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Henry Ford Health System

Henry Ford Health System Publication List – February 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 System personnel. Searches were conducted in PubMed, Embase, and Web of Science during the month, and then imported into EndNote for formatting. There are 93 unique citations listed this month, with 6 articles and 1 conference abstract on COVID-19.

Articles are listed first, followed by conference abstracts, books and book chapters, and a bibliography of publications on COVID-19. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

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Articles

Conference Abstracts

Articles

Allergy and Immunology

McCauley KE, Flynn K, DiMassa V, LaMere B, Fadrosh DW, Lynch KV, Gill MA, Pongracic JA, Khurana Hershey GK, Kercsmar CM, Liu AH, **Johnson CC**, **Kim H**, Kattan M, O'Connor GT, Bacharier LB, Teach SJ, Gergen PJ, Wheatley LM, Togias A, LeBeau P, Calatroni A, Presnell S, Boushey HA, Busse WW, Gern JE, Jackson DJ, Altman MC, and Lynch SV. Seasonal Airway Microbiome and Transcriptome Interactions Promote Childhood Asthma Exacerbations. *J Allergy Clin Immunol* 2022; Epub ahead of print. PMID: 35149044. Full Text

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Children's National Hospital, Washington, DC, USA.
Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA.
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BACKGROUND: Seasonal variation in respiratory illnesses and exacerbations in pediatric populations with asthma is well described, though whether upper airway microbes play season-specific roles in these events is unknown. OBJECTIVE: We hypothesized that nasal microbiota composition is seasonally dynamic and that discrete microbial-host interactions modify risk of asthma exacerbation in a season-specific manner. METHODS: Repeated nasal samples from children with exacerbation-prone asthma collected during periods of respiratory health (Baseline; n=181 samples) or first captured respiratory illness (n=97) across all seasons, underwent bacterial (16S rRNA gene) and fungal (ITS2) biomarker sequencing. Virus detection was performed by multiplex PCR. Paired nasal transcriptome data was examined for seasonal dynamics and integrative analyses. RESULTS: Upper airway bacterial and fungal microbiota and rhinovirus detection exhibited significant seasonal dynamics. In seasonally-adjusted analysis, variation in both baseline and respiratory illness microbiota related to subsequent exacerbation. Specifically in the fall, when respiratory illness and exacerbation events were most frequent, several Moraxella and Haemophilus members were enriched both in viral positive respiratory illnesses and those that progressed to exacerbations. The abundance of two discrete bacterial networks, characteristically comprising either Streptococcus or Staphylococcus exhibited opposing interactions with an exacerbation-associated SMAD3 nasal epithelial transcriptional module to significantly increase odds of subsequent exacerbation [OR=14.7, 95% CI: 1.50-144, P=0.02; OR=39.17, 95% CI: 2.44-626, P=0.008, respectively]. CONCLUSIONS: Upper airway microbiomes co-vary with season and with seasonal trends in respiratory illnesses and asthma exacerbations. Seasonally-adjusted analyses reveal specific bacterial-host interactions that significantly increase risk of asthma exacerbation in these children.

Anesthesiology
Cohen B, Rivas E, Yang D, Mascha EJ, **Ahuja S**, Turan A, and Sessler DI. Intraoperative Hypotension and Myocardial Injury After Noncardiac Surgery in Adults With or Without Chronic Hypertension: A Retrospective Cohort Analysis. *Anesth Analg* 2022; Epub ahead of print. PMID: 35130198. Full Text

From the Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio.
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BACKGROUND: The risk of myocardial injury progressively increases at intraoperative mean arterial pressures (MAPs) ≤65 mm Hg. Higher pressures might be required in chronically hypertensive patients. We aimed to test the hypothesis that the harm threshold is higher in patients with chronic hypertension than in normotensive patients. METHODS: We conducted a single-center retrospective cohort analysis of adults >45 years old who had noncardiac surgery between 2010 and 2018 and scheduled, rather than symptom-driven, postoperative troponin measurements. The MAP thresholds under which risk started to increase were compared between patients with chronic hypertension (baseline MAP ≥110 mm Hg) and normotensive patients (baseline MAP <110 mm Hg). The primary outcome was a composite of in-hospital mortality and myocardial injury within 30 days, defined by any postoperative 4th-generation troponin T measurement ≥0.03 ng/mL apparently due to cardiac ischemia. Multivariable logistic regression and moving average smoothing methods were used to evaluate confounder-adjusted associations between the composite outcome and the lowest intraoperative MAP sustained for either 5 or 10 cumulative minutes, and whether the relationship depended on baseline pressure (normotensive versus hypertensive). RESULTS: Among 4576 eligible surgeries, 2066 were assigned to the normotensive group with mean (standard deviation [SD]) baseline MAP of 100 (7) mm Hg, and 2510 were assigned to the hypertensive group with mean baseline MAP of 122 (10) mm Hg. The overall incidence of the composite outcome was 5.6% in normotensive and 6.0% in hypertensive patients (P = .55). The relationship between intraoperative hypotension and the composite outcome was not found to depend on baseline MAP in a multivariable mixed effects logistic regression model. Furthermore, no statistical change points were found for either baseline MAP group. CONCLUSIONS: Baseline blood pressure of the hypertensive patients was only moderately increased on average, and the event rate was low. Nonetheless, we were not able to demonstrate a difference in the harm threshold between normotensive and chronically hypertensive patients. Our results do not support the theory that hypertensive patients should be kept at higher intraoperative pressures than normotensive patients.

Anesthesiology
Frisoli TM, **Chiang M**, Eng MH, **Gonzalez PE**, **Szymanski T**, **Villablanca PA**, **O'Neill B**, **Lee JC**, **Wang DD**, and **O'Neill WW**. Percutaneous Aspiration Thrombectomy of Thrombus Attached to Left Atrial Surface of a Watchman FLX Device. *JACC Clin Electrophysiol* 2022; 8(2):277-279. PMID: 35210092. Full Text

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Behavioral Health Services/Psychiatry/Neuropsychology
Rossom RC, Richards JE, Sterling S, **Ahmedani B**, Boggs JM, Yarborough BJH, Beck A, Lloyd K, **Frank C**, Liu V, Clinch SB, Patke LD, and Simon GE. Connecting Research and Practice: Implementation of Suicide Prevention Strategies in Learning Health Care Systems. *Psychiatr Serv* 2022; 73(2):219-222. PMID: 34189931. Full Text

HealthPartners Institute, Minneapolis (Rossom); Kaiser Permanente Washington Health Research Institute, Seattle (Richards, Simon); Kaiser Permanente Northern California Division of Research, Oakland (Sterling, Liu); Henry Ford Health System, Behavioral Health Services and Center for Health Policy and Health Services Research, Detroit (Ahmedani, Frank); Kaiser Permanente Colorado Institute for Health Research, Denver (Boggs, Beck); Kaiser Permanente Northwest Center for Health Research, Portland, Oregon (Yarborough); HealthPartners Behavioral Health Plan, Minneapolis (Lloyd); private practice, Eden Prairie, Minnesota (Lloyd); Kaiser Permanente Colorado Medical Group, Denver (Clinch); Kaiser Permanente Colorado Behavioral Health, Denver (Patke). Debra A. Pinals, M.D., Enrico G. Castillo, M.D., M.S.H.P.M., and Ayorkor Gaba, Psy.D., are editors of this column.

The health care systems affiliated with the Mental Health Research Network strive to be learning health care systems that identify and address evidence gaps of importance to clinicians, patients, and funders. This column describes how research guides clinical care and clinical care guides research in the area of suicide prevention as well as some of the challenges of conducting embedded research.

Behavioral Health Services/Psychiatry/Neuropsychology
Shen C, Li H, Li M, Niu Y, Liu J, Zhu L, **Gui H**, Han W, Wang H, Zhang W, Wang X, Luo X, Sun Y, Yan J, and Guan F. DLRAPom: a hybrid pipeline of Optimized XGBoost-guided integrative multiomics analysis for identifying targetable disease-related lncRNA-miRNA-mRNA regulatory axes. *Brief Bioinform* 2022; Epub ahead of print. PMID: 35224615. Request Article

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The lack of a reliable and easy-to-operate screening pipeline for disease-related noncoding RNA regulatory axis is a problem that needs to be solved urgently. To address this, we designed a hybrid pipeline, disease-related lncRNA-miRNA-mRNA regulatory axis prediction from multiomics (DLRAPom), to identify risk biomarkers and disease-related lncRNA-miRNA-mRNA regulatory axes by adding a novel machine learning model on the basis of conventional analysis and combining experimental validation. The pipeline consists of four parts, including selecting hub biomarkers by conventional bioinformatics analysis, discovering the most essential protein-coding biomarkers by a novel machine learning model, extracting the key lncRNA-miRNA-mRNA axis and validating experimentally. Our study is the first one to propose a new pipeline predicting the interactions between lncRNA and miRNA and mRNA by combining WGCNA and XGBoost. Compared with the methods reported previously, we developed an Optimized XGBoost model to reduce the degree of overfitting in multiomics data, thereby improving the generalization ability of the overall model for the integrated analysis of multiomics data. With applications to gestational diabetes mellitus (GDM), we predicted nine risk protein-coding biomarkers and some potential lncRNA-miRNA-mRNA regulatory axes, which all correlated with GDM. In those regulatory axes, the MALAT1/hsa-miR-144-3p/IRS1 axis was predicted to be the key axis and was identified as being

associated with GDM for the first time. In short, as a flexible pipeline, DLRAPom can contribute to molecular pathogenesis research of diseases, effectively predicting potential disease-related noncoding RNA regulatory networks and providing promising candidates for functional research on disease pathogenesis.

Cardiology/Cardiovascular Research
Ananthasubramaniam G, and **Ananthasubramaniam K**. Stress electrocardiography testing in coronary artery disease: Is it time for its swan song or to redefine its role in the modern era ? *Indian Heart J* 2022; Epub ahead of print. PMID: 35167825. Full Text

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Stress electrocardiography (sECG) or treadmill stress testing is a well validated noninvasive diagnostic modality available to clinicians at low cost yet providing valuable functional data for coronary artery disease (CAD) diagnostic and prognostic evaluation. With the advances in cardiac imaging in both functional and anatomic fronts and the existing limitations of sECG testing, this modality appears less favored worldwide as reflected in some recent guideline updates. We review the past present and future of sECG to provide a viewpoint on where it stands in CAD evaluation and if it will remain relevant as a diagnostic modality or be retired going forward. We also provide our perspectives on how sECG can co-exist with other modalities such as calcium scoring and discuss the role of such testing in the Indian population.

Cardiology/Cardiovascular Research
Atluri P, Silvestry SC, Teuteberg JJ, Milano CA, Selzman CH, and **Cowger JA**. What If the Destination Is Transplant? Outcomes of Destination Therapy Patients Who Were Transplanted. *Asaio j* 2022; 68(2):178-183. PMID: 35089262. Full Text

From the Hospital of the University of Pennsylvania, Philadelphia, PA.
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We sought to characterize patients who underwent heart transplant (HTx) following destination therapy (DT) implant in the combined ENDURANCE/ENDURANCE Supplemental Trials (DT/DT2). A post hoc analysis of the DT/DT2 trials was performed. Baseline characteristics and adverse events between the HTx and no-HTx cohorts were analyzed. Reasons for transplant were examined. Time to HTx was compared with contemporaneous HVAD BTT trial patients. Of the 604 DT/DT2 HVAD patients, 80 (13%) underwent HTx. The HTx cohort was younger (53.6 ± 11.1 vs. 65.2 ± 10.8, P < 0.0001) with fewer Caucasians (60.0% vs. 76.5%, P = 0.002), less ischemic cardiomyopathy (42.5% vs. 58.8%, P = 0.01), and atrial fibrillation (38.8% vs. 54.4%, P = 0.01). The HTx cohort had longer 6-minute walk distances (183.6 vs. 38.0 m, P = 0.02). Most HTx in DT/DT2 were categorized as elective (n = 63, 79%) and, of these, 70% were due to modification of behavioral issues and weight loss. Adverse events were the main indication for urgent HTx (n = 17, 21%). Median times to HTx were longer in DT/DT2 (550.0 days) versus BTT/lateral (285.2 days). In this post hoc analysis of the DT/DT2 trials, over 1 in 10 underwent heart transplantation within 3 years of HVAD support. In DT therapy patients, consideration for transplant following DT VAD implant may be feasible.

Cardiology/Cardiovascular Research
Elbadawi A, Sedhom R, **Megaly M**, Eid M, Omran A, and Elgendy IY. Estimate and Temporal Trends of Buerger Disease Hospitalizations in the United States. *Am J Cardiol* 2022; Epub ahead of print. PMID: 35168750. Full Text

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Cardiology/Cardiovascular Research

Frisoli TM, **Chiang M**, Eng MH, **Gonzalez PE**, **Szymanski T**, **Villablanca PA**, **O'Neill B**, **Lee JC**, **Wang DD**, and **O'Neill WW**. Percutaneous Aspiration Thrombectomy of Thrombus Attached to Left Atrial Surface of a Watchman FLX Device. *JACC Clin Electrophysiol* 2022; 8(2):277-279. PMID: 35210092. Full Text

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Cardiology/Cardiovascular Research

Gorgis S, **Lemor A**, **Kolski B**, **Lalonde T**, **Kaki A**, **Marso S**, **Senter S**, **Rahman A**, **Gorwara S**, **Nazir R**, **Zuberi O**, **Justice L**, **Srivastava N**, **Padgett R**, **O'Neill W**, and **Basir MB**. Antiplatelet Therapy in Acute Myocardial Infarction and Cardiogenic Shock: Insights From the National Cardiogenic Shock Initiative. *J Invasive Cardiol* 2022; Epub ahead of print. PMID: 35157607. Request Article

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BACKGROUND: Patients presenting with acute myocardial infarction complicated by cardiogenic shock (AMI-CS) are at high risk for impaired antiplatelet activity secondary to malabsorption, systemic hypoperfusion, hypothermia, need for mechanical ventilation, and high use of analgesics. The use of antiplatelet therapy in these high-risk patients is not well studied. METHODS: Using the National Cardiogenic Shock Initiative database, we analyzed patients who presented with AMI-CS at 60 hospitals from March 2018 to December 2020. All patients were treated using a standard shock protocol. Herein, the patterns of antiplatelet use are described. RESULTS: A total of 204 patients were included in the analysis, of which 174 (85.3%) presented with ST-segment elevation myocardial infarction (STEMI). The majority (84.3%) received antiplatelet therapy before percutaneous coronary intervention (PCI); of those who received antiplatelets, 77.9% received aspirin, 55.2% received an oral P2Y12 inhibitor, and 19.2% received intravenous (IV) antiplatelet therapy. Ticagrelor was the most common P2Y12 inhibitor administered (41.9%), followed by clopidogrel (12.2%) and prasugrel (1.2%). Only 18.6% of oral antiplatelet agents were crushed. Baseline characteristics of patients who received IV vs non-IV antiplatelet agents were similar. Thrombolysis in Myocardial Infarction (TIMI) 0 flow was present in 69.6% of patients before PCI and aspiration thrombectomy was performed in 24.5% of patients. The presence of STEMI, cardiac arrest, cardiopulmonary resuscitation, hypothermia, vasopressor use, elevated lactate levels, or number of vessels treated did not influence the use of IV antiplatelet agents. CONCLUSIONS: The use of crushed and IV antiplatelet agents in AMI-CS is low. Further studies are needed in this high-risk population to assess whether more potent antiplatelet inhibition will improve outcomes.

