban health system during the year 2020. Demographics were extracted from the medical record. Multivariate logistic regression analyses were conducted to examine demographic predictors for (1) telehealth video visits vs. audio only telehealth visits and (2) in-person vs. telehealth visits (both video and audio). RESULTS: Older patients, Black patients, and those with Medicare and Medicaid were more likely to complete audio only telehealth visits vs. video visits. There were no significant demographic predictors when comparing in-person vs. telehealth (both video and audio). DISCUSSION: Some underserved and vulnerable patient populations are more likely to utilize audio-only integrated psychological visits to video visits. The utilization of audio visits over video for certain demographics speaks to the need to better understand how this type of care may benefit psychological services in the future and continued advocacy to extend audio mental health visits beyond the public health emergency to address patient populations with significant mental health needs.

Cardiology/Cardiovascular Research

Gupta K, and **Ananthasubramaniam K**. If you don't kill pollution it could kill you: pathophysiologic insights into pollution mediated cardiovascular risk through FDG PET imaging. *J Nucl Cardiol* 2022; 1-4. Epub ahead of print. PMID: 35859225. Full Text

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Cardiology/Cardiovascular Research

Kanwar MK, Pagani FD, Mehra MR, Estep JD, Pinney SP, Silvestry SC, Uriel N, Goldstein DJ, Long J, Cleveland JC, Jr., Kormos RL, Wang A, Chuang J, and **Cowger JA**. Center Variability in Patient Outcomes Following HeartMate 3 Implantation: An Analysis of the MOMENTUM 3 Trial. *J Card Fail* 2022; 28(7):1158-1168. PMID: 35504508. Full Text

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BACKGROUND: As left ventricular assist device (LVAD) survival rates continue to improve, evaluating site-specific variability in outcomes can facilitate identifying targets for quality-improvement initiative opportunities in the field. METHODS: Deidentified center-specific outcomes were analyzed for HeartMate 3 (HM3) patients enrolled in the MOMENTUM 3 pivotal and continued access protocol trials. Centers < 25th percentile for HM3 volumes were excluded. Variability in risk-adjusted center mortality was assessed at 90 days and 2 years (conditional upon 90-day survival). Adverse event (AE) rates were compared across centers. RESULTS: In the 48 included centers (1958 patients), study-implant volumes ranged between 17 and 106 HM3s. Despite similar trial-inclusion criteria, patient demographics varied across sites, including age quartile ((Q)1-Q3:57-62 years), sex (73%-85% male), destination therapy intent (60%-

84%), and INTERMACS profile 1-2 (16%-48%). Center mortality was highly variable, nadiring at ≤ 3.6% (≤ 25th percentile) and peaking at ≥ 10.4% (≥ 75th percentile) at 90 days and ≤ 10.2% and ≥ 18.7%, respectively, at 2 years. Centers with low mortality rates tended to have lower 2-year AE rates, but no center was a top performer for all AEs studied. CONCLUSIONS: Mortality and AEs were highly variable across MOMENTUM 3 centers. Studies are needed to improve our understanding of the drivers of outcome variability and to ascertain best practices associated with high-performing centers across the continuum of intraoperative to chronic stages of LVAD support.

Cardiology/Cardiovascular Research

Keteyian SJ, and **Michaels A**. Heart Failure in Cardiac Rehabilitation: A REVIEW AND PRACTICAL CONSIDERATIONS. *J Cardiopulm Rehabil Prev* 2022; Epub ahead of print. PMID: 35836338. Full Text

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PURPOSE: Exercise cardiac rehabilitation (CR) represents an evidence-based therapy for patients with heart failure with reduced ejection fraction (HFrEF) and this article provides a concise review of the relevant exercise testing and CR literature, including aspects unique to their care. CLINICAL CONSIDERATIONS: A hallmark feature of HFrEF is exercise intolerance (eg, early-onset fatigue). Drug therapies for HFrEF target neurohormonal pathways to blunt negative remodeling of the cardiac architecture and restore favorable loading conditions. Guideline drug therapy includes β-adrenergic blocking agents; blockade of the renin-angiotensin system; aldosterone antagonism; sodium-glucose cotransport inhibition; and diuretics, as needed. EXERCISE TESTING AND TRAINING: Various assessments are used to quantify exercise capacity in patients with HFrEF, including peak oxygen uptake measured during an exercise test and 6-min walk distance. The mechanisms responsible for the exercise intolerance include abnormalities in (a) central transport (chronotropic response, stroke volume) and (b) the diffusion/utilization of oxygen in skeletal muscles. Cardiac rehabilitation improves exercise capacity, intermediate physiologic measures (eg, endothelial function and sympathetic nervous system activity), health-related quality of life (HRQoL), and likely clinical outcomes. The prescription of exercise in patients with HFrEF is generally similar to that for other patients with cardiovascular disease; however, patients having undergone an advanced surgical therapy do present with features that require attention. SUMMARY: Few patients with HFrEF enroll in CR and as such, many miss the derived benefits, including improved exercise capacity, a likely reduction in risk for subsequent clinical events (eg, rehospitalization), improved HRQoL, and adoption of disease management strategies.

Cardiology/Cardiovascular Research

Megaly M, Buda K, Mashayekhi K, Werner GS, Grantham JA, Rinfret S, McEntegart M, Brilakis ES, and **Alaswad K**. Comparative Analysis of Patient Characteristics in Chronic Total Occlusion Revascularization Studies: Trials vs Real-World Registries. *JACC Cardiovasc Interv* 2022; 15(14):1441-1449. PMID: 35863793. Full Text

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BACKGROUND: The few randomized controlled trials (RCTs) on chronic total occlusion (CTO) percutaneous coronary intervention (PCI) are subject to selection bias. OBJECTIVES: The purpose of this study was to evaluate the differences between real-world CTO patients and those enrolled in RCTs. METHODS: This study performed a meta-analysis of national and dedicated CTO PCI registries and

compared patient characteristics and outcomes with those of RCTs that randomized patients to CTO PCI versus medical therapy. Given the large sample size differences between RCTs and registries, the study focused on the absolute numbers and their clinical significance. The study considered a 5% relative difference between groups to be potentially clinically relevant. RESULTS: From 2012 to 2022, 6 RCTs compared CTO PCI versus medical therapy (n = 1,047) and were compared with 15 registries (5 national and 10 dedicated CTO PCI registries). Compared with registry patients, RCT patients had fewer comorbidities, including diabetes, hypertension, previous myocardial infarction, and prior coronary artery bypass graft surgery. RCT patients had shorter CTO length (29.6 ± 19.7 mm vs 32.6 ± 23.0 mm, a relative difference of 9.2%) and lower Japan-Chronic Total Occlusion Score scores (2.0 ± 1.1 vs 2.3 ± 1.2, a relative difference of 13%) compared with those enrolled in dedicated CTO registries. Procedural success was similar between RCTs (84.5%) and dedicated CTO registries (81.4%) but was lower in national registries (63.9%). CONCLUSIONS: There is a paucity of randomized data on CTO PCI outcomes (6 RCTs, n = 1,047). These patients have lower risk profiles and less complex CTOs than those in real-world registries. Current evidence from RCTs may not be representative of real-world patients and should be interpreted within its limitation.

Cardiology/Cardiovascular Research

Megaly M, Sedhom R, Elbadawi A, Buda K, **Basir MB**, Garcia S, Brilakis ES, Rinfret S, and **Alaswad K**. Trends and Outcomes of Myocardial Infarction in Patients With Previous Coronary Artery Bypass Surgery. *Am J Cardiol* 2022; Epub ahead of print. PMID: 35870988. Full Text

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Data on myocardial infarction (MI) treatment in patients with previous coronary artery bypass grafting (CABG) is limited. We queried the Nationwide Readmissions Database to identify hospitalizations of patients with MI from 2016 to 2019. Among hospitalized patients presenting with MI, 10.3% had previous CABG. Patients with MI who had previous CABG were less likely to be revascularized than those without previous CABG for both ST-segment elevation MI (STEMI) (46.4% vs 68.4%) and non-ST-segment elevation MI (NSTEMI) (30.8% vs 36.7%). CABG was associated with a lower risk of death in NSTEMI patients (odds ratio [OR] 0.84, 95% confidence interval [CI] 0.82 to 0.86), but a higher risk in STEMI patients (OR 1.06, 95% CI 1.01 to 1.13). Revascularization was associated with a lower risk of in-hospital death in patients with previous CABG presenting with STEMI (OR 0.30, 95% CI 0.26 to 0.35) and NSTEMI (OR 0.21, 95% CI 0.19 to 0.23).

Cardiology/Cardiovascular Research

Napp LC, Westenfeld R, Møller JE, Pappalardo F, Ibrahim K, Bonello L, Wilkins C, Pershad A, Mannino SF, Schreiber TL, Hall PA, Medjamia AM, Haurand JM, Sieweke JT, Schäfer A, Grines CL, Burkhoff D, Moses JW, Ohman EM, **O'Neill WW**, Kapur NK, and Bauersachs J. Impella Mechanical Circulatory Support for Takotsubo Syndrome With Shock: A Retrospective Multicenter Analysis. *Cardiovasc Revasc Med* 2022; 40:113-119. PMID: 34916157. Full Text

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OBJECTIVES: To analyze the characteristics and outcome of Impella mechanical circulatory support (MCS) for Takotsubo syndrome (TS) with cardiogenic shock. BACKGROUND: TS is an acute heart failure syndrome characterized by transient severe reduction of left ventricular (LV) systolic function, with cardiogenic shock occurring in around 10% of patients. Since inotropes should be avoided due to their role in TS pathogenesis and aggravation of LV outflow tract obstruction, the use of MCS as treatment is a viable treatment option, however, studies are lacking. METHODS: The catheter-based ventricular assist device (cVAD) registry and local MCS databases were screened for TS patients with cardiogenic shock (TS-CS) supported with an Impella percutaneous ventricular assist device (pVAD). Patient and treatment characteristics and in-hospital outcomes were retrospectively analyzed. RESULTS: At 10 US and European centers, 16 TS-CS patients supported with an Impella pVAD were identified between December 2013 and May 2018 (mean age, 61.8 ± 15.5 years; 87.5% women). LV ejection fraction (LVEF) at presentation was severely reduced (mean, 19.4 ± 8.3%). Prior to MCS, 13 patients (81.3%) were mechanically ventilated, 4 patients (25.0%) had been resuscitated, and mean serum lactate was 4.7 ± 3.5 mmol/L. Mean duration of Impella support was 1.9 ± 1.0 days (range, 1-4 days). Thirteen patients (81.3%) survived to discharge, and all survivors experienced cardiac recovery with significant improvement of LVEF at discharge compared to baseline (20.4 ± 8.8 vs. 52.9 ± 12.0, $P < 0.001$). CONCLUSIONS: This is the first series of TS-CS patients supported with an Impella pVAD. Mortality was low, and LV systolic function recovered in all survivors. Prospective studies of Impella support in this special condition are warranted.

Cardiology/Cardiovascular Research
O'Neill WW, **Wang DD**, Polak S, Moses JW, Josephy N, **Koenig G**, Kim RJ, Lansky A, Bellumkonda L, Douglas PS, and Kapur NK. Left Ventricular Remodeling After Anterior-STEMI PCI: Imaging Observations in the Door-to-Unload (DTU) Pilot Trial. *J Invasive Cardiol* 2022; 34(8):E611-e619. PMID: 35830361.

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OBJECTIVES: To determine the predictive value of cardiac magnetic resonance (CMR) and echocardiographic parameters on left ventricular (LV) remodeling in ST-segment elevation myocardial infarction (STEMI) patients without cardiogenic shock and treated with mechanical LV unloading followed by immediate or delayed percutaneous coronary intervention (PCI)-mediated reperfusion. BACKGROUND: In STEMI, infarct size (IS) directly correlates with major cardiovascular outcomes. Preclinical models demonstrate mechanical LV unloading before reperfusion reduces IS. The door-to-unload (DTU)-STEMI pilot trial evaluated the safety and feasibility of LV unloading and delayed reperfusion in patients with STEMI. METHODS: This multicenter, prospective, randomized, safety and feasibility trial evaluated patients with anterior STEMI randomized 1:1 to LV unloading with the Impella CP (Abiomed) followed by immediate reperfusion vs delayed reperfusion after 30 minutes of unloading. Patients were assessed by CMR at 3-5 days and 30 days post PCI. Echocardiographic evaluations were

performed at 3-5 and 90 days post PCI. At 3-5 days post PCI, patients were compared based on IS as percentage of LV mass (group 1 ≤25%, group 2 >25%). Selection of IS threshold was performed post hoc. RESULTS: Fifty patients were enrolled from April 2017 to May 2018. At 90 days, group 1 (IS ≤25%) exhibited improved LV ejection fraction (from 53.1% to 58.9%; P=.001) and group 2 (IS >25%) demonstrated no improvement (from 37.6% to 39.1%; P=.55). LV end-diastolic volume and end-systolic volume were unchanged in group 1 and worsened in group 2. There was correlation between 3-5 day and 30-day CMR measurements of IS and 90-day echocardiography-derived LV ejection fraction. CONCLUSIONS: Immediate 3-5 day post-therapy IS by CMR correlates with 90-day echocardiographic LVEF and indices of remodeling. Patients with post-therapy IS >25% demonstrated evidence of adverse remodeling. Larger studies are needed to corroborate these findings with implications on patient management and prognosis.

Cardiology/Cardiovascular Research

Qintar M, **Wang DD**, **Lee J**, **Villablanca P**, **Eng MH**, **Frisoli T**, **O'Neill BP**, and **O'Neill WW**. Transcatheter vacuum-assisted left-sided mass extraction with the AngioVac system. *Catheter Cardiovasc Interv* 2022; Epub ahead of print. PMID: 35900207. Full Text

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OBJECTIVES: To study the safety and efficacy of AngioVac for left-sided transcatheter vacuum-assisted mass extraction (TVME). BACKGROUND: The AngioVac system is approved for right-sided TVME and has emerged as an effective and safe alternative for open surgical treatment. The use of the AngioVac device for aspiration of left-sided TVME has been limited. METHODS: Consecutive patients from two Michigan centers who underwent left-sided TVME were included. Data on patient demographics, procedural information, in-hospital and follow-up events were collected through electronic medical records review. Technical success was defined as aspirating of 70%-100% of the material. RESULTS: Ten patients (mean age 58.3 [±17.3] years, 50% male) were included. Indications for TMVE were in large for recurrent embolic events. All patients underwent bilateral cerebro-embolic protection using the Sentinel device. The total mean procedure time was 192.5 (±47.5) min of which the meantime for active aspiration (bypass time) was 9.3 (±4.2) min. The circuit configuration was: arteriovenous (AV) in four cases and arterioarterial (AA) in six cases. Successful aspiration was achieved in 80% of cases. No complications were reported (range follow-up 1-16 months). CONCLUSIONS: Our small case series demonstrates the feasibility and safety of the AngioVac system in left-sided mass extraction. Larger trials are needed to further demonstrate its effectiveness and safety and potentially apply for on-label use.

Cardiology/Cardiovascular Research

Rao VN, Kaltenbach LA, Granger BB, Fonarow GC, Al-Khalidi HR, Albert NM, Butler J, Allen LA, **Lanfear DE**, Ariely D, Miller JM, Brodsky MA, LaLonde TA, Lafferty JC, Granger CB, Hernandez AF, and DeVore AD. The Association of Digital Health Application Use with Heart Failure Care and Outcomes: Insights from CONNECT-HF. *J Card Fail* 2022; Epub ahead of print. PMID: 35905867. Full Text

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BACKGROUND: It is unknown if digital applications may improve guideline-directed medical therapy (GDMT) and outcomes in heart failure with reduced ejection fraction (HFrEF). METHODS AND RESULTS: CONNECT-HF included an optional, prospective ancillary study of a mobile health application among hospitalized patients for HFrEF. Digital users were matched to nonusers from the usual care group. Co-primary outcomes included change in opportunity-based composite HF quality scores and HF rehospitalization or all-cause mortality. Among 2,431 patients offered digital applications across the United States, 1,526 (63%) had limited digital access or insufficient data, 425 (17%) were digital users, and 480 (20%) declined use. Digital users were similar in age to those who declined use (mean 58 vs. 60 years, p=0.031). Digital users (N=368) versus matched nonusers (N=368) had improved composite HF quality scores (48.0% vs. 43.6%; +4.76% [3.27-6.24]; p=0.001) and composite clinical outcomes (33.0% vs. 39.6%; HR 0.76 [0.59-0.97]; p=0.027). CONCLUSIONS: Among participants in CONNECT-HF, use of digital applications was modest, yet associated with higher HF quality of care scores, including use of GDMT, and better clinical outcomes. While cause and effect cannot be determined from this study, the application of technology to guide GDMT use and dosing among patients with HFrEF warrants further investigation.

Cardiology/Cardiovascular Research

Sedhom R, Elbadawi A, **Megaly M**, Jaber WA, Cameron SJ, Weinberg I, Mamas MA, and Elgendy IY. Hospital procedural volume and outcomes with catheter-directed intervention for pulmonary embolism: a nationwide analysis. *Eur Heart J Acute Cardiovasc Care* 2022; Epub ahead of print. PMID: 35830539.
Full Text

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AIMS: There is limited data on the association between hospital catheter-directed intervention (CDI) volume and outcomes among patients with acute pulmonary embolism (PE). METHODS AND RESULTS: The Nationwide Readmissions Database years 2016-2019 was utilized to identify hospitalizations undergoing CDI for acute PE. Hospitals were divided into tertiles based on annual CDI volume; low-volume (1-3 procedures), moderate-volume (4-12 procedures) and high-volume (>12 procedures). The primary outcome was all-cause in-hospital mortality. Among 1 436 382 PE admissions, 2.6% underwent CDI; 5.6% were in low-volume, 17.3% in moderate-volume and 77.1% in high-volume hospitals. There was an inverse relationship between hospital CDI volume and in-hospital mortality (coefficient -0.344, $P < 0.001$). On multivariable regression analysis, hospitals with high CDI volume were associated with lower in-hospital mortality compared with hospitals with low CDI volume (adjusted odds ratio [OR] 0.71; 95% confidence interval [CI] 0.53, 0.95). Additionally, there was an inverse association between CDI volume and length of stay (LOS) (regression coefficient -0.023, 95% CI -0.027, -0.019) and cost (regression coefficient -74.6, 95% CI -98.8, -50.3). There were no differences in major bleeding and 30-

day unplanned readmission rates between the three groups. CONCLUSION: In this contemporary observational analysis of PE admissions undergoing CDI, there was an inverse association between hospital CDI volume and in-hospital mortality, LOS, and cost. Major bleeding and 30-day unplanned readmission rates were similar between the three groups.

Cardiology/Cardiovascular Research
Simsek B, Gorgulu S, Kostantinis S, Karacsonyi J, **Alaswad K**, Jaffer FA, Doshi D, Goktekin O, Kerrigan J, Haddad E, Patel M, Rinfret S, Jaber WA, Nicholson W, Rafeh NA, Allana S, Koutouzis M, and Brilakis ES. Radial access for chronic total occlusion percutaneous coronary intervention: Insights from the PROGRESS-CTO registry. *Catheter Cardiovasc Interv* 2022; Epub ahead of print. PMID: 35870177. Full Text

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Use of radial access for chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has been increasing. We examined the clinical characteristics and procedural outcomes of patients who underwent CTO PCI with radial versus femoral access in the Prospective Global Registry for the Study of CTO Intervention (PROGRESS-CTO, NCT02061436). Of 10,954 patients who underwent CTO PCI at 55 centers in 7 countries between 2012 and 2022, 2578 (24%) had a radial only approach. Patients who underwent radial only access were younger (63 ± 10 vs. 65 ± 10, years, $p < 0.001$), more likely to be men (84% vs. 81%, $p = 0.001$), and had significantly lower prevalence of comorbidities compared with the femoral access group including diabetes mellitus (39% vs. 45%, $p < 0.001$) and coronary artery bypass graft surgery (57% vs. 64%, $p < 0.001$). In addition, radial only cases had lower angiographic complexity with lower J-CTO and PROGRESS-CTO scores. After adjusting for potential confounders, radial only access was associated with lower risk of access site complications (odds ratio [OR]: 0.45, 95% confidence interval [CI]: 0.22-0.91), similar technical success (OR: 0.87, 95% CI: 0.74-1.04) and major adverse cardiovascular events (MACE) (OR: 0.65, 95% CI: 0.40-1.07), compared with the femoral access group. Radial only access was used in 24% of CTO PCIs and was associated with lower access site complications, and similar technical success and MACE as compared with the femoral access group.

Cardiology/Cardiovascular Research
Simsek B, Kostantinis S, Karacsonyi J, **Alaswad K**, Jaffer FA, Doshi D, Gorgulu S, Goktekin O, Kerrigan J, Haddad E, Rinfret S, Jaber WA, Nicholson W, Abi Rafeh N, Allana S, Koutouzis M, Tsiafoutis Y, and Brilakis ES. Antegrade dissection and re-entry versus parallel wiring in chronic total occlusion percutaneous coronary intervention: Insights from the PROGRESS-CTO registry. *Catheter Cardiovasc Interv* 2022; Epub ahead of print. PMID: 35900111. Full Text

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BACKGROUND: The comparative efficacy and safety of parallel wiring versus antegrade dissection and re-entry (ADR) in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is controversial. METHODS: We compared the clinical and angiographic characteristics and outcomes of parallel wiring versus ADR after failed antegrade wiring in a large, multicenter CTO PCI registry. RESULTS: A total of 1725 CTO PCI procedures with failed antegrade wiring with a single wire were approached with parallel wiring (692) or ADR (1033) at the discretion of the operator. ADR patients were older (65 ± 10 vs. 62 ± 10, years, $p < 0.001$) and had higher prevalence of comorbidities, such as diabetes mellitus (43% vs. 32%, $p < 0.001$), prior coronary artery bypass graft surgery (31% vs. 19%, $p < 0.001$), and lower left ventricular ejection fraction (50 ± 14 vs. 53 ± 11%, $p < 0.001$). The ADR group had higher J-CTO (2.8 ± 1.1 vs. 2.1 ± 1.3, $p < 0.001$) and PROGRESS-CTO (1.6 ± 1.1 vs. 1.2 ± 1.0, $p < 0.001$) scores. Equipment use including guidewires, balloons, and microcatheters was higher, and the procedures lasted longer in the ADR group. Technical success (78% vs. 75%, $p = 0.046$) and major adverse cardiovascular events (composite of all-cause mortality, stroke, acute myocardial infarction, emergency surgery or re-PCI, and pericardiocentesis) (3.7% vs. 1.9%, $p = 0.029$) were higher in the ADR group, with similar procedural success (75% vs. 73%, $p = 0.166$). CONCLUSION: In lesions that could not be crossed with antegrade wiring, ADR was associated with higher technical but not procedural success, and also higher MACE compared with parallel wiring.

Cardiology/Cardiovascular Research

Simsek B, Kostantinis S, Karacsonyi J, **Alaswad K**, Krestyaninov O, Khelimskii D, Davies R, Rier J, Goktekin O, Gorgulu S, ElGuindy A, Chandwaney RH, Patel M, Abi Rafeh N, Karmpaliotis D, Masoumi A, Khatri JJ, Jaffer FA, Doshi D, Poommipanit PB, Rangan BV, Sanvodal Y, Choi JW, Elbarouni B, Nicholson W, Jaber WA, Rinfret S, Koutouzis M, Tsiafoutis I, Yeh RW, Burke MN, Allana S, Mastrodemos OC, and Brilakis ES. Predicting Periprocedural Complications in Chronic Total Occlusion Percutaneous Coronary Intervention: The PROGRESS-CTO Complication Scores. *JACC Cardiovasc Interv* 2022; 15(14):1413-1422. PMID: 35863789. Full Text

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BACKGROUND: Chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is associated with increased risk of periprocedural complications. Estimating the risk of complications facilitates risk-benefit assessment and procedural planning. OBJECTIVES: This study sought to develop risk scores for in-hospital major adverse cardiovascular events (MACE), mortality, pericardiocentesis, and acute myocardial infarction (MI) in patients undergoing CTO PCI. METHODS: The study analyzed the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; NCT02061436) and created risk scores for MACE, mortality, pericardiocentesis, and acute MI. Logistic regression prediction modeling was used to identify independently associated variables, and models were internally validated with bootstrapping. RESULTS: The incidence of periprocedural complications among 10,480 CTO PCIs was as follows: MACE 215 (2.05%), mortality 47 (0.45%), pericardiocentesis 83 (1.08%), and acute MI 66 (0.63%). The final model for MACE included ≥65 years of age (1 point), moderate-severe calcification (1 point), blunt stump (1 point), antegrade dissection and re-entry (ADR) (1 point), female (2 points), and retrograde (2 points); the final model for mortality included ≥65 years of age (1 point), left ventricular ejection fraction ≤45% (1 point), moderate-severe calcification (1 point), ADR (1 point), and retrograde (1 point); the final model for pericardiocentesis included ≥65 years of age (1 point), female (1 point), moderate-severe calcification (1 point), ADR (1 point), and retrograde (2 points); the final model for acute MI included prior coronary artery bypass graft surgery (1 point), atrial fibrillation (1 point), and blunt stump (1 point). The C-statistics of the models were 0.74, 0.80, 0.78, 0.72 for MACE, mortality, pericardiocentesis, and acute MI, respectively. CONCLUSIONS: The PROGRESS-CTO complication risk scores can facilitate estimation of the periprocedural complication risk in patients undergoing CTO PCI.

Cardiology/Cardiovascular Research

So CY, **Kang G**, **Lee JC**, **Frisoli TM**, **O'Neill B**, **Wang DD**, Eng MH, **O'Neill W**, and **Villablanca PA**. Transcatheter edge-to-edge repair for acute mitral regurgitation with cardiogenic shock secondary to mechanical complication. *Cardiovasc Revasc Med* 2022; Epub ahead of print. PMID: 35882600. Full Text

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INTRODUCTION: Acute MR due to mechanical mitral valve (MV) complications frequently results in cardiogenic shock and requires emergency surgical intervention. There was limited evidence for alternative treatment like MitraClip for patients at prohibitive surgical risk. We aimed to study the technical features and outcomes of emergency transcatheter edge-to-edge repair (TEER) using the MitraClip system for patients with cardiogenic shock (CS) secondary to acute mitral regurgitation (MR) and mechanical MV complication. MATERIAL AND METHODS: We performed institutional review and systemic literature review to identify all TEER for CS patients due to acute mitral regurgitation and mechanical MV complication. Clinical endpoints included device success rate assessed at the end of procedure, ability to wean off MCS, all-cause and cardiovascular mortality at 30-day. RESULTS: Eight patients were identified from institutional review. Detail anatomical analysis found that patients with mechanical MV complications related to myocardial infarction had a lower transseptal height achieved during MitraClip (3.6 ± 0.1 cm vs 4.3 ± 0.3 cm, p = 0.03) than those not related. Pooled analysis for cases from institutional review (n = 8) and systemic literature review (n = 16) was performed. The device success rate was 68.8 %. Seventy-five percent (n = 18) cases required mechanical circulatory support (MCS), and 94.4 % were able to wean off MCS. At 30-day, the cardiovascular mortality was 4.5 % and the all-cause mortality was 9.1 %. CONCLUSIONS: In CS patients due to acute MR and mechanical MV complications, TEER with/without MCS was feasible with a reasonable device success rate.

Cardiology/Cardiovascular Research

Thompson MP, Yaser JM, Forrest A, **Keteyian SJ**, and Sukul D. Evaluating the Feasibility of a Statewide Collaboration to Improve Cardiac Rehabilitation Participation: THE MICHIGAN CARDIAC REHAB NETWORK. *J Cardiopulm Rehabil Prev* 2022; Epub ahead of print. PMID: 35831233. Full Text

Section of Health Services Research and Quality, Department of Cardiac Surgery (Dr Thompson) and Division of Cardiovascular Medicine, Department of Internal Medicine (Dr Sukul), Michigan Medicine, Ann Arbor; Michigan Value Collaborative, Ann Arbor (Dr Thompson and Ms Yaser); Blue Cross Blue Shield of Michigan Cardiovascular Consortium, Ann Arbor (Ms Forrest and Dr Sukul); and Division of Cardiovascular Medicine, Henry Ford Health System, Detroit, Michigan (Dr Keteyian).

PURPOSE: Regional quality improvement collaboratives may provide one solution to improving cardiac rehabilitation (CR) participation through performance benchmarking and provider engagement. The objective of this study was to evaluate the feasibility of the Michigan Cardiac Rehab Network to improve CR participation. METHODS: Multipayer claims data from the Michigan Value Collaborative were used to identify hospitals and CR facilities and assemble a multidisciplinary advisory group. Univariate analyses described participating hospital characteristics and hospital-level rates of CR performance across eligible conditions including enrollment within 1 yr, mean days to first CR visit, and mean number of CR visits within 1 yr. Three diverse CR facilities were chosen for virtual site visits to identify areas of success and barriers to improvement. RESULTS: A total of 95 hospitals and 84 CR facilities were identified, with 48 hospitals (51%) providing interventional cardiology services and 33 (35%) providing cardiac surgical services. A 17-member multidisciplinary advisory group was assembled representing 13 institutions and diverse roles. Statewide CR enrollment across eligible admissions was 33.4%, with wide variation in CR performance measures across participating hospitals and eligible admissions. Virtual site visits revealed individual successes in improving CR participation but a variety of barriers to participation related to referrals, capacity and staffing constraints, and geographic and financial barriers. CONCLUSIONS: This study demonstrated the feasibility of creating a statewide collaboration of hospitals and CR facilities centered around the goal of equitably improving CR enrollment for all eligible patients in Michigan that is supported by a multidisciplinary advisory group and performance benchmarking.

Cardiology/Cardiovascular Research

Ya'Qoub L, Elgendy IY, and Pepine CJ. Non-obstructive Plaque and Treatment of INOCA: More to Be Learned. *Curr Atheroscler Rep* 2022; Epub ahead of print. PMID: 35781776. Full Text

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PURPOSE OF REVIEW: A significant proportion of patients evaluated for chest pain have ischemia with non-obstructive coronary artery disease (INOCA). Studies have shown INOCA is associated with increased risk of major adverse cardiac events and significant burden on the health care system. RECENT FINDINGS: While there is scarce scientific evidence on management of INOCA, the CorMicA trial showed that stratified medical therapy based on the type of INOCA improved patients' symptoms and quality of life. There are multiple ongoing trials, including Women's IschemiA Trial to Reduce Events in Non-ObstRuctIve CORonary Artery Disease (WARRIOR trial), assessing the benefit of intensive medical therapy versus usual care for this increasingly recognized clinical entity. In this review, we discuss the definition of INOCA, epidemiology and risk factors, pathophysiology, and management as well as the current knowledge gaps and ongoing clinical trials in this arena.

Center for Health Policy and Health Services Research

Ahmedani BK, **Cannella CE**, **Yeh HH**, **Westphal J**, Simon GE, Beck A, Rossom RC, Lynch FL, Lu CY, Owen-Smith AA, Sala-Hamrick KJ, **Frank C**, **Akinyemi E**, **Beebani G**, **Busuito C**, Boggs JM, Daida YG, Waring S, Gui H, and **Levin AM**. Detecting and distinguishing indicators of risk for suicide using clinical records. *Transl Psychiatry* 2022; 12(1):280. PMID: 35831289. Full Text

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Health systems are essential for suicide risk detection. Most efforts target people with mental health (MH) diagnoses, but this only represents half of the people who die by suicide. This study seeks to discover and validate health indicators of suicide death among those with, and without, MH diagnoses. This case-control study used statistical modeling with health record data on diagnoses, procedures, and encounters. The study included 3,195 individuals who died by suicide from 2000 to 2015 and 249,092 randomly selected matched controls, who were age 18+ and affiliated with nine Mental Health Research Network affiliated health systems. Of the 202 indicators studied, 170 (84%) were associated with suicide in the discovery cohort, with 148 (86%) of those in the validation cohort. Malignant cancer diagnoses were risk factors for suicide in those without MH diagnoses, and multiple individual psychiatric-related indicators were unique to the MH subgroup. Protective effects across MH-stratified models included diagnoses of benign neoplasms, respiratory infections, and utilization of reproductive services. MH-stratified latent class models validated five subgroups with distinct patterns of indicators in both those with and without MH. The highest risk groups were characterized via high utilization with multiple healthcare concerns in both groups. The lowest risk groups were characterized as predominantly young, female, and high utilizers of preventive services. Healthcare data include many indicators of suicide risk for those with and without MH diagnoses, which may be used to support the identification and understanding of risk as well as targeting of prevention in health systems.