Cardiology/Cardiovascular Research

Hariri IM, Dardas T, Kanwar M, Cogswell R, Gosev I, Molina E, Myers SL, Kirklin JK, Shah P, Pagani FD, and **Cowger JA**. Long-term survival on LVAD support: Device complications and end-organ dysfunction limit long-term success. *J Heart Lung Transplant* 2022; 41(2):161-170. PMID: 34404571. Full Text

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BACKGROUND: Preoperative variables can predict short term left ventricular assist device (LVAD) survival, but predictors of extended survival remain insufficiently characterized. METHOD: Patients undergoing LVAD implant (2012-2018) in the Intermacs registry were grouped according to time on support: short-term (<1 year, n = 7,483), mid-term (MT, 1-3 years, n = 5,976) and long-term (LT, ≥3 years, n = 3,015). Landmarked hazard analyses (adjusted hazard ratio, HR) were performed to identify correlates of survival after 1 and 3 years of support. RESULTS: After surviving 1 year of support, additional LVAD survival was less likely in older (HR 1.15 per decade), Caucasian (HR 1.22) and unmarried (HR 1.16) patients ($p < 0.05$). After 3 years of support, only 3 preoperative characteristics (age, race, and history of bypass surgery, $p < 0.05$) correlated with extended survival. Postoperative events most negatively influenced achieving LT survival. In those alive at 1 year or 3 years, the occurrence of postoperative renal (creatinine HR MT = 1.09; LT HR = 1.10 per mg/dl) and hepatic dysfunction (AST HR MT = 1.29; LT HR = 1.34 per 100 IU), stroke (MT HR = 1.24; LT HR = 1.42), infection (MT HR = 1.13; LT HR = 1.10), and/or device malfunction (MT HR = 1.22; LT HR = 1.46) reduced extended survival (all $p \leq 0.03$). CONCLUSIONS: Success with LVAD therapy hinges on achieving long term survival in more recipients. After 1 year, extended survival is heavily constrained by the occurrence of adverse events and postoperative end-organ dysfunction. The growth of destination therapy intent mandates that future LVAD studies be designed with follow up sufficient for capturing outcomes beyond 24 months.

Cardiology/Cardiovascular Research

Keteyian SJ, Jackson SL, Chang A, **Brawner CA**, Wall HK, Forman DE, Sukul D, Ritchey MD, and Sperling LS. Tracking Cardiac Rehabilitation Utilization in Medicare Beneficiaries: 2017 UPDATE. *J Cardiopulm Rehabil Prev* 2022; Epub ahead of print. PMID: 35135961. Full Text

Division of Cardiovascular Medicine, Henry Ford Health System, Detroit, Michigan (Drs Keteyian and Brawner); Centers for Disease Control and Prevention, Atlanta, Georgia (Drs Jackson, Ritchey, and Sperling, Mr Chang, and Ms Wall); Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan (Dr Brawner); Divisions of Geriatrics and Cardiology, University of Pittsburgh and the VA Pittsburgh GRECC, Pittsburgh, Pennsylvania (Dr Forman); Division of Cardiovascular Diseases, University of Michigan, Ann Arbor (Dr Sukul); and Center for Heart Disease Prevention, Emory University School of Medicine, Atlanta, Georgia (Dr Sperling).

PURPOSE: This study updates cardiac rehabilitation (CR) utilization data in a cohort of Medicare beneficiaries hospitalized for CR-eligible events in 2017, including stratification by select patient demographics and state of residence. METHODS: We identified Medicare fee-for-service beneficiaries who experienced a CR-eligible event and assessed their CR participation (≥1 CR sessions in 365 d), engagement, and completion (≥36 sessions) rates through September 7, 2019. Measures were assessed overall, by beneficiary characteristics and state of residence, and by primary (myocardial infarction; coronary artery bypass surgery; heart valve repair/replacement; percutaneous coronary intervention; or heart/heart-lung transplant) and secondary (angina; heart failure) qualifying event type. RESULTS: In 2017, 412 080 Medicare beneficiaries had a primary CR-eligible event and 28.6% completed ≥1 session of CR within 365 d after discharge from a qualifying event. Among beneficiaries who completed ≥1 CR session, the mean total number of sessions was 25 ± 12 and 27.6% completed ≥36 sessions. Nebraska had the highest enrollment rate (56.1%), with four other states also achieving an enrollment rate >50% and 23 states falling below the overall rate for the United States. CONCLUSIONS: The absolute

enrollment, engagement, and program completion rates remain low among Medicare beneficiaries, indicating that many patients did not benefit or fully benefit from a class I guideline-recommended therapy. Additional research and continued widespread adoption of successful enrollment and engagement initiatives are needed, especially among identified populations.

Cardiology/Cardiovascular Research

Koechlin L, Boeddinghaus J, Nestelberger T, Lopez-Ayala P, Shrestha S, Wussler D, Haeni N, Walter JE, Twerenbold R, Eckstein FS, Reuthebuch O, **McCord J**, **Nowak RM**, Christenson RH, DeFilippi CR, Apple FS, and Mueller C. Lower diagnostic accuracy of hs-cTnI in patients with prior coronary artery bypass grafting. *Int J Cardiol* 2022; Epub ahead of print. PMID: 35189168. Full Text

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BACKGROUND: High-sensitivity cardiac troponin T (hs-cTnT) and the ESC 0/1 h-hs-cTnT-algorithm have worse performance in the early diagnosis of myocardial infarction (MI) in patients with prior coronary artery bypass grafting (CABG). It is unknown, whether this concern applies also to hs-cTnI, the most widely used analyte worldwide. METHODS: In an international multicenter diagnostic study, two cardiologists centrally adjudicated the final diagnosis in patients presenting to the emergency department with symptoms suggestive of MI according to the Third Universal Definition of MI. The objective was to compare the diagnostic accuracy of hs-cTnI assays and their performance within the ESC hs-cTnI 0/1 h-algorithms in patients with versus without prior CABG. Findings were externally validated in an U.S. multicenter diagnostic study. RESULTS: A total of 392/5'200 patients (8%) had prior coronary artery bypass grafting (CABG). Diagnostic accuracy of hs-cTnI as quantified by the area under the receiver-operating characteristics-curve (AUC) in these patients was high, but lower versus patients without prior CABG (e.g. hs-cTnI-Architect 0.91 versus 0.95; $p = 0.016$). Sensitivity/specificity of rule-out/in by the European Society of Cardiology (ESC) 0/1 h-hs-cTnI-algorithms remained very high [e.g. hs-cTnI-Architect 100% and 93.5%], but efficacy was lower (52% versus 74%, $p < 0.01$). External validation ($n = 2113$) confirmed these findings in 192 patients with prior CABG using hs-cTnI-Atellica, with 52% versus 36% ($p < 0.001$) remaining in the observe zone. CONCLUSIONS: Diagnostic accuracy of hs-cTnI and efficacy of the ESC 0/1 h-hs-cTnI-algorithms are lower in patients with prior CABG, but sensitivity/specificity remain very high. CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/ct2/show/NCT00470587, number NCT00470587.

Cardiology/Cardiovascular Research

McCord J, **Gibbs J**, **Hudson M**, **Moyer M**, **Jacobsen G**, Murtagh G, and **Nowak R**. Machine Learning to Assess for Acute Myocardial Infarction within 30 Minutes. *Crit Pathw Cardiol* 2022; Epub ahead of print. PMID: 35190507. Full Text

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Variations in high-sensitivity cardiac troponin I (hs-cTnI) by age and sex along with various sampling times can make the evaluation for acute myocardial infarction (AMI) challenging. Machine learning integrates these variables to allow a more accurate evaluation for possible AMI. The goal was to test the diagnostic and prognostic utility of a machine learning algorithm in the evaluation of possible AMI. We applied a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, sex, and hs-cTnI levels at time 0 and 30 minutes in 529 patients evaluated for possible AMI in a single urban emergency department. MI3 generates an index value from 0-100 reflecting the likelihood of AMI. Patients were followed at 30-45 days for major adverse cardiac events (MACE). There were 42 (7.9%) patients that had an AMI. Patients were divided into 3 groups by the MI3 score: low-risk (≤ 3.13), intermediate-risk (> 3.13-51.0), and high-risk (> 51.0). The sensitivity for AMI was 100% with a MI3 value ≤ 3.13 and 353 (67%) ruled-out for AMI at 30 minutes. At 30-45 days there were 2 (0.6%) MACEs (2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 AMIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 AMIs, 2 cardiac deaths). The MI3 algorithm had 100% sensitivity for AMI at 30 minutes and identified a low-risk cohort who may be considered for early discharge.

Cardiology/Cardiovascular Research

Megaly M, Buda K, **Alaswad K**, Brilakis ES, Dupont A, Naidu S, Ohman M, Napp LC, **O'Neill W**, and **Basir MB**. Comparative Analysis of Patient Characteristics in Cardiogenic Shock Studies: Differences Between Trials and Registries. *JACC Cardiovasc Interv* 2022; 15(3):297-304. PMID: 35144785. Full Text

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OBJECTIVES: This study sought to evaluate the differences in cardiogenic shock patient characteristics in trial patients and real-life patients. BACKGROUND: Cardiogenic shock (CS) is a leading cause of mortality in patients presenting with acute myocardial infarction (AMI). However, the enrollment of patients into clinical trials is challenging and may not be representative of real-world patients. METHODS: We performed a systematic review of studies in patients presenting with AMI-related CS and compared patient characteristics of those enrolled into randomized controlled trials (RCTs) with those in registries. RESULTS: We included 14 RCTs (n = 2,154) and 12 registries (n = 133,617). RCTs included more men (73% vs 67.7%, P < 0.001) compared with registries. Patients enrolled in RCTs had fewer comorbidities, including less hypertension (61.6% vs 65.9%, P < 0.001), dyslipidemia (36.4% vs 53.6%, P < 0.001), a history of stroke or transient ischemic attack (7.1% vs 10.7%, P < 0.001), and prior coronary artery bypass graft surgery (5.4% vs 7.5%, P < 0.001). Patients enrolled in RCTs also had lower lactate levels (4.7 ± 2.3 mmol/L vs 5.9 ± 1.9 mmol/L, P < 0.001) and higher mean arterial pressure (73.0 ± 8.8 mm Hg vs 62.5 ± 12.2 mm Hg, P < 0.001). Percutaneous coronary intervention (97.5% vs 58.4%, P < 0.001) and extracorporeal membrane oxygenation (11.6% vs 3.4%, P < 0.001) were used more often in RCTs. The in-hospital mortality (23.9% vs 38.4%, P < 0.001) and 30-day mortality (39.9% vs 45.9%, P < 0.001) were lower in RCT patients. CONCLUSIONS: RCTs in AMI-related CS tend to enroll fewer women and lower-risk patients compared with registries. Patients enrolled in RCTs are more likely to receive aggressive treatment with percutaneous coronary intervention and extracorporeal membrane oxygenation and have lower in-hospital and 30-day mortality.

Cardiology/Cardiovascular Research

Megaly M, Buda K, Saad M, Tawadros M, Elbadawi A, **Basir M**, Abbott JD, Rinfret S, **Alaswad K**, and Brilakis ES. Outcomes With Drug-Coated Balloons vs. Drug-Eluting Stents in Small-Vessel Coronary Artery Disease. *Cardiovasc Revasc Med* 2022; 35:76-82. PMID: 33858783. Full Text

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BACKGROUND: The use of drug-coated balloons (DCBs) in small-vessel coronary artery disease (SVD) remains controversial. METHODS: We performed a meta-analysis of all randomized controlled trials (RCTs) reporting the outcomes of DCB vs. DES in de-novo SVD. We included a total of 5 RCTs (1459 patients), with (DCB n = 734 and DES n = 725). RESULTS: Over a median follow-up duration of 6 months, DCB was associated with smaller late lumen loss (LLL) compared with DES (mean difference -0.12 mm) (95% confidence intervals (CI) [-0.21, -0.03 mm], p = 0.01). Over a median follow-up of 12 months, both modalities had similar risk of major adverse cardiovascular events (MACE) (8.7% vs. 10.2%; odds ratio (OR): 0.94, 95% CI [0.49-1.79], p = 084), all-cause mortality (1.17% vs. 2.38%; OR: 0.53, 95% CI [0.16-1.75], p = 0.30), target lesion revascularization (TLR) (7.9% vs. 3.9%; OR: 1.26, 95% CI [0.51-3.14], p = 0.62), and target vessel revascularization (TVR) (8.2% vs. 7.8%; OR: 1.06, 95% CI [0.40-2.82], p = 0.91). DCBs were associated with lower risk of myocardial infarction (MI) compared with DES (1.55% vs. 3.31%; OR: 0.48, 95% CI [0.23-1.00], p = 0.05, I2 = 0%). CONCLUSION: PCI of SVD with DCBs is associated with smaller LLL, lower risk of MI, and similar risk of MACE, death, TLR, and TVR compared with DES over one year. DCB appears as an attractive alternative to DES in patients with de-novo SVD, but long-term clinical data are still needed.

Cardiology/Cardiovascular Research

O'Neill WW, Anderson M, Burkhoff D, Grines CL, Kapur NK, Lansky AJ, Mannino S, McCabe JM, **Alaswad K**, Daggubati R, Wohns D, Meraj PM, Pinto DS, Popma JJ, Moses JW, Schreiber TL, and Magnus Ohman E. Improved Outcomes in Patients with Severely Depressed LVEF Undergoing Percutaneous Coronary Intervention with Contemporary Practices: Impella-Supported High-Risk Percutaneous Coronary Intervention in Patients with Severely Depressed LVEF. *Am Heart J* 2022; Epub ahead of print. PMID: 35192839. Full Text

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Spectrum Health, Frederik Meijer Heart and Vascular Institute, Grand Rapids, Michigan.
Northwell Health, Manhasset, New York.
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BACKGROUND: Contemporary practices for hemodynamically supported high-risk percutaneous coronary intervention (HRPCI) have evolved over the last decade. This study sought to compare outcomes of the prospective, multicenter, PROTECT III study to historic patients treated with Impella in the PROTECT II randomized controlled trial (RCT). METHODS: Of 1,134 patients enrolled in PROTECT III from March 2017 to March 2020, 504 were "PROTECT II-like" (met eligibility for PROTECT II RCT) and are referred to as PROTECT III for comparative analysis. Major adverse cardiac and cerebrovascular events (MACCE), comprising all-cause mortality, stroke/transient ischemic attack, myocardial infarction (MI), and repeat revascularization, were compared at hospital discharge and 90 days. RESULTS: Compared with PROTECT II (N=216), PROTECT III patients were less often Caucasian (77.1% vs 83.8%, p=0.045), with less prior CABG (13.7% vs 39.4%; p<0.001) and prior MI (40.7% vs 69.3%; p<0.001). More PROTECT III patients underwent rotational atherectomy (37.1% vs 14.8%, p<0.001) and duration of support was longer (median 1.6 vs 1.3 hours; p<0.001), with greater improvement achieved in myocardial ischemia jeopardy scores (7.0±2.4 vs 4.4±2.9; p<0.001) and SYNTAX scores (21.4±10.8 vs 15.7±9.5; p<0.001). In-hospital bleeding requiring transfusion was significantly lower in PROTECT III (1.8% vs 9.3%; p<0.001), as was procedural hypotension (2.2% vs 10.1%; p<0.001) and cardiopulmonary resuscitation or ventricular arrhythmia (1.6% vs 6.9%; p<0.001). At 90 days, MACCE was 15.1% and 21.9% in PROTECT III and PROTECT II, respectively (p=0.037). Following propensity score matching, Kaplan-Meier analysis showed improved 90-day MACCE rates in PROTECT III (10.4% vs 16.9%, p=0.048). CONCLUSIONS: The PROTECT III study demonstrates improved completeness of revascularization, less bleeding, and improved 90-day clinical outcomes compared to PROTECT II for Impella-supported HRPCI among patients with severely depressed LVEF.

Cardiology/Cardiovascular Research

Pack QR, Shea M, **Brawner CA**, Headley S, Hutchinson J, Madera H, and **Keteyian SJ**. Exercise Prescription Methods and Attitudes in Cardiac Rehabilitation: A NATIONAL SURVEY. *J Cardiopulm Rehabil Prev* 2022; Epub ahead of print. PMID: 35185145. Full Text

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PURPOSE: High-quality exercise training improves outcomes in cardiac rehabilitation (CR), but little is known about how most programs prescribe exercise. Thus, the aim was to describe how current CR programs prescribe exercise. METHODS: We conducted a 33-item anonymous survey of CR program directors registered with the American Association of Cardiovascular and Pulmonary Rehabilitation. We assessed the time, mode, and intensity of exercise prescribed, as well as attitudes about maximal exercise testing and exercise prescription. Results were summarized using descriptive statistics. Open-ended responses were coded and quantitated thematically. RESULTS: Of 1470 program directors, 246 (16.7%) completed the survey. In a typical session of CR, a median of 5, 35, 10, and 5 min was spent on warm-up, aerobic exercise, resistance training, and cooldown, respectively. The primary aerobic modality was the treadmill (55%) or seated dual-action step machine (40%). Maximal exercise testing and high-intensity interval training (HIIT) were infrequently reported (17 and 8% of patients, respectively). The most common method to prescribe exercise intensity was ratings of perceived exertion followed by resting heart rate +20-30 bpm, although 55 unique formulas for establishing a target heart rate or range (THRR) were reported. Moreover, variation in exercise prescription between staff members in the same program was reported in 40% of programs. Program directors reported both strongly favorable and unfavorable opinions toward maximal exercise testing, HIIT, and use of THRR. CONCLUSIONS: Cardiac rehabilitation program directors reported generally consistent exercise time and modes, but widely divergent methods and opinions toward prescribing exercise intensity. Our results suggest a need to better study and standardize exercise intensity in CR.

Cardiology/Cardiovascular Research

Toma C, Bunte MC, Cho KH, Jaber WA, Chambers J, Stegman B, Gondi S, Leung DA, Savin M, Khandhar S, Kado H, **Koenig G**, Weinberg M, Beasley RE, Roberts J, Angel W, Sarosi MG, Qaqi O, Veerina K, Brown MA, and Pollak JS. Percutaneous mechanical thrombectomy in a real-world pulmonary embolism population: Interim results of the FLASH registry. *Catheter Cardiovasc Interv* 2022; Epub ahead of print. PMID: 35114059. Full Text

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OBJECTIVES: The FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH) is a prospective multi-center registry evaluating the safety and effectiveness of percutaneous mechanical thrombectomy for treatment of pulmonary embolism (PE) in a real-world patient population (NCT03761173). This interim analysis reports outcomes for the first 250 patients enrolled in FLASH. BACKGROUND: High- and intermediate-risk PEs are characterized by high mortality rates, frequent readmissions, and long-term sequelae. Mechanical thrombectomy is emerging as a front-line therapy for PE that enables immediate thrombus reduction while avoiding the bleeding risks inherent with thrombolytics. METHODS: The primary endpoint is a composite of major adverse events (MAE) including device-related death, major bleeding, and intraprocedural device- or procedure-related adverse events at 48 h. Secondary endpoints include on-table changes in hemodynamics and longer-term measures including dyspnea, heart rate, and cardiac function. RESULTS: Patients were predominantly intermediate-risk per ESC guidelines (6.8% high-risk, 93.2% intermediate-risk). There were three MAEs (1.2%), all of which were major bleeds that resolved without sequelae, with no device-related injuries, clinical deteriorations, or deaths at 48 h. All-cause mortality was 0.4% at 30 days, with a single death that was unrelated to PE. Significant on-table improvements in hemodynamics were noted, including an average reduction in mean pulmonary artery pressure of 7.1 mmHg (22.2%, $p < 0.001$). Patient symptoms and cardiac function improved through follow-up. CONCLUSIONS: These interim results provide preliminary evidence of excellent safety in a real-world PE population. Reported outcomes suggest that mechanical thrombectomy can result in immediate hemodynamic improvements, symptom reduction, and cardiac function recovery.

Center for Health Policy and Health Services Research

Gordon SC, Teshale EH, Spradling PR, Moorman AC, Boscarino JA, Schmidt MA, Daida YG, **Rupp LB**, **Trudeau S**, **Zhang J**, and **Lu M**. Lower rates of emergency visits and hospitalizations among chronic hepatitis C patients with sustained virological response to interferon-free direct-acting antiviral therapy (2014-2018). *Clin Infect Dis* 2022; Epub ahead of print. PMID: 35147184. Full Text

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We compared rates of emergency department (ED) visits and hospitalizations between HCV patients who achieved sustained virological response (SVR) after direct-acting antiviral (DAA) therapy (cases) to matched controls. Among 3049 pairs, cases demonstrated lower rates of liver-related ED visits (P=.01) than controls; all-cause and liver-related hospitalization rates and hospitalized days were also lower in cases (P<.0001).

Center for Health Policy and Health Services Research
Jesse MT, **Gartrelle K**, **Bruschwein H**, **Hug G**, **LeTarte B**, **Lerret S**, and **Dew MA**. Non-pharmacological interventions engaging organ transplant caregivers: A systematic review. *Clin Transplant* 2022;e14611. Epub ahead of print. PMID: 35143701. Full Text

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INTRODUCTION: Lay-caregivers in organ transplantation (to candidates, recipients, and donors) are essential to pre- and postoperative care, but report significant caregiving-related stressors. This review aims to summarize studies testing nonpharmacological interventions aimed at improving organ transplant caregiver-reported outcomes. METHODS: In accordance with PRISMA, we conducted a systematic review (searched PubMed, Embase, Cochrane Central, PsycInfo, and CINAHL, no start-date restriction through 7/1/2021). Quality of comparative studies assessed by ROBS-2 or ROBINS. RESULTS: Twelve studies met inclusion. Study designs, interventions, and outcomes varied. Sample sizes were small across caregivers to adults (nine studies, five with caregiver samples ns≤50) and pediatric patients (three studies, caregiver samples ns≤16). Study designs included seven single-arm interventions, two prepost with comparison cohorts, and three randomized-controlled trials. Eight studies included transplant-specific education as the intervention, an interventional component, or as the comparison group. Outcomes included transplant specific knowledge, mental health, and intervention acceptability. Of the nine prepost caregiver assessments and/or comparison groups, four studies demonstrated no statistically significant intervention effects. CONCLUSION: Few interventions addressing the needs of organ transplant caregivers have been empirically evaluated. Existing interventions were well-received by caregivers. Given complexities of care in transplantation, research is needed evaluating interventions using rigorous trial methodology with adequate samples.

Center for Health Policy and Health Services Research
Rossom RC, Richards JE, Sterling S, **Ahmedani B**, Boggs JM, Yarborough BJH, Beck A, Lloyd K, **Frank C**, Liu V, Clinch SB, Patke LD, and Simon GE. Connecting Research and Practice: Implementation of Suicide Prevention Strategies in Learning Health Care Systems. *Psychiatr Serv* 2022; 73(2):219-222. PMID: 34189931. Full Text

HealthPartners Institute, Minneapolis (Rossom); Kaiser Permanente Washington Health Research Institute, Seattle (Richards, Simon); Kaiser Permanente Northern California Division of Research, Oakland (Sterling, Liu); Henry Ford Health System, Behavioral Health Services and Center for Health Policy and Health Services Research, Detroit (Ahmedani, Frank); Kaiser Permanente Colorado Institute for Health Research, Denver (Boggs, Beck); Kaiser Permanente Northwest Center for Health Research, Portland, Oregon (Yarborough); HealthPartners Behavioral Health Plan, Minneapolis (Lloyd); private practice, Eden Prairie, Minnesota (Lloyd); Kaiser Permanente Colorado Medical Group, Denver (Clinch); Kaiser Permanente Colorado Behavioral Health, Denver (Patke). Debra A. Pinals, M.D., Enrico G. Castillo, M.D., M.S.H.P.M., and Ayorkor Gaba, Psy.D., are editors of this column.

The health care systems affiliated with the Mental Health Research Network strive to be learning health care systems that identify and address evidence gaps of importance to clinicians, patients, and funders. This column describes how research guides clinical care and clinical care guides research in the area of suicide prevention as well as some of the challenges of conducting embedded research.

Dermatology
Fatima S, Abbas T, Refat MA, Harris JE, **Lim HW**, **Hamzavi IH**, and **Mohammad TF**. Systemic therapies in vitiligo: a review. *Int J Dermatol* 2022; Epub ahead of print. PMID: 35133006. Full Text

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Vitiligo is characterized by the development of depigmented macules and patches. Autoimmunity has been established as a factor in disease pathogenesis, leading to utilization of immunosuppressive agents. Topical immunosuppressants are commonly used; however, this treatment modality is often cumbersome and inefficient, as many patients have active disease with extensive body surface area involvement. Prompt and aggressive treatment of vitiligo is important, as this may prevent progression and improve quality of life. To meet these challenges and improve patient outcomes, interest in systemic therapies has grown. Currently, oral therapies are rarely prescribed, likely due to concerns with systemic side effects and unclear efficacy. This article provides a brief overview on the use of systemic agents in treating vitiligo in order to provide additional therapeutic options to clinicians.

Dermatology
Johns HR, **Shetty N**, Cash J, Patel T, and Pourciau C. Bowel-Associated-Dermatosis-Arthritis Syndrome (BADAS) as early presentation of ulcerative colitis in an adolescent girl. *Pediatr Dermatol* 2022; Epub ahead of print. PMID: 35191547. Full Text

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A 14-year-old girl presented with fevers, joint pain, leukocytosis, and painful, fluctuant skin lesions, preceded by a 2-week history of abdominal cramping and diarrhea. Workup revealed bowel-associated-dermatosis-arthritis syndrome (BADAS) in the setting of ulcerative colitis, a rare finding in the pediatric population.

Dermatology
Ko D, **Wang RF**, **Ozog D**, **Lim HW**, and **Mohammad TF**. Disorders of Hyperpigmentation. Part II. Review of management and treatment options for hyperpigmentation. *J Am Acad Dermatol* 2022; Epub ahead of print. PMID: 35158001. Full Text

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Key challenges in the management of pigmentary disorders such as melasma and post-inflammatory hyperpigmentation (PIH) are their resistance to treatment, tendency to recur after treatment, and the risk of exacerbating hyperpigmentation with many treatment modalities. The second article in this two-part continuing medical education series on pigmentary disorders focuses on the evidence behind medical and procedural treatments of dyschromias, including photoprotection, topical lightening agents, oral agents, chemical peels, and laser therapy.

Dermatology

Post NF, **Ezekwe N**, Narayan VS, Bekkenk MW, Van Geel N, **Hamzavi I**, Passeron T, and Wolkerstorfer A. The use of lasers in vitiligo, an overview. *J Eur Acad Dermatol Venereol* 2022; Epub ahead of print. PMID: 35176186. Full Text

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Various types of lasers have been demonstrated to be effective in the treatment of vitiligo. The mode of action of these lasers is just as varied as the purpose of intervention. Many clinicians are not aware of the unique opportunity these lasers offer to improve the outcomes of vitiligo treatment. To date, no clear overview exists of the use of lasers in vitiligo treatment. Thus, the aim of this review is to discuss the various types of lasers and provide an overview of the evidence for their efficacy. We found good evidence from a systematic review that the excimer laser is effective, induces repigmentation rates comparable to NB-UVB and has improved outcomes when combined with calcineurin inhibitors. Ablative lasers are commonly used for tissue graft or melanocyte-keratinocyte cell graft transplantation. They provide safe, fast and uniform denudation of the epidermis with propitious repigmentation outcomes. We found conflicting evidence from two systematic reviews regarding the efficacy of fractional ablative lasers for improving outcomes of NB-UVB therapy, a systematic review including only fractional ablative lasers provided evidence for efficacy. Q switched nanosecond lasers have shown to be safe and effective for inducing depigmentation, although recurrence is common and most studies were small and retrospective. Despite proven efficacy and safety, laser treatments are relatively expensive and suited for limited body surface areas and selected cases. Each type of laser has benefits and risks associated and should therefore be individually chosen based on location, extent, activity and type of vitiligo.

Dermatology

Wang RF, **Ko D**, **Friedman BJ**, **Lim HW**, and **Mohammad TF**. Disorders of Hyperpigmentation. Part I. Pathogenesis and clinical features of common pigmentary disorders. *J Am Acad Dermatol* 2022; Epub ahead of print. PMID: 35151757. Full Text

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Disorders of hyperpigmentation are common, and depending on the extent and location of involvement, can affect quality of life and pose a significant psychological burden for patients.(1,2) Given the similarities in presentation of various causes of hyperpigmentation, it is often difficult to elucidate the etiology of these conditions, which is important to guide management.(3,4) Furthermore, certain disorders such as lichen planus pigmentosus and ashy dermatosis have similar clinical and/or histologic presentations, and their classification as distinct entities has been debated, leading to additional confusion.(5-7) In this review, the authors have selected commonly encountered disorders of hyperpigmentation of the skin, subdivided into epidermal, dermal, or mixed epidermal-dermal disorders based on the location of pigment deposition. along with disorders of hyperpigmentation of the mucosa and nails. Melanocytic nevi, genetic disorders, and systemic causes of hyperpigmentation were largely

excluded and considered outside the scope of this review. We discuss the pathogenesis of hyperpigmentation, clinical features, and histology of these conditions, along with challenges encountered in diagnosis and classification. The second article in this two-part continuing medical education series focuses on medical and procedural treatments of hyperpigmentation.

Diagnostic Radiology
Hall MM, Allen GM, Allison S, **Craig J**, DeAngelis JP, Delzell PB, Finnoff JT, Frank RM, Gupta A, Hoffman D, Jacobson JA, Narouze S, Nazarian L, Onishi K, Ray JW, Sconfienza LM, Smith J, and Tagliafico A. Recommended musculoskeletal and sports ultrasound terminology: a Delphi-based consensus statement. *Br J Sports Med* 2022; Epub ahead of print. PMID: 35110328. Full Text

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The current lack of agreement regarding standardised terminology in musculoskeletal and sports ultrasound presents challenges in education, clinical practice and research. This consensus was developed to provide a reference to improve clarity and consistency in communication. A multidisciplinary expert panel was convened consisting of 18 members representing multiple specialty societies identified as key stakeholders in musculoskeletal and sports ultrasound. A Delphi process was used to reach consensus, which was defined as group level agreement of >80%. Content was organised into seven general topics including: (1) general definitions, (2) equipment and transducer manipulation, (3) anatomical and descriptive terminology, (4) pathology, (5) procedural terminology, (6) image labelling and (7) documentation. Terms and definitions which reached consensus agreement are presented herein. The historic use of multiple similar terms in the absence of precise definitions has led to confusion when conveying information between colleagues, patients and third-party payers. This multidisciplinary expert consensus addresses multiple areas of variability in diagnostic ultrasound imaging and ultrasound-guided procedures related to musculoskeletal and sports medicine.

Diagnostic Radiology
Hall MM, Allen GM, Allison S, **Craig J**, DeAngelis JP, Delzell PB, Finnoff JT, Frank RM, Gupta A, Hoffman DF, Jacobson JA, Narouze S, Nazarian LN, Onishi K, Ray JW, Sconfienza LM, Smith J, and Tagliafico A. Recommended Musculoskeletal and Sports Ultrasound Terminology: A Delphi-Based Consensus Statement. *J Ultrasound Med* 2022; Epub ahead of print. PMID: 35103998. Full Text

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OBJECTIVES: The current lack of agreement regarding standardized terminology in musculoskeletal and sports ultrasound presents challenges in education, clinical practice, and research. This consensus was developed to provide a reference to improve clarity and consistency in communication. METHODS: A multidisciplinary expert panel was convened consisting of 18 members representing multiple specialty societies identified as key stakeholders in musculoskeletal and sports ultrasound. A Delphi process was used to reach consensus which was defined as group level agreement >80%. RESULTS: Content was organized into seven general topics including: 1) General Definitions, 2) Equipment and Transducer Manipulation, 3) Anatomic and Descriptive Terminology, 4) Pathology, 5) Procedural Terminology, 6) Image Labeling, and 7) Documentation. Terms and definitions which reached consensus agreement are presented herein. CONCLUSIONS: The historic use of multiple similar terms in the absence of precise definitions has led to confusion when conveying information between colleagues, patients, and third-party payers. This multidisciplinary expert consensus addresses multiple areas of variability in diagnostic ultrasound imaging and ultrasound-guided procedures related to musculoskeletal and sports medicine.