Center for Health Policy and Health Services Research

Glanz JM, Binswanger IA, Clarke CL, Nguyen AP, Ford MA, Ray GT, Xu S, Hechter RC, Yarborough BJH, Roblin DW, **Ahmedani B**, Boscarino JA, Andrade SE, Rosa CL, and Campbell CI. The association between buprenorphine treatment duration and mortality: a multi-site cohort study of people who discontinued treatment. *Addiction* 2022; Epub ahead of print. PMID: 35815386. Full Text

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BACKGROUND AND AIMS: Buprenorphine is an effective medication for opioid use disorder that reduces mortality; however, many patients are not retained in buprenorphine treatment, and an optimal length of treatment after which patients can safely discontinue treatment has not been identified. This study measured the association between buprenorphine treatment duration and all-cause mortality among patients who discontinued treatment. Secondary objectives were to measure the association between treatment duration and drug overdose and opioid-related overdoses. DESIGN: Multi-site cohort study. SETTING: Eight US health systems. PARTICIPANTS: Patients who initiated and discontinued buprenorphine treatment between 1 January 2012 and 31 December 2018 (n = 6550). Outcomes occurring after patients discontinued buprenorphine treatment were compared between patients who initiated and discontinued treatment after 8-30, 31-90, 91-180, 181-365 and > 365 days. MEASUREMENTS: Covariate data were obtained from electronic health records (EHRs). Mortality outcomes were derived from EHRs and state vital statistics. Non-fatal opioid and drug overdoses were obtained from diagnostic codes. Four sites provided cause-of-death data to identify fatal drug and opioid-related overdoses. Adjusted frailty regression was conducted on a propensity-weighted cohort to assess associations between duration of the final treatment episode and outcomes. FINDINGS: The mortality rate after buprenorphine treatment was 1.82 per 100 person-years (n = 191 deaths). In regression analyses with > 365 days as the reference group, treatment duration was not associated with all-cause mortality and drug overdose (P > 0.05 for both). However, compared with > 365 days of treatment, 91-180 days of treatment was associated with increased opioid overdose risk (hazard ratio = 2.94, 95% confidence interval = 1.11-7.79). CONCLUSIONS: Among patients who discontinue buprenorphine treatment, there appears to be no treatment duration period associated with a reduced risk for all-cause mortality. Patients who discontinue buprenorphine treatment after 91-180 days appear to be at heightened risk for opioid overdose compared with patients who discontinue after > 365 days of treatment.

Center for Health Policy and Health Services Research
Ray GT, Altschuler A, Karmali R, Binswanger I, Glanz JM, Clarke CL, **Ahmedani B**, Andrade SE, Boscarino JA, Clark RE, Haller IV, Hechter R, Roblin DW, Sanchez K, Yarborough BJ, Bailey SR, McCarty D, Stephens KA, Rosa CL, Rubinstein AL, and Campbell CI. Development and implementation of a prescription opioid registry across diverse health systems. *JAMIA Open* 2022; 5(2):ooac030. PMID: 35651523. Full Text

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OBJECTIVE: Develop and implement a prescription opioid registry in 10 diverse health systems across the US and describe trends in prescribed opioids between 2012 and 2018. MATERIALS AND METHODS: Using electronic health record and claims data, we identified patients who had an outpatient fill for any prescription opioid, and/or an opioid use disorder diagnosis, between January 1, 2012 and December 31, 2018. The registry contains distributed files of prescription opioids, benzodiazepines and other select medications, opioid antagonists, clinical diagnoses, procedures, health services utilization, and health plan membership. Rates of outpatient opioid fills over the study period, standardized to health system demographic distributions, are described by age, gender, and race/ethnicity among members without cancer. RESULTS: The registry includes 6 249 710 patients and over 40 million outpatient opioid fills. For the combined registry population, opioid fills declined from a high of 0.718 per member-year in 2013 to 0.478 in 2018, and morphine milligram equivalents (MMEs) per fill declined from 985 MMEs per fill in 2012 to 758 MMEs in 2018. MMEs per member declined from 692 MMEs per member in 2012 to 362 MMEs per member in 2018. CONCLUSION: This study established a population-based opioid registry across 10 diverse health systems that can be used to address questions related to opioid use. Initial analyses showed large reductions in overall opioid use per member among the combined health systems. The registry will be used in future studies to answer a broad range of other critical public health issues relating to prescription opioid use.

Center for Individualized and Genomic Medicine Research

Joo J, Mak ACY, **Xiao S**, Sleiman PM, Hu D, Huntsman S, Eng C, Kan M, Diwakar AR, Lasky-Su JA, Weiss ST, Sordillo JE, Wu AC, Cloutier M, Canino G, Forno E, Celedón JC, Seibold MA, Hakonarson H, **Williams LK**, Burchard EG, and Himes BE. Genome-wide association study in minority children with asthma implicates DNAH5 in bronchodilator responsiveness. *Sci Rep* 2022; 12(1):12514. PMID: 35869121. Full Text

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Variability in response to short-acting β(2)-agonists (e.g., albuterol) among patients with asthma from diverse racial/ethnic groups may contribute to asthma disparities. We sought to identify genetic variants associated with bronchodilator response (BDR) to identify potential mechanisms of drug response and risk factors for worse asthma outcomes. Genome-wide association studies of bronchodilator response (BDR) were performed using TOPMed Whole Genome Sequencing data of the Asthma Translational Genomic Collaboration (ATGC), which corresponded to 1136 Puerto Rican, 656 Mexican and 4337 African American patients with asthma. With the population-specific GWAS results, a trans-ethnic meta-analysis was performed to identify BDR-associated variants shared across the three populations. Replication analysis was carried out in three pediatric asthma cohorts, including CAMP (Childhood Asthma Management Program; n = 560), GACRS (Genetics of Asthma in Costa Rica Study; n = 967) and HPR (Hartford-Puerto Rico; n = 417). A genome-wide significant locus (rs35661809; P = 3.61 × 10(-8)) in LINC02220, a non-coding RNA gene, was identified in Puerto Ricans. While this region was devoid of protein-coding genes, capture Hi-C data showed a distal interaction with the promoter of the DNAH5 gene in lung tissue. In replication analysis, the GACRS cohort yielded a nominal association (1-tailed P < 0.05). No genetic variant was associated with BDR at the genome-wide significant threshold in Mexicans and African Americans. Our findings help inform genetic underpinnings of BDR for understudied minority patients with asthma, but the limited availability of genetic data for racial/ethnic minority children with asthma remains a paramount challenge.

Dermatology
Geisler A, Masub N, Toker M, Nguyen J, **Seale L**, Srikantha R, Halverstam C, **Lim H**, and Jagdeo J. Skin of Color Skin Care Needs: Results of a Multi-Center-Based Survey. *J Drugs Dermatol* 2022; 21(7):709-711. PMID: Not assigned. Request Article

Dermatology
Novice T, Novice M, Portney D, Goyert J, Henry NL, Jeruss JS, and Burness ML. Factors influencing scalp cooling discussions and use at a large academic institution: a single-center retrospective review. *Support Care Cancer* 2022; Epub ahead of print. PMID: 35870021. Full Text

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PURPOSE: Chemotherapy-induced alopecia (CIA) is a stigmatizing and psychologically devasting side effect of cancer treatment. Scalp cooling therapy (SCT) is the most effective method to reduce CIA, yet it is underutilized. We investigated factors that may impact scalp cooling discussion and use. METHODS: We performed a retrospective review of cancer patients from 2000 to 2019 who had documentation of SCT discussion in the electronic medical record. The University of Michigan Rogel Cancer Center registry was used to identify the total number of cancer patients eligible for SCT during 2015-2019. Chi-square tests were used for outcome and patient characteristic comparisons (p < 0.05). RESULTS: From 2000 to 2019, 194 patients had documentation of SCT discussion. Of those, 72 (43.6%) used SCT, 93 (47.9%)

did not use SCT, and the remaining 29 (17.8%) had unknown SCT use. A total of 5615 cancer patients were eligible for SCT from 2015 to 2019. As compared to those who did not have documented SCT discussions, patients who had documentation of SCT discussions in that period (n = 161, 3.0%) were more likely to be female, have breast cancer, be less than 45 years old, and live in a zip code with average income > US $100,000 (all p < 0.0001). Between 2015 and 2019, 57 patients (1.02%) used SCT. On univariate analysis, patient-initiated conversation about SCT (p = 0.01) and age less than 65 (p = 0.03) were significantly associated with decision to use SCT. CONCLUSION: There were distinctions in the types of patients who have documented discussions about SCT. Improving patient knowledge about the availability of SCT and increasing access to this technology for all eligible cancer patients may enable more patients to achieve improved quality of life by reducing or preventing CIA.

Dermatology
Pandya AG, Harris JE, Lebwohl M, **Hamzavi IH**, Butler K, Kuo FI, Wei S, and Rosmarin D. Addition of Narrow-Band Ultraviolet Light B (UVB) Phototherapy to Ruxolitinib Cream in Patients With Vitiligo. *J Invest Dermatol* 2022; Epub ahead of print. PMID: 35787401. Full Text

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Dermatology
Reshetylo S, Narla S, Bakker C, Freeman T, Farah RS, **Hamzavi IH**, and Goldfarb N. Systematic review of photodynamic therapy for the treatment of hidradenitis suppurativa. *Photodermatol Photoimmunol Photomed* 2022. PMID: Not assigned. Full Text

Dermatology
van Geel N, **Hamzavi IH**, Pandya AG, Wolkerstorfer A, Seneschal J, Garg A, Spuls P, Terwee CB, Mallett S, Speeckaert R, Meurant JM, Eleftheriadou V, and Ezzedine K. Vitiligo International Task force for an Agreed List of core data (VITAL): study protocol of a vitiligo core outcome set (COS) and contextual factors for clinical trials, registries, and clinical practice. *Trials* 2022; 23(1):591. PMID: 35871019. Full Text

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BACKGROUND: There is a lack of consensus related to the collection of standardized data for individuals with vitiligo enrolled in clinical trials and registries as well as those seen in clinical practice which causes difficulty in accurately interpreting, comparing, and pooling of data. Several years ago, efforts to initiate work on developing core outcome sets were performed and a consensus was reached in 2015 on the first core domain set for vitiligo clinical trials. METHODS/DESIGN: This project aims to further develop a core outcome set for vitiligo clinical trials as well as create internationally agreed-upon core outcome sets for registries and clinical practice. These core outcome sets will include a core domain set and a core measurement instruments set and will be supplemented by contextual factors, including baseline and treatment-related characteristics. In a preparatory exercise, the 2015 core domain set will be re-evaluated and will serve as the basis for the list of outcome domains used to initiate the consensus process. This project will consist of two parts. Part 1 will focus on the selection of a core domain set, or "what to measure" and contextual factors, for each setting based on electronic surveys (e-Delphi technique) and a conclusive consensus meeting by a large group of international stakeholders. Part 2 will include selection of core measurement instruments, or "how to measure," and measurement details (e.g., scale and timing) for the core domain sets and contextual factors agreed upon in part 1. Part 2 will be based on consensus meetings with stakeholders involved in part 1 and will be guided by C3 (CHORD-COUSIN Collaboration), Harmonising Outcome Measures for Eczema (HOME), COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN), and Outcome Measures in Rheumatology (OMERACT) recommendations including information on measurement properties of available instruments (systematic review and expert/patient opinion). At the end of part 2, all stakeholders involved will be invited to participate in a final meeting in which the ultimate core data sets (core outcome sets and contextual factors) will be presented and the dissemination plan and implementation goals will be defined. DISCUSSION: This project will harmonize data collection between clinical trials, registries, and clinical practices, facilitating new insights in vitiligo. TRIAL REGISTRATION: This study is registered in the Core Outcome Measures for Effectiveness Trials (COMET) database and on the C3 (CHORD-COUSIN Collaboration) website.

Dermatology

Zhang X, Li X, Wang Y, Chen Y, Hu Y, Guo C, Yu Z, Xu P, Ding Y, **Mi QS**, Wu J, Gu J, and Shi Y. Abnormal lipid metabolism in epidermal Langerhans cells mediates psoriasis-like dermatitis. *JCI Insight* 2022; 7(13). PMID: 35801590. Full Text

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Psoriasis is a chronic, inflammatory skin disease, frequently associated with dyslipidemia. Lipid disturbance in psoriasis affects both circulatory system and cutaneous tissue. Epidermal Langerhans cells (LCs) are tissue-resident DCs that maintain skin immune surveillance and mediate various cutaneous disorders, including psoriasis. However, the role of LCs in psoriasis development and their lipid metabolic alternation remains unclear. Here, we demonstrate that epidermal LCs of psoriasis patients enlarge with longer dendrites and possess elevated IL-23p19 mRNA and a higher level of neutral lipids when compared with normal LCs of healthy individuals. Accordantly, epidermal LCs from imiquimod-induced psoriasis-like dermatitis in mice display overmaturation, enhanced phagocytosis, and excessive secretion of IL-23. Remarkably, these altered immune properties in lesional LCs are tightly correlated with elevated neutral lipid levels. Moreover, the increased lipid content of psoriatic LCs might result from impaired autophagy of lipids. Bulk RNA-Seq analysis identifies dysregulated genes involved in lipid metabolism, autophagy, and immunofunctions in murine LCs. Overall, our data suggest that dysregulated lipid metabolism influences LC immunofunction, which contributes to the development of

psoriasis, and therapeutic manipulation of this metabolic process might provide an effective measurement for psoriasis.

Diagnostic Radiology

Horst KK, **Leschied JR**, Janitz EM, Kim JS, Narayanan S, Setty BN, Birkemeier K, Sintim-Damoa A, Lampl BS, Pomeranz CB, and Hwang M. Neonatal neurosonography practices: a survey of active Society for Pediatric Radiology members. *Pediatr Radiol* 2022; Epub ahead of print. PMID: 35879446. Full Text

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BACKGROUND: While neonatal brain US is emerging as an imaging modality with greater portability, widespread availability and relative lower cost compared to MRI, it is unknown whether US is being maximized in infants to increase sensitivity in detecting intracranial pathology related to common indications such as hemorrhage, ischemia and ventriculomegaly. OBJECTIVE: To survey active members of the Society for Pediatric Radiology (SPR) regarding their utilization of various cranial US techniques and reporting practices in neonates. MATERIALS AND METHODS: We distributed an online 10-question survey to SPR members to assess practice patterns of neonatal cranial US including protocol details, use of additional sonographic views, perceived utility of spectral Doppler evaluation, and germinal matrix hemorrhage and ventricular size reporting preferences. RESULTS: Of the 107 institutions represented, 90% of respondents were split evenly between free-standing children's hospitals and pediatric departments attached to a general hospital. We found that most used template reporting (72/107, 67%). The anterior fontanelle approach was standard practice (107/107, 100%). We found that posterior fontanelle views (72% sometimes, rarely or never) and high-frequency linear probes to evaluate far-field structures (52% sometimes, rarely or never) were seldom used. Results revealed a range of ways to report germinal matrix hemorrhage and measure ventricular indices to assess ventricular dilatation. There was substantial intra-institutional protocol and reporting variability as well. CONCLUSION: Our results demonstrate high variability in neurosonography practice and reporting among active SPR members, aside from the anterior fontanelle views, template reporting and linear high-resolution near-field evaluation. Standardization of reporting germinal matrix hemorrhage and ventricular size would help ensure a more consistent application of neonatal US in research and clinical practice.

Diagnostic Radiology

Larivière S, Royer J, Rodríguez-Cruces R, Paquola C, Caligiuri ME, Gambardella A, Concha L, Keller SS, Cendes F, Yasuda CL, Bonilha L, Gleichgerrcht E, Focke NK, Domin M, von Podewills F, Langner S, Rummel C, Wiest R, Martin P, Kotikalapudi R, O'Brien TJ, Sinclair B, Vivash L, Desmond PM, Lui E, Vaudano AE, Meletti S, Tondelli M, Alhusaini S, Doherty CP, Cavalleri GL, Delanty N, Kälviäinen R, Jackson GD, Kowalczyk M, Mascalchi M, Semmelroch M, Thomas RH, **Soltanian-Zadeh H**, **Davoodi-Bojd E**, Zhang J, Winston GP, Griffin A, Singh A, Tiwari VK, Kreilkamp BAK, Lenge M, Guerrini R, Hamandi K, Foley S, Rüber T, Weber B, Depondt C, Absil J, Carr SJA, Abela E, Richardson MP, Devinsky O, Severino M, Striano P, Tortora D, Kaestner E, Hatton SN, Vos SB, Caciagli L, Duncan JS, Whelan CD, Thompson PM, Sisodiya SM, Bernasconi A, Labate A, McDonald CR, Bernasconi N, and Bernhardt BC. Structural network alterations in focal and generalized epilepsy assessed in a worldwide

ENIGMA study follow axes of epilepsy risk gene expression. *Nat Commun* 2022; 13(1):4320. PMID: 35896547. Full Text

Epilepsy is associated with genetic risk factors and cortico-subcortical network alterations, but associations between neurobiological mechanisms and macroscale connectomics remain unclear. This multisite ENIGMA-Epilepsy study examined whole-brain structural covariance networks in patients with epilepsy and related findings to postmortem epilepsy risk gene expression patterns. Brain network analysis included 578 adults with temporal lobe epilepsy (TLE), 288 adults with idiopathic generalized epilepsy (IGE), and 1328 healthy controls from 18 centres worldwide. Graph theoretical analysis of structural covariance networks revealed increased clustering and path length in orbitofrontal and temporal regions in TLE, suggesting a shift towards network regularization. Conversely, people with IGE showed decreased clustering and path length in fronto-temporo-parietal cortices, indicating a random network configuration. Syndrome-specific topological alterations reflected expression patterns of risk genes for hippocampal sclerosis in TLE and for generalized epilepsy in IGE. These imaging-transcriptomic signatures could potentially guide diagnosis or tailor therapeutic approaches to specific epilepsy syndromes.

Diagnostic Radiology

Lawrence R, **Soliman SB**, **Roseni K**, **Zauel R**, and **Bey MJ**. In vivo evaluation of rotator cuff internal impingement during scapular plane abduction in asymptomatic individuals. *J Orthop Res* 2022; Epub ahead of print. PMID: 35880416. Full Text

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Internal impingement - or entrapment of the undersurface of the rotator cuff tendon against the glenoid during overhead activities - is believed to contribute to articular-sided tears. However, little is known about internal impingement outside athletic populations. Therefore, the objectives of this study were to: 1) describe glenoid-to-footprint distances and proximity centers during dynamic, in vivo motion in asymptomatic individuals, and 2) determine the extent to which these measures differed between individuals with and without a rotator cuff tear. Shoulder kinematics were assessed in 37 asymptomatic individuals during scapular plane abduction using a high-speed biplane radiographic system. Glenoid-to-footprint distances and proximity center locations were calculated by combining the kinematics and CT-derived bone models. Glenoid-to-footprint contact was presumed to occur when the minimum distance was less than the estimated labral thickness. The condition of the supraspinatus tendon (intact, torn) was assessed using ultrasound. Minimum distances and proximity centers were compared over humerothoracic elevation angles (90°, 110°, 130°, 150°) and between supraspinatus pathology groups using two-factor mixed model ANOVAs. The minimum distance decreased consistently across elevation angles ($p<0.01$) without a significant difference between groups. Contact was estimated to occur in all participants. The proximity center was generally located on the anterior half of the rotator cuff footprint and the posterosuperior glenoid. Clinical Significance: Internal impingement during overhead motions may be a prevalent mechanism of rotator cuff pathology as contact appears to be common and involves the region of the rotator cuff footprint where degenerative rotator cuff tears are thought to originate.

Diagnostic Radiology

Leschied J, Nozaki T, Rosenbaum DG, and Simoni P. The Global Reading Room: A Child With Lower Extremity Pain. *AJR Am J Roentgenol* 2022; Epub ahead of print. PMID: 35895301. Full Text

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Diagnostic Radiology

Rosen KA, **Thodge A**, **Tang A**, **Franz BM**, **Klochko CL**, and **Soliman SB**. The sonographic quantitative assessment of the deltoid muscle to detect type 2 diabetes mellitus: a potential noninvasive and sensitive screening method? *BMC Endocr Disord* 2022; 22(1):193. PMID: 35897066. Full Text

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BACKGROUND: In our previous published study, we demonstrated that a qualitatively assessed elevation in deltoid muscle echogenicity on ultrasound was both sensitive for and a strong predictor of a type 2 diabetes (T2DM) diagnosis. This study aims to evaluate if a sonographic quantitative assessment of the deltoid muscle can be used to detect T2DM. METHODS: Deltoid muscle ultrasound images from 124 patients were stored: 31 obese T2DM, 31 non-obese T2DM, 31 obese non-T2DM and 31 non-obese non-T2DM. Images were independently reviewed by 3 musculoskeletal radiologists, blinded to the patient's category. Each measured the grayscale pixel intensity of the deltoid muscle and humeral cortex to calculate a muscle/bone ratio for each patient. Following a 3-week delay, the 3 radiologists independently repeated measurements on a randomly selected 40 subjects. Ratios, age, gender, race, body mass index, insulin usage and hemoglobin A(1c) were analyzed. The difference among the 4 groups was compared using analysis of variance or chi-square tests. Both univariate and multivariate linear mixed models were performed. Multivariate mixed-effects regression models were used, adjusting for demographic and clinical variables. Post hoc comparisons were done with Bonferroni adjustments to identify any differences between groups. The sample size achieved 90% power. Sensitivity and specificity were calculated based on set threshold ratios. Both intra- and inter-radiologist variability or agreement were assessed. RESULTS: A statistically significant difference in muscle/bone ratios between the groups was identified with the average ratios as follows: obese T2DM, 0.54 ($P < 0.001$); non-obese T2DM, 0.48 ($P < 0.001$); obese non-T2DM, 0.42 ($P = 0.03$); and non-obese non-T2DM, 0.35. There was excellent inter-observer agreement (intraclass correlation coefficient 0.87) and excellent intra-observer agreements (intraclass correlation coefficient 0.92, 0.95 and 0.94). Using threshold ratios, the sensitivity for detecting T2DM was 80% (95% CI 67% to 88%) with a specificity of 63% (95% CI 50% to 75%). CONCLUSIONS: The sonographic quantitative assessment of the deltoid muscle by ultrasound is sensitive and accurate for the detection of T2DM. Following further studies, this process could translate into a dedicated, simple and noninvasive screening method to detect T2DM with the prospects of identifying even a fraction of the undiagnosed persons worldwide. This could prove especially beneficial in screening of underserved and underrepresented communities.

Emergency Medicine

Hoppmann RA, Mladenovic J, Melniker L, Badea R, Blaivas M, Montorfano M, Abuhamad A, Noble V, Hussain A, Prosen G, Villen T, Via G, Nogue R, Goodmurphy C, Bastos M, Nace GS, Volpicelli G, Wakefield RJ, Wilson S, Bhagra A, Kim J, Bahner D, Fox C, Riley R, Steinmetz P, Nelson BP, Pellerito J, Nazarian LN, Wilson LB, Ma IWY, **Amponsah D**, Barron KR, Dversdal RK, Wagner M, Dean AJ, Tierney D, Tsung JW, Nocera P, Pazeli J, Liu R, Price S, Neri L, Piccirillo B, Osman A, Lee V, Naqvi N, Petrovic T, Bornemann P, Valois M, Lanctot JF, Haddad R, Govil D, Hurtado LA, Dinh VA, DePhilip RM, Hoffmann B, Lewiss RE, Parange NA, Nishisaki A, Doniger SJ, Dallas P, Bergman K, Barahona JO, Wortsman X, Smith RS, Sisson CA, Palma J, Mallin M, Ahmed L, and Mustafa H. International consensus conference recommendations on ultrasound education for undergraduate medical students. *Ultrasound J* 2022; 14(1):31. PMID: 35895165. Full Text

OBJECTIVES: The purpose of this study is to provide expert consensus recommendations to establish a global ultrasound curriculum for undergraduate medical students. METHODS: 64 multi-disciplinary ultrasound experts from 16 countries, 50 multi-disciplinary ultrasound consultants, and 21 medical

students and residents contributed to these recommendations. A modified Delphi consensus method was used that included a systematic literature search, evaluation of the quality of literature by the GRADE system, and the RAND appropriateness method for panel judgment and consensus decisions. The process included four in-person international discussion sessions and two rounds of online voting. RESULTS: A total of 332 consensus conference statements in four curricular domains were considered: (1) curricular scope (4 statements), (2) curricular rationale (10 statements), (3) curricular characteristics (14 statements), and (4) curricular content (304 statements). Of these 332 statements, 145 were recommended, 126 were strongly recommended, and 61 were not recommended. Important aspects of an undergraduate ultrasound curriculum identified include curricular integration across the basic and clinical sciences and a competency and entrustable professional activity-based model. The curriculum should form the foundation of a life-long continuum of ultrasound education that prepares students for advanced training and patient care. In addition, the curriculum should complement and support the medical school curriculum as a whole with enhanced understanding of anatomy, physiology, pathophysiological processes and clinical practice without displacing other important undergraduate learning. The content of the curriculum should be appropriate for the medical student level of training, evidence and expert opinion based, and include ongoing collaborative research and development to ensure optimum educational value and patient care. CONCLUSIONS: The international consensus conference has provided the first comprehensive document of recommendations for a basic ultrasound curriculum. The document reflects the opinion of a diverse and representative group of international expert ultrasound practitioners, educators, and learners. These recommendations can standardize undergraduate medical student ultrasound education while serving as a basis for additional research in medical education and the application of ultrasound in clinical practice.

Emergency Medicine

Kim R, Lin T, Pang G, Liu Y, Tungate AS, Hendry PL, Kurz MC, Peak DA, Jones J, Rathlev NK, Swor RA, Domeier R, Velilla MA, **Lewandowski C**, Datner E, Pearson C, Lee D, Mitchell PM, McLean SA, and Linnstaedt SD. Derivation and validation of risk prediction for posttraumatic stress symptoms following trauma exposure. *Psychol Med* 2022; 1-10. Epub ahead of print. PMID: 35775366. Request Article

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BACKGROUND: Posttraumatic stress symptoms (PTSS) are common following traumatic stress exposure (TSE). Identification of individuals with PTSS risk in the early aftermath of TSE is important to enable targeted administration of preventive interventions. In this study, we used baseline survey data from two prospective cohort studies to identify the most influential predictors of substantial PTSS. METHODS: Self-identifying black and white American women and men (n = 1546) presenting to one of

16 emergency departments (EDs) within 24 h of motor vehicle collision (MVC) TSE were enrolled. Individuals with substantial PTSS (⩾33, Impact of Events Scale - Revised) 6 months after MVC were identified via follow-up questionnaire. Sociodemographic, pain, general health, event, and psychological/cognitive characteristics were collected in the ED and used in prediction modeling. Ensemble learning methods and Monte Carlo cross-validation were used for feature selection and to determine prediction accuracy. External validation was performed on a hold-out sample (30% of total sample). RESULTS: Twenty-five percent (n = 394) of individuals reported PTSS 6 months following MVC. Regularized linear regression was the top performing learning method. The top 30 factors together showed good reliability in predicting PTSS in the external sample (Area under the curve = 0.79 ± 0.002). Top predictors included acute pain severity, recovery expectations, socioeconomic status, self-reported race, and psychological symptoms. CONCLUSIONS: These analyses add to a growing literature indicating that influential predictors of PTSS can be identified and risk for future PTSS estimated from characteristics easily available/assessable at the time of ED presentation following TSE.

Emergency Medicine

Nguyen A, **Al Hage A**, **Yu H**, and **Gunaga S**. Arterial Occlusion and Acute Deep Vein Thrombosis-Induced Acute Limb Ischemia in a COVID-19 Patient. *Cureus* 2022; 14(7):e26689. PMID: 35949755. Full Text

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Coronavirus disease 2019 (COVID-19) is a viral illness known to elicit a hypercoagulable state leading to a myriad of vascular pathologies. Over the course of the COVID-19 pandemic, widespread insults to the venous system have been well documented, with an increasing number of arterial events being reported. Despite the rising incidence of both pathological manifestations, these events are rare, but when present, serve as significant life threats to the patient in question. We report and discuss a case of a 69-year-old female with no thromboembolic risk factors or systemic signs of illness who presented with signs and symptoms consistent with acute limb ischemia (ALI). The patient was ultimately found to have occlusion of multiple arterial and venous vessels. She tested positive for COVID-19 despite being otherwise asymptomatic from a viral syndrome standpoint. To our knowledge, there are no reports in the medical literature of ALI - in the setting of arterial occlusion and concomitant deep vein thrombosis (DVT) - as the sole clinical manifestation in an asymptomatic patient without thrombotic risk factors who was only incidentally found to be COVID-19-positive. This case underscores the atypical manifestations and deleterious effects associated with COVID-19 and the need to have a high index of suspicion for a multitude of pathologies when facing this viral illness.

Emergency Medicine

Suleyman G, **Fadel R**, **Alsaadi A**, **Sueng LN**, **Ghandour A**, **Alkhatib A**, **Singh T**, **Parsons A**, **Miller J**, **Ramesh M**, **Brar I**, and **Alangaden G**. Progression to Critical Illness and Death in Patients With Breakthrough Hospitalizations. *Open Forum Infect Dis* 2022; 9(7):ofac213. PMID: 35821729. Full Text

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BACKGROUND: Characterization of disease progression and outcomes after coronavirus disease 2019 (COVID-19)-related hospitalization in vaccinated compared with unvaccinated individuals is limited. METHODS: This was a retrospective case-control study of symptomatic vaccinated (cases) and unvaccinated (controls) participants hospitalized for COVID-19 between December 30, 2020, and September 30, 2021, in Southeast Michigan. Hospitalized adult patients with lab-confirmed COVID-19 were identified through daily census report. Breakthrough infection was defined as detection of severe acute respiratory syndrome coronavirus 2 ≥14 days after completion of the primary vaccination series. The association between prior vaccination and critical COVID-19 illness (composite of intensive care unit [ICU] admission, invasive mechanical ventilation [IMV], 28-day mortality) was examined. RESULTS: Two hundred ten (39%) fully vaccinated and 325 (61%) unvaccinated patients were evaluated. Compared with controls, cases were older, had more comorbidities (4 [3-7] vs 2 [1-4]; P < .001), and were more likely to

be immunocompromised. Cases had less severe symptoms compared with controls (2 [1-2] vs 2 [2-3]; P < .001) and were less likely to progress to critical COVID-19 illness (33.3% vs 45.5%; P < .001); 28-day mortality was significantly lower in cases (11.0% vs 24.9%; P < .001). Symptom severity (odds ratio [OR], 2.59; 95% CI, 1.61-4.16; P < .001) and modified Sequential Organ Failure Assessment score on presentation (OR, 1.74; 95% CI, 1.48-2.06; P < .001) were independently associated with development of critical COVID-19 illness. Prior vaccination (OR, 0.528; 95% CI, 0.307-0.910; P = .020) was protective. CONCLUSIONS: COVID-19-vaccinated patients were less likely to develop critical COVID-19 illness and more likely to survive. Disease severity at presentation was a predictor of adverse outcomes regardless of vaccination status.

Emergency Medicine

Tanriverdi B, Gregory DF, Olino TM, Ely TD, Harnett NG, van Rooij SJH, Lebois LAM, Seligowski AV, Jovanovic T, Ressler KJ, House SL, Beaudoin FL, An X, Neylan TC, Clifford GD, Linnstaedt SD, Germine LT, Bollen KA, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Musey PI, Jr., Hendry PL, Sheikh S, Jones CW, Punches BE, Kurz MC, McGrath ME, Hudak LA, Pascual JL, Seamon MJ, Datner EM, Pearson C, Domeier RM, Rathlev NK, O'Neil BJ, Sanchez LD, Bruce SE, Miller MW, Pietrzak RH, Joormann J, Barch DM, Pizzagalli DA, Sheridan JF, Smoller JW, Harte SE, Elliott JM, McLean SA, Kessler RC, Koenen KC, Stevens JS, and Murty VP. Hippocampal Threat Reactivity Interacts with Physiological Arousal to Predict PTSD Symptoms. *J Neurosci* 2022; Epub ahead of print. PMID: 35879096. Full Text

Hippocampal impairments are reliably associated with post-traumatic stress disorder (PTSD); however, little research has characterized how increased threat-sensitivity may interact with arousal responses to alter hippocampal reactivity, and further how these interactions relate to the sequelae of trauma-related symptoms. In a sample of individuals recently exposed to trauma (N=116, 76 Female), we found that PTSD symptoms at 2-weeks were associated with decreased hippocampal responses to threat as assessed with functional magnetic resonance imaging (fMRI). Further, the relationship between hippocampal threat sensitivity and PTSD symptomology only emerged in individuals who showed transient, high threat-related arousal, as assayed by an independently collected measure of Fear Potentiated Startle. Collectively, our finding suggests that development of PTSD is associated with threat-related decreases in hippocampal function, due to increases in fear-potentiated arousal.Significance StatementAlterations in hippocampal function linked to threat-related arousal are reliably associated with post-traumatic stress disorder (PTSD); however, how these alterations relate to the sequelae of trauma-related symptoms is unknown. Prior models based on non-trauma samples suggest that arousal may impact hippocampal neurophysiology leading to maladaptive behavior. Here we show that decreased hippocampal threat sensitivity interacts with fear-potentiated startle to predict PTSD symptoms. Specifically, individuals with high fear-potentiated startle and low, transient hippocampal threat sensitivity showed the greatest PTSD symptomology. These findings bridge literatures of threat-related arousal and hippocampal function to better understand PTSD risk.

Emergency Medicine

Winthrop KL, Skolnick AW, Rafiq AM, Beegle SH, **Suszanski J**, Koehne G, Barnett-Griness O, Bibliowicz A, Fathi R, Anderson P, Raday G, Eagle G, Ben-Yair VK, Minkowitz HS, Levitt ML, and Gordon MS. Opaganib in Coronavirus Disease 2019 Pneumonia: Results of a Randomized, Placebo-Controlled Phase 2a Trial. *Open Forum Infect Dis* 2022; 9(7):ofac232. PMID: 35832268. Full Text

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BACKGROUND: Opaganib, an oral sphingosine kinase-2 inhibitor with antiviral and anti-inflammatory properties, was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication in vitro. We thus considered that opaganib could be beneficial for moderate to severe coronavirus disease 2019 (COVID-19) pneumonia. The objective of the study was to evaluate the safety of opaganib and its effect on supplemental oxygen requirements and time to hospital discharge in COVID-19 pneumonia hospitalized patients requiring supplemental oxygen. METHODS: This Phase 2a, randomized, double-blind, placebo-controlled study was conducted between July and December 2020 in 8 sites in the United States. Forty-two enrolled patients received opaganib (n = 23) or placebo (n = 19) added to standard of care for up to 14 days and were followed up for 28 days after their last dose of opaganib/placebo. RESULTS: There were no safety concerns arising in this study. The incidence of ≥Grade 3 treatment-emergent adverse events was 17.4% and 33.3% in the opaganib and placebo groups, respectively. Three deaths occurred in each group. A numerical advantage for opaganib over placebo was observed in in this nonpowered study reflected by total supplemental oxygen requirement from baseline to Day 14, the requirement for supplemental oxygen for at least 24 hours by Day 14, and hospital discharge. CONCLUSIONS: In this proof-of-concept study, hypoxic, hospitalized patients receiving oral opaganib had a similar safety profile to placebo-treated patients, with preliminary evidence of benefit for opaganib as measured by supplementary oxygen requirement and earlier hospital discharge. These findings support further evaluation of opaganib in this population.

Endocrinology and Metabolism

Kaur G, Bhadada SK, Santra M, Pal R, Sarma P, Sachdeva N, Dhiman V, Dahiya D, Saikia UN, Chakraborty A, Sood A, Prakash M, Behera A, and **Rao SD**. Multi-level annotation of germline MEN1 variants of synonymous, non-synonymous and uncertain significance in Indian patients with sporadic primary hyperparathyroidism. *J Bone Miner Res* 2022; Epub ahead of print. PMID: 35856247. Full Text

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Primary hyperthyroidism (PHPT) is third most common endocrine disorder characterized by hypercalcemia with elevated or non-suppressed parathyroid hormone levels by parathyroid tumors. Familial PHPT, as part of multiple endocrine type-1, occurs due to the germline mutation in the MEN1 gene. The involvement and the role of germline MEN1 variations in sporadic PHPT of Indian PHPT patients are unknown. Precise classifications of different types of MEN1 variations are fundamental for determining clinical relevance and diagnostic role. This prospective cohort study was performed on 82 patients with PHPT (with no clinical or history of MEN1) who underwent screening for MEN 1 variations through Sanger sequencing. Multilevel computational analysis was performed to determine the structure-function relationship of synonymous, non-synonymous, and variants of uncertain significance. Of the 82 PHPT patients, 42 (51%) had 26 germline MEN1 variants, including 8 non-synonymous, 7 synonymous, 9 Variants of uncertain significance (VUS), one-splice site, and one regulatory variation. Five most common germline variations (c.1838A>G, c.1817C>T, c.1525C>A, c.-35A>T, and c.250T>C) were observed in this study. c.-35A>T(5'UTR region) was associated with recurrence of PHPT (OR = 5.4; p = 0.04 and

subsequent detection of other endocrine tumors (OR = 13.6, p = 0.035). c.1525C>A was associated with multi glandular parathyroid tumor (OR = 13.6, p = 0.035). Align-GVDV, FATHMM and mutation taster analysis reported the disease-specific potential of VUS and synonymous variations. Significant linkage disequilibrium was observed in c.1785G>A and c.1817C>T (r(2) =0.3859, p= 0.0001), c.1475C>G and c.1525C>A (r(2) =0.385, p= 0.0004) and c.1569T>C and c.1838A>G (r(2) =0.488, p= 0.0001). The detection of MEN1 variations, especially those with disease-specific potential, can prompt early screening for other MEN1-related tumors and disease recurrence.

Endocrinology and Metabolism

Mikkilineni P, **Simon R**, **Bhan A**, and **Rao SD**. Patient Perspectives on the COVID-19 Vaccine: A Pilot Survey Study of Patients in Endocrinology Clinics. *Endocr Pract* 2022; Epub ahead of print. PMID: 35787467. Full Text

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OBJECTIVE: Vaccine hesitancy is an impediment to fighting the COVID-19 pandemic. Endocrinology clinics routinely see patients who are at high risk of a more aggressive form of COVID-19, including patients with diabetes, obesity, and hypertension. As patients with endocrine-related conditions often require multiple visits each year, endocrinology clinics provide a significant opportunity for vaccine education. The aim of our study was to evaluate patient perspectives about COVID-19 vaccination in outpatient endocrinology clinics. METHODS: A pilot survey study of patients who visited 3 endocrinology clinics between May 31, 2021, and June 18, 2021. A 7-item questionnaire explored the patients' perspectives and behaviors regarding COVID-19 vaccination. Data were analyzed with descriptive statistics. RESULTS: A total of 446 patients from 3 clinic locations (1 urban and 2 suburbans) completed our survey. There were 361 (81%) patients who indicated that they were planning to or had already received the COVID-19 vaccination, 56 (13%) reported no intent for vaccination, and 29 (7%) were unsure. Of the 85 patients who were unsure or did not intend to be vaccinated, 43 (51%) were Black, 30 (35%) were White, and 4 (5%) had other racial/ethnic identities. When asked about vaccine hesitancy, 25 (29%) wanted to wait and see how the others responded to the vaccine, 20 (24%) had concerns about the side effects, 12 (14%) did not believe in vaccines, and 11 (13%) felt that COVID-19 was not as bad as the media had portrayed it. Significantly more Black patients had vaccine hesitancy than White patients (P = .035). CONCLUSION: Although most endocrinology patients were amenable to COVID-19 vaccination, a subpopulation still expressed vaccine hesitancy, indicating that endocrinology clinics may be an ideal place for targeted vaccine education.

Gastroenterology

Carter M, Solsrud K, **Yeddula S**, **Fitzmaurice MG**, **Singh A**, **Nagai S**, and **Jafri SM**. Hepatitis E Diagnosis and Management After Liver, Kidney, or Heart Transplant: A Single-Center Experience. *Transplant Proc* 2022; Epub ahead of print. PMID: 35907694. Full Text

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BACKGROUND: Transplant-related hepatitis E virus (HEV) infection is a rarely recognized phenomenon with significant clinical importance given its potential to result in chronic hepatitis posttransplant. METHODS: We retrospectively evaluated HEV diagnosis and treatment after liver, kidney, and heart transplant in a single center. We identified patients diagnosed with HEV by serologic testing and evaluated their treatment regimens. RESULTS: Fifteen transplant recipients (12 liver, 2 kidney, and 1 heart) presented with elevated liver enzymes and were positive for HEV IgM antibody. Liver enzymes

normalized in 4 patients after being treated with ribavirin. One of the 4 patients had 2 recurrences with positive HEV RNA results following ribavirin treatment but recovered after 12 months of ribavirin therapy. After treatment with reduction in immunosuppression without antiviral treatment, 6 of 8 patients' liver enzymes normalized. One of these patients died of acute pancreatitis 2 months after testing positive for HEV IgM antibody. CONCLUSIONS: The potential for complications related to active HEV infections in transplant recipients necessitates prompt diagnosis and treatment to prevent irreversible damage. Diagnosis with HEV reverse transcriptase-polymerase chain reaction should follow a positive HEV IgM antibody test. This manuscript provides evidence that ribavirin antiviral therapy and reducing immunosuppression are effective treatments for HEV infections in liver, kidney, and heart transplant recipients, which has not been sufficiently investigated in the population of the United States. Larger multicenter studies are needed to confirm the risks and benefits of using ribavirin antiviral therapy as first-line therapy of HEV posttransplant.

Gastroenterology
Kiran RP, Kochhar GS, Kariv R, Rex DK, Sugita A, Rubin DT, Navaneethan U, Hull TL, Ko HM, Liu X, Kachnic LA, Strong S, Iacucci M, Bemelman W, Fleshner P, Safyan RA, Kotze PG, D'Hoore A, Faiz O, Lo S, Ashburn JH, Spinelli A, Bernstein CN, Kane SV, Cross RK, **Schairer J**, McCormick JT, Farraye FA, Chang S, Scherl EJ, Schwartz DA, Bruining DH, Philpott J, Bentley-Hibbert S, Tarabar D, El-Hachem S, Sandborn WJ, Silverberg MS, Pardi DS, Church JM, and Shen B. Management of pouch neoplasia: consensus guidelines from the International Ileal Pouch Consortium. *Lancet Gastroenterol Hepatol* 2022; 7(9):871-893. PMID: 35798022. Full Text

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Surveillance pouchoscopy is recommended for patients with restorative proctocolectomy with ileal pouch-anal anastomosis in ulcerative colitis or familial adenomatous polyposis, with the surveillance interval depending on the risk of neoplasia. Neoplasia in patients with ileal pouches mainly have a glandular source and less often are of squamous cell origin. Various grades of neoplasia can occur in the prepouch ileum, pouch body, rectal cuff, anal transition zone, anus, or perianal skin. The main treatment modalities are endoscopic polypectomy, endoscopic ablation, endoscopic mucosal resection, endoscopic submucosal dissection, surgical local excision, surgical circumferential resection and re-anastomosis, and pouch excision. The choice of the treatment modality is determined by the grade, location, size, and features of neoplastic lesions, along with patients' risk of neoplasia and comorbidities, and local endoscopic and surgical expertise.

Gastroenterology
Parikh ND, Mehta N, Hoteit MA, Yang JD, John BV, Moon AM, **Salgia RJ**, Pillai A, Kassab I, Saeed N, Thyssen E, Nathani P, McKinney J, Chan W, Durkin C, Connor M, Alsudaney M, Konjeti R, Durand B, Nissen NN, Kim HP, Paknikar R, Rich NE, Schipper MJ, and Singal AG. Association between sustained virological response and clinical outcomes in patients with hepatitis C infection and hepatocellular carcinoma. *Cancer* 2022; Epub ahead of print. PMID: 35796530. Full Text

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BACKGROUND: Sustained viral response (SVR) improves survival for patients with hepatitis C (HCV) and hepatocellular carcinoma (HCC) after curative treatment; however, the benefit of SVR in those with

active HCC with a significant competing risk of mortality is unknown. This study aimed to evaluate the association between SVR and outcomes in patients with active HCC. METHODS: The authors performed a multicenter, retrospective cohort study including consecutive adults with HCV cirrhosis and treatment-naive HCC diagnosed between 2014 and 2018. Patients were stratified into two groups: active viremia (n = 431) and SVR before HCC diagnosis (n = 135). All patients underwent nonsurgical therapy as their initial treatment and were followed until liver transplantation, last follow-up, or death. The primary outcome was incident or worsening hepatic decompensation within 6 months and the secondary outcome was overall survival. All analyses used inverse probability of treatment weights (IPTW) to account for differences between the nonrandomized cohorts. RESULTS: Post-SVR patients had significantly lower odds of hepatic decompensation compared to viremic patients (odds ratio [OR], 0.18; 95% confidence interval [CI], 0.06-0.59). Results were consistent among subgroups of patients with Child Pugh A cirrhosis (OR, 0.22; 95% CI, 0.04-0.77), Barcelona Clinic Liver Cancer stage B/C HCC (OR, 0.20; 95% CI, 0.04-0.65), and those receiving nonablative HCC therapies (OR, 0.21; 95% CI, 0.07-0.67). However, in IPTW multivariable Cox regression, SVR was not associated with improved survival (hazard ratio, 0.79; 95% CI, 0.56-1.12). CONCLUSIONS: Patients with HCV-related HCC and SVR are less likely to experience hepatic decompensation than viremic patients, suggesting patients with HCC who are undergoing nonsurgical therapies may benefit from DAA treatment.

Gastroenterology

Trudeau S, **Mendiratta V**, **Dababneh Y**, **Hollingsworth J**, and **Gordon SC**. Letter to the Editor: Successful treatment of multidrug resistant hepatitis C after >12 months of continuous therapy with direct-acting antivirals. *Hepatology* 2022; Epub ahead of print. PMID: 35894159. Full Text

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Hematology-Oncology

Hinton T, Karnak D, Tang M, Jiang R, Luo Y, Boonstra P, Sun Y, Nancarrow DJ, Sandford E, Ray P, Maurino C, Matuszak M, Schipper MJ, Green MD, **Yanik GA**, Tewari M, Naqa IE, Schonewolf CA, Haken RT, Jolly S, Lawrence TS, and Ray D. Improved prediction of radiation pneumonitis by combining biological and radiobiological parameters using a data-driven Bayesian network analysis. *Transl Oncol* 2022; 21:101428. PMID: 35460942. Full Text

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Grade 2 and higher radiation pneumonitis (RP2) is a potentially fatal toxicity that limits efficacy of radiation therapy (RT). We wished to identify a combined biomarker signature of circulating miRNAs and cytokines which, along with radiobiological and clinical parameters, may better predict a targetable RP2 pathway. In a prospective clinical trial of response-adapted RT for patients (n = 39) with locally advanced non-small cell lung cancer, we analyzed patients' plasma, collected pre- and during RT, for microRNAs (miRNAs) and cytokines using array and multiplex enzyme linked immunosorbent assay (ELISA), respectively. Interactions between candidate biomarkers, radiobiological, and clinical parameters were analyzed using data-driven Bayesian network (DD-BN) analysis. We identified alterations in specific

miRNAs (miR-532, -99b and -495, let-7c, -451 and -139-3p) correlating with lung toxicity. High levels of soluble tumor necrosis factor alpha receptor 1 (sTNFR1) were detected in a majority of lung cancer patients. However, among RP patients, within 2 weeks of RT initiation, we noted a trend of temporary decline in sTNFR1 (a physiological scavenger of TNFα) and ADAM17 (a shedding protease that cleaves both membrane-bound TNFα and TNFR1) levels. Cytokine signature identified activation of inflammatory pathway. Using DD-BN we combined miRNA and cytokine data along with generalized equivalent uniform dose (gEUD) to identify pathways with better accuracy of predicting RP2 as compared to either miRNA or cytokines alone. This signature suggests that activation of the TNFα-NFκB inflammatory pathway plays a key role in RP which could be specifically ameliorated by etanercept rather than current therapy of non-specific leukotoxic corticosteroids.

Hematology-Oncology

Modonutti D, **Majdalany SE**, **Corsi N**, **Li P**, **Sood A**, **Dalela D**, **Jamil ML**, **Hwang C**, **Menon M**, **Rogers CG**, Trinh QD, **Novara G**, and **Abdollah F**. A novel prognostic model predicting overall survival in patients with metastatic castration-resistant prostate cancer receiving standard chemotherapy: A multi-trial cohort analysis. *Prostate* 2022; Epub ahead of print. PMID: 35790016. Full Text

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PURPOSE: Generalizable, updated, and easy-to-use prognostic models for patients with metastatic castration-resistant prostate cancer (mCRPC) are lacking. We developed a nomogram predicting the overall survival (OS) of mCRPC patients receiving standard chemotherapy using data from five randomized clinical trials (RCTs). METHODS: Patients enrolled in the control arm of five RCTs (ASCENT 2, VENICE, CELGENE/MAINSAIL, ENTHUSE 14, and ENTHUSE 33) were randomly split between training (n = 1636, 70%) and validation cohorts (n = 700, 30%). In the training cohort, Cox regression tested the prognostic significance of all available variables as a predictor of OS. Independent predictors of OS on multivariable analysis were used to construct a novel multivariable model (nomogram). The accuracy of this model was tested in the validation cohort using time-dependent area under the curve (tAUC) and calibration curves. RESULTS: Most of the patients were aged 65-74 years (44.5%) and the median (interquartile range) follow-up time was 13.9 (8.9-20.2) months. At multivariable analysis, the following were independent predictors of OS in mCRPC patients: sites of metastasis (visceral vs. bone metastasis, hazard ratio [HR]: 1.24), prostate-specific antigen (HR: 1.00), aspartate transaminase (HR: 1.01), alkaline phosphatase (HR: 1.00), body mass index (HR: 0.97), and hemoglobin (≥13 g/dl vs. <11 g/dl, HR: 0.41; all $p < 0.05$). A nomogram based on these variables was developed and showed favorable discrimination (tAUC at 12 and 24 months: 73% and 72%, respectively) and calibration characteristics on external validation. CONCLUSION: A new prognostic model to predict OS of patients with mCRPC undergoing first line chemotherapy was developed. This can help urologists/oncologists in counseling patients and might be useful to better stratify patients for future clinical trials.

Hematology-Oncology

Noé J, Bordogna W, Archer V, Smoljanovic V, Hilton M, Woodhouse R, Mocci S, and **Gadgeel SM**. Concordance Between Tissue ALK Detection by Immunohistochemistry and Plasma ALK Detection by Next-Generation Sequencing in the Randomized Phase 3 ALEX Study in Patients With Treatment-Naive Advanced ALK-Positive NSCLC. *JTO Clin Res Rep* 2022; 3(7):100341. PMID: 35756755. Full Text

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INTRODUCTION: The Blood First Assay Screening Trial revealed the clinical applicability of blood-based next-generation sequencing to identify patients with ALK-positive NSCLC for alectinib treatment. To understand the relationship between tissue-based versus blood-based testing, we retrospectively investigated concordance between VENTANA ALK (D5F3) CDx immunohistochemistry and the FoundationACT (FACT; Foundation Medicine, Inc.) plasma assay, and compared clinical efficacy between phase 3 ALEX study subpopulations. METHODS: Patients with advanced ALK-positive (by immunohistochemistry) NSCLC were randomized 1:1 to alectinib 600 mg or crizotinib 250 mg, twice daily. Assessable baseline plasma samples were analyzed for ALK positivity by FACT; positive percent agreement with immunohistochemistry was evaluated. Progression-free survival (PFS), duration of response, and objective response rate were compared between intention-to-treat (ITT) and biomarker-evaluable populations, and plasma ALK-positive and plasma ALK-negative subpopulations. RESULTS: In the ITT population (303 patients; alectinib, 152; crizotinib, 151), all patients had ALK-positive tumors by immunohistochemistry. In the biomarker-evaluable population (149 patients; alectinib, 76; crizotinib, 73), 105 had plasma ALK-positive and 44 had plasma ALK-negative tumors. Positive percent agreement between immunohistochemistry and FACT was 70.5% (105 of 149; 95% confidence interval: 62.5-77.7). Baseline characteristics were generally balanced, with some exceptions, notably tumor burden. Median PFS in plasma ALK-positive and ALK-negative patients was 22.4 months and not estimable with alectinib and 7.3 months and 12.9 months with crizotinib, respectively; median duration of response was 25.9 months and not estimable with alectinib and 5.6 months and 11.5 months with crizotinib, respectively. CONCLUSIONS: Reasonable concordance between FACT and immunohistochemistry was observed; both methods are valuable in identifying ALK-positive patients, separately or concurrently. Alectinib was found to have superior PFS in the plasma ALK-positive population, as in the ITT population.

Hematology-Oncology
Pu CY, Lusk CM, **Neslund-Dudas C**, **Gadgeel S**, Soubani AO, and Schwartz AG. Lung Cancer Screening Criteria and Cardiopulmonary Comorbidities. *JTO Clin Res Rep* 2022; 3(8):100377. PMID: 35880085. Full Text

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INTRODUCTION: Lung cancer screening criteria should select candidates with minimal cardiopulmonary comorbidities who are fit for curative lung cancer resection. METHODS: We retrospectively analyzed 728 patients with lung cancer for screening eligibility using the U.S. Preventive Services Task Force (USPSTF) 2013 criteria (n = 370). If ineligible for screening, they were further assessed for eligibility using the USPSTF 2021 (n = 121) and National Comprehensive Cancer Network group 2 (NCCN gp 2) (n = 155). Comparisons of cardiopulmonary comorbidities between patients selected by the different lung cancer screening criteria were performed. Excluding missing data, a similar comparison was done between USPSTF 2013 (n = 283) and PLCOm2012 (risk threshold ≥1.51%) (n = 118). RESULTS: Patients eligible for USPSTF 2021 and NCCN gp 2 had lower rates of airflow obstruction (forced expiratory volume in 1 s [FEV1]/forced vital capacity <0.7) compared with those in USPSTF 2013 (55.4% and 56.8% versus 70.5%). Both USPSTF 2021 and NCCN gp 2 groups had less severe airflow obstruction; only 11.6% and 12.9% of patients, respectively, had percent-predicted FEV1 less than 50% versus 20.3% in the USPSTF 2013 group. Comparing USPSTF 2013 and PLCOm2012 revealed no significant differences in age or the rate of airflow obstruction ($p = 0.06$ and $p = 0.09$ respectively). Nevertheless, rates of percent-predicted FEV1 less than 50% and diffusing capacity of the lungs for carbon monoxide less than 50% were lower in the PLCOm2012 group compared with those in the USPSTF 2013 group (22.3% versus 10.2% and 32.6% versus 20.0%), respectively. CONCLUSIONS: The

USPSTF 2021 qualifies an additional group of screening candidates who are healthier with better lung reserve, translating to better surgical candidacy but potentially more overdiagnosis. The PLCOm2012, with its better accuracy in selecting patients at risk of cancer, selects an older group with chronic obstructive pulmonary disease but with good lung reserve and potentially less overdiagnosis.

Hospital Medicine

Haymart B, Barnes GD, Kong X, Ali M, Kline-Rogers E, DeCamillo D, and **Kaatz S**. Comparison of Patient Outcomes Before and After Switching From Warfarin to a Direct Oral Anticoagulant Based on Time in Therapeutic Range Guideline Recommendations. *JAMA Netw Open* 2022; 5(7):e2222089. PMID: 35834255. Full Text

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This cohort study evaluates stroke and major bleeding rates before and after switching from warfarin to a direct oral anticoagulant (DOAC) in patients grouped by pre-switch time-in-therapeutic range guideline thresholds.

Hospital Medicine

Porres-Aguilar M, Rosovsky RP, Rivera-Lebron BN, **Kaatz S**, Mukherjee D, Anaya-Ayala JE, Jimenez D, and Jerjes-Sánchez C. Pulmonary embolism response teams: Changing the paradigm in the care for acute pulmonary embolism. *J Thromb Haemost* 2022; Epub ahead of print. PMID: 35895858. Full Text

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Pulmonary embolism response teams (PERTs) have emerged as a multidisciplinary, multispecialty team of experts in the care of highly complex symptomatic acute pulmonary embolism (PE), with a centralized unique activation process, providing rapid multimodality assessment and risk stratification, formulating the best individualized diagnostic and therapeutic approach, streamlining the care in challenging clinical case scenarios (e.g. intermediate-high risk and high-risk PE), and facilitating the implementation of the recommended therapeutic strategies on time. PERTs are currently changing how complex acute PE cases are approached. The structure, organization, and function of a given PERT may vary from hospital to hospital, depending on local expertise, specific resources and infrastructure for a given academic hospital center. Current emerging data demonstrate the value of PERTs in improving time to PE diagnosis, shorter time to intiation of anticoagulation reducing hospital length of stay, increasing use of advanced therapies without an increase in bleeding and in some reports, decreasing mortality. Importantly, PERTs are positively impacting outcomes by changing the paradigm of care for acute PE through global adoption by the health-care community.

Hospital Medicine

Schulman S, Sholzberg M, Spyropoulos AC, Zarychanski R, Resnick HE, Bradbury CA, Broxmeyer L, Connors JM, Falanga A, Iba T, **Kaatz S**, Levy JH, Middeldorp S, Minichiello T, Ramacciotti E, Samama CM, and Thachil J. ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost* 2022; Epub ahead of print. PMID: 35906716. Full Text

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Antithrombotic agents reduce risk of thromboembolism in severely ill patients. Patients with coronavirus disease 2019 (COVID-19) may realize additional benefits from heparins. Optimal dosing and timing of these treatments and benefits of other antithrombotic agents remain unclear. In October 2021, ISTH assembled an international panel of content experts, patient representatives, and a methodologist to develop recommendations on anticoagulants and antiplatelet agents for patients with COVID-19 in different clinical settings. We used the American College of Cardiology Foundation/American Heart Association methodology to assess level of evidence (LOE) and class of recommendation (COR). Only recommendations with LOE A or B were included. Panelists agreed on 12 recommendations: three for non-hospitalized, five for non-critically ill hospitalized, three for critically ill hospitalized, and one for post-discharge patients. Two recommendations were based on high-quality evidence, the remainder on moderate-quality evidence. Among non-critically ill patients hospitalized for COVID-19, the panel gave a strong recommendation (a) for use of prophylactic dose of low molecular weight heparin or unfractionated heparin (LMWH/UFH) (COR 1); (b) for select patients in this group, use of therapeutic dose LMWH/UFH in preference to prophylactic dose (COR 1); but (c) against the addition of an antiplatelet agent (COR 3). Weak recommendations favored (a) sulodexide in non-hospitalized patients, (b) adding an antiplatelet agent to prophylactic LMWH/UFH in select critically ill, and (c) prophylactic rivaroxaban for select patients after discharge (all COR 2b). Recommendations in this guideline are based on high-/moderate-quality evidence available through March 2022. Focused updates will incorporate future evidence supporting changes to these recommendations.

Infectious Diseases

Bergin SP, Calvert SB, Farley J, Sun JL, Chiswell K, Dieperink W, Kluytmans J, Lopez-Delgado JC, Leon-Lopez R, **Zervos MJ**, Kollef MH, Sims M, Kabchi BA, Rubin D, Santiago J, Natarajan M, Tenaerts P, Fowler VG, Holland TL, Bonten MJ, and Hullegie SJ. PROPHETIC EU: Prospective Identification of Pneumonia in Hospitalized Patients in the Intensive Care Unit in European and United States Cohorts. *Open Forum Infect Dis* 2022; 9(7):ofac231. PMID: 35836748. Full Text

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University Medical Center Utrecht, Utrecht, the Netherlands.

BACKGROUND: The prospective identification of patients at high risk for hospital-acquired/ventilator-associated bacterial pneumonia may improve clinical trial feasibility and foster antibacterial development. In a prior study conducted in the United States, clinical criteria were used to prospectively identify these patients; however, these criteria have not been applied in a European population. METHODS: Adults considered high risk for pneumonia (treatment with ventilation or high levels of supplemental oxygen) in the intensive care units of 7 European hospitals were prospectively enrolled from June 12 to December 27, 2017. We estimated the proportion of high-risk patients developing pneumonia according to US Food and Drug Administration guidance and a subset potentially eligible for antibacterial trial enrollment. We compared patient characteristics, treatment exposures, and pneumonia incidence in a European cohort and a previously described US cohort. RESULTS: Of 888 high-risk patients, 211/888 (24%) were treated for possible pneumonia, and 150/888 (17%) met the Food and Drug Administration definition for hospital-acquired/ventilator-associated bacterial pneumonia. A higher proportion of European patients treated for possible pneumonia met the pneumonia definition (150/211 [71%] vs 537/1464 [37%]; P < .001). Among patients developing pneumonia, a higher proportion of European patients met antibacterial trial eligibility criteria (124/150 [83%] vs 371/537 [69%]; P < .001). CONCLUSIONS: Clinical criteria prospectively identified high-risk patients with high rates of pneumonia in the European cohort. Despite higher rates of established risk factors and incident pneumonia, European patients were significantly less likely to receive antibiotics for possible pneumonia than US patients. Different treatment practices may contribute to lower rates of antibacterial trial enrollment in the United States.

Infectious Diseases

Birk NK, **Jain S**, **Massoud L**, **Ramesh D**, **Monday L**, **Muma B**, **Williams J**, **Alangaden G**, and **Ramesh M**. Real-world Experience of Sotrovimab in High-risk, Immunocompromised COVID-19 Patients. *Open Forum Infect Dis* 2022; 9(7):ofac282. PMID: 35859992. Full Text

Division of Infectious Diseases, Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA.

We completed a real-world analysis of 498 consecutive high-risk nonimmunocompromised and immunocompromised patients who received sotrovimab during the B.1.1.529 surge. Emergency department visits/hospitalizations and 30-day all-cause mortality between the 2 groups were similar. When administered early, sotrovimab is effective at preventing coronavirus disease 2019 progression in immunocompromised and nonimmunocompromised patients.

Infectious Diseases

Greenlee SB, **Kenney RM**, **Makowski CT**, **Bulat E**, **Brar I**, and **Davis SL**. Evaluating the Impact of Substance Use Disorder Resources on Outcomes of Persons Who Inject Drugs with Infections. *J Addict Med* 2022; Epub ahead of print. PMID: 35802753. Full Text

From the Department of Pharmacy, Henry Ford Hospital, Detroit, MI (SBG, RMK, CTM, SLD); Department of Pharmacy, Houston Methodist Hospital, Houston, TX (SBG); Department of Addiction Medicine, Henry Ford Maplegrove Center, West Bloomfield, MI (EB); Department of Infectious Diseases, Henry Ford Hospital, Detroit, MI (IB); and Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI (SLD).

OBJECTIVE: The aim of the study is to evaluate the impact of inpatient substance use disorder (SUD) resources on outcomes of persons who inject stimulants and/or opioids (PWIDs) with infections. METHODS: This retrospective cohort evaluated PWIDs hospitalized from July 1, 2020, to May 31, 2021, and prescribed an antimicrobial course. The patients were compared based on inpatient implementation of SUD resources, including consultation of addiction medicine/behavioral health, implementation of an opioid withdrawal treatment protocol, or continuation/initiation of medications for opioid use disorder. The primary outcome was a composite of antibiotic completion, no unplanned discharge, and no 30-day readmission. Notable secondary outcomes included length of stay and presence of stigmatizing language in the electronic medical record. RESULTS: A total of 119 patients were analyzed-74 (62.2%) received SUD resources. The primary outcome was met by 43 patients with SUD resources implemented (58.1%) and 19 patients without resources (42.2%, P = 0.093). After adjustment for infection type, implementation of SUD resources (adjusted odds ratio, 2.593; 95% confidence interval, 1.162-5.789) was independently associated with primary outcome success. The patients who received SUD resources had a median length of stay of 7 days (4-13.3) compared with 4 days (2-6.5) in those without resources (P < 0.001). Stigmatizing language was present in 98% of patient electronic medical records. CONCLUSIONS: Patient care provided to PWIDs with infections is optimized when SUD resources are implemented. This study further supports the necessity of improving SUD management when PWIDs are admitted to healthcare facilities.