Emergency Medicine

Ball MT, Powell JR, Collard L, York DK, and Panchal AR. Administrative and Educational Characteristics of Paramedic Programs in the United States. *Prehosp Disaster Med* 2022; 1-5. Epub ahead of print. PMID: 35105406. Request Article

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INTRODUCTION: Paramedics are a vital component of the Emergency Medical Services (EMS) workforce and the United States health care system. The continued provision of high-quality care

demands constantly improving education at accredited institutions. To date, only limited characteristics of paramedic education in the United States have been documented and studied in the literature. The objective of this study was to describe the educational infrastructure of accredited paramedic programs in the United States in 2018. METHODS: This is a retrospective, cross-sectional evaluation of the 2018 paramedic program annual report from The Committee on Accreditation of Educational Programs for the EMS Professions (CoAEMSP; Rowlett, Texas USA). The dataset includes detailed program metrics. Additionally, questions concerning program characteristics, demographics, and resources were asked as part of the evaluation. Resource availability was assessed via the Resource Assessment Matrix (RAM) with a benchmark of 80%. Included in the analysis are all paramedic programs with students enrolled. Descriptive statistics were calculated (median, [interquartile range/IQR]). RESULTS: A total of 677 programs submitted data (100% response rate). Of these, 626 met inclusion criteria, totaling 17,422 students. Program annual enrollment varied greatly from one to 362 with most programs having small sizes (18 students [IQR 12-30]). Program duration was 12 months [IQR 12-16] with total hours of instruction being approximately 1,174 [IQR 1069-1304], 19% of which were dedicated to clinical experience. Full-time faculty sizes were small (two faculty members [IQR 1-3]) with most programs (80%) having annual operating budgets below USD$500,000. For programs with an annual budget below USD$100,000 (34% of programs), annual enrollment was approximately 14 students [IQR 9-21]. Degrees conferred by programs included certificates (90%), associate degrees (55%), and bachelor's degree (2%). Simulation access was assessed with nearly all (100%) programs reporting simple task trainers and 84% of programs investing in advanced simulation manikins. Seventy-eight percent of programs met the RAM benchmark. CONCLUSION: Most paramedic educational programs in the United States have small annual enrollments with low numbers of dedicated faculty and confer certificates and associate degrees. Nearly one-quarter of paramedic educational programs are not adequately resourced. This study is limited by self-reported data to the national accreditation agency. Future work is needed to identify program characteristics that are associated with high performance.

Emergency Medicine

Horiuchi Y, Wettersten N, van Veldhuisen DJ, Mueller C, Filippatos G, **Nowak R**, Hogan C, Kontos MC, Cannon CM, Müeller GA, Birkhahn R, Taub P, Vilke GM, Barnett O, McDonald K, Mahon N, Nuñez J, Briguori C, Passino C, Duff S, Maisel A, and Murray PT. Decongestion, kidney injury and prognosis in patients with acute heart failure. *Int J Cardiol* 2022; Epub ahead of print. PMID: 35202737. Full Text

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BACKGROUND: In patients with acute heart failure (AHF), the development of worsening renal function with appropriate decongestion is thought to be a benign functional change and not associated with poor prognosis. We investigated whether the benefit of decongestion outweighs the risk of concurrent kidney tubular damage and leads to better outcomes. METHODS: We retrospectively analyzed data from the AKINESIS study, which enrolled AHF patients requiring intravenous diuretic therapy. Urine neutrophil gelatinase-associated lipocalin (uNGAL) and B-type natriuretic peptide (BNP) were serially measured during the hospitalization. Decongestion was defined as ≥30% BNP decrease at discharge compared to admission. Univariable and multivariable Cox models were assessed for one-year mortality. RESULTS: Among 736 patients, 53% had ≥30% BNP decrease at discharge. Levels of uNGAL and BNP at each collection time point had positive but weak correlations ($r \leq 0.133$). Patients without decongestion and with higher discharge uNGAL values had worse one-year mortality, while those with decongestion had better outcomes regardless of uNGAL values (p for interaction 0.018). This interaction was also significant when the change in BNP was analyzed as a continuous variable ($p < 0.001$). Although higher peak and discharge uNGAL were associated with mortality in univariable analysis, only ≥30% BNP decrease was a significant predictor after multivariable adjustment. CONCLUSIONS: Among AHF patients treated with diuretic therapy, decongestion was generally not associated with kidney tubular damage assessed by uNGAL. Kidney tubular damage with adequate decongestion does not impact outcomes; however, kidney injury without adequate decongestion is associated with a worse prognosis.

Emergency Medicine

Koechlin L, Boeddinghaus J, Nestelberger T, Lopez-Ayala P, Shrestha S, Wussler D, Haeni N, Walter JE, Twerenbold R, Eckstein FS, Reuthebuch O, **McCord J**, **Nowak RM**, Christenson RH, DeFilippi CR, Apple FS, and Mueller C. Lower diagnostic accuracy of hs-cTnI in patients with prior coronary artery bypass grafting. *Int J Cardiol* 2022; Epub ahead of print. PMID: 35189168. Full Text

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BACKGROUND: High-sensitivity cardiac troponin T (hs-cTnT) and the ESC 0/1 h-hs-cTnT-algorithm have worse performance in the early diagnosis of myocardial infarction (MI) in patients with prior coronary artery bypass grafting (CABG). It is unknown, whether this concern applies also to hs-cTnI, the most

widely used analyte worldwide. METHODS: In an international multicenter diagnostic study, two cardiologists centrally adjudicated the final diagnosis in patients presenting to the emergency department with symptoms suggestive of MI according to the Third Universal Definition of MI. The objective was to compare the diagnostic accuracy of hs-cTnI assays and their performance within the ESC hs-cTnI 0/1 h-algorithms in patients with versus without prior CABG. Findings were externally validated in an U.S. multicenter diagnostic study. RESULTS: A total of 392/5'200 patients (8%) had prior coronary artery bypass grafting (CABG). Diagnostic accuracy of hs-cTnI as quantified by the area under the receiver-operating characteristics-curve (AUC) in these patients was high, but lower versus patients without prior CABG (e.g. hs-cTnI-Architect 0.91 versus 0.95; p = 0.016). Sensitivity/specificity of rule-out/in by the European Society of Cardiology (ESC) 0/1 h-hs-cTnI-algorithms remained very high [e.g. hs-cTnI-Architect 100% and 93.5%], but efficacy was lower (52% versus 74%, p < 0.01). External validation (n = 2113) confirmed these findings in 192 patients with prior CABG using hs-cTnI-Atellica, with 52% versus 36% (p < 0.001) remaining in the observe zone. CONCLUSIONS: Diagnostic accuracy of hs-cTnI and efficacy of the ESC 0/1 h-hs-cTnI-algorithms are lower in patients with prior CABG, but sensitivity/specificity remain very high. CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/ct2/show/NCT00470587, number NCT00470587.

Emergency Medicine

McCord J, **Gibbs J**, **Hudson M**, **Moyer M**, **Jacobsen G**, Murtagh G, and **Nowak R**. Machine Learning to Assess for Acute Myocardial Infarction within 30 Minutes. *Crit Pathw Cardiol* 2022; Epub ahead of print. PMID: 35190507. Full Text

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Variations in high-sensitivity cardiac troponin I (hs-cTnI) by age and sex along with various sampling times can make the evaluation for acute myocardial infarction (AMI) challenging. Machine learning integrates these variables to allow a more accurate evaluation for possible AMI. The goal was to test the diagnostic and prognostic utility of a machine learning algorithm in the evaluation of possible AMI. We applied a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, sex, and hs-cTnI levels at time 0 and 30 minutes in 529 patients evaluated for possible AMI in a single urban emergency department. MI3 generates an index value from 0-100 reflecting the likelihood of AMI. Patients were followed at 30-45 days for major adverse cardiac events (MACE). There were 42 (7.9%) patients that had an AMI. Patients were divided into 3 groups by the MI3 score: low-risk (≤ 3.13), intermediate-risk (> 3.13-51.0), and high-risk (> 51.0). The sensitivity for AMI was 100% with a MI3 value ≤ 3.13 and 353 (67%) ruled-out for AMI at 30 minutes. At 30-45 days there were 2 (0.6%) MACEs (2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 AMIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 AMIs, 2 cardiac deaths). The MI3 algorithm had 100% sensitivity for AMI at 30 minutes and identified a low-risk cohort who may be considered for early discharge.

Emergency Medicine

Rosario J, Lewiss RE, Stolz LA, Del Rios M, Acuña J, Adhikari S, **Amponsah D**, Dessie AS, Gottlieb M, Huang RD, Jones J, Landry A, Liu RB, Ng L, Panebianco NL, Weekes AJ, and Knight S. Creating a more racial-ethnic inclusive clinical ultrasound community. *Am J Emerg Med* 2022; 54:208-211. PMID: 35176660. Full Text

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Endocrinology and Metabolism

Herrgott GA, **Asmaro KP**, **Wells M**, **Sabedot TS**, **Malta TM**, **Mosella MS**, **Nelson K**, **Scarpace L**, Barnholtz-Sloan JS, Sloan AE, Selman WR, **deCarvalho AC**, **Poisson LM**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Snyder J**, **Walbert T**, **Rosenblum M**, **Mikkelsen T**, **Bhan A**, **Craig J**, **Kalkanis S**, **Rock J**, **Noushmehr H**, and **Castro AV**. Detection of Tumor-specific DNA Methylation Markers in the Blood of Patients with Pituitary Neuroendocrine Tumors. *Neuro Oncol* 2022; Epub ahead of print. PMID: 35212383. Full Text

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BACKGROUND: DNA methylation abnormalities are pervasive in pituitary neuroendocrine tumors (PitNETs). The feasibility to detect methylome alterations in circulating cell-free DNA (cfDNA) has been reported for several central nervous system tumors but not across PitNETs. The aim of the study was to use the liquid biopsy approach to detect PitNET-specific methylation signatures to differentiate these tumors from other sellar diseases. METHOD: We profiled the cfDNA methylome (EPIC array) of 59 serum and 41 plasma liquid biopsy specimens from patients with PitNETs and other CNS diseases (sellar tumors and other pituitary non-neoplastic diseases, lower-grade gliomas and skull base meningiomas) or nontumor conditions, grouped as non-PitNET. RESULTS: Our results indicated that, despite quantitative and qualitative differences between serum and plasma cfDNA composition, both sources of liquid biopsy showed that patients with PitNETs presented a distinct methylome landscape compared to non-PitNETs. In addition, liquid biopsy methylomes captured epigenetic features reported in PitNET tissue and provided information about cell type composition. Using liquid biopsy-derived PitNETs-specific signatures as input to develop machine-learning predictive models, we generated scores which distinguished PitNETs from non-PitNETs conditions, including sellar tumor and non-neoplastic pituitary diseases, with accuracies

above ~93% in independent cohort sets. CONCLUSIONS: Our results underpin the potential application of methylation-based liquid biopsy profiling as a noninvasive approach to identify clinically relevant epigenetic markers to diagnose and potentially impact the prognostication and management of patients with PitNETs.

Gastroenterology
Gordon SC, Teshale EH, Spradling PR, Moorman AC, Boscarino JA, Schmidt MA, Daida YG, **Rupp LB**, **Trudeau S**, **Zhang J**, and **Lu M**. Lower rates of emergency visits and hospitalizations among chronic hepatitis C patients with sustained virological response to interferon-free direct-acting antiviral therapy (2014-2018). *Clin Infect Dis* 2022; Epub ahead of print. PMID: 35147184. Full Text

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We compared rates of emergency department (ED) visits and hospitalizations between HCV patients who achieved sustained virological response (SVR) after direct-acting antiviral (DAA) therapy (cases) to matched controls. Among 3049 pairs, cases demonstrated lower rates of liver-related ED visits (P=.01) than controls; all-cause and liver-related hospitalization rates and hospitalized days were also lower in cases (P<.0001).

Gastroenterology
Ichkhanian Y, Gutierrez OB, Roman S, Yoo IK, Canakis A, Pawa R, Koch K, Su B, Ujiki M, **Alsheik E**, **Zuchelli T**, **Piraka C**, Ghandour B, Zhang L, Sloan JA, and Khashab MA. Role of Functional Luminal Imaging Probe (FLIP) in the Management of post Myotomy Clinical Failure. *Gastrointest Endosc* 2022; Epub ahead of print. PMID: 35149045. Full Text

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INTRODUCTION: Small percentage of patients with esophageal dysmotility disorders (EDD) fail to improve or relapse following management by laparoscopic Heller myotomy (LHM) and peroral endoscopic myotomy (POEM). In this study, we aimed to describe the role of functional luminal imaging probe (FLIP) in identifying the patients who might benefit from LES-directed re-treatment. METHODS: This was a retrospective study at 6 tertiary care centers (4 USA, 1 Europe, 1 Asia) between 01/2015 and 04/2021 involving patients with prior failed myotomy. The primary outcome was the impact of FLIP utilization on

the management of patients with prior failed myotomy. RESULTS: A total of 123 patients [F 62 (50%), mean age 53±21.1 years] who underwent LHM (n=53, 43%) or POEM (n=70, 57%) for the management of achalasia, (n=98) or other EDD (n=25) had clinical failure at a median time of 10.8 (IQR: 0.8-17.3) months post-procedure. A total of 29 patients had apposing "abnormal" diagnoses in terms of integrated relaxation pressure (IRP) > 15mmHg on HRM and distensibility index (DI) < 2.8 mm(2)/mmHg on FLIP, with ultimate change in management noted in 15 patients (10 directed towards conservative management, 5 directed towards LES directed re-treatment). The impact of FLIP on both the diagnosis and management was noted in 15/29 (52%) patients. In the subgroup analysis of patients who underwent LES-directed re-treatment (n=44), clinical success was highest among patients with both abnormal IRP and DI, 21/25 (84%) vs. patients with only abnormal IRP, 8/14 (57%), or only abnormal DI, 3/5 (60%), (p=0.04), with DI at 40 ml distension volume on FLIP identified as an independent predictor of clinical success, (OR 1.51; 95% CI 1.02-2.1, p=0.03). CONCLUSION: The finding of this study further suggests the important role of using FLIP in addition to HRM in evaluating patients with clinical failure post myotomy.