Infectious Diseases

Shrestha R, Luterbach CL, Dai WX, Komarow L, Earley M, Weston G, **Herc E**, Jacob JT, Salata R, Wong D, Anderson D, Rydell KB, Arias CA, Chen L, van Duin D, and Investigators M. Characteristics of community-acquired carbapenem-resistant Enterobacterales. *J Antimicrob Chemother* 2022. PMID: Not assigned. Full Text

Infectious Diseases

Suleyman G, **Fadel R**, **Alsaadi A**, **Sueng LN**, **Ghandour A**, **Alkhatib A**, **Singh T**, **Parsons A**, **Miller J**, **Ramesh M**, **Brar I**, and **Alangaden G**. Progression to Critical Illness and Death in Patients With Breakthrough Hospitalizations. *Open Forum Infect Dis* 2022; 9(7):ofac213. PMID: 35821729. Full Text

Division of Infectious Disease, Henry Ford Hospital, Detroit, Michigan, USA.
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BACKGROUND: Characterization of disease progression and outcomes after coronavirus disease 2019 (COVID-19)-related hospitalization in vaccinated compared with unvaccinated individuals is limited. METHODS: This was a retrospective case-control study of symptomatic vaccinated (cases) and unvaccinated (controls) participants hospitalized for COVID-19 between December 30, 2020, and September 30, 2021, in Southeast Michigan. Hospitalized adult patients with lab-confirmed COVID-19 were identified through daily census report. Breakthrough infection was defined as detection of severe acute respiratory syndrome coronavirus 2 ≥14 days after completion of the primary vaccination series. The association between prior vaccination and critical COVID-19 illness (composite of intensive care unit [ICU] admission, invasive mechanical ventilation [IMV], 28-day mortality) was examined. RESULTS: Two hundred ten (39%) fully vaccinated and 325 (61%) unvaccinated patients were evaluated. Compared with

controls, cases were older, had more comorbidities (4 [3-7] vs 2 [1-4]; P < .001), and were more likely to be immunocompromised. Cases had less severe symptoms compared with controls (2 [1-2] vs 2 [2-3]; P < .001) and were less likely to progress to critical COVID-19 illness (33.3% vs 45.5%; P < .001); 28-day mortality was significantly lower in cases (11.0% vs 24.9%; P < .001). Symptom severity (odds ratio [OR], 2.59; 95% CI, 1.61-4.16; P < .001) and modified Sequential Organ Failure Assessment score on presentation (OR, 1.74; 95% CI, 1.48-2.06; P < .001) were independently associated with development of critical COVID-19 illness. Prior vaccination (OR, 0.528; 95% CI, 0.307-0.910; P = .020) was protective. CONCLUSIONS: COVID-19-vaccinated patients were less likely to develop critical COVID-19 illness and more likely to survive. Disease severity at presentation was a predictor of adverse outcomes regardless of vaccination status.

Internal Medicine

August BA, **Griebe KM**, **Stine JJ**, **Hauser CD**, **Hunsaker T**, **Jones MC**, **Martz C**, **Peters MA**, **To L**, **Belanger R**, **Schlacht S**, **Swiderek J**, **Davis SL**, **Mlynarek ME**, and **Smith ZR**. Evaluating the impact of severe sepsis 3-hour bundle compliance on 28-day in-hospital mortality: A propensity adjusted, nested case-control study. *Pharmacother* 2022. PMID: Not assigned. Full Text

Internal Medicine

Beydoun SB, Lee AH, Durudogan L, Kaufman V, Potter M, **Askar F**, Tsouvalas C, Reed B, and Sherwin RL. A Detroit Student-Run Free Clinic's Management of Select Chronic Diseases. *Cureus* 2022; 14(7):e26701. PMID: 35959186. Full Text

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AIM: The Cass Clinic is a student-run free clinic in Detroit, Michigan that treats chronic diseases including hypertension (HTN), diabetes mellitus (DM), and obesity. Our study aims to quantify the effectiveness of our clinic in managing chronic diseases. SUBJECT AND METHODS: This study assessed selected health outcomes for 137 patients who visited our clinic between September 1, 2017 and August 31, 2018 based on initial and most recent surrogate markers including manual blood pressure, hemoglobin A1c (HbA1c), and body mass index (BMI) recorded in the clinic's medical record system dating back to 2012. RESULTS: Patients were divided into two groups: occasionally seen patients (OSP) and frequently seen patients (FSP). FSP with HTN had systolic blood pressure (SBP) decreased by an average of 14.1 mmHg and diastolic blood pressure (DBP) decreased by 9.8 mmHg, which were statistically associated with the number of clinic visits. Additionally, all patients treated at Cass Clinic saw a decrease in their HbA1c and BMI. HbA1c in OSP decreased by 0.50%. HbA1c in the FSP decreased by 1.7%. Patients with at least two recorded BMIs (n=73) saw a decrease of 0.13 kg/m(2). CONCLUSION: The data from our analysis support that a student-run free clinic model like Cass Clinic provides long-term value for patients who frequently utilize the clinic. These clinics also act as an important resource for the community by making positive strides toward better health in multiple measurable outcomes, including HTN and DM management.

Internal Medicine

Blackmond N, Provencher E, Provencher S, Zoma M, **Goodman BD**, and **Silverman A**. Complicated Open Wound Management in a Free Clinic Setting. *Cureus* 2022; 14(7):e26605. PMID: 35936122. Full Text

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Wound healing is a complex and integrated process that involves several interdependent overlapping stages, including hemostasis, inflammation, proliferation, and vascularization. Cellulitis and skin abscesses are among the most common skin and soft tissue infections. Cellulitis typically involves the deeper dermis of subcutaneous fat and tends to have a more indolent course with the development of localized symptoms over a few days. Skin abscesses are described as a collection of pus within the dermis or subcutaneous space. Diabetes mellitus (DM) is the leading cause of impaired wound healing and consequently has higher rates of patients developing soft tissue infections. Diabetic patients experience decreased early inflammatory cell infiltration but increased numbers of neutrophils and macrophages. Complications include bacteremia, metastatic infection, sepsis, and toxic shock syndrome. In this case, we describe a 50-year-old Caucasian uninsured male who was referred to the Gary Burnstein Clinic (GBC) from a nearby hospital for wound management after an incision and drainage of a large back abscess and uncontrolled type 2 diabetes mellitus (T2DM). The patient presented with a large erythematous, indurated lesion with a cruciate incision that spanned from his mid-thoracic spine to the medial border of his left scapula. The wound management course required strict follow-up to the clinic every 48-72 hours for debridement and monitoring. This was complicated by the GBC's limited resources along with the volunteer nurses' and physicians' availability. To avoid the patient being lost to follow-up, shared decision-making was utilized to create a schedule that was advantageous for both the patient and the clinic. Ultimately, the patient made a full recovery without any adverse events. This case highlights the gaps in care for the medically uninsured. We also showcase the passion and dedication our medical volunteers exhibit to care for the community. The GBC provides high-quality healthcare to bridge gaps in access to care by offering broad specialist access while ensuring continuity of care.

Internal Medicine

Greenlee SB, **Kenney RM**, **Makowski CT**, **Bulat E**, **Brar I**, and **Davis SL**. Evaluating the Impact of Substance Use Disorder Resources on Outcomes of Persons Who Inject Drugs with Infections. *J Addict Med* 2022; Epub ahead of print. PMID: 35802753. Full Text

From the Department of Pharmacy, Henry Ford Hospital, Detroit, MI (SBG, RMK, CTM, SLD); Department of Pharmacy, Houston Methodist Hospital, Houston, TX (SBG); Department of Addiction Medicine, Henry Ford Maplegrove Center, West Bloomfield, MI (EB); Department of Infectious Diseases, Henry Ford Hospital, Detroit, MI (IB); and Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI (SLD).

OBJECTIVE: The aim of the study is to evaluate the impact of inpatient substance use disorder (SUD) resources on outcomes of persons who inject stimulants and/or opioids (PWIDs) with infections. METHODS: This retrospective cohort evaluated PWIDs hospitalized from July 1, 2020, to May 31, 2021, and prescribed an antimicrobial course. The patients were compared based on inpatient implementation of SUD resources, including consultation of addiction medicine/behavioral health, implementation of an opioid withdrawal treatment protocol, or continuation/initiation of medications for opioid use disorder. The primary outcome was a composite of antibiotic completion, no unplanned discharge, and no 30-day readmission. Notable secondary outcomes included length of stay and presence of stigmatizing language in the electronic medical record. RESULTS: A total of 119 patients were analyzed-74 (62.2%) received SUD resources. The primary outcome was met by 43 patients with SUD resources implemented (58.1%) and 19 patients without resources (42.2%, P = 0.093). After adjustment for infection type, implementation of SUD resources (adjusted odds ratio, 2.593; 95% confidence interval, 1.162-5.789) was independently associated with primary outcome success. The patients who received SUD resources had a median length of stay of 7 days (4-13.3) compared with 4 days (2-6.5) in those without resources (P < 0.001). Stigmatizing language was present in 98% of patient electronic medical records. CONCLUSIONS: Patient care provided to PWIDs with infections is optimized when SUD resources are implemented. This study further supports the necessity of improving SUD management when PWIDs are admitted to healthcare facilities.

Internal Medicine

Gupta K, and **Ananthasubramaniam K**. If you don't kill pollution it could kill you: pathophysiologic insights into pollution mediated cardiovascular risk through FDG PET imaging. *J Nucl Cardiol* 2022; 1-4. Epub ahead of print. PMID: 35859225. Full Text

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Internal Medicine

Suleyman G, **Fadel R**, **Alsaadi A**, **Sueng LN**, **Ghandour A**, **Alkhatib A**, **Singh T**, **Parsons A**, **Miller J**, **Ramesh M**, **Brar I**, and **Alangaden G**. Progression to Critical Illness and Death in Patients With Breakthrough Hospitalizations. *Open Forum Infect Dis* 2022; 9(7):ofac213. PMID: 35821729. Full Text

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BACKGROUND: Characterization of disease progression and outcomes after coronavirus disease 2019 (COVID-19)-related hospitalization in vaccinated compared with unvaccinated individuals is limited. METHODS: This was a retrospective case-control study of symptomatic vaccinated (cases) and unvaccinated (controls) participants hospitalized for COVID-19 between December 30, 2020, and September 30, 2021, in Southeast Michigan. Hospitalized adult patients with lab-confirmed COVID-19 were identified through daily census report. Breakthrough infection was defined as detection of severe acute respiratory syndrome coronavirus 2 ≥14 days after completion of the primary vaccination series. The association between prior vaccination and critical COVID-19 illness (composite of intensive care unit [ICU] admission, invasive mechanical ventilation [IMV], 28-day mortality) was examined. RESULTS: Two hundred ten (39%) fully vaccinated and 325 (61%) unvaccinated patients were evaluated. Compared with controls, cases were older, had more comorbidities (4 [3-7] vs 2 [1-4]; P < .001), and were more likely to be immunocompromised. Cases had less severe symptoms compared with controls (2 [1-2] vs 2 [2-3]; P < .001) and were less likely to progress to critical COVID-19 illness (33.3% vs 45.5%; P < .001); 28-day mortality was significantly lower in cases (11.0% vs 24.9%; P < .001). Symptom severity (odds ratio [OR], 2.59; 95% CI, 1.61-4.16; P < .001) and modified Sequential Organ Failure Assessment score on presentation (OR, 1.74; 95% CI, 1.48-2.06; P < .001) were independently associated with development of critical COVID-19 illness. Prior vaccination (OR, 0.528; 95% CI, 0.307-0.910; P = .020) was protective. CONCLUSIONS: COVID-19-vaccinated patients were less likely to develop critical COVID-19 illness and more likely to survive. Disease severity at presentation was a predictor of adverse outcomes regardless of vaccination status.

Internal Medicine

Tobin ET, **Hadwiger A**, **DiChiara A**, **Entz A**, and **Miller-Matero LR**. Demographic Predictors of Telehealth Use for Integrated Psychological Services in Primary Care During the COVID-19 Pandemic. *J Racial Ethn Health Disparities* 2022; Epub ahead of print. PMID: 35794514. Full Text

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OBJECTIVE: Prior to the COVID-19 pandemic, growing mental health needs were well documented, particularly those of diverse patient populations. The current study aims to better understand racial and psychosocial factors associated with patient utilization of integrated psychological services via telehealth

during the COVID-19 pandemic within a diverse primary care clinic. METHODS: Retrospective chart reviews were completed for patients seen by an integrated psychology team within a general internal medicine clinic at a large urban health system during the year 2020. Demographics were extracted from the medical record. Multivariate logistic regression analyses were conducted to examine demographic predictors for (1) telehealth video visits vs. audio only telehealth visits and (2) in-person vs. telehealth visits (both video and audio). RESULTS: Older patients, Black patients, and those with Medicare and Medicaid were more likely to complete audio only telehealth visits vs. video visits. There were no significant demographic predictors when comparing in-person vs. telehealth (both video and audio). DISCUSSION: Some underserved and vulnerable patient populations are more likely to utilize audio-only integrated psychological visits to video visits. The utilization of audio visits over video for certain demographics speaks to the need to better understand how this type of care may benefit psychological services in the future and continued advocacy to extend audio mental health visits beyond the public health emergency to address patient populations with significant mental health needs.

Internal Medicine

Trudeau S, **Mendiratta V**, **Dababneh Y**, **Hollingsworth J**, and **Gordon SC**. Letter to the Editor: Successful treatment of multidrug resistant hepatitis C after >12 months of continuous therapy with direct-acting antivirals. *Hepatology* 2022; Epub ahead of print. PMID: 35894159. Full Text

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Nephrology

Drawz PE, Rai NK, Lenoir KM, Suarez M, Powell JR, Raj DS, Beddhu S, Agarwal AK, **Soman S**, Whelton PK, Lash J, Rahbari-Oskoui FF, Dobre M, Parkulo MA, Rocco MV, McWilliams A, Dwyer JP, Thomas G, Rahman M, Oparil S, Horwitz E, Pajewski NM, and Ishani A. Effect of Intensive versus Standard BP Control on AKI and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study. *Kidney360* 2022; 3(7):1253-1262. PMID: 35919535. Full Text

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BACKGROUND: Adjudication of inpatient AKI in the Systolic Blood Pressure Intervention Trial (SPRINT) was based on billing codes and admission and discharge notes. The purpose of this study was to evaluate the effect of intensive versus standard BP control on creatinine-based inpatient and outpatient AKI, and whether AKI was associated with cardiovascular disease (CVD) and mortality. METHODS: We linked electronic health record (EHR) data from 47 clinic sites with trial data to enable creatinine-based adjudication of AKI. Cox regression was used to evaluate the effect of intensive BP control on the incidence of AKI, and the relationship between incident AKI and CVD and all-cause mortality. RESULTS: A total of 3644 participants had linked EHR data. A greater number of inpatient AKI events were identified using EHR data (187 on intensive versus 155 on standard treatment) as compared with serious adverse event (SAE) adjudication in the trial (95 on intensive versus 61 on standard treatment). Intensive treatment increased risk for SPRINT-adjudicated inpatient AKI (HR, 1.51; 95% CI, 1.09 to 2.08) and for creatinine-based outpatient AKI (HR, 1.40; 95% CI, 1.15 to 1.70), but not for creatinine-based inpatient AKI (HR, 1.20; 95% CI, 0.97 to 1.48). Irrespective of the definition (SAE or creatinine based), AKI was associated with increased risk for all-cause mortality, but only creatinine-based inpatient AKI was associated with increased risk for CVD. CONCLUSIONS: Creatinine-based ascertainment of AKI, enabled by EHR data, may be more sensitive and less biased than traditional SAE adjudication. Identifying ways to prevent AKI may reduce mortality further in the setting of intensive BP control.

Nephrology
Silberzweig J, Bhat JG, Dittrich MO, Durvasula R, Giullian J, Hymes JL, Johnson D, Schiller B, Spech R, Spry L, Walker GS, Watnick S, **Yee J**, and Freedman BI. Collaboration between Dialysis Providers. *J Am Soc Nephrol* 2022. PMID: Not assigned. Full Text

Nephrology
Srour O, Beran A, Mhanna M, Malhas SE, Khokher W, Alhasanat O, and **Srour K**. Effects of Curcumin Supplementation on Inflammation and Metabolic Profiles in Hemodialysis Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am J Ther* 2022; Epub ahead of print. PMID: 35849060. Full Text

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Neurology
Alsrouji OK, and **Chebl AB**. Acute Neurointervention for Ischemic Stroke. *Interv Cardiol Clin* 2022; 11(3):339-347. PMID: 35710287. Full Text

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Acute ischemic stroke (AIS) is one of the major causes of death worldwide and a leading cause of disability. Until recently treatment of AIS was supportive, and in a minority of patients intravenous thrombolysis was available but with marginal clinical benefit. With the advent of stent retrievers, distal aspiration catheters as well as improved patient selection neurologic outcomes have greatly improved. However, the care of patients with AIS is still challenging and requires the early recognition of stroke symptoms, extensive diagnostic testing, early intervention, and advanced nursing and critical care.

Neurology
Cox BC, **Khattak JF**, Starnes K, Brinkmann BH, Tatum WO, Noe KH, Van Gompel JJ, Miller KJ, Marsh WR, Grewal SS, Zimmerman RS, So EL, Wong-Kisiel LC, and Burkholder DB. Subclinical seizures on stereotactic EEG: characteristics and prognostic value. *Seizure* 2022; 101:96-102. PMID: 35939857. Full Text

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OBJECTIVE: Although stereotactic EEG (sEEG) has become a widely used intracranial EEG technique, the significance of subclinical seizures (SCS) recorded on sEEG is unclear and studies examining this finding on sEEG are limited. We investigated (1) the prevalence of SCS in patients undergoing sEEG and clinical factors associated with their presence, (2) how often the subclinical seizure onset zone (SOZ) colocalizes with clinical SOZ, (3) the association of SCS and surgical outcomes, and (4) the influence of resection of the subclinical SOZ on surgical outcome. METHODS: We reviewed all patients who underwent intracranial monitoring with sEEG at our institution from 2015 through 2020 (n=169). Patient and seizure characteristics were recorded, as was concordance of subclinical and clinical seizures and post-surgical outcomes. RESULTS: SCS were observed during sEEG monitoring in 84 of 169 patients (50%). There was no difference in the prevalence of SCS based on imaging abnormalities, temporal vs extratemporal SOZ, number of electrodes, or pathology. SCS were more common in females than males (62% vs 40%, p=0.0054). SCS had complete concordance with clinical SOZ in 40% of patients, partial concordance in 29%, overlapping in 19%, and discordant in 12%. Eighty-three patients had surgery, 44 of whom had SCS. There was no difference in excellent outcome (ILAE 12 or 2) based on the presence of SCS or SCS concordance with clinical SOZ; however, there were improved outcomes in patients with complete resection of the subclinical SOZ compared with patients with incomplete resection (p =0.013). SIGNIFICANCE: These findings demonstrate that SCS are common during sEEG and colocalize with the clinical SOZ in most patients. Discordance with clinical SOZ does not necessarily predict poor surgical outcome; rather, complete surgical treatment of the subclinical SOZ correlates with excellent outcome. For unclear reasons, subclinical seizures occurred more commonly in females than males.

Neurology
Decker BM, Turco A, **Xu J**, Terman SW, Kosaraju N, Jamil A, Davis KA, Litt B, Ellis CA, Khankhanian P, and Hill CE. Development of a natural language processing algorithm to extract seizure types and frequencies from the electronic health record. *Seizure* 2022; 101:48-51. PMID: 35882104. Full Text

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OBJECTIVE: To develop a natural language processing (NLP) algorithm to abstract seizure types and frequencies from electronic health records (EHR). BACKGROUND: Seizure frequency measurement is an epilepsy quality metric. Yet, abstraction of seizure frequency from the EHR is laborious. We present an NLP algorithm to extract seizure data from unstructured text of clinic notes. Algorithm performance was

assessed at two epilepsy centers. METHODS: We developed a rules-based NLP algorithm to recognize terms related to seizures and frequency within the text of an outpatient encounter. Algorithm output (e.g. number of seizures of a particular type within a time interval) was compared to seizure data manually annotated by two expert reviewers ("gold standard"). The algorithm was developed from 150 clinic notes from institution #1 (development set), then tested on a separate set of 219 notes from institution #1 (internal test set) with 248 unique seizure frequency elements. The algorithm was separately applied to 100 notes from institution #2 (external test set) with 124 unique seizure frequency elements. Algorithm performance was measured by recall (sensitivity), precision (positive predictive value), and F1 score (geometric mean of precision and recall). RESULTS: In the internal test set, the algorithm demonstrated 70% recall (173/248), 95% precision (173/182), and 0.82 F1 score compared to manual review. Algorithm performance in the external test set was lower with 22% recall (27/124), 73% precision (27/37), and 0.40 F1 score. CONCLUSIONS: These results suggest NLP extraction of seizure types and frequencies is feasible, though not without challenges in generalizability for large-scale implementation.

Neurology

Hu J, Shen Y, **Fahmy LM**, Krishnamurthy S, Li J, **Zhang L**, Chen Y, Haacke EM, and **Jiang Q**. The role of the parenchymal vascular system in cerebrospinal fluid tracer clearance. *Eur Radiol* 2022; Epub ahead of print. PMID: 35852578. Full Text

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OBJECTIVES: The current understanding of cerebral waste clearance (CWC) involves cerebrospinal fluid (CSF) participation but lacks convincing evidence for the direct participation of the parenchymal vascular system. The objective of this study was to evaluate the role of the parenchymal vascular system in CSF tracer clearance in rats. METHODS: We used superparamagnetic iron oxide-enhanced susceptibility-weighted imaging (SPIO-SWI) and quantitative susceptibility mapping (QSM) methods to simultaneously study 7 T MRI signal changes in parenchymal veins, arteries, and their corresponding para-vascular spaces in 26 rats, following intra-cisterna magna (ICM) infusion of different CSF tracers (FeREX, Ferumoxytol, Fe-Dextran) to determine the amount of tracer in the artery and vein quantitatively. RESULTS: We observed that the parenchymal venous system participated in CSF tracer clearance following ICM infusion of different MRI tracers with different concentrations of iron. Parenchymal venous participation was more obvious when 75 μg iron was injected. In the parenchymal veins, the relative mean (± SE) value of the susceptibility increased by 13.5 (± 1.0)% at 15 min post-tracer infusion ($p < 0.01$), and 33.6 (± 6.7)% at 45 min post-tracer infusion ($p = 0.01$), compared to baseline. In contrast to the parenchymal veins, a negligible amount of CSF tracer entered the parenchymal arteries: 1.3 (± 2.6)% at 15 min post-tracer infusion ($p = 0.6$), and 12 (± 19)% at 45 min post-tracer infusion ($p = 0.5$), compared to baseline. CONCLUSIONS: MRI tracers can enter the parenchymal vascular system and more MRI tracers were observed in the cerebral venous than arterial vessels, suggesting the direct participation of parenchymal vascular system in CWC. KEY POINTS: • MRI results revealed that the parenchymal venous system directly participates in cerebrospinal fluid tracer clearance following ICM infusion of MRI tracer. • Different sizes of MRI tracers can enter the parenchymal venous system.

Neurology

Larivière S, Royer J, Rodríguez-Cruces R, Paquola C, Caligiuri ME, Gambardella A, Concha L, Keller SS, Cendes F, Yasuda CL, Bonilha L, Gleichgerrcht E, Focke NK, Domin M, von Podewills F, Langner S, Rummel C, Wiest R, Martin P, Kotikalapudi R, O'Brien TJ, Sinclair B, Vivash L, Desmond PM, Lui E, Vaudano AE, Meletti S, Tondelli M, Alhusaini S, Doherty CP, Cavalleri GL, Delanty N, Kälviäinen R, Jackson GD, Kowalczyk M, Mascalchi M, Semmelroch M, Thomas RH, **Soltanian-Zadeh H**, **Davoodi-**

Bojd E, Zhang J, Winston GP, Griffin A, Singh A, Tiwari VK, Kreilkamp BAK, Lenge M, Guerrini R, Hamandi K, Foley S, Rüber T, Weber B, Depondt C, Absil J, Carr SJA, Abela E, Richardson MP, Devinsky O, Severino M, Striano P, Tortora D, Kaestner E, Hatton SN, Vos SB, Caciagli L, Duncan JS, Whelan CD, Thompson PM, Sisodiya SM, Bernasconi A, Labate A, McDonald CR, Bernasconi N, and Bernhardt BC. Structural network alterations in focal and generalized epilepsy assessed in a worldwide ENIGMA study follow axes of epilepsy risk gene expression. *Nat Commun* 2022; 13(1):4320. PMID: 35896547. Full Text

Epilepsy is associated with genetic risk factors and cortico-subcortical network alterations, but associations between neurobiological mechanisms and macroscale connectomics remain unclear. This multisite ENIGMA-Epilepsy study examined whole-brain structural covariance networks in patients with epilepsy and related findings to postmortem epilepsy risk gene expression patterns. Brain network analysis included 578 adults with temporal lobe epilepsy (TLE), 288 adults with idiopathic generalized epilepsy (IGE), and 1328 healthy controls from 18 centres worldwide. Graph theoretical analysis of structural covariance networks revealed increased clustering and path length in orbitofrontal and temporal regions in TLE, suggesting a shift towards network regularization. Conversely, people with IGE showed decreased clustering and path length in fronto-temporo-parietal cortices, indicating a random network configuration. Syndrome-specific topological alterations reflected expression patterns of risk genes for hippocampal sclerosis in TLE and for generalized epilepsy in IGE. These imaging-transcriptomic signatures could potentially guide diagnosis or tailor therapeutic approaches to specific epilepsy syndromes.

Neurology

Orozco E, Guo Y, Chen JJ, Dubey D, **Howell B**, Moutvic M, St Louis EK, and McKeon A. Clinical Reasoning: A 43-Year-Old Man With Subacute Onset of Vision Disturbances, Jaw Spasms, Balance, and Sleep Difficulties. *Neurology* 2022; Epub ahead of print. PMID: 35794020. Full Text

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A brainstem syndrome is recognizable in patients presenting with a combination of visual disturbances, incoordination, gait problems, speech and swallowing difficulties and new onset sleep symptomatology. Brainstem disorders of subacute onset (onset and progression with accumulation of disabling deficits in 6-12 weeks) are generally of autoimmune, infectious, inflammatory or infiltrative neoplastic cause. An autoimmune or infectious brainstem disorder may be referred to as brainstem encephalitis or rhombencephalitis. We describe a patient with a paraneoplastic autoimmune rhombencephalitis, in whom diagnostic clues included: diverse visual and sleep symptoms, trismus and choking in the history; see-saw nystagmus, opsoclonus, dysarthria, jaw dystonia and episodic laryngospasm on examination; subtle but longitudinal and non-enhancing T2 MRI abnormalities in the brainstem and upper cervical cord, and oligoclonal bands in CSF. His movement disorder-specific neural IgG profile revealed ANNA-2 (anti-Ri) and KLHL-11-IgG. Both are biomarkers of paraneoplastic brainstem encephalitis, and KLCHL-11-IgG has been reported to accompany germ cell tumors, which was found in a solitary metastasis to the left inguinal lymph node in our patient, along with an atrophic left testis. Multidisciplinary treatment (autoimmune neurology, sleep medicine, ophthalmology, and physiatry) led to significant clinical improvements. This case provides a framework for evaluation of patients with subacute onset brainstem syndromes, and the investigation and management of those with paraneoplastic and other autoimmune diseases.

Neurology

Plawecki AM, Saleem A, **Zvirbulis D**, **Peterson EL**, Yoo F, **Ali A**, and **Craig JR**. Clinical Features and Headache Diagnoses in Patients With Chief Complaint of Craniofacial Pain. *Ann Otol Rhinol Laryngol* 2022; Epub ahead of print. PMID: 35794798. Full Text

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OBJECTIVES: Investigate the use of nasal endoscopy, sinus imaging, and neurologic evaluation in patients presenting to a rhinologist primarily for craniofacial pain. METHODS: This was a retrospective analysis of consecutive outpatients presenting to a rhinologist between 2016 and 2019 with chief complaints of craniofacial pain with or without other sinonasal symptoms, who were then referred to and evaluated by headache specialists. Data analyzed included sinusitis symptoms, Sino-Nasal Outcome Test (SNOT-22) scores (and facial pain subscores), pain location, nasal endoscopy, computed tomography (CT) findings, and headache diagnoses made by headache specialists. RESULTS: Of the 134 patients with prominent craniofacial pain, the majority of patients were diagnosed with migraine (50%) or tension-type (22%) headache, followed by multiple other non-sinogenic headache disorders. Approximately 5% of patients had headaches attributed to sinusitis. Amongst all patients, 90% had negative nasal endoscopies. Patients with negative endoscopies were significantly less likely to report smell loss ($P = .003$) compared to those with positive endoscopies. Poor agreement was demonstrated between self-reported pain locations and sinus findings on CT (kappa values < 0.20). Negative nasal endoscopy showed high concurrence with negative CT findings (80%-97%). CONCLUSIONS: Patients presenting with chief complaints of craniofacial pain generally met criteria for various non-sinogenic headache disorders. Nasal endoscopy was negative in 90% of patients, and CT demonstrated poor agreement with pain locations. Nasal endoscopy and CT shared high concurrence rates for negative sinus findings. The value of nasal endoscopy over sinus imaging in craniofacial pain evaluation should be explored in future studies.

Neurology

Reddi Nagesh M, Gatasheh MK, **Hoda N**, and Vijayakumar N. Mutagenicity assessment of Salacia chinensis by bacterial reverse mutation assay using histidine dependent Salmonella typhimurium tester strains. *Saudi J Biol Sci* 2022; 29(8):103370. PMID: 35846385. Full Text

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BACKGROUND AND OBJECTIVE: Genotoxicity analysis is one of the most important non-clinical environmental safety investigations required for pharmaceutical and agrochemical product registration. Any medicinal product must undergo a risk evaluation to determine its mutagenicity and carcinogenicity. MATERIALS AND METHODS: The Ames test is a commonly used in vitro test for determining a test chemical's mutagenic activity. Histidine-dependent Salmonella typhimurium strains with a defective gene that causes the bacteria to synthesis the necessary amino acid histidine for life were tested for mutagenic potential. In order to reveal pro-mutagens and mutagens, the mutagenic potential of both plate integration and pre-incubation techniques was examined in the presence and absence of metabolizing system. Salacia chinensis has been widely used in ayurveda to treat various ailments. However, the information of mutagenicity of Salacia chinensis is scarce as per available literature. RESULTS: The mutagenicity of a Salacia chinensis root extract was investigated utilizing the Ames assay with plate incorporation and pre-incubation protocols using the appropriate Salmonella typhimurium tester strains: TA98, TA100, TA1537, TA1535, and TA102 in the presence and absence of S9. The concentrations used were 0.3123, 0.625, 1.25, 2.5 and 5 mg/plate. The extract of Salacia chinensis root did not show any mutagenic effect in any

of the Salmonella typhimurium strains at the concentrations tested in the absence or presence of metabolic activation. CONCLUSION: The root of Salacia chinensis was hence confirmed to be non-mutagenic and at least according to the results of this genotoxicity evaluation can be regarded as being safe for human use.