Gastroenterology
Kim WR, Telep LE, Jump B, **Lu M**, Ramroth H, Flaherty J, Gaggar A, Chokkalingam AP, and **Gordon SC**. Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States. *Aliment Pharmacol Ther* 2022; Epub ahead of print. PMID: 35137422. Full Text

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BACKGROUND: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are the first-line treatment agents for chronic hepatitis B virus (HBV). Recently, whether the degree to which the risk of hepatocellular carcinoma (HCC) may be reduced by ETV vs TDF has been debated. We compared the incidence of HCC among treatment-naïve patients receiving TDF vs ETV in the United States. METHODS: From a large administrative medical claims database of commercially insured patients, we identified 166,933 adults with a diagnosis of chronic hepatitis B and a minimum of 12 months of prior enrolment, of whom 3934 and 6127 initiated ETV and TDF respectively. Fine-Gray hazard regression models incorporating treatment propensity scores (PS) were used to estimate the risk of HCC incidence associated with TDF vs ETV; variables considered for adjustment included demographic characteristics, concomitant medication use and baseline comorbidities, as well as competing events including liver transplantation and medication changes. RESULTS: After PS weighting, the TDF and ETV groups were well-matched. During the follow-up, 90 patients developed HCC, including 50 receiving ETV and 40 receiving TDF, giving rise to crude incidence rates of 0.62 per 100 person-years (PY) and 0.30 per 100 PY respectively. In PS-weighted, multivariable analysis, TDF was associated with a subdistribution hazard ratio for HCC of 0.58 (95% confidence interval [CI]: 0.38-0.89) compared to ETV. Results were similar when patients ≥40 years and men and women were analysed separately. CONCLUSION: Among commercially insured, treatment-naïve patients with chronic hepatitis B in the United States, treatment with TDF was associated with significantly lower risk of HCC than ETV.

Gastroenterology
Kitajima T, **Kuno Y**, **Ivanics T**, **Lu M**, **Moonka D**, **Shimada S**, **Shamaa T**, **Abouljoud MS**, and **Nagai S**. Improved Survival With Higher-risk Donor Grafts in Liver Transplant With Acute-on-chronic Liver Failure. *Transplant Direct* 2022; 8(2):e1283. PMID: 35187210. Full Text

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Use of higher-risk grafts in liver transplantation for patients with acute-on-chronic liver failure (ACLF) has been associated with poor outcomes. This study analyzes trends in liver transplantation outcomes for ACLF over time based on the donor risk index (DRI). METHODS: Using the Organ Procurement and

Transplantation Network and the United Network for Organ Sharing registry, 17 300 ACLF patients who underwent liver transplantation between 2002 and 2019 were evaluated. Based on DRI, adjusted hazard ratios for 1-y patient death were analyzed in 3 eras: Era 1 (2002-2007, n = 4032), Era 2 (2008-2013, n = 6130), and Era 3 (2014-2019, n = 7138). DRI groups were defined by DRI <1.2, 1.2-1.6, 1.6-2.0, and >2.0. RESULTS: ACLF patients had significantly lower risks of patient death within 1 y in Era 2 (adjusted hazard ratio, 0.69; 95% confidence interval, 0.61-0.78; P < 0.001) and Era 3 (adjusted hazard ratio, 0.48; 95% confidence interval, 0.42-0.55; P < 0.001) than in Era 1. All DRI groups showed lower hazards in Era 3 than in Era 1. Improvement of posttransplant outcomes were found both in ACLF-1/2 and ACLF-3 patients. In ACLF-1/2, DRI 1.2 to 1.6 and >2.0 had lower adjusted risk in Era 3 than in Era 1. In ACLF-3, DRI 1.2 to 2.0 had lower risk in Era 3. In the overall ACLF cohort, the 2 categories with DRI >1.6 had significantly higher adjusted risks of 1-y patient death than DRI <1.2. When analyzing hazards in each era, DRI > 2.0 carried significantly higher adjusted risks in Eras 1 and 3' whereas DRI 1.2 to 2.0 had similar adjusted risks throughout eras. Similar tendency was found in ACLF-1/2. In the non-ACLF cohort, steady improvement of posttransplant outcomes was obtained in all DRI categories. Similar results were obtained when only hepatitis C virus-uninfected ACLF patients were evaluated. CONCLUSIONS: In ACLF patients, posttransplant outcomes have significantly improved, and outcomes with higher-risk organs have improved in all ACLF grades. These results might encourage the use of higher-risk donors in ACLF patients and provide improved access to transplant.

Gastroenterology

Lim YS, Seto WK, Kurosaki M, Fung S, Kao JH, Hou J, **Gordon SC**, Flaherty JF, Yee LJ, Zhao Y, Agarwal K, and Lampertico P. Review: switching patients with chronic hepatitis B to tenofovir alafenamide-a review of current data. *Aliment Pharmacol Ther* 2022; Epub ahead of print. PMID: 35178711. Full Text

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BACKGROUND: The nucleos(t)ide analogues (NAs) entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are preferred treatment options for patients with chronic hepatitis B infection (CHB). However, resistance to ETV has been reported, especially with prior exposure to other NAs, and long-term TDF treatment has been associated with decline in renal function and loss of bone mineral density in some patients. Consequently, TAF may be preferable to ETV, TDF or other NAs in specific circumstances such as in patients with risk of bone or renal complications, elderly patients or those with previous NA experience. AIM: To provide a summary of the available efficacy and safety data following switch to TAF from other NAs in patients with CHB in clinical studies and real-world settings. METHODS: Literature searches were performed on PubMed and abstracts from three major international liver congresses between 2019 and 2021. Studies that included efficacy and/or safety data for patients with CHB switching from any NA to TAF were selected. RESULTS: Thirty-six papers and abstracts were included in this narrative review. Switching from TDF to TAF maintained or improved virological and biochemical responses with improved bone and renal safety. Switching from ETV or other NAs to TAF maintained or improved virological and biochemical responses and varying results for bone and renal safety. CONCLUSIONS: Switching to TAF appears to maintain or improve virological, biochemical and bone- and renal-related safety outcomes. These data support the concept of switching to TAF in some patients with CHB based on their individual circumstances.

Gastroenterology

Montano-Loza AJ, Ronca V, Ebadi M, Hansen BE, Hirschfield G, Elwir S, Alsaed M, Milkiewicz P, Janik MK, Marschall HU, Burza MA, Efe C, Calışkan AR, Harputluoglu M, Kabaçam G, Terrabuio D, de Quadros Onofrio F, Selzner N, Bonder A, Parés A, Llovet L, Akyıldız M, Arikan C, Manns MP, Taubert R, Weber AL, Schiano TD, Haydel B, Czubkowski P, Socha P, Ołdak N, Akamatsu N, Tanaka A, Levy C, Martin EF, Goel A, Sedki M, Jankowska I, Ikegami T, Rodriguez M, Sterneck M, Weiler-Normann C, Schramm C, Donato MF, Lohse A, Andrade RJ, Patwardhan VR, van Hoek B, Biewenga M, Kremer AE, Ueda Y, Deneau M, Pedersen M, Mayo MJ, Floreani A, Burra P, Secchi MF, Beretta-Piccoli BT, Sciveres M, Maggiore G, **Jafri SM**, Debray D, Girard M, Lacaille F, Lytvyak E, Mason AL, Heneghan M, and Oo YH. Risk factors and outcomes associated with recurrent autoimmune hepatitis following liver transplantation. *J Hepatol* 2022; Epub ahead of print. PMID: 35143897. Full Text

BACKGROUND & AIMS: The impact of recurrent autoimmune hepatitis (AIH) post-liver transplant on patient and graft survival is not well characterised. We evaluated a large, international multi-center cohort to identify the probability and risk factors associated with recurrent AIH and the association between recurrent disease and patient and graft survival. METHODS: We included 736 patients (77% female, mean age, 42±1 years) with AIH who underwent LT from January 1987 through June 2020, among 33 centers in North America, South America, Europe and Asia. Clinical data before and after LT, biochemical data within the first 12 months after LT, and immunosuppression after LT were analyzed to identify patients with higher risk of recurrence of AIH based on histological diagnosis. RESULTS: AIH recurred in 20% of patients after 5 years and 31% after 10 years. Age at LT ≤42 years (HR, 3.15; 95% CI, 1.22-8.16; p=0.02), use of mycophenolate mofetil post-LT (HR, 3.06; 95% CI, 1.39-6.73; p=0.005), donor and recipient sex mismatch (HR, 2.57; 95% CI, 1.39-4.76; p=0.003) and high IgG pre-LT (HR, 1.04; 95% CI, 1.01-1.06; p=0.004) were associated with higher risk of AIH recurrence after adjusting for other confounders. In multivariate Cox regression with time-dependent covariate, recurrent AIH significantly associated with graft loss (HR, 10.79, 95% CI 5.37-21.66, p<0.001) and death (HR, 2.53, 95% CI 1.48-4.33, p=0.001). CONCLUSION: Recurrence of AIH following transplant is frequent and is associated with younger age at LT, use of mycophenolate mofetil post-LT, sex mismatch and high IgG pre-LT. We demonstrate an association between disease recurrence and impaired graft and overall survival in patients with AIH, highlighting ongoing efforts to better characterize, prevent and treat recurrent AIH. LAY ABSTRACT: Recurrent autoimmune hepatitis following liver transplant is frequent and is associated with some recipient features and the type of antirejection medications. Recurrent autoimmune hepatitis negatively affects the outcome after liver transplant.

Gastroenterology

Nagai S, Nallabasannagari AR, **Moonka D**, Reddiboina M, **Yeddula S**, **Kitajima T**, **Francis I**, and **Abouljoud M**. Use of Neural Network Models to Predict Liver Transplant Waitlist Mortality. *Liver Transpl* 2022; Epub ahead of print. PMID: 35224855. Full Text

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Current liver transplant (LT) organ allocation relies on MELD-Na scores to predict mortality in patients awaiting LT. This study aims to develop Neural Network (NN) models that more accurately predict LT waitlist mortality. The study evaluates patients listed for LT between February 27(th) , 2002 and June 30(th) , 2021 using the OPTN/UNOS registry. We excluded patients listed with MELD exception scores and those listed for multi-organ transplant, except for liver-kidney transplant. Subset of data from the waitlist was used to create a mortality prediction model at 90 days after listing with 105,140 patients. A total of 28 variables were selected for model creation. The data was split using random sampling into training, validation, and test datasets in a 60:20:20 ratio. The performance of the model was assessed using Area Under Receiver Operating Curve (AUC-ROC) and Area Under Precision-Recall curve (PR-AUC). AUC-ROC for 90-Day mortality was 0.936 (0.934-0.937, 95% CI), and PR-AUC was 0.758 (0.754-0.762, 95% CI). The NN 90-Day Mortality model outperformed MELD-based models for both AUC-ROC and PR-AUC. The 90-Day Mortality model specifically identified more waitlist deaths with a

higher Recall (Sensitivity) of 0.807 (0.803-0.811, 95% CI) vs 0.413 (0.409 - 0.418, 95% CI) (P<0.001). The performance metrics were compared by breaking the test dataset into multiple patient subsets by Ethnicity, Gender, Region, Age, Diagnosis Group, and Year of listing. The NN 90-Day Mortality model outperformed MELD-based models across all subsets in predicting mortality. In conclusion, organ allocation based on NN modeling has the potential to decrease waitlist mortality and lead to more equitable allocation systems in LT.

Gastroenterology
Rehana RW, **Fahad H**, **Sadiq O**, and **Schairer J**. Outcomes of Gastrointestinal Bleeding During the COVID-19 Pandemic. *Gastro Hep Adv* 2022; Epub ahead of print. PMID: 35174367. Full Text

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Gastroenterology
Shimada S, **Ivanics T**, **Kitajima T**, **Shamaa T**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, **Moonka D**, **Zhang J**, **Lu M**, and **Nagai S**. Improvements in liver transplant outcomes in patients with HCV/HIV coinfection after the introduction of direct-acting antiviral therapies. *Transpl Infect Dis* 2022; e13808. Epub ahead of print. PMID: 35157334. Full Text

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan, USA.
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BACKGROUND: In recipients with HCV/HIV coinfection, the impact that the wider use of direct-acting antivirals (DAAs) has had on post-liver transplant (LT) outcomes has not been evaluated. We investigated the impact of DAAs introduction on post-LT outcome in patients with HCV/HIV coinfection. METHODS: Using Organ Procurement and Transplant Network/United Network for Organ Sharing data, we compared post-LT outcomes in patients with HCV and/or HIV pre- and post-DAAs introduction. We categorized these patients into two eras: pre-DAA (2008-2012 [pre-DAA era]) and post-DAA (2014-2019 [post-DAA era]). To study the impact of DAAs introduction, inverse probability of treatment weighting was used to adjust patient characteristics. RESULTS: A total of 17 215 LT recipients were eligible for this study (HCV/HIV [n = 160]; HIV mono-infection [n = 188]; HCV mono-infection [n = 16 867]). HCV/HIV coinfection and HCV mono-infection had a significantly lower hazard of 1- and 3-year graft loss post-DAA, compared pre-DAA (1-year: adjusted hazard ratio [aHR] 0.29, 95% confidence interval (CI) 0.16-0.53 in HIV/HCV, aHR 0.58, 95% CI 0.54-0.63, respectively; 3-year: aHR 0.30, 95% CI 0.14-0.61, aHR 0.64, 95% CI 0.58-0.70, respectively). The hazards of 1- and 3-year graft loss post-DAA in HIV mono-infection were comparable to those in pre-DAA. HCV/HIV coinfection had significantly lower patient mortality post-DAA, compared to pre-DAA (1-year: aHR 0.30, 95% CI 0.17-0.55; 3-year: aHR 0.31, 95% CI 0.15-0.63). CONCLUSIONS: Post-LT outcomes in patients with coinfection significantly improved and became comparable to those with HCV mono-infection after introducing DAA therapy. The introduction of DAAs supports the use of LT in the setting of HCV/HIV coinfection.

Gastroenterology
Shimada S, **Kitajima T**, **Suzuki Y**, **Kuno Y**, **Shamaa T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, **Moonka D**, and **Nagai S**. Impact on Waitlist Outcomes from Changes in the Medical Eligibility of Candidates for Simultaneous Liver-Kidney Transplantation Following Implementation of the 2017 Organ Procurement and Transplantation Network/United Network for Organ Sharing Policy in the United States. *Ann Transplant* 2022; 27. PMID: 35177580. Full Text

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BACKGROUND The new simultaneous liver-kidney transplantation (SLK) listing criteria in the United States was implemented in 2017. We aimed to investigate the impact on waitlist and post-transplantation

outcomes from changes in the medical eligibility of candidates for SLK after policy implementation in the United States. MATERIAL AND METHODS We analyzed adult primary SLK candidates between January 2015 and March 2019 using the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) registry. We compared waitlist practice, post-transplantation outcomes, and final transplant graft type in SLK candidates before and after the policy. RESULTS A total of 4641 patients were eligible, with 2975 and 1666 registered before and after the 2017 policy, respectively. The daily number of SLK candidates was lower after the 2017 policy (3.25 vs 2.89, P=0.01); 1956 received SLK and 95 received liver transplant alone (LTA). The proportion of patients who eventually received LTA was higher after the 2017 policy (7.9% vs 3.0%; P<0.001). The 1-year graft survival rate was worse in patients with LTA than in those with SLK (80.5% vs 90.4%; P=0.003). The adjusted risk of 1-year graft failure in patients with LTA was 2.01 (95% confidence interval 1.13-3.58, P=0.01) compared with patients with SLK among the SLK candidates. CONCLUSIONS Although the number of registrations for SLK increased, the number of SLK transplants decreased, and the number of liver transplants increased. LTA in this patient cohort was associated with worse post-transplantation outcomes.

Hematology-Oncology

Elkrief A, Hennessy C, Kuderer NM, Rubinstein SM, Wulff-Burchfield E, Rosovsky RP, Vega-Luna K, Thompson MA, Panagiotou OA, Desai A, Rivera DR, Khaki AR, Tachiki L, Lynch RC, Stratton C, Elias R, Batist G, Kasi A, Shah DP, Bakouny Z, Cabal A, Clement J, Crowell J, Dixon B, Friese CR, Fry SL, Grover P, Gulati S, Gupta S, **Hwang C**, Khan H, Kim SJ, Klein EJ, Labaki C, McKay RR, Nizam A, Pennell NA, Puc M, Schmidt AL, Shahrokni A, Shaya JA, Su CT, Wall S, Williams N, Wise-Draper TM, Mishra S, Grivas P, French B, Warner JL, and Wildes TM. Geriatric risk factors for serious COVID-19 outcomes among older adults with cancer: a cohort study from the COVID-19 and Cancer Consortium. *Lancet Healthy Longev* 2022; Epub ahead of print. PMID: 35187516. Full Text

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BACKGROUND: Older age is associated with poorer outcomes of SARS-CoV-2 infection, although the heterogeneity of ageing results in some older adults being at greater risk than others. The objective of this study was to quantify the association of a novel geriatric risk index, comprising age, modified Charlson comorbidity index, and Eastern Cooperative Oncology Group performance status, with COVID-19 severity and 30-day mortality among older adults with cancer. METHODS: In this cohort study, we enrolled patients aged 60 years and older with a current or previous cancer diagnosis (excluding those with non-invasive cancers and premalignant or non-malignant conditions) and a current or previous laboratory-confirmed COVID-19 diagnosis who reported to the COVID-19 and Cancer Consortium (CCC19) multinational, multicentre, registry between March 17, 2020, and June 6, 2021. Patients were also excluded for unknown age, missing data resulting in unknown geriatric risk measure, inadequate data quality, or incomplete follow-up resulting in unknown COVID-19 severity. The exposure of interest was the CCC19 geriatric risk index. The primary outcome was COVID-19 severity and the secondary outcome was 30-day all-cause mortality; both were assessed in the full dataset. Adjusted odds ratios (ORs) and 95% CIs were estimated from ordinal and binary logistic regression models. FINDINGS: 5671 patients with cancer and COVID-19 were included in the analysis. Median follow-up time was 56 days (IQR 22-120), and median age was 72 years (IQR 66-79). The CCC19 geriatric risk index identified 2365 (41·7%) patients as standard risk, 2217 (39·1%) patients as intermediate risk, and 1089 (19·2%) as high risk. 36 (0·6%) patients were excluded due to non-calculable geriatric risk index. Compared with standard-risk patients, high-risk patients had significantly higher COVID-19 severity (adjusted OR 7·24; 95% CI 6·20-8·45). 920 (16·2%) of 5671 patients died within 30 days of a COVID-19 diagnosis, including 161 (6·8%) of 2365 standard-risk patients, 409 (18·5%) of 2217 intermediate-risk patients, and 350 (32·1%) of 1089 high-risk patients. High-risk patients had higher adjusted odds of 30-day mortality (adjusted OR 10·7; 95% CI 8·54-13·5) than standard-risk patients. INTERPRETATION: The CCC19 geriatric risk index was strongly associated with COVID-19 severity and 30-day mortality. Our CCC19 geriatric risk index, based on readily available clinical factors, might provide clinicians with an easy-to-use risk stratification method to identify older adults most at risk for severe COVID-19 as well as mortality. FUNDING: US National Institutes of Health National Cancer Institute Cancer Center.

Hematology-Oncology

Gierach GL, Sak M, Fan S, Pfeiffer RM, Palakal M, Ramin C, Bey-Knight L, Simon MS, Gorski D, **Ali H**, Littrup P, Sherman ME, and Duric N. Rapid Reductions in Breast Density following Tamoxifen Therapy as Evaluated by Whole-Breast Ultrasound Tomography. *J Clin Med* 2022; 11(3). PMID: 35160244. Full Text

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PURPOSE: Women whose mammographic breast density declines within 12-18 months of initiating tamoxifen for chemoprevention or adjuvant treatment show improved therapeutic responses compared with those whose density is unchanged. We tested whether measuring changes in sound speed (a surrogate of breast density) using ultrasound tomography (UST) could enable rapid identification of favorable responses to tamoxifen. METHODS: We evaluated serial density measures at baseline and at 1 to 3, 4 to 6, and 12+ months among 74 women (aged 30-70 years) following initiation of tamoxifen for clinical indications, including an elevated risk of breast cancer (20%) and diagnoses of in situ (39%) or invasive (40%) breast carcinoma, enrolled at Karmanos Cancer Institute and Henry Ford Health System (Detroit, MI, USA). For comparison, we evaluated an untreated group with screen negative mammography and frequency-matched on age, race, and menopausal status (n = 150), at baseline and 12 months. Paired t-tests were used to assess differences in UST sound speed over time and between tamoxifen-treated and untreated patients. RESULTS: Sound speed declined steadily over the 12 month

period among patients receiving tamoxifen (mean (SD): -3.0 (8.2) m/s; p = 0.001), whereas density remained unchanged in the untreated group (mean (SD): 0.4 (7.1) m/s; p = 0.75 (relative change between groups: p = 0.0009)). In the tamoxifen group, we observed significant sound speed reductions as early as 4-6 months after tamoxifen initiation (mean (SD): -2.1 (6.8) m/s; p = 0.008). Sound speed reductions were greatest among premenopausal patients (P-interaction = 0.0002) and those in the middle and upper tertiles of baseline sound speed (P-interaction = 0.002). CONCLUSIONS: UST can image rapid declines in sound speed following initiation of tamoxifen. Given that sound speed and mammographic density are correlated, we propose that UST breast imaging may capture early responses to tamoxifen, which in turn may have utility in predicting therapeutic efficacy.

Hematology-Oncology

Ou SI, Jänne PA, Leal TA, **Rybkin, II**, Sabari JK, Barve MA, Bazhenova LA, Johnson ML, Velastegui KL, Cilliers C, Christensen JG, Yan X, Chao RC, and Papadopoulos KP. First-in-Human Phase I/IB Dose-Finding Study of Adagrasib (MRTX849) in Patients With Advanced KRAS(G12C) Solid Tumors (KRYSTAL-1). *J Clin Oncol* 2022; Epub ahead of print. PMID: 35167329. Full Text

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Mary Crowley Cancer Center, Dallas, TX.
University of California San Diego, Moores Cancer Center, La Jolla, CA.
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PURPOSE: Adagrasib (MRTX849) is an oral, highly selective, small-molecule, covalent inhibitor of KRAS(G12C). We report results from a phase I/IB study of adagrasib in non-small-cell lung cancer, colorectal cancer, and other solid tumors harboring the KRAS(G12C) mutation. MATERIALS AND METHODS: Patients with advanced KRAS(G12C)-mutant solid tumors were treated with adagrasib 150 mg orally once daily, 300 mg once daily, 600 mg once daily, 1,200 mg once daily, or 600 mg orally twice a day using an accelerated titration design, which transitioned to a modified toxicity probability interval design when a predefined degree of toxicity was observed or target adagrasib exposure was achieved. Safety, pharmacokinetics, and clinical activity were evaluated. RESULTS: Twenty-five patients were enrolled and received at least one dose of adagrasib. The recommended phase II dose (RP2D) was 600 mg twice a day on the basis of safety, tolerability, and observed pharmacokinetics properties. No maximum tolerated dose was formally defined. After a median follow-up of 19.6 months, eight of 15 patients (53.3%; 95% CI, 26.6 to 78.7) with RECIST-evaluable KRAS(G12C)-mutant non-small-cell lung cancer treated at 600 mg twice a day achieved a confirmed partial response. The median duration of response was 16.4 months (95% CI, 3.1 to not estimable). The median progression-free survival was 11.1 months (95% CI, 2.6 to not estimable). One of two patients with KRAS(G12C)-mutant colorectal cancer treated at 600 mg twice a day achieved a partial response (duration of response, 4.2 months). At the RP2D, the most common treatment-related adverse events (any grade) were nausea (80.0%), diarrhea (70.0%), vomiting (50.0%), and fatigue (45.0%). The most common grade 3-4 treatment-related adverse event was fatigue (15.0%). CONCLUSION: Adagrasib 600 mg twice a day was well tolerated and exhibited antitumor activity in patients with advanced solid tumors harboring the KRAS(G12C) mutation.

Hematology-Oncology

Satyanarayana G, Enriquez KT, Sun T, Klein EJ, Abidi M, Advani SM, Awosika J, Bakouny Z, Bashir B, Berg S, Bernardes M, Egan PC, Elkrief A, Feldman LE, Friese CR, Goel S, Gomez CG, Grant KL, Griffiths EA, Gulati S, Gupta S, **Hwang C**, Jain J, Jani C, Kaltsas A, Kasi A, Khan H, Knox N, Koshkin VS, Kwon DH, Labaki C, Lyman GH, McKay RR, McNair C, Nagaraj G, Nakasone ES, Nguyen R, Nonato TK, Olszewski AJ, Panagiotou OA, Puc M, Razavi P, Robilotti EV, Santos-Dutra M, Schmidt AL, Shah DP, Shah SA, Vieira K, Weissmann LB, Wise-Draper TM, Wu U, Wu JT, Choueiri TK, Mishra S, Warner JL,

French B, and Farmakiotis D. Coinfections in Patients With Cancer and COVID-19: A COVID-19 and Cancer Consortium (CCC19) Study. *Open Forum Infect Dis* 2022; 9(3). PMID: 35198648. Full Text

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Loma Linda University Cancer Center, Loma Linda, California, USA.
Virtua Health, Mt. Holly, New Jersey, USA.
Mays Cancer Center at UT Health San Antonio MD Anderson Cancer Center, San Antonio, Texas, USA.
Stanford Cancer Institute at Stanford University, Stanford, California, USA.

BACKGROUND: The frequency of coinfections and their association with outcomes have not been adequately studied among patients with cancer and coronavirus disease 2019 (COVID-19), a high-risk group for coinfection. METHODS: We included adult (≥18 years) patients with active or prior hematologic or invasive solid malignancies and laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection, using data from the COVID-19 and Cancer Consortium (CCC19, NCT04354701). We captured coinfections within ±2 weeks from diagnosis of COVID-19, identified factors cross-sectionally associated with risk of coinfection, and quantified the association of coinfections with 30-day mortality. RESULTS: Among 8765 patients (hospitalized or not; median age, 65 years; 47.4% male), 16.6% developed coinfections: 12.1% bacterial, 2.1% viral, 0.9% fungal. An additional 6.4% only had clinical diagnosis of a coinfection. The adjusted risk of any coinfection was positively associated with age >50 years, male sex, cardiovascular, pulmonary, and renal comorbidities, diabetes, hematologic malignancy, multiple malignancies, Eastern Cooperative Oncology Group Performance Status, progressing cancer, recent cytotoxic chemotherapy, and baseline corticosteroids; the adjusted risk of superinfection was positively associated with tocilizumab administration. Among hospitalized patients, high neutrophil count and C-reactive protein were positively associated with bacterial coinfection risk, and high or low neutrophil count with fungal coinfection risk. Adjusted mortality rates were significantly higher among patients with bacterial (odds ratio [OR], 1.61; 95% CI, 1.33-1.95) and fungal (OR, 2.20; 95% CI, 1.28-3.76) coinfections. CONCLUSIONS: Viral and fungal coinfections are infrequent among patients with cancer and COVID-19, with the latter associated with very high mortality rates. Clinical and laboratory parameters can be used to guide early empiric antimicrobial therapy, which may improve clinical outcomes.

Hospital Medicine

Angelini DE, **Kaatz S**, Rosovsky RP, Zon RL, **Pillai S**, Robertson WE, Elavalakanar P, Patell R, and Khorana A. COVID-19 and venous thromboembolism: A narrative review. *Res Pract Thromb Haemost* 2022; 6(2):e12666. PMID: 35224417. Full Text

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COVID-19 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) is associated with coagulopathy through numerous mechanisms. The reported incidence of venous thromboembolism (VTE) in hospitalized patients with COVID-19 has varied widely, and several meta-analyses have been performed to assess the overall prevalence of VTE. The novelty of this coronavirus strain along with its unique mechanisms for microvascular and macrovascular thrombosis has led to uncertainty as to how to diagnose, prevent, and treat thrombosis in patients affected by this virus. This review discusses the epidemiology and pathophysiology of thrombosis in the setting of SARS-CoV-2 infection along with an updated review on the preventative and treatment strategies for VTE associated with SARS-CoV-2 infection.

Infectious Diseases

Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, Brown SM, Knowlton KU, Self WH, Files DC, Jain MK, Benfield T, Bowdish ME, Leshnower BG, Baker JV, Jensen JU, Gardner EM, Ginde AA, Harris ES, Johansen IS, **Markowitz N**, Matthay MA, Østergaard L, Chang CC, Goodman AL, Chang W, Dewar RL, Gerry NP, Higgs ES, Highbarger H, Murray DD, Murray TA, Natarajan V, Paredes R, Parmar MKB, Phillips AN, Reilly C, Rupert AW, Sharma S, Shaw-Saliba K, Sherman BT, Teitelbaum M, Wentworth D, Cao H, Klekotka P, Babiker AG, Davey VJ, Gelijns AC, Kan VL, Polizzotto MN, Thompson BT, Lane HC, and Neaton JD. Responses to a Neutralizing Monoclonal Antibody for Hospitalized Patients With COVID-19 According to Baseline Antibody and Antigen Levels : A Randomized Controlled Trial. *Ann Intern Med* 2022; 175(2):234-243. PMID: 34928698. Full Text

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BACKGROUND: In a randomized, placebo-controlled, clinical trial, bamlanivimab, a SARS-CoV-2-neutralizing monoclonal antibody, given in combination with remdesivir, did not improve outcomes among hospitalized patients with COVID-19 based on an early futility assessment. OBJECTIVE: To evaluate the a priori hypothesis that bamlanivimab has greater benefit in patients without detectable levels of endogenous neutralizing antibody (nAb) at study entry than in those with antibodies, especially if viral levels are high. DESIGN: Randomized, placebo-controlled trial. (ClinicalTrials.gov: NCT04501978). SETTING: Multicenter trial. PATIENTS: Hospitalized patients with COVID-19 without end-organ failure. INTERVENTION: Bamlanivimab (7000 mg) or placebo. MEASUREMENTS: Antibody, antigen, and viral RNA levels were centrally measured on stored specimens collected at baseline. Patients were followed for 90 days for sustained recovery (defined as discharge to home and remaining home for 14 consecutive days) and a composite safety outcome (death, serious adverse events, organ failure, or serious infections). RESULTS: Among 314 participants (163 receiving bamlanivimab and 151 placebo), the median time to sustained recovery was 19 days and did not differ between the bamlanivimab and placebo

groups (subhazard ratio [sHR], 0.99 [95% CI, 0.79 to 1.22]; sHR > 1 favors bamlanivimab). At entry, 50% evidenced production of anti-spike nAbs; 50% had SARS-CoV-2 nucleocapsid plasma antigen levels of at least 1000 ng/L. Among those without and with nAbs at study entry, the sHRs were 1.24 (CI, 0.90 to 1.70) and 0.74 (CI, 0.54 to 1.00), respectively (nominal P for interaction = 0.018). The sHR (bamlanivimab vs. placebo) was also more than 1 for those with plasma antigen or nasal viral RNA levels above median level at entry and was greatest for those without antibodies and with elevated levels of antigen (sHR, 1.48 [CI, 0.99 to 2.23]) or viral RNA (sHR, 1.89 [CI, 1.23 to 2.91]). Hazard ratios for the composite safety outcome (<1 favors bamlanivimab) also differed by serostatus at entry: 0.67 (CI, 0.37 to 1.20) for those without and 1.79 (CI, 0.92 to 3.48) for those with nAbs. LIMITATION: Subgroup analysis of a trial prematurely stopped because of futility; small sample size; multiple subgroups analyzed. CONCLUSION: Efficacy and safety of bamlanivimab may differ depending on whether an endogenous nAb response has been mounted. The limited sample size of the study does not allow firm conclusions based on these findings, and further independent trials are required that assess other types of passive immune therapies in the same patient setting. PRIMARY FUNDING SOURCE: U.S. government Operation Warp Speed and National Institute of Allergy and Infectious Diseases.