Neurology

Siegel DR, **Van Harn M**, **Taguchi M**, **Bansal P**, **Cerghet M**, and **Memon AB**. Clinical and diagnostic spectrum of optic neuritis: A single-center retrospective study of disorders associated with multiple sclerosis, anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies. *Clin Neurol Neurosurg* 2022; 221:107381. PMID: 35901556. Full Text

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OBJECTIVE: Optic neuritis (ON) is an immune-mediated optic neuropathy associated with multiple immune-mediated neurological conditions. Our aim was to characterize the clinical and diagnostic features of first or initial episodes of ON associated with multiple sclerosis (MS)-associated (typical) and antibody-related (atypical) ON. METHODS: Retrospective, single institution, medical record review. We analyzed demographic, clinical, laboratory, and radiographic findings of 139 patients who presented with first episodes of MS-associated ON (MS-ON), aquaporin 4 antibody-associated ON (AQP4-ON), and myelin oligodendrocyte glycoprotein antibody-associated ON (MOG-ON) between January 2015 and October 2019 without preceding diagnosis. Simple hypothesis testing assessed differences between groups were performed. RESULTS: Of 139 patients (109 [79 %] women; 29 [21 %] men; mean age 47 [SD, 14] years), 106 had MS-ON, 25 had AQP4-ON, and 8 had MOG-ON. Patients with MOG-ON had the highest recurrence rate (88 %) relative to MS-ON (28 %) and AQP4-ON (56 %) patients ($P < .001$). Patients with AQP4-ON had the highest mean visual functional system scores (4.3 [SD, 1.8]) relative to MS-ON (2.0 [SD, 1.9]) and MOG-ON patients (2.8 [SD, 2.0]) ($P < .001$). CONCLUSION: Patients presenting with initial episodes of ON exhibit a range radiographic and laboratory feature depending on the underlying associated disease. Understanding the variable characteristics of typical (MS-associated) and atypical (antibody-associated) ON may help physicians accurately diagnose and effectively treat ON.

Neurology

Zhang L, **Li C**, **Huang R**, **Teng H**, **Zhang Y**, **Zhou M**, **Liu X**, **Fan B**, **Luo H**, **He A**, **Zhao A**, **Lu M**, **Chopp M**, and **Zhang ZG**. Cerebral endothelial cell derived small extracellular vesicles improve cognitive function in aged diabetic rats. *Front Aging Neurosci* 2022; 14:926485. PMID: 35912073. Full Text

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Small extracellular vesicles (sEVs) mediate cell-cell communication by transferring their cargo biological materials into recipient cells. Diabetes mellitus (DM) induces cerebral vascular dysfunction and neurogenesis impairment, which are associated with cognitive decline and an increased risk of developing dementia. Whether the sEVs are involved in DM-induced cerebral vascular disease, is unknown. Therefore, we studied sEVs derived from cerebral endothelial cells (CEC-sEVs) of aged DM rats (DM-CEC-sEVs) and found that DM-CEC-sEVs robustly inhibited neural stem cell (NSC) generation of new neuroblasts and damaged cerebral endothelial function. Treatment of aged DM-rats with CEC-

sEVs derived from adult healthy normal rats (N-CEC-sEVs) ameliorated cognitive deficits and improved cerebral vascular function and enhanced neurogenesis. Intravenously administered N-CEC-sEVs crossed the blood brain barrier and were internalized by neural stem cells in the neurogenic region, which were associated with augmentation of miR-1 and -146a and reduction of myeloid differentiation primary response gene 88 and thrombospondin 1 proteins. In addition, uptake of N-CEC-sEVs by the recipient cells was mediated by clathrin and caveolin dependent endocytosis signaling pathways. The present study provides ex vivo and in vivo evidence that DM-CEC-sEVs induce cerebral vascular dysfunction and neurogenesis impairment and that N-CEC-sEVs have a therapeutic effect on improvement of cognitive function by ameliorating dysfunction of cerebral vessels and increasing neurogenesis in aged DM rats, respectively.

Neurosurgery

Alsrouji OK, and **Chebl AB**. Acute Neurointervention for Ischemic Stroke. *Interv Cardiol Clin* 2022; 11(3):339-347. PMID: 35710287. Full Text

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Acute ischemic stroke (AIS) is one of the major causes of death worldwide and a leading cause of disability. Until recently treatment of AIS was supportive, and in a minority of patients intravenous thrombolysis was available but with marginal clinical benefit. With the advent of stent retrievers, distal aspiration catheters as well as improved patient selection neurologic outcomes have greatly improved. However, the care of patients with AIS is still challenging and requires the early recognition of stroke symptoms, extensive diagnostic testing, early intervention, and advanced nursing and critical care.

Neurosurgery

Dmytriw AA, Ghozy S, Sweid A, Piotin M, Bekelis K, Sourour N, Raz E, Vela-Duarte D, Linfante I, Dabus G, **Kole M**, Martínez-Galdámez M, Nimjee SM, Lopes DK, Hassan AE, Kan P, Ghorbani M, Levitt MR, Escalard S, Missios S, Shapiro M, Clarençon F, Elhorany M, **Tahir RA**, Youssef PP, Pandey AS, Starke RM, El Naamani K, Abbas R, Mansour OY, Galvan J, Billingsley JT, Mortazavi A, Walker M, Dibas M, Settecase F, Heran MKS, Kuhn AL, Puri AS, Menon BK, Sivakumar S, Mowla A, D'Amato S, Zha AM, Cooke D, Vranic JE, Regenhardt RW, Rabinov JD, Stapleton CJ, Goyal M, Wu H, Cohen J, Turkel-Parella D, Xavier A, Waqas M, Tutino V, Siddiqui A, Gupta G, Nanda A, Khandelwal P, Tiu C, Portela PC, Perez de la Ossa N, Urra X, de Lera M, Arenillas JF, Ribo M, Requena M, Piano M, Pero G, De Sousa K, Al-Mufti F, Hashim Z, Nayak S, Renieri L, Du R, Aziz-Sultan MA, Liebeskind D, Nogueira RG, Abdalkader M, Nguyen TN, Vigilante N, Siegler JE, Grossberg JA, Saad H, Gooch MR, Herial NA, Rosenwasser RH, Tjoumakaris S, Patel AB, Tiwari A, and Jabbour P. International controlled study of revascularization and outcomes following COVID-positive mechanical thrombectomy. *Eur J Neurol* 2022; Epub ahead of print. PMID: 35818781. Full Text

BACKGROUND AND PURPOSE: Previous studies suggest that mechanisms and outcomes in patients with COVID-19-associated stroke differ from those in patients with non-COVID-19-associated strokes, but there is limited comparative evidence focusing on these populations. The aim of this study, therefore, was to determine if a significant association exists between COVID-19 status with revascularization and functional outcomes following thrombectomy for large vessel occlusion (LVO), after adjustment for potential confounding factors. METHODS: A cross-sectional, international multicenter retrospective study was conducted in consecutively admitted COVID-19 patients with concomitant acute LVO, compared to a control group without COVID-19. Data collected included age, gender, comorbidities, clinical characteristics, details of the involved vessels, procedural technique, and various outcomes. A multivariable-adjusted analysis was conducted. RESULTS: In this cohort of 697 patients with acute LVO, 302 had COVID-19 while 395 patients did not. There was a significant difference ($p < 0.001$) in the mean age (in years) and gender of patients, with younger patients and more males in the COVID-19 group. In terms of favorable revascularization (modified Thrombolysis in Cerebral Infarction [mTICI] grade 3),

COVID-19 was associated with lower odds of complete revascularization (odds ratio 0.33, 95% confidence interval [CI] 0.23-0.48; p < 0.001), which persisted on multivariable modeling with adjustment for other predictors (adjusted odds ratio 0.30, 95% CI 0.12-0.77; p = 0.012). Moreover, endovascular complications, in-hospital mortality, and length of hospital stay were significantly higher among COVID-19 patients (p < 0.001). CONCLUSION: COVID-19 was an independent predictor of incomplete revascularization and poor functional outcome in patients with stroke due to LVO. Furthermore, COVID-19 patients with LVO were more often younger and had higher morbidity/mortality rates.

Neurosurgery
Hamilton TM, **Reese JC**, and **Air EL**. Health Care Disparity in Pain. *Neurosurg Clin N Am* 2022; 33(3):251-260. PMID: 35718394. Full Text

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Disparity in the treatment of chronic pain has become increasingly pertinent in health care, given the large burden of disease and its economic costs to society. That disease burden is disproportionally carried by minorities and those of lower socioeconomic status for a host of historical and systemic reasons. Only by understanding the cause of such disparities, collecting accurate and thorough data that illuminate all contributing factors, and diversifying the health care workforce, can we achieve more equitable treatment and reduce the burden of chronic pain.

Neurosurgery
Liu EM, Shi ZF, Li KK, **Malta TM**, Chung NY, Chen H, Chan JY, Poon MF, Kwan JS, Chan DT, **Noushmehr H**, Mao Y, and Ng HK. Molecular landscape of IDH-wild type, pTERT-wild type adult glioblastomas. *Brain Pathol* 2022; e13107. Epub ahead of print. PMID: 35815721. Full Text

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Telomerase reverse transcriptase (TERT) promoter (pTERT) mutation has often been described as a late event in gliomagenesis and it has been suggested as a prognostic biomarker in gliomas other than 1p19q codeleted tumors. However, the characteristics of isocitrate dehydrogenase (IDH) wild type (wt) (IDHwt), pTERTwt glioblastomas are not well known. We recruited 72 adult IDHwt, pTERTwt glioblastomas and performed methylation profiling, targeted sequencing, and fluorescence in situ hybridization (FISH) for TERT structural rearrangement and ALT (alternative lengthening of telomeres). There was no significant difference in overall survival (OS) between our cohort and a the Cancer Genome Atlas (TCGA) cohort of IDHwt, pTERT mutant (mut) glioblastomas, suggesting that pTERT mutation on its own is not a prognostic factor among IDHwt glioblastomas. Epigenetically, the tumors clustered into classic-like (11%), mesenchymal-like (32%), and LGm6-glioblastoma (GBM) (57%), the latter far exceeding the corresponding proportion seen in the TCGA cohort of IDHwt, pTERTmut glioblastomas. LGm6-GBM-clustered tumors were enriched for platelet derived growth factor receptor alpha (PDGFRA) amplification or mutation (p = 0.008), and contained far fewer epidermal growth factor receptor (EGFR) amplification (p < 0.01), 10p loss (p = 0.001) and 10q loss (p < 0.001) compared with cases not clustered to this group. LGm6-GBM cases predominantly showed ALT (p = 0.038). In the whole cohort, only 35% cases showed EGFR amplification and no case showed combined chromosome +7/-10. Since the cases were already pTERTwt, so the three molecular properties of EGFR amplification, +7/-10, and pTERT mutation may not cover all IDHwt glioblastomas. Instead, EGFR and PDGFRA amplifications covered 67% and together with their mutations covered 71% of cases of this cohort. Homozygous deletion of cyclin dependent

kinase inhibitor 2A (CDKN2A)/B was associated with a worse OS (p = 0.031) and was an independent prognosticator in multivariate analysis (p = 0.032). In conclusion, adult IDHwt, pTERTwt glioblastomas show epigenetic clustering different from IDHwt, pTERTmut glioblastomas, and IDHwt glioblastomas which are pTERTwt may however not show EGFR amplification or +7/-10 in a significant proportion of cases. CDKN2A/B deletion is a poor prognostic biomarker in this group.

Neurosurgery

Lubanska D, Alrashed S, Mason GT, Nadeem F, Awada A, DiPasquale M, Sorge A, Malik A, Kojic M, Soliman MAR, **deCarvalho AC**, Shamisa A, Kulkarni S, Marquardt D, Porter LA, and Rondeau-Gagné S. Impairing proliferation of glioblastoma multiforme with CD44+ selective conjugated polymer nanoparticles. *Sci Rep* 2022; 12(1):12078. PMID: 35840697. Full Text

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Glioblastoma is one of the most aggressive types of cancer with success of therapy being hampered by the existence of treatment resistant populations of stem-like Tumour Initiating Cells (TICs) and poor blood-brain barrier drug penetration. Therapies capable of effectively targeting the TIC population are in high demand. Here, we synthesize spherical diketopyrrolopyrrole-based Conjugated Polymer Nanoparticles (CPNs) with an average diameter of 109 nm. CPNs were designed to include fluorescein-conjugated Hyaluronic Acid (HA), a ligand for the CD44 receptor present on one population of TICs. We demonstrate blood-brain barrier permeability of this system and concentration and cell cycle phase-dependent selective uptake of HA-CPNs in CD44 positive GBM-patient derived cultures. Interestingly, we found that uptake alone regulated the levels and signaling activity of the CD44 receptor, decreasing stemness, invasive properties and proliferation of the CD44-TIC populations in vitro and in a patient-derived xenograft zebrafish model. This work proposes a novel, CPN- based, and surface moiety-driven selective way of targeting of TIC populations in brain cancer.

Neurosurgery

Macki M, **Hamilton T**, **Massie L**, **Bazydlo M**, **Schultz L**, **Seyfried D**, Park P, Aleem I, **Abdulhak M**, **Chang VW**, and **Schwalb JM**. Characteristics and outcomes of patients undergoing lumbar spine surgery for axial back pain in the Michigan Spine Surgery Improvement Collaborative. *Spine J* 2022; Epub ahead of print. PMID: 35803577. Full Text

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BACKGROUND CONTEXT: The indications for surgical intervention of axial back pain without leg pain for degenerative lumbar disorders have been limited in the literature, as most study designs allow some degree of leg symptoms in the inclusion criteria. PURPOSE: To determine the outcome of surgery (decompression only vs. fusion) for pure axial back pain without leg pain. STUDY DESIGN/SETTING: Prospectively collected data in the Michigan Spine Surgery Improvement Collaborative (MSSIC). PATIENT SAMPLE: Patients with pure axial back pain without leg pain underwent lumbar spine surgery for primary diagnoses of lumbar disc herniation, lumbar stenosis, and isthmic or degenerative spondylolisthesis ≤ grade II. OUTCOME MEASURES: Minimally clinically important difference (MCID) for back pain, Numeric Rating Scale of back pain, Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF), MCID of PROMIS-PF, and patient satisfaction on the North American Spine Surgery Patient Satisfaction Index were collected at 90 days, 1 year, and 2 years after surgery. METHODS: Log-Poisson generalized estimating equation models were constructed with patient-reported outcomes as the independent variable, reporting adjusted risk ratios (RR(adj)). RESULTS: Of the 388 patients at 90 days, multi-level versus single level lumbar surgery decreased the likelihood of obtaining a MCID in back pain by 15% (RR(adj)=0.85, p=.038). For every one-unit increase in preoperative back pain, the likelihood for a favorable outcome increased by 8% (RR(adj)=1.08, p<.001). Of the 326 patients at 1 year, symptom duration > 1 year decreased the likelihood of a MCID in back pain by 16% (RR(adj)=0.84, p=.041). The probability of obtaining a MCID in back pain increased by 9% (RR(adj)=1.09, p<.001) for every 1-unit increase in baseline back pain score and by 14% for fusions versus decompression alone (RR(adj)=1.14, p=.0362). Of the 283 patients at 2 years, the likelihood of obtaining MCID in back pain decreased by 30% for patients with depression (RR(adj)=0.70, p<.001) and increased by 8% with every one-unit increase in baseline back pain score (RR(adj)=1.08, p<.001). CONCLUSIONS: Only the severity of preoperative back pain was associated with improvement in MCID in back pain at all time points, suggesting that surgery should be considered for selected patients with severe axial pain without leg pain. Fusion surgery versus decompression alone was associated with improved patient-reported outcomes at 1 year only, but not at the other time points.

Neurosurgery
Schwalb JM. Financial Sustainability of Neuromodulation for Pain. *Neurosurg Clin N Am* 2022; 33(3):281-286. PMID: 35718397. Full Text

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When considering the financial sustainability of neuromodulation for pain, one needs to consider the varying costs involved with this therapy. These include comparisons between different types of neuromodulation, comparisons between neuromodulation and conventional therapy, and comparisons between neuromodulation and other invasive modalities. In addition, any consideration of cost also needs to take quality into account. Even if a therapy is expensive, it can be considered cost-effective if it leads to significant increase in quality of life and economic productivity of the patient. This review considers these questions, methodologies used to assess them, and variations between different health delivery systems.

Nursing
August BA, **Griebe KM**, **Stine JJ**, **Hauser CD**, **Hunsaker T**, **Jones MC**, **Martz C**, **Peters MA**, **To L**, **Belanger R**, **Schlacht S**, **Swiderek J**, **Davis SL**, **Mlynarek ME**, and **Smith ZR**. Evaluating the impact of severe sepsis 3-hour bundle compliance on 28-day in-hospital mortality: A propensity adjusted, nested case-control study. *Pharmacother* 2022; Epub ahead of print. PMID: Not assigned. Full Text

Nursing
Turmell M, Cooley A, Yap TL, Alderden J, Sabol VK, Lin JA, and Kennerly SM. Improving Pressure Injury Prevention by Using Wearable Sensors to Cue Critical Care Patient Repositioning. *Am J Crit Care* 2022; 31(4):295-305. PMID: 35773199. Full Text

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Tracey L. Yap is an associate professor, Duke University School of Nursing, Durham, North Carolina.
Jenny Alderden is an associate professor, Boise State University School of Nursing, Boise, Idaho.
Valerie K. Sabol is a professor and division chair, Healthcare in Adult Populations, Duke University School of Nursing.
Jiunn-Ru (Angela) Lin is a data analyst, Smith & Nephew, Fort Worth, Texas.
Susan M. Kennerly is a professor, East Carolina University College of Nursing, Greenville, North Carolina.

BACKGROUND: Repositioning patients at regular intervals is the standard of care for pressure injury prevention, yet compliance with routine repositioning schedules can be hard to achieve in busy critical care environments. Cueing technology may help improve repositioning compliance. OBJECTIVE: To determine whether using wearable patient sensors to cue nurses about patients' repositioning needs could improve compliance with an every-2-hour repositioning protocol. METHODS: A sequential pretest-posttest study design was used in a 12-bed medical intensive care unit. The study occurred in 2 phases. In phase 1, eligible patients wore a triaxial accelerometer-based sensor; nurses were blinded to the data. In phase 2, the sensor technology provided staff with visual cues about patients' positions and repositioning needs. The primary measure was repositioning protocol compliance, which was compared between phase 1 and phase 2 with weighted t tests. Unit staff members were surveyed before the start of phase 1 and at the end of phase 2. RESULTS: In phase 1, 25 patients met the inclusion criteria. Phase 2 began 1 day after phase 1 and included 29 patients. In phase 1, repositioning compliance was 55%, and the mean repositioning interval was 3.8 hours. In phase 2, repositioning protocol compliance increased to 89%, and the mean repositioning interval was 2.3 hours. Nursing staff survey results showed improved teamwork in phase 2. CONCLUSION: Visual cueing about patients' mobility needs is associated with increased compliance with the facility repositioning protocol.

Obstetrics, Gynecology and Women's Health Services

Ayyash M, **Kole M**, **Le Q**, **Shen Y**, and **Swain M**. Partial Molar Pregnancy Presenting as a Tubal Ectopic Pregnancy. *Case Rep Obstet Gynecol* 2022; 2022:7414190. PMID: 35845975. Full Text

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BACKGROUND: Tubal molar pregnancy is extremely rare, with no more than 200 cases reported in the literature. The incidence is approximated at 1.5 per 1,000,000 pregnancies. CASE: We report the case of a 22-year-old woman with an overall initial stable clinical presentation who was noted to have a ruptured ectopic pregnancy. She was surgically treated, and pathology revealed partial hydatidiform molar ectopic pregnancy. At the time of surgical intervention, the treating physicians had not considered molar ectopic pregnancy within the differential diagnosis, since this is a very rare presentation. Once the pathology was discovered, the patient was contacted to be scheduled for close follow-up and counseling to reduce progression to choriocarcinomas. CONCLUSION: This case report highlights the importance of sending, reviewing, and following up on pathologic specimens for all patients undergoing surgical intervention for presumed ectopic pregnancy and ensuring that appropriate follow-up is in place for those patients.

Ophthalmology and Eye Care Services

Li Y, **Gappy S**, **Liu X**, **Sassalos T**, **Zhou T**, **Hsu A**, **Zhang A**, **Edwards PA**, **Gao H**, and **Qiao X**. Metformin suppresses pro-inflammatory cytokines in vitreous of diabetes patients and human retinal vascular endothelium. *PLoS One* 2022; 17(7):e0268451. PMID: 35802672. Full Text

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Metformin is a traditional anti-hyperglycemic medication that has recently been shown to benefit vascular complications of diabetes via an anti-inflammatory mechanism other than glycemic control. This study aims to test the hypothesis that metformin suppresses diabetic retinopathy (DR) associated intraocular inflammation. Human vitreous from control and proliferative diabetic retinopathy (PDR) patients with or without long-term metformin treatment (> 5 years) were collected for multiple inflammatory cytokines measurements with a cytokine array kit. The vast majority of the measurable cytokines in PDR vitreous has a lower level in metformin group than non-metformin group. Although the p values are not significant

due to a relatively small sample size and large deviations, the 95% confidence interval (CI) for the mean difference between the two groups shows some difference in the true values should not be neglected. Using quantitative ELISA, soluble intercellular adhesion molecule -1 (ICAM-1) and monocyte chemoattractant protein -1 (MCP-1) presented with significantly lower concentrations in metformin group versus non-metformin group. Metformin group also has significantly less up-regulated cytokines and diminished positive correlations among the cytokines when compared to non-metformin group. Possible role of AMP-activated protein kinase (AMPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in metformin's anti-inflammatory effects were studied in human retinal vascular endothelial cells (hRVECs) cultured in normal glucose (NG) and high glucose (HG) conditions. Metformin inhibited HG-induced ICAM-1, IL-8, and MCP-1 via AMPK activation, whereas pharmacological AMPK inhibition had no effect on its inhibition of NF-κB p65, sICAM-1, and tumor necrosis factor-α (TNF-α). Metformin-induced suppression of the inflammatory cytokines could also be mediated through its direct inhibition of NF-κB, independent of AMPK pathway. This is a proof-of-concept study that found metformin treatment was associated with reduced inflammatory responses in vitreous of diabetes patients and retinal vascular endothelial cells, supporting the rationale for using metformin to treat DR at an early stage.

Ophthalmology and Eye Care Services

Siegel DR, **Van Harn M**, **Taguchi M**, **Bansal P**, **Cerghet M**, and **Memon AB**. Clinical and diagnostic spectrum of optic neuritis: A single-center retrospective study of disorders associated with multiple sclerosis, anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies. *Clin Neurol Neurosurg* 2022; 221:107381. PMID: 35901556. Full Text

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OBJECTIVE: Optic neuritis (ON) is an immune-mediated optic neuropathy associated with multiple immune-mediated neurological conditions. Our aim was to characterize the clinical and diagnostic features of first or initial episodes of ON associated with multiple sclerosis (MS)-associated (typical) and antibody-related (atypical) ON. METHODS: Retrospective, single institution, medical record review. We analyzed demographic, clinical, laboratory, and radiographic findings of 139 patients who presented with first episodes of MS-associated ON (MS-ON), aquaporin 4 antibody-associated ON (AQP4-ON), and myelin oligodendrocyte glycoprotein antibody-associated ON (MOG-ON) between January 2015 and October 2019 without preceding diagnosis. Simple hypothesis testing assessed differences between groups were performed. RESULTS: Of 139 patients (109 [79 %] women; 29 [21 %] men; mean age 47 [SD, 14] years), 106 had MS-ON, 25 had AQP4-ON, and 8 had MOG-ON. Patients with MOG-ON had the highest recurrence rate (88 %) relative to MS-ON (28 %) and AQP4-ON (56 %) patients ($P < .001$). Patients with AQP4-ON had the highest mean visual functional system scores (4.3 [SD, 1.8]) relative to MS-ON (2.0 [SD, 1.9]) and MOG-ON patients (2.8 [SD, 2.0]) ($P < .001$). CONCLUSION: Patients presenting with initial episodes of ON exhibit a range radiographic and laboratory feature depending on the underlying associated disease. Understanding the variable characteristics of typical (MS-associated) and atypical (antibody-associated) ON may help physicians accurately diagnose and effectively treat ON.

Orthopedics/Bone and Joint Center

Lawrence R, **Soliman SB**, **Roseni K**, **Zauel R**, and **Bey MJ**. In vivo evaluation of rotator cuff internal impingement during scapular plane abduction in asymptomatic individuals. *J Orthop Res* 2022; Epub ahead of print. PMID: 35880416. Full Text

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Internal impingement - or entrapment of the undersurface of the rotator cuff tendon against the glenoid during overhead activities - is believed to contribute to articular-sided tears. However, little is known about internal impingement outside athletic populations. Therefore, the objectives of this study were to: 1) describe glenoid-to-footprint distances and proximity centers during dynamic, in vivo motion in asymptomatic individuals, and 2) determine the extent to which these measures differed between individuals with and without a rotator cuff tear. Shoulder kinematics were assessed in 37 asymptomatic individuals during scapular plane abduction using a high-speed biplane radiographic system. Glenoid-to-footprint distances and proximity center locations were calculated by combining the kinematics and CT-derived bone models. Glenoid-to-footprint contact was presumed to occur when the minimum distance was less than the estimated labral thickness. The condition of the supraspinatus tendon (intact, torn) was assessed using ultrasound. Minimum distances and proximity centers were compared over humerothoracic elevation angles (90°, 110°, 130°, 150°) and between supraspinatus pathology groups using two-factor mixed model ANOVAs. The minimum distance decreased consistently across elevation angles ($p<0.01$) without a significant difference between groups. Contact was estimated to occur in all participants. The proximity center was generally located on the anterior half of the rotator cuff footprint and the posterosuperior glenoid. Clinical Significance: Internal impingement during overhead motions may be a prevalent mechanism of rotator cuff pathology as contact appears to be common and involves the region of the rotator cuff footprint where degenerative rotator cuff tears are thought to originate.

Orthopedics/Bone and Joint Center
Meadows AM, **Skinner MM**, **Faraj MT**, **Hazime AA**, **Day RG**, **Fore JA**, and **Day CS**. Racial, Ethnic, and Gender Diversity in Academic Orthopaedic Surgery Leadership. *J Bone Joint Surg Am* 2022; 104(13):1157-1165. PMID: 35793794. Full Text

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BACKGROUND: Multiple investigations in the past 50 years have documented a lack of racial/ethnic and gender diversity in the orthopaedic surgery workforce when compared with other specialties. Studies in other industries suggest that diversification of leadership can help diversify the underlying workforce. This study investigates changes in racial/ethnic and gender diversity of orthopaedic surgery leadership from 2007 to 2019 and compares leadership diversity to that of other surgical and nonsurgical specialties, specifically in terms of chairpersons and program directors. METHODS: Demographic data were collected from The Journal of the American Medical Association and the Association of American Medical Colleges. Aggregate data were utilized to determine the racial, ethnic, and gender composition of academic leadership for 8 surgical and nonsurgical specialties in 2007 and 2019. Comparative analysis was conducted to identify changes in diversity among chairpersons between the 2 years. Furthermore, current levels of diversity in orthopaedic leadership were compared with those of other specialties. RESULTS: A comparative analysis of diversity among program directors revealed that orthopaedic surgery had significantly lower minority representation (20.5%) when compared with the nonsurgical specialties (adjusted $p < 0.01$ for all) and, with the exception of neurological surgery, had the lowest proportion of female program directors overall, at 9.0% (adjusted $p < 0.001$ for all). From 2007 to 2019, orthopaedic surgery experienced no change in minority representation among chairpersons (adjusted $p = 0.73$) but a significant increase in female representation among chairpersons, from 0.0% (0 of 102) to 4.1% (5 of 122) (adjusted $p = 0.04$). Lastly, a significant decrease in minority and female representation was observed when comparing the diversity of 2019 orthopaedic faculty to orthopaedic leadership in 2019/2020 ($p < 0.05$ for all). CONCLUSIONS: Diversity in orthopaedic surgery leadership has improved on some key fronts, specifically in gender diversity among chairpersons. However, a significant decrease in minority and gender representation was observed between 2019 orthopaedic faculty and 2019/2020 orthopaedic

leadership ($p < 0.05$), which was a trend shared by other specialties. These findings may suggest a more pervasive problem in diversity of medical leadership that is not only limited to orthopaedic surgery.

Orthopedics/Bone and Joint Center
Moeller JL. Pelvic Avulsion Fractures in Adolescent Athletes: Analyzing the Effect of Delay in Diagnosis. *Clin J Sport Med* 2022; 32(4):368-374. PMID: 35762861. Full Text

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OBJECTIVE: To evaluate whether delay in the diagnosis of pelvic avulsion fractures in young athletes leads to prolonged treatment and prolonged return toward sport activities, whether fractures at certain locations are associated with a greater risk of diagnostic delay, and what reasons may exist for delay in diagnosis. DESIGN: Retrospective chart review of young patients who presented with pelvic region avulsion fracture to a community-based sports medicine clinic over a 19-year period. SETTING: Private practice, primary care sports medicine clinic. PATIENTS: Patients younger than 20 years diagnosed with pelvic region avulsion fracture. INTERVENTIONS: None, this was a retrospective study. MAIN OUTCOME MEASURES: Clearance for return toward sport activities. RESULTS: Two hundred twenty-five cases were reviewed for reasons for delay in diagnosis; 208 cases met criteria for the duration of treatment and return to play activities portions of the study. The mean time from date of injury diagnosis was 19.59 days, and the mean duration from date of injury to clearance for return to play advancement was 67.20 days. Duration of treatment varied slightly depending on timing of diagnosis, whereas duration from date of injury to clearance for return to play advancement varied greatly depending on diagnostic delay. Those who did not sense a "pop" at the time of injury were more likely to experience diagnostic delay, as were athletes with ischial tuberosity fractures. The most common cause of diagnostic delay was patient/family decision on when to seek care; misdiagnosis as a muscle strain was also common. CONCLUSIONS: Diagnostic delay of adolescent pelvic avulsion fractures may unnecessarily prevent athletes from returning to play within an optimal time frame. Our observations highlight a need for educating athletes and their families on when to seek initial or follow-up medical care as well as educating medical providers regarding the diagnosis of pelvic avulsion fractures.

Orthopedics/Bone and Joint Center
Tavallaee G, Lively S, Rockel JS, **Ali SA**, Im M, Sarda C, Mitchell GM, Rossomacha E, Nakamura S, Potla P, Gabrial S, Matelski J, Ratneswaran A, Perry K, Hinz B, Gandhi R, Jurisica I, and Kapoor M. Contribution of microRNA-27b-3p to synovial fibrotic responses in knee osteoarthritis. *Arthritis Rheumatol* 2022; Epub ahead of print. PMID: 35791923. Full Text

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OBJECTIVES: Synovial fibrosis contributes to osteoarthritis (OA) pathology but the underlying mechanisms remain unknown. We have observed increased microRNA (miR)-27b-3p levels in synovial fluid of late-stage radiographic knee OA patients. Here, we determined the contribution of miR-27b-3p to synovial fibrosis. METHODS: Synovium sections obtained from Kellgren-Lawrence-graded knee OA patients and a mouse model of knee OA (destabilization of medial meniscus; DMM) were stained for miR-27b-3p using in situ hybridization. Effects of intra-articular injections of miR-27b-3p mimic into naïve mouse knee joints, and miR-27b-3p inhibitor in the DMM model were also examined. MiR-27b-3p mimic or inhibitor transfection experiments were performed on human OA fibroblast-like synoviocytes (FLS)

using RT-qPCR array, RNA sequencing, RT-qPCR, Western blotting, immunofluorescence and migration assays. RESULTS: MiR-27b-3p expression increased in the synovium of knee OA patients and after DMM surgery in mice. Intra-articular injections of miR-27b-3p mimic injected in mouse knee joints induced a synovial fibrosis-like phenotype with increased synovitis scores and increased COL1A1 and α-SMA expression. In the DMM model, miR-27b-3p inhibitor decreased α-SMA with unchanged COL1A1 expression and synovitis scores. MiR-27b-3p mimic treatment of human OA FLS induced pro-fibrotic responses including increased migration and expression of key extracellular matrix (ECM) genes, while inhibitor transfection had opposite effects. RNA-sequencing identified a PPARG/ADAMTS8 signaling axis regulated by miR-27b-3p in OA FLS. MiR-27b-3p mimic-transfected OA FLS treated with the PPARG agonist rosiglitazone or ADAMTS8-siRNA exhibited altered expression of select ECM genes. CONCLUSIONS: This study demonstrates a key role of miR-27b-3p in ECM regulation associated with synovial fibrosis during OA.