Internal Medicine

Rehana RW, **Fahad H**, **Sadiq O**, and **Schairer J**. Outcomes of Gastrointestinal Bleeding During the COVID-19 Pandemic. *Gastro Hep Adv* 2022; Epub ahead of print. PMID: 35174367. Full Text

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Nephrology

Novak JE, and Ellison DH. Diuretics in States of Volume Overload: Core Curriculum 2022. *Am J Kidney Dis* 2022; Epub ahead of print. PMID: 35190215. Full Text

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Volume overload, defined as excess total body sodium and water with expansion of extracellular fluid volume, characterizes common disorders such as congestive heart failure, end-stage liver disease, chronic kidney disease, and nephrotic syndrome. Diuretics are the cornerstone of therapy for volume overload and comprise several classes whose mechanisms of action, pharmacokinetics, indications, and adverse effects are essential principles of nephrology. Loop diuretics are typically the first-line treatment in the management of hypervolemia, with additional drug classes indicated in cases of diuretic resistance and electrolyte or acid-base disorders. Separately, clinical trials highlight improved outcomes in some states of volume overload, such as loop diuretics and sodium/glucose cotransporter 2 inhibitors in patients with congestive heart failure. Resistance to diuretics is a frequent, multifactorial clinical challenge that requires creative and physiology-based solutions. In this installment of AJKD's Core Curriculum in Nephrology, we discuss the pharmacology and therapeutic use of diuretics in states of volume overload and strategies to overcome diuretic resistance.

Nephrology

Sohaney R, Yin H, Shahinian V, Saran R, Burrows NR, Pavkov ME, Banerjee T, Hsu CY, Powe N, Steffick D, Zivin K, and Heung M. In-Hospital and 1-Year Mortality Trends in a National Cohort of US Veterans with Acute Kidney Injury. *Clin J Am Soc Nephrol* 2022; 17(2):184-193. PMID: 35131927. Full Text

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BACKGROUND AND OBJECTIVES: AKI, a frequent complication among hospitalized patients, confers excess short- and long-term mortality. We sought to determine trends in in-hospital and 1-year mortality associated with AKI as defined by Kidney Disease Improving Global Outcomes consensus criteria. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: This retrospective cohort study used data from the national Veterans Health Administration on all patients hospitalized from October 1, 2008 to September 31, 2017. AKI was defined by Kidney Disease Improving Global Outcomes serum creatinine criteria. In-hospital and 1-year mortality trends were analyzed in patients with and without AKI using Cox regression with year as a continuous variable. RESULTS: We identified 1,688,457 patients and 2,689,093 hospitalizations across the study period. Among patients with AKI, 6% died in hospital, and 28% died within 1 year. In contrast, in-hospital and 1-year mortality rates were 0.8% and 14%, respectively, among non-AKI hospitalizations. During the study period, there was a slight decline in crude in-hospital AKI-associated mortality (hazard ratio, 0.98 per year; 95% confidence interval, 0.98 to 0.99) that was attenuated after accounting for patient demographics, comorbid conditions, and acute hospitalization characteristics (adjusted hazard ratio, 0.99 per year; 95% confidence interval, 0.99 to 1.00). This stable temporal trend in mortality persisted at 1 year (adjusted hazard ratio, 1.00 per year; 95% confidence interval, 0.99 to 1.00). CONCLUSIONS: AKI associated mortality remains high, as greater than one in four patients with AKI died within 1 year of hospitalization. Over the past decade, there seems to have been no significant progress toward improving in-hospital or long-term AKI survivorship.

Neurology

Ding G, **Li L**, **Zhang L**, **Chopp M**, **Davoodi-Bojd E**, **Li Q**, **Li C**, **Wei M**, **Zhang Z**, and **Jiang Q**. MRI Metrics of Cerebral Endothelial Cell Derived Exosomes for the Treatment of Cognitive Dysfunction Induced in Ageing Rats Subjected to Type-2 Diabetes. *Diabetes* 2022; Epub ahead of print. PMID: 35175337. Full Text

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Ongoing neurovascular dysfunction contributes to type-2 diabetes mellitus (T2DM) induced cognitive deficits. However, it is not known whether early post onset of T2DM interventions may reduce evolving neurovascular dysfunction and thereby lead to diminution of T2DM induced cognitive deficits. Using multiple MRI metrics, we evaluated neurovascular changes in T2DM rats treated with exosomes derived from cerebral endothelial cells (CEC-Exos). Two months after induction of T2DM in middle age male rats by administration of streptozotocin-nicotinamide, rats were randomly treated with CEC-Exos or saline for 4 consecutive weeks (n=10/group). MRI measurements were performed at the end of the treatment, which included CBF, contrast enhanced T1-weighted imaging, and relaxation time constants T1 and T2. MRI analysis showed that compared with the controls, the CEC-Exo treated T2DM rats exhibited significant elevation of T2 and CBF in white matter and significant augmentation of T1 and reduction of BBB permeability in gray matter. In the hippocampus, CEC-Exo treatment significantly increased T1 and CBF. Furthermore, CEC-Exo treatment significantly reduced T2DM-induced cognitive deficits measured by the Morris water maze and odor recognition tests. Collectively, our corresponding MRI data demonstrate that treatment of T2DM rats with CEC-Exos robustly reduced neurovascular dysfunction in gray and white matter, and the hippocampus.

Neurology

Minen MT, Khanns D, Guiracocha J, Ehrlich A, Khan FA, **Ali AS**, Birlea M, Singh NN, Peretz A, and Larry Charleston IV. The role of urgent care centers in headache management: a quality improvement project. *BMC Health Serv Res* 2022; 22(1):162. PMID: 35135555. Full Text

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BACKGROUND: Patients with headache often seek urgent medical care to treat pain and associated symptoms that do not respond to therapeutic options at home. Urgent Cares (UCs) may be suitable for the evaluation and treatment of such patients but there is little data on how headache is evaluated in UC settings and what types of treatments are available. We conducted a study to evaluate the types of care available for patients with headache presenting to UCs. DESIGN: Cross-Sectional. METHODS: Headache specialists across the United States contacted UCs to collect data on a questionnaire. Questions asked about UC staffing (e.g. number and backgrounds of staff, hours of operation), average length of UC visits for headache, treatments and tests available for patients presenting with headache, and disposition including to the ED. RESULTS: Data from 10 UC programs comprised of 61 individual UC sites revealed: The vast majority (8/10; 80%) had diagnostic testing onsite for headache evaluation. A small majority (6/10; 60%) had the American Headache Society recommended intravenous medications for acute migraine available. Half (5/10) had a headache protocol in place. The majority (6/10; 60%) had no follow up policy after UC discharge. CONCLUSIONS: UCs have the potential to provide expedited care for patients presenting for evaluation and treatment of headache. However, considerable variability exists amongst UCs in their abilities to manage headaches. This study reveals many opportunities for future research including the development of protocols and professional partnerships to help guide the evaluation, triage, and treatment of patients with headache in UC settings.

Neurosurgery

Herrgott GA, **Asmaro KP**, **Wells M**, **Sabedot TS**, **Malta TM**, **Mosella MS**, **Nelson K**, **Scarpace L**, Barnholtz-Sloan JS, Sloan AE, Selman WR, **deCarvalho AC**, **Poisson LM**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Snyder J**, **Walbert T**, **Rosenblum M**, **Mikkelsen T**, **Bhan A**, **Craig J**, **Kalkanis S**, **Rock J**, **Noushmehr H**, and **Castro AV**. Detection of Tumor-specific DNA Methylation Markers in the Blood of Patients with Pituitary Neuroendocrine Tumors. *Neuro Oncol* 2022; Epub ahead of print. PMID: 35212383. Full Text

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BACKGROUND: DNA methylation abnormalities are pervasive in pituitary neuroendocrine tumors (PitNETs). The feasibility to detect methylome alterations in circulating cell-free DNA (cfDNA) has been reported for several central nervous system tumors but not across PitNETs. The aim of the study was to use the liquid biopsy approach to detect PitNET-specific methylation signatures to differentiate these tumors from other sellar diseases. METHOD: We profiled the cfDNA methylome (EPIC array) of 59 serum and 41 plasma liquid biopsy specimens from patients with PitNETs and other CNS diseases (sellar tumors and other pituitary non-neoplastic diseases, lower-grade gliomas and skull base meningiomas) or nontumor conditions, grouped as non-PitNET. RESULTS: Our results indicated that, despite quantitative and qualitative differences between serum and plasma cfDNA composition, both sources of liquid biopsy showed that patients with PitNETs presented a distinct methylome landscape compared to non-PitNETs. In addition, liquid biopsy methylomes captured epigenetic features reported in PitNET tissue and provided information about cell type composition. Using liquid biopsy-derived PitNETs-specific signatures as input to develop machine-learning predictive models, we generated scores which distinguished PitNETs from non-PitNETs conditions, including sellar tumor and non-neoplastic pituitary diseases, with accuracies above ~93% in independent cohort sets. CONCLUSIONS: Our results underpin the potential application of methylation-based liquid biopsy profiling as a noninvasive approach to identify clinically relevant epigenetic markers to diagnose and potentially impact the prognostication and management of patients with PitNETs.

Nursing
Julin MJ, Ochoa S, Cooper D, and Dabney B. Using the Oncology Care Model to Manage Cancer Pain at an Outpatient Oncology Clinic. *Clin J Oncol Nurs* 2022; 26(1):E7-e13. PMID: 35073299. Full Text

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BACKGROUND: Cancer prevalence and the incidence of cancer pain are increasing. Although individualized care plans have been proposed to help manage cancer pain, minimal research has evaluated their effectiveness. OBJECTIVES: This quality improvement project assessed whether an education session on pain management guidelines from the Centers for Medicare and Medicaid Services Oncology Care Model (OCM) increased provider use of care plans and pain management options and patient satisfaction. METHODS: A pre-/postintervention analysis was performed in an outpatient oncology clinic with patients reporting cancer pain. Staff received an education session on the OCM. Quizzes documented staff knowledge, and chart reviews documented use of care plans and pain management options. Patients' pain management satisfaction was assessed via survey. FINDINGS: There was no significant increase in provider use of pain management care plans, and patients' pain scores increased in the postintervention period. These findings likely were affected by the COVID-19 pandemic. However, patients' pain management satisfaction scores and provider use of nonpharmacologic treatment options increased postintervention.

Ophthalmology and Eye Care Services
Hou A, **Jin ML**, and **Goldman D**. The Protective Effects of Soft Contact Lenses for Contact Sports: A Novel Porcine Model for Corneal Abrasion Biomechanics. *Eye Contact Lens* 2022; Epub ahead of print. PMID: 35220351. Full Text

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PURPOSE: The aim of this study was to determine whether soft contact lenses provide protection for the corneal surface. METHODS: Fresh porcine eyes were inflated to intraocular pressures of 11 to 22 mm Hg

and secured to a Styrofoam head. Newton meters affixed with artificial acrylic nails were placed at angles of 0°, 45°, and 90° from a porcine corneal surface. The force of impact was recorded at which corneal abrasions were induced. The experiment was repeated with Senofilcon A and Lotrafilcon A soft contact lenses placed upon porcine eyes. RESULTS: The mean forces required to induce a corneal abrasion with force at 0°, 45°, and 90° from corneal surface were 11±5.09, 9.18±2.76, and 7.72±2.61 Newtons, respectively. With soft contact lens barrier, the maximum measurable force of 50 Newtons could not produce a corneal abrasion. CONCLUSION: The force required to create corneal abrasions varies depending on the angle of the force vector. The use of contact lenses can withstand a minimum of five times the average force needed to create corneal abrasions.

Orthopedics/Bone and Joint Center

Gardinier JD, **Chougule A**, and **Zhang C**. The mechanotransduction of MLO-Y4 cells is disrupted by the senescence-associated secretory phenotype of neighboring cells. *J Cell Physiol* 2022; Epub ahead of print. PMID: 35102547. Full Text

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Age-related bone loss is attributed to the accumulation of senescent cells and their increasing production of inflammatory cytokines as part of the senescence-associated secretory phenotype (SASP). In otherwise healthy individuals, osteocytes play a key role in maintaining bone mass through their primary function of responding to skeletal loading. Given that osteocytes' response to loading is known to steadily decline with age, we hypothesized that the increasing presence of senescent cells and their SASP inhibit osteocytes' response to loading. To test this hypothesis, we developed two in vitro models of senescent osteocytes and osteoblasts derived from MLO-Y4 and MC3T3 cell lines, respectively. The senescent phenotype was unique to each cell type based on distinct changes in cell cycle inhibitors and SASP profile. The SASP profile of senescent osteocytes was in part dependent on nuclear factor-κB signaling and presents a new potential mechanism to target the SASP in bone. Nonsenescent MLO-Y4 cells cultured with the SASP of each senescent cell type failed to exhibit changes in gene expression as well as ERK phosphorylation and prostaglandin E2 release. The SASP of senescent osteocytes had the largest effect and neutralizing interleukin-6 (IL-6) as part of the SASP restored osteocytes' response to loading. The loss in mechanotransduction due to IL-6 was attributed to a decrease in P2X7 expression and overall sensitivity to purinergic signaling. Altogether, these findings demonstrate that the SASP of senescent cells have a negative effect on the mechanotransduction of osteocytes and that IL-6 is a key SASP component that contributes to the loss in mechanotransduction.

Orthopedics/Bone and Joint Center

Koolmees DS, Ramkumar PN, **Solsrud K**, **Yedulla NR**, **Elhage KG**, **Cross AG**, and **Makhni EC**. Time-Driven Activity-Based Costing Accurately Determines Bundle Cost for Rotator Cuff Repair. *Arthroscopy* 2022; Epub ahead of print. PMID: 35189303. Full Text

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PURPOSE: The purpose of this study was to determine the cost of the episode of care for primary RCR from day of surgery to 90 days post-operatively using the time driven activity-based costing (TDABC) method. The secondary purpose of this study was to identify the main drivers of cost for both phases of care. METHODS: This retrospective case series study used the TDABC method to determine the bundled cost of care for a RCR. First, a process map of the RCR episode of care was constructed in order to determine drivers of fixed (i.e. rent, power), direct variable (i.e. healthcare personnel), and indirect costs (i.e. marketing, building maintenance). The study was performed at a Midwestern tertiary care medical system, and patients were included in the study if they underwent a RCR from January 2018-January 2019 with at least 90 days of post-operative follow-up. In this manuscript all costs were included, but we did not account for fees to provider and professional groups RESULTS: The TDABC method calculated a

cost of $10,569 for a bundled RCR, with 76% arising from the operative phase and 24% from the post-operative phase. The main driver of cost within the operative phase was the direct fixed costs, which accounted for 35% of the cost in this phase, and the largest contributor to cost within this category was the cost of implants, which accounted for 55%. In the post-operative phase of care, physical therapy visits were the greatest contributor to cost at 59%. CONCLUSION: In a bundled cost of care for RCR, the largest cost driver occurs on the day of surgery for direct fixed costs, in particularly the implant. Physical therapy represents over half the costs of the episode of care. Better understanding the specific cost of care for RCR will facilitate optimization with appropriately designed payment models and policies that safeguard the interests of the patient, physician, and payer.