Orthopedics/Bone and Joint Center

Tramer JS, **Khalil LS**, **Jildeh TR**, **Abbas MJ**, **McGee A**, **Lau MJ**, **Moutzouros V**, and Okoroha KR. Blood Flow Restriction Therapy For Two Weeks Prior to Anterior Cruciate Ligament Reconstruction Did Not Impact Quadriceps Strength Compared to Standard Therapy. *Arthroscopy* 2022; Epub ahead of print. PMID: 35842062. Full Text

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PURPOSE: To evaluate the efficacy of a two-week home-based blood flow restriction (BFR) prehabiliation program on quadriceps strength and patient reported outcomes prior to anterior cruciate ligament (ACL) reconstruction. METHODS: Patients presenting with an ACL tear were randomized into two groups, BFR and control, at their initial clinic visit. Quadriceps strength was measured utilizing a handheld dynamometer in order to calculate peak force, average force and time to peak force during seated leg extension at the initial clinic visit and repeated on the day of surgery. All patients were provided education on standardized exercises to be performed 5 days per week for two weeks between the initial clinic visit and date of surgery. The BFR group was instructed to perform these exercises with a pneumatic cuff set to 80% of limb occlusion pressure placed over the proximal thigh. Patient Reported Outcome Measurement System Physical Function (PROMIS-PF), knee range of motion and quadriceps circumference were gathered at the initial clinic visit /day of surgery and patients were monitored for adverse effects. RESULTS: A total 45 patients met inclusion criteria and elected to participate. There were 23 patients randomized to the BFR group and 22 patients randomized into the control group. No significant differences were noted between the BFR and control groups in any demographic characteristics (48% versus 64% male ($p=0.271$) and average age 26.5 ± 12.0 versus 27.0 ± 11.0 ($p=0.879$) in BFR and control respectively). During the initial clinic visit there were no significant differences in quadriceps circumference, peak quadriceps force generation, time to peak force, average force, pain and PROMIS scales ($P>0.05$ for all). Following completion of a two week home prehabilitation protocol all patients indeterminant of cohort demonstrated decreased strength loss in the operative leg compared to the non-operative leg ($p<0.05$ for both) However, there were no significant differences in any strength or outcome measures between the BFR and control groups ($P>0.05$ for all). There were no complications experienced in either group, and both were compliant with the home-based prehabilitation program. CONCLUSIONS: A two week standardized prehabilitation protocol preceding ACL reconstruction resulted in a significant improvement in personal quadriceps peak force measurements, both with and without the use of BFR. No difference in quadriceps circumference, strength, or patient reported outcomes were found between the BFR and the control group. The home-based BFR prehabiliation protocol was found to be feasible, accessible, and well tolerated by patients.

Orthopedics/Bone and Joint Center

Warren JR, **Khalil LS**, **Pietroski AD**, **Burdick GB**, **McIntosh MJ**, **Guthrie ST**, and **Muh SJ**. Perceived effectiveness of video interviews for orthopaedic surgery residency during COVID-19. *BMC Med Educ* 2022; 22(1):566. PMID: 35869546. Full Text

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BACKGROUND: During the 2020-21 residency interview season, interviews were conducted through virtual platforms due to the COVID-19 pandemic. The purpose of this study is to assess the general perceptions of applicants, residents and attendings at a single, large, metropolitan orthopaedic residency with regards to the video interview process before and after the interview season. METHODS: Surveys were sent to all orthopaedic applicants, residents, and attendings before the interview season. Applicants who received interviews and responded to the first survey (46) and faculty who responded to the first survey (28) were sent a second survey after interviews to assess how their perceptions of video interviews changed. RESULTS: Initially, 50% of applicants (360/722) and 50% of faculty and residents (28/56) responded before interview season. After interviews, 55% of interviewees (25/46) and 64% of faculty and residents (18/28) responded. Before interviews, 91% of applicants stated they would prefer in-person interviews and 71% were worried that video interviews would prevent them from finding the best program fit. Before interviews, 100% of faculty and residents stated they would rather conduct in-person interviews and 86% felt that residencies would be less likely to find applicants who best fit the program. Comparing responses before and after interviews, 16% fewer applicants ($p = 0.01$) perceived that in-person interviews provide a better sense of a residency program and faculty and residents' perceived ability to build rapport with interviewees improved in 11% of respondents ($p = 0.01$). However, in-person interviews were still heavily favored by interviewees (84%) and faculty and residents (88%) after the interview season. CONCLUSIONS: In-person interviews for Orthopaedic Surgery Residency are perceived as superior and are preferred among the overwhelming majority of applicants, residents, and interviewers. Nevertheless, perceptions toward video interviews improved in certain domains after interview season, identifying potential areas of improvement and alternative interview options for future applicants.

Orthopedics/Bone and Joint Center

Warren JR, **Khalil LS**, **Pietroski AD**, and **Muh SJ**. Injection of adipose stem cells in the treatment of rotator cuff disease - a narrative review of current evidence. *Regen Med* 2022; 17(7):477-489. PMID: 35586993. Full Text

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The purpose of this study is to summarize evidence for the use of adipose stem cell (ASC) injections in the treatment of rotator cuff tears (RCT) and identify future areas of study. A thorough literature search was performed to identify studies investigating the use of ASC injections in the treatment of RCTs. Among animal trials, it is unclear whether ASCs are of benefit for rotator cuff repair. In clinical trials, ASC injection may reduce retear rate with otherwise equivocal clinical outcomes. Although ASC injection may be safe, the literature does not provide a clear consensus as to the efficacy of ASC injections, nor does it delineate which patients would benefit most from this treatment.
The purpose of this paper is to review available studies that look at the effects of adipose stem cell (ASC) injections in the treatment of rotator cuff tears (RCT). A thorough literature search of all available studies was performed. Among lab studies in animals, it is unclear if ASCs help improve the outcomes of rotator cuff repair. In studies using live patients, ASC injection may reduce retear rate, but it is unclear whether there are any other benefits to ASC injection. ASC injection is safe in humans, but the literature does not provide a clear consensus as to how much benefit this treatment provides for rotator cuff repair, nor does it delineate which patients would benefit most from this treatment.

Otolaryngology – Head and Neck Surgery

Douglas JE, Patel T, Rullan-Oliver B, Ungerer H, Hinh L, **Peterson EL**, Kohanski MA, Kennedy DW, Palmer JN, Adappa ND, and **Craig JR**. Odontogenic Sinusitis is a Common Cause of Operative Extra-Sinus Infectious Complications. *Am J Rhinol Allerg* 2022. PMID: Not assigned. Full Text

Otolaryngology – Head and Neck Surgery

Plawecki AM, Saleem A, **Zvirbulis D**, **Peterson EL**, Yoo F, **Ali A**, and **Craig JR**. Clinical Features and Headache Diagnoses in Patients With Chief Complaint of Craniofacial Pain. *Ann Otol Rhinol Laryngol* 2022; Epub ahead of print. PMID: 35794798. Full Text

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OBJECTIVES: Investigate the use of nasal endoscopy, sinus imaging, and neurologic evaluation in patients presenting to a rhinologist primarily for craniofacial pain. METHODS: This was a retrospective analysis of consecutive outpatients presenting to a rhinologist between 2016 and 2019 with chief complaints of craniofacial pain with or without other sinonasal symptoms, who were then referred to and evaluated by headache specialists. Data analyzed included sinusitis symptoms, Sino-Nasal Outcome Test (SNOT-22) scores (and facial pain subscores), pain location, nasal endoscopy, computed tomography (CT) findings, and headache diagnoses made by headache specialists. RESULTS: Of the 134 patients with prominent craniofacial pain, the majority of patients were diagnosed with migraine (50%) or tension-type (22%) headache, followed by multiple other non-sinogenic headache disorders. Approximately 5% of patients had headaches attributed to sinusitis. Amongst all patients, 90% had negative nasal endoscopies. Patients with negative endoscopies were significantly less likely to report smell loss ($P = .003$) compared to those with positive endoscopies. Poor agreement was demonstrated between self-reported pain locations and sinus findings on CT (kappa values < 0.20). Negative nasal endoscopy showed high concurrence with negative CT findings (80%-97%). CONCLUSIONS: Patients presenting with chief complaints of craniofacial pain generally met criteria for various non-sinogenic headache disorders. Nasal endoscopy was negative in 90% of patients, and CT demonstrated poor agreement with pain locations. Nasal endoscopy and CT shared high concurrence rates for negative sinus findings. The value of nasal endoscopy over sinus imaging in craniofacial pain evaluation should be explored in future studies.

Pathology and Laboratory Medicine

Acosta AM, Sangoi AR, Maclean F, Trpkov K, Osunkoya AO, Collins K, Miyamoto H, Hirsch MS, Chan E, Tretiakova M, Mohanty SK, Kaushal S, Cornejo KM, Aron M, Quiroga-Garza G, Arora K, **Nguyen JK**, **Williamson SR**, Epstein JI, and Matoso A. Prostatic malakoplakia: clinicopathological assessment of a multi-institutional series of 49 patients. *Histopathology* 2022; Epub ahead of print. PMID: 35876721. Full Text

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Prostatic malakoplakia (MP) is rare, with only case reports and small series (< five patients) available in the literature. In this study we analysed an international multi-institutional series of 49 patients with prostatic MP to more clearly define its clinicopathological features. The median age was 67 years and the median serum prostate-specific antigen (PSA) was 7.5 ng/ml. MP was clinically manifest in most cases (28 of 45 patients with data available, 62%). Of 43 patients with detailed clinical history available, 21 (49%) had concurrent or metachronous malignancies (including prostate cancer). Diabetes or insulin resistance was present in 11 patients (26%). Additionally, three patients had a history of solid organ transplantation and one had HIV. Of note, six of 34 patients (18%) without concurrent prostate cancer had an abnormal digital rectal examination and/or lesions on magnetic resonance imaging (MRI) with prostate imaging reporting and data system (PIRADS) scores 4-5. The initial diagnosis was made on core biopsies (25 of 49, 51%), transurethal resection specimens (12 of 49, 24%), radical prostatectomies (10 of 49, 20%), Holmium-laser enucleation (one of 49, 2%) and cystoprostatectomy (one of 49, 2%). Tissue involvement was more commonly diffuse or multifocal (40 of 49, 82%). Von Kossa and periodic acid-Schiff stains were positive in 35 of 38 (92%) and 26 of 27 lesions (96%), respectively. Of note, two cases were received in consultation by the authors with a preliminary diagnosis of mesenchymal tumour/tumour of the specialised prostatic stroma. The present study suggests that prostatic MP is often associated with clinical findings that may mimic those of prostate cancer in a subset of patients. Moreover, MP may be found incidentally in patients with concurrent prostate cancer.

Pathology and Laboratory Medicine

Ayyash M, **Kole M**, **Le Q**, **Shen Y**, and **Swain M**. Partial Molar Pregnancy Presenting as a Tubal Ectopic Pregnancy. *Case Rep Obstet Gynecol* 2022; 2022:7414190. PMID: 35845975. Full Text

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BACKGROUND: Tubal molar pregnancy is extremely rare, with no more than 200 cases reported in the literature. The incidence is approximated at 1.5 per 1,000,000 pregnancies. CASE: We report the case of a 22-year-old woman with an overall initial stable clinical presentation who was noted to have a ruptured ectopic pregnancy. She was surgically treated, and pathology revealed partial hydatidiform molar ectopic pregnancy. At the time of surgical intervention, the treating physicians had not considered molar ectopic pregnancy within the differential diagnosis, since this is a very rare presentation. Once the pathology was discovered, the patient was contacted to be scheduled for close follow-up and counseling to reduce progression to choriocarcinomas. CONCLUSION: This case report highlights the importance of sending, reviewing, and following up on pathologic specimens for all patients undergoing surgical intervention for presumed ectopic pregnancy and ensuring that appropriate follow-up is in place for those patients.

Pediatrics
Gamarel KE, Rebchook G, McCree BM, Jadwin-Cakmak L, **Connolly M**, Reyes LA, and Sevelius JM. The ethical imperative to reduce HIV stigma through community-engaged, status-neutral interventions designed with and for transgender women of colour in the United States. *J Int AIDS Soc* 2022; 25 Suppl 1(Suppl 1):e25907. PMID: 35818894. Full Text

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INTRODUCTION: In the era of biomedical HIV prevention and treatment technologies, such as treatment as prevention (TasP) and pre-exposure prophylaxis (PrEP), there is momentum to develop and rigorously evaluate interventions focused on PrEP among those at risk for HIV acquisition and antiretroviral therapy (ART) adherence among people living with HIV. While HIV status-specific interventions focused on PrEP or ART provide valuable information, status-segregated interventions can create, perpetuate, and even increase HIV stigma among transgender women of colour and other marginalized communities in the United States (US). DISCUSSION: Due largely to community advocacy, discourses that support status-neutral approaches have emerged in the scientific literature. Although US-based funding mechanisms have typically designated awards focused on a specific HIV status, intervention developers and implementing agencies find creative ways to design and implement status-neutral programmes despite such restrictions. We present our experience with intervention research in New York, Detroit, New Orleans, Puerto Rico and the San Francisco Bay Area, all Ending the HIV Epidemic (EHE) priority jurisdictions. Kickin it with the Gurlz' was developed to be status-neutral through two grants due to community demands for a unifying approach. The Transgender Women Engagement and Entry to (TWEET) Care Project was designed to improve HIV care engagement for transgender women living with HIV, but developers realized the importance of including participants of any HIV status. Healthy Divas was designed for transgender women living with HIV but subsequent implementing agencies prioritized adapting it to be status-neutral. These examples support the urgency of designing, implementing and evaluating status-neutral interventions. CONCLUSIONS: Community-based organizations strive for inclusivity in their programming and are rightly often reluctant to segregate services based on the HIV status of their clients. As researchers, we have an ethical imperative to work to reduce HIV stigma and respond to the needs of those most impacted by HIV, including transgender women of colour. As such, we call upon funders to develop mechanisms that support the development and testing of HIV status-neutral interventions to reduce HIV stigma and support community building, thereby increasing the possibility of fully realizing the benefits of biomedical HIV prevention and treatment technologies for all.

Pharmacy
August BA, **Griebe KM**, **Stine JJ**, **Hauser CD**, **Hunsaker T**, **Jones MC**, **Martz C**, **Peters MA**, **To L**, **Belanger R**, **Schlacht S**, **Swiderek J**, **Davis SL**, **Mlynarek ME**, and **Smith ZR**. Evaluating the impact of severe sepsis 3-hour bundle compliance on 28-day in-hospital mortality: A propensity adjusted, nested case-control study. *Pharmacother* 2022. PMID: Not assigned. Full Text

Pharmacy
Carter M, Solsrud K, **Yeddula S**, **Fitzmaurice MG**, **Singh A**, **Nagai S**, and **Jafri SM**. Hepatitis E Diagnosis and Management After Liver, Kidney, or Heart Transplant: A Single-Center Experience. *Transplant Proc* 2022; Epub ahead of print. PMID: 35907694. Full Text

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BACKGROUND: Transplant-related hepatitis E virus (HEV) infection is a rarely recognized phenomenon with significant clinical importance given its potential to result in chronic hepatitis posttransplant. METHODS: We retrospectively evaluated HEV diagnosis and treatment after liver, kidney, and heart transplant in a single center. We identified patients diagnosed with HEV by serologic testing and evaluated their treatment regimens. RESULTS: Fifteen transplant recipients (12 liver, 2 kidney, and 1 heart) presented with elevated liver enzymes and were positive for HEV IgM antibody. Liver enzymes normalized in 4 patients after being treated with ribavirin. One of the 4 patients had 2 recurrences with positive HEV RNA results following ribavirin treatment but recovered after 12 months of ribavirin therapy. After treatment with reduction in immunosuppression without antiviral treatment, 6 of 8 patients' liver enzymes normalized. One of these patients died of acute pancreatitis 2 months after testing positive for HEV IgM antibody. CONCLUSIONS: The potential for complications related to active HEV infections in transplant recipients necessitates prompt diagnosis and treatment to prevent irreversible damage. Diagnosis with HEV reverse transcriptase-polymerase chain reaction should follow a positive HEV IgM antibody test. This manuscript provides evidence that ribavirin antiviral therapy and reducing immunosuppression are effective treatments for HEV infections in liver, kidney, and heart transplant recipients, which has not been sufficiently investigated in the population of the United States. Larger multicenter studies are needed to confirm the risks and benefits of using ribavirin antiviral therapy as first-line therapy of HEV posttransplant.

Pharmacy

Chang F, O'Connell MB, Mills ME, **Hwang JM**, **Khreizat HS**, Garwood CL, and Houser A. Preventive health therapy and behavior outcomes from a brown bag medication review for older adults. *J Am Geriatr Soc* 2022; Epub ahead of print. PMID: 35906965. Full Text

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BACKGROUND: Morbidity and mortality associated with preventable diseases can be reduced with the use of preventive health services. We evaluated the uptake and retention of preventive health behaviors and management of accidental medication poisonings in older adults after a health prevention educational component was combined with a brown bag medication review. METHODS: This study used a cohort design and was conducted in six urban senior centers and three independent senior living communities in Detroit, Michigan. Participants included 85 older adults (>60 years old) taking five or more medications with 63 participants returning follow up materials. Pharmacy personnel conducted brown bag medication reviews that were combined with a preventive health education component. Information was collected on medications, vaccinations, supplement use, and accidental medication poisoning management. Participants were given written recommendations on prescription medications and preventive health therapies to improve health and medication use. An investigator developed program satisfaction survey was administered immediately after the review. An investigator-developed follow-up preventive health implementation survey was conducted at least 3 months later to assess recommendation implementation. RESULTS: Participants' mean age was 75.9 ± 8.5 years. Fifty-six older adults had 124 recommendations in preventive health in total (1-5/participant). Eleven participants had no recommendations. Sixty-three participants (74%) returned follow-up preventive health surveys. Twenty-three percent of recommendations were already implemented with 34% planned to be done in the future. Poisoning management knowledge increased for 13 participants, reporting they would call the poison control center. The program was well received, with participants reporting high satisfaction scores

(4.8 ± 0.7 out of 5). CONCLUSIONS: Brown bag medication reviews can be an effective method to promote the uptake of preventive health behaviors among older adults, but additional accidental medication poisoning management education is still needed.

Pharmacy
Greenlee SB, **Kenney RM**, **Makowski CT**, **Bulat E**, **Brar I**, and **Davis SL**. Evaluating the Impact of Substance Use Disorder Resources on Outcomes of Persons Who Inject Drugs with Infections. *J Addict Med* 2022; Epub ahead of print. PMID: 35802753. Full Text

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OBJECTIVE: The aim of the study is to evaluate the impact of inpatient substance use disorder (SUD) resources on outcomes of persons who inject stimulants and/or opioids (PWIDs) with infections. METHODS: This retrospective cohort evaluated PWIDs hospitalized from July 1, 2020, to May 31, 2021, and prescribed an antimicrobial course. The patients were compared based on inpatient implementation of SUD resources, including consultation of addiction medicine/behavioral health, implementation of an opioid withdrawal treatment protocol, or continuation/initiation of medications for opioid use disorder. The primary outcome was a composite of antibiotic completion, no unplanned discharge, and no 30-day readmission. Notable secondary outcomes included length of stay and presence of stigmatizing language in the electronic medical record. RESULTS: A total of 119 patients were analyzed-74 (62.2%) received SUD resources. The primary outcome was met by 43 patients with SUD resources implemented (58.1%) and 19 patients without resources (42.2%, P = 0.093). After adjustment for infection type, implementation of SUD resources (adjusted odds ratio, 2.593; 95% confidence interval, 1.162-5.789) was independently associated with primary outcome success. The patients who received SUD resources had a median length of stay of 7 days (4-13.3) compared with 4 days (2-6.5) in those without resources (P < 0.001). Stigmatizing language was present in 98% of patient electronic medical records. CONCLUSIONS: Patient care provided to PWIDs with infections is optimized when SUD resources are implemented. This study further supports the necessity of improving SUD management when PWIDs are admitted to healthcare facilities.

Pharmacy
Veve MP, Mercuro NJ, Sangiovanni RJ, Santarossa M, and Patel N. Prevalence and Predictors of Pseudomonas aeruginosa Among Hospitalized Patients With Diabetic Foot Infections. *Open Forum Infect Dis* 2022; 9(7). PMID: Not assigned. Full Text

Public Health Sciences
Ahmedani BK, **Cannella CE**, **Yeh HH**, **Westphal J**, Simon GE, Beck A, Rossom RC, Lynch FL, Lu CY, Owen-Smith AA, Sala-Hamrick KJ, **Frank C**, **Akinyemi E**, **Beebani G**, **Busuito C**, Boggs JM, Daida YG, Waring S, Gui H, and **Levin AM**. Detecting and distinguishing indicators of risk for suicide using clinical records. *Transl Psychiatry* 2022; 12(1):280. PMID: 35831289. Full Text

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Health systems are essential for suicide risk detection. Most efforts target people with mental health (MH) diagnoses, but this only represents half of the people who die by suicide. This study seeks to discover and validate health indicators of suicide death among those with, and without, MH diagnoses. This case-control study used statistical modeling with health record data on diagnoses, procedures, and encounters. The study included 3,195 individuals who died by suicide from 2000 to 2015 and 249,092 randomly selected matched controls, who were age 18+ and affiliated with nine Mental Health Research Network affiliated health systems. Of the 202 indicators studied, 170 (84%) were associated with suicide in the discovery cohort, with 148 (86%) of those in the validation cohort. Malignant cancer diagnoses were risk factors for suicide in those without MH diagnoses, and multiple individual psychiatric-related indicators were unique to the MH subgroup. Protective effects across MH-stratified models included diagnoses of benign neoplasms, respiratory infections, and utilization of reproductive services. MH-stratified latent class models validated five subgroups with distinct patterns of indicators in both those with and without MH. The highest risk groups were characterized via high utilization with multiple healthcare concerns in both groups. The lowest risk groups were characterized as predominantly young, female, and high utilizers of preventive services. Healthcare data include many indicators of suicide risk for those with and without MH diagnoses, which may be used to support the identification and understanding of risk as well as targeting of prevention in health systems.

Public Health Sciences
Douglas JE, Patel T, Rullan-Oliver B, Ungerer H, Hinh L, **Peterson EL**, Kohanski MA, Kennedy DW, Palmer JN, Adappa ND, and **Craig JR**. Odontogenic Sinusitis is a Common Cause of Operative Extra-Sinus Infectious Complications. *Am J Rhinol Allerg* 2022. PMID: Not assigned. Full Text

Public Health Sciences
Khatri B, Tessneer KL, Rasmussen A, Aghakhanian F, Reksten TR, Adler A, Alevizos I, Anaya JM, Aqrawi LA, Baecklund E, Brun JG, Bucher SM, Eloranta ML, Engelke F, Forsblad-d'Elia H, Glenn SB, Hammenfors D, Imgenberg-Kreuz J, Jensen JL, Johnsen SJA, Jonsson MV, Kvarnström M, Kelly JA, Li H, Mandl T, Martín J, Nocturne G, Norheim KB, Palm Ø, Skarstein K, Stolarczyk AM, Taylor KE, Teruel M, Theander E, Venuturupalli S, Wallace DJ, Grundahl KM, Hefner KS, Radfar L, Lewis DM, Stone DU, Kaufman CE, Brennan MT, Guthridge JM, James JA, Scofield RH, Gaffney PM, Criswell LA, Jonsson R, Eriksson P, Bowman SJ, Omdal R, Rönnblom L, Warner B, Rischmueller M, Witte T, Farris AD, Mariette X, Alarcon-Riquelme ME, Shiboski CH, Wahren-Herlenius M, Ng WF, Sivils KL, **Adrianto I**, Nordmark G, and Lessard CJ. Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. *Nat Commun* 2022; 13(1):4287. PMID: 35896530. Full Text

Sjögren's disease is a complex autoimmune disease with twelve established susceptibility loci. This genome-wide association study (GWAS) identifies ten novel genome-wide significant (GWS) regions in Sjögren's cases of European ancestry: CD247, NAB1, PTTG1-MIR146A, PRDM1-ATG5, TNFAIP3, XKR6, MAPT-CRHR1, RPTOR-CHMP6-BAIAP6, TYK2, SYNGR1. Polygenic risk scores yield predictability (AUROC = 0.71) and relative risk of 12.08. Interrogation of bioinformatics databases refine the associations, define local regulatory networks of GWS SNPs from the 95% credible set, and expand the implicated gene list to >40. Many GWS SNPs are eQTLs for genes within topologically associated domains in immune cells and/or eQTLs in the main target tissue, salivary glands.

Public Health Sciences
Lee Y, Jehangir Q, **Lin CH**, **Li P**, Sule AA, **Poisson L**, Balijepally V, Halabi AR, Patel K, Krishnamoorthy G, and Nair GB. 3D-PAST: Risk Assessment Model for Predicting Venous Thromboembolism in COVID-19. *J Clin Med* 2022; 11(14). PMID: 35887713. Full Text

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Hypercoagulability is a recognized feature in SARS-CoV-2 infection. There exists a need for a dedicated risk assessment model (RAM) that can risk-stratify hospitalized COVID-19 patients for venous thromboembolism (VTE) and guide anticoagulation. We aimed to build a simple clinical model to predict VTE in COVID-19 patients. This large-cohort, retrospective study included adult patients admitted to four hospitals with PCR-confirmed SARS-CoV-2 infection. Model training was performed on 3531 patients hospitalized between March and December 2020 and validated on 2508 patients hospitalized between January and September 2021. Diagnosis of VTE was defined as acute deep vein thrombosis (DVT) or pulmonary embolism (PE). The novel RAM was based on commonly available parameters at hospital admission. LASSO regression and logistic regression were performed, risk scores were assigned to the significant variables, and cutoffs were derived. Seven variables with assigned scores were delineated as: DVT History = 2; High D-Dimer (>500-2000 ng/mL) = 2; Very High D-Dimer (>2000 ng/mL) = 5; PE History = 2; Low Albumin (<3.5 g/dL) = 1; Systolic Blood Pressure <120 mmHg = 1, Tachycardia (heart rate >100 bpm) = 1. The model had a sensitivity of 83% and specificity of 53%. This simple, robust clinical tool can help individualize thromboprophylaxis for COVID-19 patients based on their VTE risk category.

Public Health Sciences

Macki M, **Hamilton T**, **Massie L**, **Bazydlo M**, **Schultz L**, **Seyfried D**, Park P, Aleem I, **Abdulhak M**, **Chang VW**, and **Schwalb JM**. Characteristics and outcomes of patients undergoing lumbar spine surgery for axial back pain in the Michigan Spine Surgery Improvement Collaborative. *Spine J* 2022; Epub ahead of print. PMID: 35803577. Full Text

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BACKGROUND CONTEXT: The indications for surgical intervention of axial back pain without leg pain for degenerative lumbar disorders have been limited in the literature, as most study designs allow some degree of leg symptoms in the inclusion criteria. PURPOSE: To determine the outcome of surgery (decompression only vs. fusion) for pure axial back pain without leg pain. STUDY DESIGN/SETTING: Prospectively collected data in the Michigan Spine Surgery Improvement Collaborative (MSSIC). PATIENT SAMPLE: Patients with pure axial back pain without leg pain underwent lumbar spine surgery for primary diagnoses of lumbar disc herniation, lumbar stenosis, and isthmic or degenerative spondylolisthesis ≤ grade II. OUTCOME MEASURES: Minimally clinically important difference (MCID) for back pain, Numeric Rating Scale of back pain, Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF), MCID of PROMIS-PF, and patient satisfaction on the North American Spine Surgery Patient Satisfaction Index were collected at 90 days, 1 year, and 2 years after surgery. METHODS: Log-Poisson generalized estimating equation models were constructed with patient-reported outcomes as the independent variable, reporting adjusted risk ratios (RR(adj)). RESULTS: Of the 388 patients at 90 days, multi-level versus single level lumbar surgery decreased the likelihood of obtaining a MCID in back pain by 15% (RR(adj)=0.85, p=.038). For every one-unit increase in preoperative back pain, the likelihood for a favorable outcome increased by 8% (RR(adj)=1.08, p<.001).

Of the 326 patients at 1 year, symptom duration > 1 year decreased the likelihood of a MCID in back pain by 16% (RR(adj)=0.84, p=.041). The probability of obtaining a MCID in back pain increased by 9% (RR(adj)=1.09, p<.001) for every 1-unit increase in baseline back pain score and by 14% for fusions versus decompression alone (RR(adj)=1.14, p=.0362). Of the 283 patients at 2 years, the likelihood of obtaining MCID in back pain decreased by 30% for patients with depression (RR(adj)=0.70, p<.001) and increased by 8% with every one-unit increase in baseline back pain score (RR(adj)=1.08, p<.001). CONCLUSIONS: Only the severity of preoperative back pain was associated with improvement in MCID in back pain at all time points, suggesting that surgery should be considered for selected patients with severe axial pain without leg pain. Fusion surgery versus decompression alone was associated with improved patient-reported outcomes at 1 year only, but not at the other time points.

Public Health Sciences

Modonutti D, **Majdalany SE**, **Corsi N**, **Li P**, **Sood A**, **Dalela D**, **Jamil ML**, **Hwang C**, **Menon M**, **Rogers CG**, Trinh QD, **Novara G**, and **Abdollah F**. A novel prognostic model predicting overall survival in patients with metastatic castration-resistant prostate cancer receiving standard chemotherapy: A multi-trial cohort analysis. *Prostate* 2022; Epub ahead of print. PMID: 35790016. Full Text

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PURPOSE: Generalizable, updated, and easy-to-use prognostic models for patients with metastatic castration-resistant prostate cancer (mCRPC) are lacking. We developed a nomogram predicting the overall survival (OS) of mCRPC patients receiving standard chemotherapy using data from five randomized clinical trials (RCTs). METHODS: Patients enrolled in the control arm of five RCTs (ASCENT 2, VENICE, CELGENE/MAINSAIL, ENTHUSE 14, and ENTHUSE 33) were randomly split between training (n = 1636, 70%) and validation cohorts (n = 700, 30%). In the training cohort, Cox regression tested the prognostic significance of all available variables as a predictor of OS. Independent predictors of OS on multivariable analysis were used to construct a novel multivariable model (nomogram). The accuracy of this model was tested in the validation cohort using time-dependent area under the curve (tAUC) and calibration curves. RESULTS: Most of the patients were aged 65-74 years (44.5%) and the median (interquartile range) follow-up time was 13.9 (8.9-20.2) months. At multivariable analysis, the following were independent predictors of OS in mCRPC patients: sites of metastasis (visceral vs. bone metastasis, hazard ratio [HR]: 1.24), prostate-specific antigen (HR: 1.00), aspartate transaminase (HR: 1.01), alkaline phosphatase (HR: 1.00), body mass index (HR: 0.97), and hemoglobin (≥13 g/dl vs. <11 g/dl, HR: 0.41; all p < 0.05). A nomogram based on these variables was developed and showed favorable discrimination (tAUC at 12 and 24 months: 73% and 72%, respectively) and calibration characteristics on external validation. CONCLUSION: A new prognostic model to predict OS of patients with mCRPC undergoing first line chemotherapy was developed. This can help urologists/oncologists in counseling patients and might be useful to better stratify patients for future clinical trials.

Public Health Sciences

Plawecki AM, Saleem A, **Zvirbulis D**, **Peterson EL**, Yoo F, **Ali A**, and **Craig JR**. Clinical Features and Headache Diagnoses in Patients With Chief Complaint of Craniofacial Pain. *Ann Otol Rhinol Laryngol* 2022; Epub ahead of print. PMID: 35794798. Full Text

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OBJECTIVES: Investigate the use of nasal endoscopy, sinus imaging, and neurologic evaluation in patients presenting to a rhinologist primarily for craniofacial pain. METHODS: This was a retrospective analysis of consecutive outpatients presenting to a rhinologist between 2016 and 2019 with chief complaints of craniofacial pain with or without other sinonasal symptoms, who were then referred to and evaluated by headache specialists. Data analyzed included sinusitis symptoms, Sino-Nasal Outcome Test (SNOT-22) scores (and facial pain subscores), pain location, nasal endoscopy, computed tomography (CT) findings, and headache diagnoses made by headache specialists. RESULTS: Of the 134 patients with prominent craniofacial pain, the majority of patients were diagnosed with migraine (50%) or tension-type (22%) headache, followed by multiple other non-sinogenic headache disorders. Approximately 5% of patients had headaches attributed to sinusitis. Amongst all patients, 90% had negative nasal endoscopies. Patients with negative endoscopies were significantly less likely to report smell loss (P = .003) compared to those with positive endoscopies. Poor agreement was demonstrated between self-reported pain locations and sinus findings on CT (kappa values < 0.20). Negative nasal endoscopy showed high concurrence with negative CT findings (80%-97%). CONCLUSIONS: Patients presenting with chief complaints of craniofacial pain generally met criteria for various non-sinogenic headache disorders. Nasal endoscopy was negative in 90% of patients, and CT demonstrated poor agreement with pain locations. Nasal endoscopy and CT shared high concurrence rates for negative sinus findings. The value of nasal endoscopy over sinus imaging in craniofacial pain evaluation should be explored in future studies.

Public Health Sciences

Pu CY, Lusk CM, **Neslund-Dudas C**, **Gadgeel S**, Soubani AO, and Schwartz AG. Lung Cancer Screening Criteria and Cardiopulmonary Comorbidities. *JTO Clin Res Rep* 2022; 3(8):100377. PMID: 35880085. Full Text

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INTRODUCTION: Lung cancer screening criteria should select candidates with minimal cardiopulmonary comorbidities who are fit for curative lung cancer resection. METHODS: We retrospectively analyzed 728 patients with lung cancer for screening eligibility using the U.S. Preventive Services Task Force (USPSTF) 2013 criteria (n = 370). If ineligible for screening, they were further assessed for eligibility using the USPSTF 2021 (n = 121) and National Comprehensive Cancer Network group 2 (NCCN gp 2) (n = 155). Comparisons of cardiopulmonary comorbidities between patients selected by the different lung cancer screening criteria were performed. Excluding missing data, a similar comparison was done between USPSTF 2013 (n = 283) and PLCOm2012 (risk threshold ≥1.51%) (n = 118). RESULTS: Patients eligible for USPSTF 2021 and NCCN gp 2 had lower rates of airflow obstruction (forced expiratory volume in 1 s [FEV1]/forced vital capacity <0.7) compared with those in USPSTF 2013 (55.4% and 56.8% versus 70.5%). Both USPSTF 2021 and NCCN gp 2 groups had less severe airflow obstruction; only 11.6% and 12.9% of patients, respectively, had percent-predicted FEV1 less than 50% versus 20.3% in the USPSTF 2013 group. Comparing USPSTF 2013 and PLCOm2012 revealed no significant differences in age or the rate of airflow obstruction (p = 0.06 and p = 0.09 respectively). Nevertheless, rates of percent-predicted FEV1 less than 50% and diffusing capacity of the lungs for carbon monoxide less than 50% were lower in the PLCOm2012 group compared with those in the USPSTF 2013 group (22.3% versus 10.2% and 32.6% versus 20.0%), respectively. CONCLUSIONS: The USPSTF 2021 qualifies an additional group of screening candidates who are healthier with better lung reserve, translating to better surgical candidacy but potentially more overdiagnosis. The PLCOm2012, with its better accuracy in selecting patients at risk of cancer, selects an older group with chronic obstructive pulmonary disease but with good lung reserve and potentially less overdiagnosis.

Public Health Sciences

Rosen KA, **Thodge A**, **Tang A**, **Franz BM**, **Klochko CL**, and **Soliman SB**. The sonographic quantitative assessment of the deltoid muscle to detect type 2 diabetes mellitus: a potential noninvasive and sensitive screening method? *BMC Endocr Disord* 2022; 22(1):193. PMID: 35897066. Full Text

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BACKGROUND: In our previous published study, we demonstrated that a qualitatively assessed elevation in deltoid muscle echogenicity on ultrasound was both sensitive for and a strong predictor of a type 2 diabetes (T2DM) diagnosis. This study aims to evaluate if a sonographic quantitative assessment of the deltoid muscle can be used to detect T2DM. METHODS: Deltoid muscle ultrasound images from 124 patients were stored: 31 obese T2DM, 31 non-obese T2DM, 31 obese non-T2DM and 31 non-obese non-T2DM. Images were independently reviewed by 3 musculoskeletal radiologists, blinded to the patient's category. Each measured the grayscale pixel intensity of the deltoid muscle and humeral cortex to calculate a muscle/bone ratio for each patient. Following a 3-week delay, the 3 radiologists independently repeated measurements on a randomly selected 40 subjects. Ratios, age, gender, race, body mass index, insulin usage and hemoglobin A(1c) were analyzed. The difference among the 4 groups was compared using analysis of variance or chi-square tests. Both univariate and multivariate linear mixed models were performed. Multivariate mixed-effects regression models were used, adjusting for demographic and clinical variables. Post hoc comparisons were done with Bonferroni adjustments to identify any differences between groups. The sample size achieved 90% power. Sensitivity and specificity were calculated based on set threshold ratios. Both intra- and inter-radiologist variability or agreement were assessed. RESULTS: A statistically significant difference in muscle/bone ratios between the groups was identified with the average ratios as follows: obese T2DM, 0.54 ($P < 0.001$); non-obese T2DM, 0.48 ($P < 0.001$); obese non-T2DM, 0.42 ($P = 0.03$); and non-obese non-T2DM, 0.35. There was excellent inter-observer agreement (intraclass correlation coefficient 0.87) and excellent intra-observer agreements (intraclass correlation coefficient 0.92, 0.95 and 0.94). Using threshold ratios, the sensitivity for detecting T2DM was 80% (95% CI 67% to 88%) with a specificity of 63% (95% CI 50% to 75%). CONCLUSIONS: The sonographic quantitative assessment of the deltoid muscle by ultrasound is sensitive and accurate for the detection of T2DM. Following further studies, this process could translate into a dedicated, simple and noninvasive screening method to detect T2DM with the prospects of identifying even a fraction of the undiagnosed persons worldwide. This could prove especially beneficial in screening of underserved and underrepresented communities.

Public Health Sciences

Siegel DR, **Van Harn M**, **Taguchi M**, **Bansal P**, **Cerghet M**, and **Memon AB**. Clinical and diagnostic spectrum of optic neuritis: A single-center retrospective study of disorders associated with multiple sclerosis, anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies. *Clin Neurol Neurosurg* 2022; 221:107381. PMID: 35901556. Full Text

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OBJECTIVE: Optic neuritis (ON) is an immune-mediated optic neuropathy associated with multiple immune-mediated neurological conditions. Our aim was to characterize the clinical and diagnostic features of first or initial episodes of ON associated with multiple sclerosis (MS)-associated (typical) and antibody-related (atypical) ON. METHODS: Retrospective, single institution, medical record review. We analyzed demographic, clinical, laboratory, and radiographic findings of 139 patients who presented with first episodes of MS-associated ON (MS-ON), aquaporin 4 antibody-associated ON (AQP4-ON), and myelin oligodendrocyte glycoprotein antibody-associated ON (MOG-ON) between January 2015 and October 2019 without preceding diagnosis. Simple hypothesis testing assessed differences between groups were performed. RESULTS: Of 139 patients (109 [79 %] women; 29 [21 %] men; mean age 47 [SD, 14] years), 106 had MS-ON, 25 had AQP4-ON, and 8 had MOG-ON. Patients with MOG-ON had the highest recurrence rate (88 %) relative to MS-ON (28 %) and AQP4-ON (56 %) patients ($P < .001$). Patients with AQP4-ON had the highest mean visual functional system scores (4.3 [SD, 1.8]) relative to MS-ON (2.0 [SD, 1.9]) and MOG-ON patients (2.8 [SD, 2.0]) ($P < .001$). CONCLUSION: Patients presenting with initial episodes of ON exhibit a range radiographic and laboratory feature depending on the underlying associated disease. Understanding the variable characteristics of typical (MS-associated) and atypical (antibody-associated) ON may help physicians accurately diagnose and effectively treat ON.

Public Health Sciences

Trudeau S, **Mendiratta V**, **Dababneh Y**, **Hollingsworth J**, and **Gordon SC**. Letter to the Editor: Successful treatment of multidrug resistant hepatitis C after >12 months of continuous therapy with direct-acting antivirals. *Hepatology* 2022; Epub ahead of print. PMID: 35894159. Full Text

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Public Health Sciences

Zhang L, **Li C**, **Huang R**, **Teng H**, **Zhang Y**, **Zhou M**, **Liu X**, **Fan B**, **Luo H**, **He A**, **Zhao A**, **Lu M**, **Chopp M**, and **Zhang ZG**. Cerebral endothelial cell derived small extracellular vesicles improve cognitive function in aged diabetic rats. *Front Aging Neurosci* 2022; 14:926485. PMID: 35912073. Full Text

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Small extracellular vesicles (sEVs) mediate cell-cell communication by transferring their cargo biological materials into recipient cells. Diabetes mellitus (DM) induces cerebral vascular dysfunction and neurogenesis impairment, which are associated with cognitive decline and an increased risk of developing dementia. Whether the sEVs are involved in DM-induced cerebral vascular disease, is unknown. Therefore, we studied sEVs derived from cerebral endothelial cells (CEC-sEVs) of aged DM rats (DM-CEC-sEVs) and found that DM-CEC-sEVs robustly inhibited neural stem cell (NSC) generation of new neuroblasts and damaged cerebral endothelial function. Treatment of aged DM-rats with CEC-sEVs derived from adult healthy normal rats (N-CEC-sEVs) ameliorated cognitive deficits and improved cerebral vascular function and enhanced neurogenesis. Intravenously administered N-CEC-sEVs crossed the blood brain barrier and were internalized by neural stem cells in the neurogenic region, which were associated with augmentation of miR-1 and -146a and reduction of myeloid differentiation primary response gene 88 and thrombospondin 1 proteins. In addition, uptake of N-CEC-sEVs by the recipient cells was mediated by clathrin and caveolin dependent endocytosis signaling pathways. The present study provides ex vivo and in vivo evidence that DM-CEC-sEVs induce cerebral vascular dysfunction and neurogenesis impairment and that N-CEC-sEVs have a therapeutic effect on improvement of cognitive function by ameliorating dysfunction of cerebral vessels and increasing neurogenesis in aged DM rats, respectively.

Pulmonary and Critical Care Medicine

Chrissian AA, **Diaz-Mendoza J**, and **Simoff MJ**. Restenosis Following Bronchoscopic Airway Stenting for Complex Tracheal Stenosis. *J Bronchology Interv Pulmonol* 2022; Epub ahead of print. PMID: 35856939. Full Text

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BACKGROUND: Nonsurgical patients with complex postintubation tracheal stenosis (PITS) and tracheostomy-associated tracheal stenosis (PTTS) often require airway stenting. However, the optimal approach is unknown. Identifying patients at higher risk for restenosis after stent removal may allow the treating physician to individualize the vigilance and duration of airway stenting, and help optimize outcomes. METHODS: This was a single-center retrospective analysis of prospectively collected data on all patients with complex PITS and/or PTTS treated with protocolized bronchoscopic airway stenting over a consecutive 16-year period. The primary outcome analyzed was restenosis rate at 1 year after stent removal. Predictors for restenosis and factors influencing risk for death during stent therapy were also assessed. RESULTS: Of the 181 subjects treated with silicone airway stenting, 128 were available for analysis of the primary outcome. Restenosis by 1 year after stent removal occurred in 58%. Independent predictors for restenosis were coexisting diabetes [odd ratio (OR)=3.10, 95% confidence interval (CI)=1.04-9.24; P=0.04], morbid obesity (OR=3.13, 95% CI=1.20-8.17; P=0.02), and occurrence of stent-associated complications requiring bronchoscopic management (OR=2.13, 95% CI=1.12-4.03; P=0.02). The overall mortality during the initial stenting period was 14%, and a silicone Y-stent was associated with a higher risk of death (OR=3.58, 95% CI=1.40-9.14; P=0.008). CONCLUSION: Tracheal restenosis after silicone stent therapy for complex PITS and PTTS is common and more likely to occur in patients with diabetes, morbid obesity, and frequent stent-associated complications. Mortality risk during stent therapy is not negligible, and a Y-stent should be utilized only after careful consideration. These findings may be incorporated into the approach to bronchoscopic airway stenting in these patients.

Pulmonary and Critical Care Medicine

Shakaroun DA, **Lazar MH**, Horowitz JC, and **Jennings JH**. Serum Ferritin as a Predictor of Outcomes in Hospitalized Patients with Covid-19 Pneumonia. *J Intensive Care Med* 2022. PMID: Not assigned. Full Text

Radiation Oncology

Chetty IJ, **Doemer AJ**, **Dolan JL**, **Kim JP**, **Cunningham JM**, **Dragovic J**, **Feldman A**, **Walker EM**, **Elshaikh M**, **Adil K**, **Movsas B**, and **Parikh PJ**. MRI-guided Radiotherapy (MRgRT) for treatment of Oligometastases: Review of clinical applications and challenges. *Int J Radiat Oncol Biol Phys* 2022; Epub ahead of print. PMID: 35901978. Full Text

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PURPOSE: Early clinical results on the application of magnetic resonance imaging (MRI) coupled with a linear accelerator to deliver MR-guided radiation therapy (MRgRT) have demonstrated feasibility for safe delivery of stereotactic body radiotherapy (SBRT) in treatment of oligometastatic disease. Here we set out to review the clinical evidence and challenges associated with MRgRT in this setting. METHODS AND MATERIALS: We performed a systematic review of the literature pertaining to clinical experiences and trials on the use of MRgRT primarily for the treatment of oligometastatic cancers. We reviewed the opportunities and challenges associated with the use of MRgRT. RESULTS: Benefits of MRgRT pertaining to superior soft-tissue contrast, real-time imaging and gating, and online adaptive radiotherapy facilitate safe and effective dose escalation to oligometastatic tumors while simultaneously sparing surrounding healthy tissues. Challenges concerning further need for clinical evidence and technical considerations related to planning, delivery, quality assurance (QA) of hypofractionated doses, and safety

in the MRI environment must be considered. CONCLUSIONS: The promising early indications of safety and effectiveness of MRgRT for SBRT-based treatment of oligometastatic disease in multiple treatment locations should lead to further clinical evidence to demonstrate the benefit of this technology.

Radiation Oncology

Kim H, Olsen JR, Green OL, Chin RI, Hawkins WG, Fields RC, Hammill C, Doyle MB, Chapman W, Suresh R, Tan B, Pedersen K, Jansen B, DeWees TA, Lu E, Henke LE, Badiyan S, **Parikh PJ**, Roach MC, Wang-Gillam A, and Lim KH. MR-guided radiation therapy with concurrent gemcitabine / nab-paclitaxel chemotherapy in inoperable pancreatic cancer: a TITE-CRM phase I trial. *Int J Radiat Oncol Biol Phys* 2022; Epub ahead of print. PMID: 35878713. Full Text

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BACKGROUND: Ablative radiation therapy for borderline resectable or locally advanced pancreatic ductal adenocarcinoma (BR/LA-PDAC) may limit concurrent chemotherapy dosing and usually is only safely deliverable to tumors distant from gastrointestinal organs. MR-guided radiation therapy (MRgRT) may safely permit radiation and chemotherapy dose escalation. METHODS: We conducted a single-arm phase I study to determine the maximum tolerated dose (MTD) of ablative hypofractionated radiation with full-dose gemcitabine/nab-paclitaxel in patients with BR/LA-PDAC. Patients were treated with gemcitabine/nab-paclitaxel (1000/125 mg/m(2)) x 1c then concurrent gemcitabine/nab-paclitaxel and radiation. Gemcitabine/nab-paclitaxel and radiation doses were escalated per time-to-event continual reassessment method from 40-45 Gy / 25 fxs with chemotherapy (600-800/75 mg/m(2)) to 60-67.5 Gy / 15 fractions and concurrent gemcitabine/nab-paclitaxel (1000/100 mg/m(2)). The primary endpoint was MTD of radiation as defined by 60-day dose limiting toxicity (DLT). DLT was treatment-related G5, G4 hematologic or G3 gastrointestinal requiring hospitalization >3 days. Secondary endpoints included resection rates, local progression free survival (LPFS), distant metastasis free survival (DMFS), and overall survival (OS). RESULTS: Thirty patients enrolled (3/2015-2/2019), with 26 evaluable patients (2 progressed before radiation, 1 determined ineligible for radiation during planning, 1 withdrew consent). One DLT was observed. The DLT rate was 14.1% [3.3%-24.9%] with a maximum tolerated dose of gemcitabine/nab-paclitaxel (1000/100 mg/m(2)) and 67.5 Gy / 15 fractions. At a median follow-up of 40.6 months for living patients the median OS was 14.5 months (95% CI, 10.9-28.2 months). The median OS for patients with ECOG 0 and CA 19-9 <90 were 34.1 (95% CI, 13.6-54.1) and 43.0 (95% CI, 8.0-not reached) months, respectively. 2-year LPFS and DMFS were 85% (95% CI, 63-94%) and 57% (95% CI, 34-73%), respectively. CONCLUSIONS: Full-dose gemcitabine/nab-paclitaxel with ablative MRgRT dosing is safe in patients with BR/LA-PDAC, with promising LPFS and DMFS. CLINICALTRIALS: gov NCTXXXXXXXX.

Research Administration

Larivière S, Royer J, Rodríguez-Cruces R, Paquola C, Caligiuri ME, Gambardella A, Concha L, Keller SS, Cendes F, Yasuda CL, Bonilha L, Gleichgerrcht E, Focke NK, Domin M, von Podewills F, Langner S, Rummel C, Wiest R, Martin P, Kotikalapudi R, O'Brien TJ, Sinclair B, Vivash L, Desmond PM, Lui E, Vaudano AE, Meletti S, Tondelli M, Alhusaini S, Doherty CP, Cavalleri GL, Delanty N, Kälviäinen R, Jackson GD, Kowalczyk M, Mascalchi M, Semmelroch M, Thomas RH, **Soltanian-Zadeh H**, **Davoodi-Bojd E**, Zhang J, Winston GP, Griffin A, Singh A, Tiwari VK, Kreilkamp BAK, Lenge M, Guerrini R,

Hamandi K, Foley S, Rüber T, Weber B, Depondt C, Absil J, Carr SJA, Abela E, Richardson MP, Devinsky O, Severino M, Striano P, Tortora D, Kaestner E, Hatton SN, Vos SB, Caciagli L, Duncan JS, Whelan CD, Thompson PM, Sisodiya SM, Bernasconi A, Labate A, McDonald CR, Bernasconi N, and Bernhardt BC. Structural network alterations in focal and generalized epilepsy assessed in a worldwide ENIGMA study follow axes of epilepsy risk gene expression. *Nat Commun* 2022; 13(1):4320. PMID: 35896547. Full Text

Epilepsy is associated with genetic risk factors and cortico-subcortical network alterations, but associations between neurobiological mechanisms and macroscale connectomics remain unclear. This multisite ENIGMA-Epilepsy study examined whole-brain structural covariance networks in patients with epilepsy and related findings to postmortem epilepsy risk gene expression patterns. Brain network analysis included 578 adults with temporal lobe epilepsy (TLE), 288 adults with idiopathic generalized epilepsy (IGE), and 1328 healthy controls from 18 centres worldwide. Graph theoretical analysis of structural covariance networks revealed increased clustering and path length in orbitofrontal and temporal regions in TLE, suggesting a shift towards network regularization. Conversely, people with IGE showed decreased clustering and path length in fronto-temporo-parietal cortices, indicating a random network configuration. Syndrome-specific topological alterations reflected expression patterns of risk genes for hippocampal sclerosis in TLE and for generalized epilepsy in IGE. These imaging-transcriptomic signatures could potentially guide diagnosis or tailor therapeutic approaches to specific epilepsy syndromes.

Sleep Medicine
Mahr G, and **Drake CL**. Singing in tune: Carl Jung and The Red Book. *Sleep Health* 2022; Epub ahead of print. PMID: 35831228. Full Text

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Sleep Medicine
Reffi AN, **Cheng P**, **Kalmbach DA**, Jovanovic T, Norrholm SD, **Roth T**, and **Drake CL**. Is a blunted cortisol response to stress a premorbid risk for insomnia? *Psychoneuroendocrinology* 2022; 144:105873. PMID: 35905512. Full Text

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STUDY OBJECTIVES: Vulnerability to stress-related sleep disturbances (sleep reactivity) is an established heritable risk factor for insomnia disorder with unclear biological underpinnings. Preliminary research points to a blunted cortisol response to stress as a biological predisposition to familial risk for insomnia, but the role of cortisol response in sleep reactivity is unknown. Therefore, the current studies examined whether sleep reactivity is associated with a blunted cortisol response to two laboratory stressors among participants without insomnia. METHODS: Two community samples of adults with no lifetime history of insomnia completed the Trier Social Stress Test (N = 35) or the Cold Pressor Task (N = 34). Participants were grouped by insomnia-risk using sleep reactivity scores from the Ford Insomnia Response to Stress Test (FIRST). Physiological responses were measured via markers of the hypothalamic-pituitary-adrenal (HPA) axis (salivary cortisol) and autonomic nervous system (ANS; heart rate, mean arterial pressure, and salivary alpha amylase). RESULTS: Participants with high insomnia-risk (FIRST score > 18) exhibited blunted cortisol responses to both stressors. There were no group differences in ANS responses across stressors. CONCLUSIONS: Insomnia-risk as indicated by sleep reactivity is associated with blunted cortisol responses to psychosocial and physical laboratory stressors among premorbid adults without insomnia disorder. This study replicates previous research and supports a blunted cortisol response to stress as a biomarker for insomnia vulnerability that may be detected using

the FIRST. Prospective research is needed to elucidate whether a blunted cortisol response to stress is one mechanism by which sleep reactive individuals may be at risk of developing insomnia.

Sleep Medicine

Walker JL, Vargas I, **Drake CL**, Ellis JG, Muench A, and Perlis ML. The Natural History of Insomnia: High Sleep Reactivity Interacts with Greater Life Stress to Predict the Onset of Acute Insomnia. *Sleep* 2022; Epub ahead of print. PMID: 35776964. Full Text

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STUDY OBJECTIVES: Prior research suggests that some individuals have a predisposition to experience insomnia following acute stressors (i.e., sleep reactivity). The present study was a proof of concept and specifically aimed to provide additional empirical evidence that the link between stressful life events and the onset of acute insomnia is moderated by sleep reactivity. METHODS: 1,225 adults with a history of good sleep (Mage = 53.2 years, 68% female, 83% white) were recruited nationwide for an online study on sleep health. Participants completed surveys to assess sleep reactivity (baseline), sleep patterns (daily sleep diary), and stressful life events (weekly survey). All daily and weekly measures were completed for a one-year period. Sleep diary data were used to identify sleep initiation/maintenance difficulties, including whether they met criteria for acute insomnia at any point during the one-year interval. RESULTS: Participants with high sleep reactivity compared to low sleep reactivity were at 76% increased odds of developing acute insomnia during the one-year interval. In general, greater weekly stressful life events were associated with greater insomnia during the subsequent week. Those participants with high sleep reactivity demonstrated a stronger relationship between weekly stressful life events and insomnia, such that they reported the greatest levels of insomnia following weeks where they experienced a greater number of stressful life events. CONCLUSIONS: These results further support the sleep reactivity model of insomnia, and specifically, provide evidence that sleep reactivity predicts the incidence of acute insomnia in a sample of participants with no history of insomnia.

Surgery

Abbassi F, Gero D, Muller X, Bueno A, Figiel W, Robin F, Laroche S, Picard B, Shankar S, **Ivanics T**, van Reeven M, van Leeuwen OB, Braun HJ, Monbaliu D, Breton A, Vachharajani N, Bonaccorsi Riani E, Nowak G, McMillan RR, Abu-Gazala S, Nair A, Bruballa R, Paterno F, Weppler Sears D, Pinna AD, Guarrera JV, de Santibañes E, de Santibañes M, Hernandez-Alejandro R, Olthoff K, Ghobrial RM, Ericzon BG, Ciccarelli O, Chapman WC, Mabrut JY, Pirenne J, Müllhaupt B, Ascher NL, Porte RJ, de Meijer VE, Polak WG, Sapisochin G, Attia M, Weiss E, Adam RA, Cherqui D, Boudjema K, Zienewicz K, Jassem W, Dutkowski P, and Clavien PA. Novel Benchmark Values for Redo Liver Transplantation. Does the Outcome Justify the Effort? *Ann Surg* 2022; Epub ahead of print. PMID: 35894428. Full Text

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OBJECTIVE: To define benchmark cutoffs for redo liver transplantation (redo-LT). BACKGROUND: In the era of organ shortage, redo-LT is frequently discussed in terms of expected poor outcome and wasteful resources. However, there is a lack of benchmark data to reliably evaluate outcomes after redo-LT. METHODS: We collected data on redo-LT between January 2010 and December 2018 from 22 high-volume transplant centers. Benchmark cases were defined as recipients with MELD score ≤25, absence of portal vein thrombosis, no mechanical ventilation at the time of surgery, receiving a graft from a donor after brain death. Also, high-urgent priority and early redo-LT including those for primary non-function (PNF) or hepatic artery thrombosis were excluded. Benchmark cutoffs were derived from the 75th percentile of the medians of all benchmark centers. RESULTS: Out of 1110 redo-LT, 373 (34%) cases qualified as benchmark cases. Among these cases, the rate of postoperative complications until discharge was 76%, and increased up to 87% at 1-year, respectively. One-year overall survival rate was excellent with 90%. Benchmark cutoffs included Comprehensive Complication Index (CCI®) at 1-year of ≤72, and in-hospital and 1-year mortality rates of ≤13% and ≤15%, respectively. In contrast, patients who received a redo-LT for PNF showed worse outcomes with some values dramatically outside the redo-LT benchmarks. CONCLUSION: This study shows that redo-LT achieves good outcome when looking at benchmark scenarios. However, this figure changes in high-risk redo-LT, as for example in PNF. This major analysis objectifies for the first-time results and efforts for redo-LT and can serve as a basis for discussion about the use of scarce resources.

Surgery

Carter M, Solsrud K, **Yeddula S**, **Fitzmaurice MG**, **Singh A**, **Nagai S**, and **Jafri SM**. Hepatitis E Diagnosis and Management After Liver, Kidney, or Heart Transplant: A Single-Center Experience. *Transplant Proc* 2022; Epub ahead of print. PMID: 35907694. Full Text

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BACKGROUND: Transplant-related hepatitis E virus (HEV) infection is a rarely recognized phenomenon with significant clinical importance given its potential to result in chronic hepatitis posttransplant. METHODS: We retrospectively evaluated HEV diagnosis and treatment after liver, kidney, and heart transplant in a single center. We identified patients diagnosed with HEV by serologic testing and evaluated their treatment regimens. RESULTS: Fifteen transplant recipients (12 liver, 2 kidney, and 1

heart) presented with elevated liver enzymes and were positive for HEV IgM antibody. Liver enzymes normalized in 4 patients after being treated with ribavirin. One of the 4 patients had 2 recurrences with positive HEV RNA results following ribavirin treatment but recovered after 12 months of ribavirin therapy. After treatment with reduction in immunosuppression without antiviral treatment, 6 of 8 patients' liver enzymes normalized. One of these patients died of acute pancreatitis 2 months after testing positive for HEV IgM antibody. CONCLUSIONS: The potential for complications related to active HEV infections in transplant recipients necessitates prompt diagnosis and treatment to prevent irreversible damage. Diagnosis with HEV reverse transcriptase-polymerase chain reaction should follow a positive HEV IgM antibody test. This manuscript provides evidence that ribavirin antiviral therapy and reducing immunosuppression are effective treatments for HEV infections in liver, kidney, and heart transplant recipients, which has not been sufficiently investigated in the population of the United States. Larger multicenter studies are needed to confirm the risks and benefits of using ribavirin antiviral therapy as first-line therapy of HEV posttransplant.

Surgery

Ehlers AP, Bonham AJ, Ghaferi AA, Finks JF, **Carlin AM**, and Varban OA. Impact of hiatal hernia repair technique on patient-reported gastroesophageal reflux symptoms following laparoscopic sleeve gastrectomy. *Surg Endosc* 2022; Epub ahead of print. PMID: 35854122. Full Text

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INTRODUCTION: Repairing a hiatal hernia at the time of laparoscopic sleeve gastrectomy (SG) can reduce or even prevent gastroesophageal reflux disease (GERD) symptoms in the post-operative period. Several different hiatal hernia repair techniques have been described but their impact on GERD symptoms after SG is unclear. METHODS: Surgeons (n = 74) participating in a statewide quality collaborative were surveyed on their typical technique for repair of hiatal hernias during SG. Options included posterior repair with mesh (PRM), posterior repair (PR), and anterior repair (AR). Patients who underwent SG with concurrent hiatal hernia repair (n = 7883) were compared according to their surgeon's reported technique. Patient characteristics, baseline and 1-year GERD health-related quality of life surveys, weight loss and 30-day risk-adjusted complications were analyzed. RESULTS: The most common technique reported by surgeons for hiatal hernia repair was PR (n = 64, 85.3%), followed by PRM (n = 7, 9.3%) and AR (n = 4, 5.3%). Patients who underwent SG by surgeons who perform AR had lower rates of baseline GERD diagnosis (AR 55.3%, PR 59.5%, PRM 64.8%, $p < 0.01$), but were more likely to experience worsening GERD symptoms at 1 year (AR 29.8%, PR 28.7%, PRM 28.2%, $p < 0.0001$), despite similar weight loss (AR 29.8%, PR 28.7%, PRM 28.2%, $p = 0.08$). Satisfaction with GERD symptoms at 1 year was high (AR 73.2%, PR 76.3%, PRM 75.7%, $p = 0.43$), and risk-adjusted 30-day outcomes were similar among all groups. CONCLUSIONS: Patients undergoing SG with concurrent hiatal hernia repair by surgeons who typically perform an AR were more likely to report worsening GERD at 1 year despite excellent weight loss. Surgeons who typically performed an AR had nearly one-half of their patients report increased GERD severity after surgery despite similar weight loss. While GERD symptom control may be multifactorial, technical approach to hiatal hernia repair at the time of SG may play a role and a posterior repair is recommended.

Surgery

Jasien JV, Laurie SS, Lee SMC, Martin DS, Kemp DT, Ebert DJ, Ploutz-Snyder RJ, Marshall-Goebel K, Alferova IV, Sargsyan AE, Danielson RW, Hargens AR, **Dulchavsky SA**, Stenger MB, and Macias BR. Noninvasive Indicators of Intracranial Pressure Before, During, and After Long-Duration Spaceflight. *J Appl Physiol (1985)* 2022; Epub ahead of print. PMID: 35861522. Request Article

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Weightlessness induces a cephalad shift of blood and cerebrospinal fluid that may increase intracranial pressure (ICP) during spaceflight, while lower body negative pressure (LBNP) may provide an opportunity to caudally redistribute fluids and lower ICP. To investigate the effects of spaceflight and LBNP on noninvasive indicators of ICP (nICP), we studied thirteen crewmembers before and after spaceflight in seated, supine, and 15° head-down tilt postures, and at ~45 and ~150 days of spaceflight with and without 25 mmHg LBNP. We used 4 techniques to quantify nICP: cerebral and cochlear fluid pressure (CCFP), otoacoustic emissions (OAE), ultrasound measures of optic nerve sheath diameter (ONSD), and ultrasound-based internal jugular vein pressure (IJVp). On flight day 45, two nICP measures were lower than preflight supine posture (CCFP: mean difference -98.5 -nl [CI: -190.8 to -6.1 -nl], $p = 0.037$]; OAE: -19.7 degrees [CI: -10.4 to -29.1 degrees], $p < 0.001$), but not significantly different from preflight seated measures. Conversely, ONSD was not different than any preflight posture, whereas IJVp was significantly greater than preflight seated measures (14.3 mmHg [CI: 10.1 to 18.5mmHg], $p < 0.001$), but not significantly different than preflight supine measures. During spaceflight, acute LBNP application did not cause a significant change in nICP indicators. These data suggest that during spaceflight nICP is not elevated above values observed in the seated posture on Earth. Invasive measures would be needed to provide absolute ICP values and more precise indications of ICP change during various phases of spaceflight.

Surgery

Scales MK, Velez-Delgado A, Steele NG, Schrader HE, Stabnick AM, Yan W, Mercado Soto NM, Nwosu ZC, Johnson C, Zhang Y, Salas-Escabillas DJ, Menjivar RE, Maurer HC, **Crawford HC**, Bednar F, Olive KP, Pasca di Magliano M, and Allen BL. Combinatorial Gli activity directs immune infiltration and tumor growth in pancreatic cancer. *PLoS Genet* 2022; 18(7):e1010315. PMID: 35867772. Full Text

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Proper Hedgehog (HH) signaling is essential for embryonic development, while aberrant HH signaling drives pediatric and adult cancers. HH signaling is frequently dysregulated in pancreatic cancer, yet its role remains controversial, with both tumor-promoting and tumor-restraining functions reported. Notably, the GLI family of HH transcription factors (GLI1, GLI2, GLI3), remain largely unexplored in pancreatic cancer. We therefore investigated the individual and combined contributions of GLI1-3 to pancreatic

cancer progression. At pre-cancerous stages, fibroblast-specific Gli2/Gli3 deletion decreases immunosuppressive macrophage infiltration and promotes T cell infiltration. Strikingly, combined loss of Gli1/Gli2/Gli3 promotes macrophage infiltration, indicating that subtle changes in Gli expression differentially regulate immune infiltration. In invasive tumors, Gli2/Gli3 KO fibroblasts exclude immunosuppressive myeloid cells and suppress tumor growth by recruiting natural killer cells. Finally, we demonstrate that fibroblasts directly regulate macrophage and T cell migration through the expression of Gli-dependent cytokines. Thus, the coordinated activity of GLI1-3 directs the fibroinflammatory response throughout pancreatic cancer progression.

Surgery

Talan DA, Moran GJ, Krishnadasan A, Monsell SE, Faine BA, Uribe L, Kaji AH, DeUgarte DA, Self WH, Shapiro NI, Cuschieri J, Glaser J, Park PK, Price TP, Siparsky N, Sanchez SE, Machado-Aranda DA, Victory J, Ayoung-Chee P, Chiang W, Corsa J, Evans HL, Ferrigno L, Garcia L, Hatch Q, Horton MD, **Johnson J**, Jones A, Kao LS, Kelly A, Kim D, Kutcher ME, Liang MK, Maghami N, McGrane K, Minko E, Mohr C, Neufeld M, **Patton JH**, Rog C, Rushing A, Sabbatini AK, Salzberg M, Thompson CM, Tichter A, Wisler J, Bizzell B, Fannon E, Lawrence SO, Voldal EC, Lavallee DC, Comstock BA, Heagerty PJ, Davidson GH, Flum DR, and Kessler LG. Analysis of Outcomes Associated With Outpatient Management of Nonoperatively Treated Patients With Appendicitis. *JAMA Netw Open* 2022; 5(7):e2220039. PMID: 35796152. Full Text

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IMPORTANCE: In the Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial, which found antibiotics to be noninferior, approximately half of participants randomized to receive antibiotics had outpatient management with hospital discharge within 24 hours. If outpatient management is safe, it could increase convenience and decrease health care use and costs. OBJECTIVE: To assess the use and safety of outpatient management of acute appendicitis. DESIGN, SETTING, AND PARTICIPANTS: This cohort study, which is a secondary analysis of the CODA trial, included 776 adults with imaging-confirmed appendicitis who received antibiotics at 25 US hospitals from May 1, 2016, to February 28, 2020. EXPOSURES: Participants randomized to antibiotics (intravenous then oral) could be discharged from the emergency department based on clinician judgment and prespecified criteria (hemodynamically stable, afebrile, oral intake tolerated, pain controlled, and follow-up confirmed). Outpatient management and hospitalization were defined as discharge within or after 24 hours, respectively. MAIN OUTCOMES AND MEASURES: Outcomes compared among patients receiving outpatient vs inpatient care included serious adverse events (SAEs), appendectomies, health care encounters, satisfaction, missed workdays at 7 days, and EuroQol 5-dimension (EQ-5D) score at 30 days. In addition, appendectomy incidence among outpatients and inpatients, unadjusted and adjusted for illness severity, was compared. RESULTS: Among 776 antibiotic-randomized participants, 42 (5.4%) underwent appendectomy within 24 hours and 8 (1.0%) did not receive their first antibiotic dose within 24 hours, leaving 726 (93.6%) comprising the study population (median age, 36 years; range, 18-86 years; 462 [63.6%] male; 437 [60.2%] White). Of these participants, 335 (46.1%; site range, 0-89.2%) were discharged within 24 hours, and 391 (53.9%) were discharged after 24 hours. Over 7 days, SAEs occurred in 0.9 (95% CI, 0.2-2.6) per 100 outpatients and 1.3 (95% CI, 0.4-2.9) per 100 inpatients; in the appendicolith subgroup, SAEs occurred in 2.3 (95% CI, 0.3-8.2) per 100 outpatients vs 2.8 (95% CI, 0.6-7.9) per 100 inpatients. During this period, appendectomy occurred in 9.9% (95% CI, 6.9%-13.7%) of outpatients and 14.1% (95% CI, 10.8%-18.0%) of inpatients; adjusted analysis demonstrated a similar difference in incidence (-4.0 percentage points; 95% CI, -8.7 to 0.6). At 30 days, appendectomies occurred in 12.6% (95% CI, 9.1%-16.7%) of outpatients and 19.0% (95% CI, 15.1%-23.4%) of inpatients. Outpatients missed fewer workdays (2.6 days; 95% CI, 2.3-2.9 days) than did inpatients (3.8 days; 95% CI, 3.4-4.3 days) and had similar frequency of return health care visits and high satisfaction and EQ-5D scores. CONCLUSIONS AND RELEVANCE: These findings support that outpatient antibiotic management is safe for selected adults with acute appendicitis, with no greater risk of complications or appendectomy than hospital care, and should be included in shared decision-making discussions of patient preferences for outcomes associated with nonoperative and operative care. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02800785.

Surgery

Vitous CA, **Carlin AM**, Waljee J, Stricklen A, Ross R, Ghaferi A, and Ehlers AP. Factors that influence discharge opioid prescribing among bariatric surgeons across Michigan. *Am J Surg* 2022; Epub ahead of print. PMID: 35933183. Full Text

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BACKGROUND: Opioid prescribing following bariatric surgery has been a focus due to its association with new persistent opioid use (NPOU) and worse outcomes. Guidelines have led to a reduction in opioids prescribed, but there remains variation in prescribing practices. METHODS: We conducted interviews with 20 bariatric surgeons across Michigan. Transcripts were analyzed using descriptive content analysis. RESULTS: At the patient level, surgeons described the role of surgical history and pain tolerance. At the provider level, surgeons discussed patient dissatisfaction, reputation, and workload. At the institution level, surgeons discussed colleagues, resources, and administration. At a collaborative level, surgeons described the role of evidence and performance measures. There was lack of consensus on whether NPOU is a problem facing patients undergoing bariatric surgery. CONCLUSION: Despite efforts aimed at addressing opioid prescribing, variability exists in prescribing practices. Understanding determinants that impact stakeholder alignment is critical to increasing adherence to guideline-concordant care.

Urology
Atiemo HO. Editorial Commentary. *Urol Pract* 2022; 9(4):312. PMID: Not assigned. Full Text

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Urology
Canvasser NE, River M, Bechis SK, Ingimarsson J, Knoedler J, Stern K, Stoughton CL, Wollin D, Borofsky M, Bhojani N, Tayeb ME, Kamphuis G, **Leavitt D**, Hsi RS, and Scotland KB. Over-the-counter alkali agents to raise urine pH and citrate excretion: a prospective crossover study in healthy adults. *Urology* 2022; Epub ahead of print. PMID: 35843354. Full Text

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OBJECTIVE: To assess the effect of two over-the-counter alkalizing agents on 24-hour urinary parameters. MATERIALS AND METHODS: Ten healthy volunteers without a history of kidney stones were recruited to complete a baseline 24-hour urinalysis with a four-day diet inventory. Participants then maintained the same diet on either LithoLyte® (20 mEq two times per day) or KSPtabs(TM) (1 tablet two times per day) and submitted another 24-hour urinalysis. The process was repeated with the other supplement. Urinary alkali parameters were compared to baseline, and side effects were elicited with a questionnaire. RESULTS: LithoLyte® intake resulted in a non-significant increase in citrate (597 to 758 mg/day, p=0.058, an increase in urine pH (6.46 to 6.66, p=0.028), and a decrease in urine ammonium (41 to 36 mmol/day, p=0.005) compared to baseline. KSPtabs(TM) resulted in an increase in citrate (597 to 797 mg/day, p=0.037) and urine pH (6.46 to 6.86, p=0.037), with a non-significant decrease in ammonium (41 to 34 mmol/day, p=0.059). No significant differences were seen comparing urinary analytes between LithoLyte® and KSPtabs(TM). With Litholyte®, no side effects, mild, moderate, and severe side effects were seen in 50%, 40%, 10%, and 0%, respectively. With KSPtabs(TM), rates were 60%, 20%, 10%, and 10%, respectively. CONCLUSIONS: In healthy participants without a history of kidney stones, LithoLyte® and KSPtabs(TM) are effective over-the-counter alkali supplements, with a similar side effect profile to prescription potassium citrate.

Urology

Chen I, **Arora S**, **Alhayek K**, **Leavitt D**, and **Dabaja A**. Diagnosis and management of testicular compartment syndrome caused by tension hydrocele. *Urol Case Rep* 2022; 43:102091. PMID: 35520029. Full Text

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A hydrocele is an abnormal collection of fluid within the tunica vaginalis which may either be congenital or acquired. Hydroceles are usually painless and don't require immediate intervention unless they impact activities of daily living. This case demonstrates a rare complication of hydroceles termed tension hydrocele which presented with scrotal swelling and acute pain. Unlike the classic presentation of hydroceles with minimal pain or discomfort, it is important to recognize tension hydroceles as an extremely rare but possible cause of acute scrotum, which needs to be emergently diagnosed and treated.

Urology

Grauer R, Gorin MA, **Sood A**, **Butaney M**, **Olson P**, **Farah G**, **Hanna Cole R**, **Jeong W**, **Abdollah F**, and **Menon M**. Impact of prostate biopsy technique on outcomes of the precision prostatectomy procedure. *BMJ Surg Interv Health Technol* 2022; 4(1):e000122. PMID: 35892060. Full Text

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OBJECTIVE: To assess the impact of iterative changes in preoperative and postoperative biopsy techniques on the outcomes of men undergoing the precision prostatectomy procedure. Precision prostatectomy is a novel surgical treatment for prostate cancer that aims to maximally preserve erectogenic nerves via partial preservation of the prostate capsule. DESIGN: Retrospective. SETTING: Single tertiary care center. PARTICIPANTS: This study included 120 patients who consented to undergo prostate cancer treatment with the precision prostatectomy procedure. Patients were originally enrolled in one of two separate prospective protocols studying precision prostatectomy. INTERVENTIONS: Preoperatively, 60 patients were screened with transrectal (TR) biopsy and 60 were screened by transperineal (TP) biopsy. Ultimately, 117 patients underwent precision prostatectomy. Of the 43 postoperative biopsies, 19 were TR; 17 were TP with ultrasound; and 7 were TP with microultrasound (mUS). MAIN OUTCOME MEASURES: Preoperatively, we evaluated whether the transition to TP biopsy was associated with differences in postoperative treatment failure defined as a neoplasm-positive postoperative biopsy. Postoperative biopsies were compared with respect to their ability to sample the remnant tissue, specifically percentage of cores positive for prostate tissue. RESULTS: Preoperatively, 9/60 (15%) positive postoperative biopsies occurred in the TR group and 6/60 (10%) in the TP group; Kaplan-Meier survival estimates did not differ between groups (p=0.69 by log rank). Postoperatively, the numbers of cores positive for prostate tissue were 99/160 (62%), 63/107 (59%), and 36/39 (92%) in the TR biopsy, TP with ultrasound, and TP with mUS groups, respectively; this difference was statistically significant versus the rate in the TR and standard TP groups (p=0.0003 and 0.0002). CONCLUSION: We found no significant improvement in patient screening, preoperatively-though limited by small sample size and relatively short follow-up. The incorporation of high-frequency mUS for postoperative biopsies improved the ability to sample the remnant tissue with a higher efficiency.

Urology

Kovacevic L, **Kovacevic N**, and Lakshmanan Y. Proteomic analysis of inhibitory protein profiles in the urine of children with nephrolithiasis: implication for disease prevention. *Int Urol Nephrol* 2022. PMID: Not assigned. Full Text

Urology

Modonutti D, **Majdalany SE**, **Corsi N**, **Li P**, **Sood A**, **Dalela D**, **Jamil ML**, **Hwang C**, **Menon M**, **Rogers CG**, Trinh QD, **Novara G**, and **Abdollah F**. A novel prognostic model predicting overall survival in patients with metastatic castration-resistant prostate cancer receiving standard chemotherapy: A multi-trial cohort analysis. *Prostate* 2022; Epub ahead of print. PMID: 35790016. Full Text

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PURPOSE: Generalizable, updated, and easy-to-use prognostic models for patients with metastatic castration-resistant prostate cancer (mCRPC) are lacking. We developed a nomogram predicting the overall survival (OS) of mCRPC patients receiving standard chemotherapy using data from five randomized clinical trials (RCTs). METHODS: Patients enrolled in the control arm of five RCTs (ASCENT 2, VENICE, CELGENE/MAINSAIL, ENTHUSE 14, and ENTHUSE 33) were randomly split between training (n = 1636, 70%) and validation cohorts (n = 700, 30%). In the training cohort, Cox regression tested the prognostic significance of all available variables as a predictor of OS. Independent predictors of OS on multivariable analysis were used to construct a novel multivariable model (nomogram). The accuracy of this model was tested in the validation cohort using time-dependent area under the curve (tAUC) and calibration curves. RESULTS: Most of the patients were aged 65-74 years (44.5%) and the median (interquartile range) follow-up time was 13.9 (8.9-20.2) months. At multivariable analysis, the following were independent predictors of OS in mCRPC patients: sites of metastasis (visceral vs. bone metastasis, hazard ratio [HR]: 1.24), prostate-specific antigen (HR: 1.00), aspartate transaminase (HR: 1.01), alkaline phosphatase (HR: 1.00), body mass index (HR: 0.97), and hemoglobin (≥13 g/dl vs. <11 g/dl, HR: 0.41; all $p < 0.05$). A nomogram based on these variables was developed and showed favorable discrimination (tAUC at 12 and 24 months: 73% and 72%, respectively) and calibration characteristics on external validation. CONCLUSION: A new prognostic model to predict OS of patients with mCRPC undergoing first line chemotherapy was developed. This can help urologists/oncologists in counseling patients and might be useful to better stratify patients for future clinical trials.

Urology

Sharma G, Shah M, Ahluwalia P, Dasgupta P, Challacombe BJ, Bhandari M, Ahlawat R, Rawal S, Buffi NM, Sivaraman A, Porter JR, **Rogers C**, Mottrie A, Abaza R, Rha KH, Moon D, Yuvaraja TB, Parekh DJ, Capitanio U, Maes KK, Porpiglia F, Turkeri L, and Gautam G. Comparison of perioperative outcomes following transperitoneal versus retroperitoneal robot-assisted partial nephrectomy: a propensity-matched analysis of VCQI database. *World J Urol* 2022; Epub ahead of print. PMID: 35867142. Full Text

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OBJECTIVE: To compare perioperative outcomes following retroperitoneal robot-assisted partial nephrectomy (RPRAPN) and transperitoneal robot-assisted partial nephrectomy (TPRAPN). METHODS: With this Vattikuti Collective Quality Initiative (VCQI) database, study propensity scores were calculated according to the surgical access (TPRAPN and RPRAPN) for the following independent variables, i.e., age, sex, side of the surgery, RENAL nephrometry scores (RNS), estimated glomerular filtration rate (eGFR) and serum creatinine. The study's primary outcome was the comparison of trifecta between the two groups. RESULTS: In this study, 309 patients who underwent RPRAPN were matched with 309 patients who underwent TPRAPN. The two groups matched well for age, sex, tumor side, polar location of the tumor, RNS, preoperative creatinine and eGFR. Operative time and warm ischemia time were significantly shorter with RPRAPN. Intraoperative blood loss and need for blood transfusion were lower with RPRAPN. There was a significantly higher number of intraoperative complications with RPRAPN. However, there was no difference in the two groups for postoperative complications. Trifecta outcomes were better with RPRAPN (70.2% vs. 53%, $p < 0.0001$) compared to TPRAPN. We noted no significant change in overall results when controlled for tumor location (anteriorly or posteriorly). The surgical approach, tumor size and RNS were identified as independent predictors of trifecta on multivariate analysis. CONCLUSION: RPRAPN is associated with superior perioperative outcomes in well-selected patients compared to TPRAPN. However, the data for the retroperitoneal approach were contributed by a few centers with greater experience with this technique, thus limiting the generalizability of the results of this study.

Urology
Sood A, **Zhang LT**, **Keeley J**, **Butaney M**, **Stricker M**, Andrews JR, Grauer R, **Peabody JO**, **Rogers CG**, **Menon M**, and **Abdollah F**. Optimizing anti-androgen treatment use among men with pathologic lymph-node positive prostate cancer treated with radical prostatectomy: the importance of postoperative PSA kinetics. *Prostate Cancer Prostatic Dis* 2022; Epub ahead of print. PMID: 35794359. Request Article

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BACKGROUND: Optimal postsurgical management of prostate cancer (PCa) patients with nodal metastasis at the time of radical prostatectomy remains unclear. We sought to examine the role of postoperative PSA kinetics and pathologic tumor characteristics in guiding additional hormonal therapy use in pN1 men. METHODS: In total, 297 pN1 PCa patients treated with radical prostatectomy and

ePLND between 2002 and 2018 were identified within our prospectively maintained institutional cancer data-registry. Following surgery, these patients were managed with either immediate androgen deprivation therapy (iADT) or observation with deferred ADT (dADT). The former was defined as ADT given within ≤6 months of surgery and the latter as >6 months. The primary outcome was metastasis. Regression-tree analysis was used to stratify patients into novel risk-groups based on post-prostatectomy tumor characteristics and PSA kinetics and the corresponding metastasis risk. Multivariable Cox regression analyses tested the impact of iADT versus observation ± dADT on metastasis, cancer-specific mortality, and overall mortality within each risk-group separately. RESULTS: The median follow-up was 6.1 years (IQR 3.2-9.0). Regression-tree analysis stratified patients into 3 novel risk-groups (Harrell's C-index 0.79) based on PSA-nadir and time to biochemical failure: group 1 (low-risk) included patients with time to biochemical recurrence >6 months (n = 115), while groups 2 and 3 included patients with biochemical failure within ≤6 months with a postoperative PSA-nadir <1.05 ng/mL (group 2 [intermediate-risk], n = 125) or ≥1.05 ng/mL (group 3 [high-risk], n = 57), respectively. No other patient or tumor characteristics were significant for risk stratification. Within each risk-group, the 10-year metastasis-free survival rates with iADT versus observation ± dADT use were: group 1, 100% versus 95.4% (Log-rank p = 0.738), group 2, 80.6% versus 53.5% (Log-rank p = 0.016), and group 3, 41.5% versus 0% (Log-rank p = 0.015), respectively. Adjusted Cox regression analyses confirmed the benefit of iADT utilization in reducing metastasis in group 2 (p = 0.029) and group 3 (p = 0.008) patients, with no benefit for group 1 patients (p = 0.918). Similar results were noted for cancer-specific and overall mortality. CONCLUSIONS: Following radical prostatectomy, early postoperative PSA kinetics may provide valuable information for guiding the timing of ADT initiation-this may reduce over- and undertreatment of pN1 PCa men.

Conference Abstracts

Cardiology/Cardiovascular Research

Sabbah HN, **Zhang K**, **Xu J**, **Gupta RC**, Nguyen N, and Adams J. Intravenous infusion of the beta-3 adrenergic receptor antagonist APD418 improves left ventricular function in dogs with systolic heart failure despite long-term therapy with beta-blockers. *Eur J Heart Fail* 2022; 24:104-104.

Center for Health Policy and Health Services Research

Nau CL, Hong BD, Padilla A, Waters H, Houle CR, Penfold RB, Rossom R, and **Braciszewski JM**. P9 Social Determinants of Health and Disruptive Life Events Among Patients with Schizophrenia or Bipolar Disorder. *Value in Health* 2022; 25(7):S288-S289. Full Text

Objective: To assess risk of disruptive life events (DLEs) and the effects of social determinants of health (SDoH) on DLEs in patients with schizophrenia (SCZ) or bipolar I disorder (BP-I). Methods: Multi-site retrospective, cohort study using electronic medical record data from Kaiser Permanente Southern California and Henry Ford Health System matched to DLE data (address changes, judgements, lien filings, bankruptcy, arrests) from TransUnion. Adults with SCZ or BP-I were matched to major depressive disorder (MDD) and general health (GH) controls based on date of incident or first prevalent diagnosis and demographic characteristics. Generalized estimating equation regression models assessed impact of covariates on outcomes. Results: Samples included 15,634 patients with SCZ and 29,380 patients with BP-I matched to MDD controls and 16,095 patients with SCZ and 29,850 patients with BP-I matched to GH controls. Differences in DLEs were found between patients with SCZ and BP-I and their control groups. Comparing patients with SCZ and BP-I to their matched controls, the likelihood of experiencing DLEs differed by race, age, and gender. Compared to white patients, Asian patients were less likely to experience any DLE, while Black patients were more likely to experience any DLE. Patients currently under age 65 (vs. ≥65) were more likely to move, have judgements, declare bankruptcy, and have been arrested. Odds of having a lien were less for patients 18-44 years but more for those 45-64 years (both vs. ≥65). Findings for gender were mixed based on comparator cohort. Conclusions: Further research is warranted to understand the role of social determinants of health on the occurrence of DLEs among patients with mental illness to develop policies and clinical pathways that help improve equitable access to care.

Gastroenterology

Moonka D, **Kitajima T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Long-term outcomes of donation after cardiac death and living donor liver transplant for primary sclerosing cholangitis. *J Hepatol* 2022; 77:S778-S779.

Gastroenterology

Younossi Z, Yılmaz Y, Yu ML, Wong VWS, Castellanos-Fernandez M, Isakov V, Duseja AK, Méndez-Sánchez N, Eguchi Y, Bugianesi E, Burra P, George J, Fan JG, Papatheodoridis G, Chan WK, Alswat K, Hamid SS, Singal A, Gomez MR, **Gordon SC**, Roberts S, El Kassas M, Kugelmas M, Ong J, Alqahtani S, Ziayee M, Lam B, Younossi I, Racila A, Henry L, and Stepanova M. Lean non-alcoholic fatty liver disease patients from the global NASH registry. *J Hepatol* 2022; 77:S154-S155. Full Text

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Background and aims: Although vast majority of patients with NAFLD are overweight and obese, NAFLD can be seen among lean individuals. The aim was to assess prevalence of lean NAFLD in different regions of the world. Method: The Global NASH Registry enrolled patients with an established diagnosis of NAFLD from real-world practices in 18 countries (Australia, China, Cuba, Egypt, Greece, Hong Kong, India, Italy, Japan, Saudi Arabia, Malaysia, Mexico, Pakistan, Russia, Spain, Taiwan, Turkey, USA) in 6 out of 7 Global Burden of Disease (GBD) super-regions. Clinical and patient-reported outcomes (PRO) data (CLDQ-NASH, FACIT-F,WPAI)were collected. Lean NAFLDwas defined as NAFLD in patients with BMI <25 kg/m2, or 23 kg/m2 for patients of East Asian origin. Results: There were 6096 NAFLD patients included (as of November 10, 2021): 48% from High-Income super-region, 24% Middle East and North Africa (MENA), 12% Southeast Asia, 7% Latin America, 6% from Eastern Europe and Central Asia, and

3% South Asia super-region. Of these, 7.3% were lean. The rates of lean NAFLD were the highest in Southeast Asia (12%) and South Asia (31%), the lowest in Eastern Europe and Central Asia (<2%) and MENA (4%) ($p < 0.0001$). In comparison to overweight/obese patients, lean NAFLD patients were older (mean age 53 vs. 51 years) and predominantly of Asian race (48% vs. 18%) ($p < 0.01$). Furthermore, lean patients had lower rates of diabetes (28% vs. 41%), hypertension (35% vs. 52%), hyperlipidemia (40% vs. 50%), sleep apnea (8% vs. 33%), clinically overt fatigue (25% vs. 36%), and histologic cirrhosis (10% vs. 15%), but more abdominal pain (25% vs. 18%) and higher FIB-4 scores (mean 1.8 vs. 1.3) (all $p \leq 0.02$). In multivariate analysis, having lean NAFLD (as opposed to overweight/ obese NAFLD) was independently associated with older age (OR = 1.019 (1.008–1.030) per year), enrollment outside of MENA region (OR = 0.43 (0.31–0.58)) and from South Asia (OR = 5.01 (3.42– 7.45)) sites (reference: High-Income), absence of type 2 diabetes (OR = 0.61 (0.46–0.80)) and hypertension (OR = 0.46 (0.35–0.60)), and presence of regular exercise (OR = 1.55 (1.21–2.00)) (all $p < 0.01$). Lean NAFLD also had higher PRO scores than overweight/obese NAFLD (all domains of CLDQ-NASH and FACIT-F) (all $p < 0.01$) (Figure). In multivariate analysis, lower total CLDQ-NASH scores (range 1–7) in lean NAFLD patients were independently associated with enrollment from MENA region, history of anxiety, depression, fatigue, and abdominal pain (beta from − 0.40 to − 0.67 for each condition) ($p < 0.01$). (Figure Presented) Conclusion: Lean NAFLD patients seen in real-world practices across the world have different clinical and PRO profiles in comparison to NAFLD patients who are overweight or obese.

Nephrology

Choudhury A, Arora V, **Mishra K**, Tevethia H, Kaushik V, Prasad B, Kumar M, and Sarin SK. Predicting prognosis in large cohort of decompensated cirrhosis of liver (DCLD)- a machine learning (ML) approach. *J Hepatol* 2022; 77:S53. Full Text

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Background and aims: Onset of decompensation in cirrhosis is associated with poor outcome. The current clinico-biochemical tools have limited accuracy in predicting outcomes reliably. Identifying the predictors with precision model on the big data using artificial intelligence may improve predictability. We aimed to develop a machine learning (ML) based prognostic model for predicting 90 day survival in patients of cirrhosis presenting with decompensation. Method: We analysed electronic medical records retrospectively of hospitalised cirrhosis patients at the ILBS, with a complete 90-day follow-up. Clinical data, laboratory parameters and organ involvement were serially noted. AI-modelling was done after appropriate mining, feature engineering, splitted randomly into train and testsets (20:80). The class imbalance problem was handled by random over-sampling technique, to make balanced 50:50 ratios. After 10- fold cross validation, 3 repetitions and grid search for optimal hyper parameters, the XGB-CV model was chosen. AUC was the primary selection criteria and confusion matrix was used to compare AUCs between AI-models and existing indices; CTP and MELD-score. Results: Total of 6326 patients [mean age 48.2 ± 11.5 years, 84% male, Mean CTP 10.4 ± 2.2 and MELD Na-30.4 ± 11.9, alcohol 49.4%] were included. Ninety day mortality was 29.2%. Acute insultwas identified in 80% cases; of which extra-hepatic 49%, hepatic 46% and unknown 5% cases respectively. The XGB-CV model had the best accuracy for prediction of 90 days event in the train set 0.90 (0.90–0.93), validation set 0.80 (0.79–0.81) and for overall dataset 0.80 (0.79– 0.81). The AUC of the XGB-CV model was better than CTP and MELD Na-score by 16% and 15% respectively. The prediction model considered 43 variables; 18 of which predicted the outcome, and 10 maximum contributors are shown in concordance classifier. The most contributors to poor outcome included, index presentation as HE, diagnosis of AD/ACLF/ESLD, PT-INR, serum creatinine, total bilirubin, acute insult etiology, prior decompensation, acute hepatic or extrahepatic insult, leukocyte count and present duration of illness. In the Decision Tree Model, the presence of HE, PT-INR and syndromic diagnosis of AD or ACLF/ESLD was able to stratify the patients into low (22%), intermediate (23–46%) and high risk (>75%) of mortality at 90 days. Conclusion: The AI based current model developed using a large data base of CLD patients presenting with decompensation immensely adds to the current indices of liver disease severity and can stratify patients at admission. Simple ML algorithms using HE and INR besides syndromic presentation, could help treatment decisions and prognostication.

Neurology

Monternier P, **Singh J**, DeWitt S, Gluais P, Moller DE, and Hallakou-Bozec S. Deuterium-Stabilized (R)-Pioglitazone, PXL065, for Treatment of X-Linked Adrenoleukodystrophy (ALD). *Eur J Neurol* 2022; 29:293. Full Text

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Background and aims: X-linked Adrenoleukodystrophy (ALD) is a rare neurometabolic disorder caused by ABCD1- gene mutations, leading to Very-Long-Chain Fatty Acids (VLCFA; in particular C26:0) accumulation, inflammation, mitochondrial impairment and demyelination. PXL065, a clinical-stage deuterium-stabilized(R)-stereoisomer of pioglitazone, retains pioglitazone non-genomic actions but lacks PPARγ activity. As pioglitazone exhibits beneficial effects in ALD models and PXL065 may avoid PPARγ-related side effects, we investigated PXL065 effects of in preclinical models. Methods: Patient-derived fibroblasts and lymphocytes and Abcd1-KO mouse glial cells were exposed to PXL065 (5-10μM) and pioglitazone (10μM) for 7 days. VLCFA content was measured by mass spectrometry, selected gene expression by RT-qPCR, and mitochondrial function using a Seahorse Analyzer (after 72hr). PXL065 or pioglitazone (15mg/kg QD) were administered to 6-8-week or 13-month old Abcd1-KO mice for 8 and 12 weeks, respectively. VLCFA content (mass spectrometry), sciatic nerve axonal morphology (electronic microscopy), and locomotor function (open field test) were measured. Results: In patient and mouse glial cells, PXL065 and pioglitazone corrected C26:0, improved mitochondrial function, increased compensatory Abcd2-3 transporter gene expression, and decreased inflammatory gene expression. In Abcd1-KO mice, C26:0 levels were normalized in plasma and decreased in spinal cord (-55%, $p<0.01$) and brain (-49%, $p<0.0001$). Pioglitazone had no effect in spinal cord. Following PXL065 and pioglitazone treatment, abnormal axonal morphology (stellate-shaped cells) was improved but only PXL065 showed significantly improved locomotor test results. Conclusion: Despite reduced PPARγ activity, PXL065 showed substantial signs of efficacy and superior therapeutic potential vs. pioglitazone (in vivo) supporting clinical development for ALD. A Phase 2a study is planned in 2022.

Surgery

Ivanics T, Claasen M, Al-Adra D, and Sapisochin G. Immunotherapy before solid organ transplantation: an international transplant community-focused survey. *J Hepatol* 2022; 77:S800-S801.

Surgery

Ivanics T, So D, Claasen M, Wallace D, Patel M, Gravely A, Walker K, Cowling T, Erdman L, and Sapisochin G. Evaluating the predictive performance and transferability of machine learning-based prediction models using national liver transplant data registries. *J Hepatol* 2022; 77:S801-S802.

Surgery

Moonka D, **Kitajima T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Long-term outcomes of donation after cardiac death and living donor liver transplant for primary sclerosing cholangitis. *J Hepatol* 2022; 77:S778-S779.

Books and Book Chapters

Nephrology

Jalota Sahota R, and Soos MP. Subclavian Vein Thrombosis. *StatPearls*. StatPearls Publishing; 2022. PMID: 32644695. Full Text

Subclavian vein thrombosis (SCVT) is a condition where a blood clot forms in the subclavian vein. SCVT can occur from multiple etiologies and is a potentially life-threatening pathology if not treated in a timely manner. SCVT occurs due to either a primary etiology or a secondary etiology. Primary thrombosis is further delineated as effort induced (Paget-Schroetter syndrome) or idiopathic (frequently associated with undiagnosed malignancy). Secondary subclavian vein thrombosis is associated with catheters or lines in the vein. While primary thrombosis is rare, the incidence of secondary thrombosis continues to rise as a consequence of complex cardiac devices and long term central venous catheters (CVC) placement in cancer patients. SCVT has high rates of acute mortality and long term disability without proper and timely treatment. Early diagnosis and treatment are essential in preventing fatal acute complications, such as pulmonary embolism and long term morbidity related to venous inflow restriction.