Orthopedics/Bone and Joint Center

Shaw JH, **Rahman TM**, **Wesemann LD**, **Jiang C**, **Darrith B**, and **Davis JJ**. Comparison of Postoperative Instability and Acetabular Cup Positioning in Robotic Assisted versus Traditional Total Hip Arthroplasty. *J Arthroplasty* 2022; Epub ahead of print. PMID: 35143923. Full Text

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BACKGROUND: Robotic-assisted total hip arthroplasty (R-THA) affords precision yet uncertain clinical benefits. This study compares dislocation rates and related revisions between R-THA and manual total hip arthroplasty (M-THA). Secondarily we evaluated cup position, patient-reported outcome measures (PROMs), and postoperative complications. METHODS: A three-surgeon cohort study was conducted on 2,247 consecutive patients (1724 M-THA and 523 R-THA) who received a primary THA between January 2014 and June 2020 at a single hospital. Demographics, PROMs, emergency department visits, readmissions, and 90-day complications were collected via the Michigan Arthroplasty Registry Collaborative Quality Initiative. Chart review yielded instability occurrence with average follow-up of 4 years. Multivariate regression analysis was performed and a sample of 368 radiographs including all dislocations were assessed. RESULTS: There were significantly lower rates of dislocation in R-THA (0.6%) versus M-THA (2.5%; Multivariate odds ratio 3.74, $p < .046$). All cases of unstable R-THA were successfully treated conservatively, whereas 46% of unstable M-THA were revised for recurrent instability. Cup anteversion (25.6° ± 5.4° R-THA vs. 20.6° ± 7.6° M-THA) was greater and cup inclination (42.5° ± 5.3° R-THA vs. 47.0° ± 6.7° M-THA) was lower in the R-THA group ($p < .05$). No significant differences were noted for demographics, PROMs, or other complications ($p > .05$). CONCLUSION: R-THA resulted in less than one-fourth the dislocation rate compared to M-THA and no revision for instability. It was associated with no difference in PROMs or other early complications. The influence of R-THA on stability goes beyond simply cup positioning and deserves further study.

Orthopedics/Bone and Joint Center

Shaw JH, **Wesemann LD**, **Kadri OM**, **Les CM**, **North WT**, and **Charters MA**. Multiple Venous Thromboembolism Pharmacologic Agents Are Associated with an Increased Risk for Early Postoperative Complications following a Total Joint Arthroplasty. *Adv Orthop* 2022; 2022:8318595. PMID: 35178256. Full Text

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The purpose of this study was to determine the effect that concurrent venous thromboembolism (VTE) medications had on early outcomes following primary total joint arthroplasty (TJA). 2653 total knee and hip arthroplasties were reviewed at a tertiary medical center. The study performed a multivariable comparison of outcomes in patients on 2 or more VTE medications, as well as a logistic regression on outcomes following each addition of a VTE medication postoperatively (number of VTE medications was 1-4). Controlling for gender, age, body mass index, and preoperative American Society of Anesthesiologists score throughout the analysis, patients who received 2 or more VTE prophylaxis medications had increased LOS ($p < 0.001$), transfusions ($p < 0.001$), emergency department visits

(p=0.001), readmissions (p < 0.001), 90dPOE (p < 0.001), and PE (p < 0.001). Every additional postoperative VTE medication incrementally increased the risk for longer LOS (p < 0.001), transfusions (p < 0.001), 90dPOE (p < 0.001), deep vein thrombosis (p=0.049), PE (p < 0.001), emergency department visits (p=0.005), and readmission (p=0.010). Patients on multiple VTE medications following TJA demonstrate significantly poorer outcomes. The current study's findings caution the use of multiple VTE medications whenever possible immediately following a TJA.

Orthopedics/Bone and Joint Center

Tramer JS, **Yedulla NR**, **Ziedas AC**, **Patel M**, **Franovic S**, **Muh SJ**, and **Makhni EC**. Risk Factors for Failure to Achieve Minimal Clinically Important Difference and Significant Clinical Benefit in PROMIS CAT Domains in Patients Undergoing Rotator Cuff Repair. *J Shoulder Elbow Surg* 2022; Epub ahead of print. PMID: 35172206. Full Text

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BACKGROUND: The Patient-Reported Outcomes Measurement Information System (PROMIS) has emerged as a valid and efficient means of collecting outcomes in patients with rotator cuff tears. The purpose of this study was to establish threshold score changes to determine minimal clinically important difference (MCID) and substantial clinical benefit (SCB) in PROMIS computer adaptive test (CAT) scores following rotator cuff repair (RCR). Additionally, we sought to identify potential risk factors for failing to achieve MCID and SCB. METHODS: Patients undergoing arthroscopic RCR were identified over a 24-month period. Only patients that completed both preoperative and postoperative PROMIS CAT assessments were included in this cohort. PROMIS CAT forms for upper extremity physical function (PROMIS-UE), pain interference (PROMIS-PI), and depression (PROMIS-D) were utilized with minimum of 1.5 year follow-up. Statistical analysis was performed to determine threshold score changes to determine anchor-based MCID and SCB, as well as risk factors for failure to achieve significant clinical improvement following surgery. RESULTS: Of 198 eligible patients, 168 (84.8%) were included in analysis. Delta PROMIS-UE values of 5.8 and 9.7 (area under the curve (AUC) = 0.906 and 0.949, respectively) and delta PROMIS-PI values of -11.4 and -12.9 (AUC = 0.875 and 0.938, respectively) were identified as threshold predictors of MCID and SCB achievement. On average, 81%, 65%, and 55% of patients achieved MCID for PROMIS-UE, PROMIS-PI, and PROMIS-D while 71%, 61%, and 38% of patients in the cohort respectively achieved SCB. MCID achievement in PROMIS-UE significantly differed according to risk factors including smoking status (LR: 9.8, p=0.037), tear size (LR: 10.4, p<0.001), distal clavicle excision (LR: 6.1, p=0.005), and prior shoulder surgery (LR: 19.2, p<0.001). Factors influencing SCB achievement for PROMIS-UE were smoking status (LR: 9.3, p=0.022), tear size (LR: 8.0, p=0.039), and prior shoulder surgery (11.9, p<0.001). Significantly different rates of MCID and SCB achievement in PROMIS-PI for smoking status (LR: 7.0, p=0.030 and LR: 5.2, p=0.045) and prior shoulder surgery (LR: 9.1, p=0.002 and LR: 7.4, p=0.006) were also identified. DISCUSSION AND CONCLUSION: The majority of patients showed clinically significant improvements that exceeded the established MCID for PROMIS-UE and PROMIS-PI following RCR. Patients with larger tear sizes, a history of prior shoulder surgery, tobacco users, and those who received concomitant distal clavicle excision were at risk for failing to achieve MCID in PROMIS-UE. Additionally, smokers and patients who underwent prior shoulder surgery demonstrated significantly lower improvements in pain scores following surgery.

Otolaryngology – Head and Neck Surgery

Goyal N, Day A, Epstein J, Goodman J, Graboyes E, Jalisi S, Kiess AP, Ku JA, Miller MC, Panwar A, Patel VA, Sacco A, Sandulache V, **Williams AM**, Deschler D, Farwell DG, Nathan CA, Fakhry C, and Agrawal N. Head and neck cancer survivorship consensus statement from the American Head and Neck Society. *Laryngoscope Investig Otolaryngol* 2022; 7(1):70-92. PMID: 35155786. Full Text

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OBJECTIVES: To provide a consensus statement describing best practices and evidence regarding head and neck cancer survivorship. METHODS: Key topics regarding head and neck cancer survivorship were identified by the multidisciplinary membership of the American Head and Neck Society Survivorship, Supportive Care & Rehabilitation Service. Guidelines were generated by combining expert opinion and a review of the literature and categorized by level of evidence. RESULTS: Several areas regarding survivorship including dysphonia, dysphagia, fatigue, chronic pain, intimacy, the ability to return to work, financial toxicity, lymphedema, psycho-oncology, physical activity, and substance abuse were identified and discussed. Additionally, the group identified and described the role of key clinicians in survivorship including surgical, medical and radiation oncologists; dentists; primary care physicians; psychotherapists; as well as physical, occupational, speech, and respiratory therapists. CONCLUSION: Head and neck cancer survivorship is complex and requires a multidisciplinary approach centered around patients and their caregivers. As survival related to head and neck cancer treatment improves, addressing post-treatment concerns appropriately is critically important to our patient's quality of life. There continues to be a need to define effective and efficient programs that can coordinate this multidisciplinary effort toward survivorship.

Otolaryngology – Head and Neck Surgery
Herrgott GA, **Asmaro KP**, **Wells M**, **Sabedot TS**, **Malta TM**, **Mosella MS**, **Nelson K**, **Scarpace L**, Barnholtz-Sloan JS, Sloan AE, Selman WR, **deCarvalho AC**, **Poisson LM**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Snyder J**, **Walbert T**, **Rosenblum M**, **Mikkelsen T**, **Bhan A**, **Craig J**, **Kalkanis S**, **Rock J**, **Noushmehr H**, and **Castro AV**. Detection of Tumor-specific DNA Methylation Markers in the Blood of Patients with Pituitary Neuroendocrine Tumors. *Neuro Oncol* 2022; Epub ahead of print. PMID: 35212383. Full Text

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Department of Otolaryngology, Co-director of the Skull Base, Pituitary and Endoscopy Center.

BACKGROUND: DNA methylation abnormalities are pervasive in pituitary neuroendocrine tumors (PitNETs). The feasibility to detect methylome alterations in circulating cell-free DNA (cfDNA) has been reported for several central nervous system tumors but not across PitNETs. The aim of the study was to use the liquid biopsy approach to detect PitNET-specific methylation signatures to differentiate these tumors from other sellar diseases. METHOD: We profiled the cfDNA methylome (EPIC array) of 59 serum and 41 plasma liquid biopsy specimens from patients with PitNETs and other CNS diseases (sellar tumors and other pituitary non-neoplastic diseases, lower-grade gliomas and skull base meningiomas) or nontumor conditions, grouped as non-PitNET. RESULTS: Our results indicated that, despite quantitative and qualitative differences between serum and plasma cfDNA composition, both sources of liquid biopsy showed that patients with PitNETs presented a distinct methylome landscape compared to non-PitNETs. In addition, liquid biopsy methylomes captured epigenetic features reported in PitNET tissue and provided information about cell type composition. Using liquid biopsy-derived PitNETs-specific signatures as input to develop machine-learning predictive models, we generated scores which distinguished PitNETs from non-PitNETs conditions, including sellar tumor and non-neoplastic pituitary diseases, with accuracies above ~93% in independent cohort sets. CONCLUSIONS: Our results underpin the potential application of methylation-based liquid biopsy profiling as a noninvasive approach to identify clinically relevant epigenetic markers to diagnose and potentially impact the prognostication and management of patients with PitNETs.

Otolaryngology – Head and Neck Surgery

Larrabee KA, Kao AS, **Barbetta BT**, and **Jones LR**. Midface Including Le Fort Level Injuries. *Facial Plast Surg Clin North Am* 2022; 30(1):63-70. PMID: 34809887. Full Text

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Le Fort fractures occur at uniform weak areas in the midface often due to blunt impact to the face. Sporting injuries are a common cause of facial trauma; however, use of protective equipment has reduced the number of sports-related injuries. All patients with traumatic injuries should be evaluated using Advanced Trauma Life Support protocol. Le Fort fractures can contribute to airway obstruction, and urgent intubation may be indicated. Surgery is indicated for most displaced Le Fort fractures to restore function and facial harmony. To facilitate reduction, the original occlusive relationship should be restored by placing the patient in MMF.

Pathology and Laboratory Medicine

Al-Obaidy KI, Saleeb RM, Trpkov K, Williamson SR, Sangoi AR, Nassiri M, Hes O, Montironi R, Cimadamore A, Acosta AM, Alruwaii ZI, Alkashash A, **Hassan O**, **Gupta N**, Osunkoya AO, Sen JD, Baldrige LA, Sakr WA, Idrees MT, Eble JN, Grignon DJ, and Cheng L. Recurrent KRAS mutations are early events in the development of papillary renal neoplasm with reverse polarity. *Mod Pathol* 2022; Epub ahead of print. PMID: 35152262. Full Text

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We evaluated the clinicopathologic and molecular characteristics of mostly incidentally detected, small, papillary renal neoplasms with reverse polarity (PRNRP). The cohort comprised 50 PRNRP from 46 patients, divided into 2 groups. The clinically undetected (<5 mm) neoplasms (n = 34; 68%) had a median size of 1.1 mm (range 0.2-4.3 mm; mean 1.4 mm), and the clinically detected (≥5 mm) neoplasms (n = 16; 32%) which had a median size of 13 mm (range 9-30 mm; mean 16 mm). Neoplasms were positive for GATA3 (n = 47; 100%) and L1CAM (n = 34/38; 89%) and were negative for vimentin (n = 0/44; 0%) and, to a lesser extent, AMACR [(n = 12/46; 26%; weak = 9, weak/moderate = 3)]. KRAS mutations were found in 44% (n = 15/34) of the clinically undetected PRNRP and 88% of the clinically detected PRNRP (n = 14/16). The two clinically detected PRNRP with wild-type KRAS gene were markedly cystic and contained microscopic intracystic tumors. In the clinically undetected PRNRP, the detected KRAS mutations rate was higher in those measuring ≥1 mm vs <1 mm [n = 14/19 (74%) vs n = 1/15 (7%)]. Overall, the KRAS mutations were present in exon 2-codon 12: c.35 G > T (n = 21), c.34 G > T (n = 3), c.35 G > A (n = 2), c.34 G > C (n = 2) resulting in p.Gly12Val, p. Gly12Asp, p.Gly12Cys and p.Gly12Arg, respectively. One PRNRP had a G12A/V/D complex mutation. Twenty-six PRNRP were concurrently present with other tumors of different histologic subtypes in the ipsilateral kidney; molecular testing of 8 of the latter showed wild-type KRAS gene despite the presence of KRAS mutations in 5 concurrent PRNRP. On follow up, no adverse pathologic events were seen (range 1-160 months; mean 44 months). In conclusion, the presence of KRAS mutations in small, clinically undetected PRNRP provides a unique finding to this entity and supports its being an early event in the development of these neoplasms.

Pathology and Laboratory Medicine

Herrgott GA, **Asmaro KP**, **Wells M**, **Sabedot TS**, **Malta TM**, **Mosella MS**, **Nelson K**, **Scarpace L**, Barnholtz-Sloan JS, Sloan AE, Selman WR, **deCarvalho AC**, **Poisson LM**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Snyder J**, **Walbert T**, **Rosenblum M**, **Mikkelsen T**, **Bhan A**, **Craig J**, **Kalkanis S**, **Rock J**, **Noushmehr H**, and **Castro AV**. Detection of Tumor-specific DNA Methylation Markers in the Blood of Patients with Pituitary Neuroendocrine Tumors. *Neuro Oncol* 2022; Epub ahead of print. PMID: 35212383. Full Text

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Department of Otolaryngology, Co-director of the Skull Base, Pituitary and Endoscopy Center.

BACKGROUND: DNA methylation abnormalities are pervasive in pituitary neuroendocrine tumors (PitNETs). The feasibility to detect methylome alterations in circulating cell-free DNA (cfDNA) has been reported for several central nervous system tumors but not across PitNETs. The aim of the study was to use the liquid biopsy approach to detect PitNET-specific methylation signatures to differentiate these tumors from other sellar diseases. METHOD: We profiled the cfDNA methylome (EPIC array) of 59 serum and 41 plasma liquid biopsy specimens from patients with PitNETs and other CNS diseases (sellar tumors and other pituitary non-neoplastic diseases, lower-grade gliomas and skull base meningiomas) or nontumor conditions, grouped as non-PitNET. RESULTS: Our results indicated that, despite quantitative and qualitative differences between serum and plasma cfDNA composition, both sources of liquid biopsy showed that patients with PitNETs presented a distinct methylome landscape compared to non-PitNETs. In addition, liquid biopsy methylomes captured epigenetic features reported in PitNET tissue and provided information about cell type composition. Using liquid biopsy-derived PitNETs-specific signatures as input to develop machine-learning predictive models, we generated scores which distinguished PitNETs from non-PitNETs conditions, including sellar tumor and non-neoplastic pituitary diseases, with accuracies above ~93% in independent cohort sets. CONCLUSIONS: Our results underpin the potential application of methylation-based liquid biopsy profiling as a noninvasive approach to identify clinically relevant epigenetic markers to diagnose and potentially impact the prognostication and management of patients with PitNETs.

Pharmacy

George J, **Lobkovich A**, **Nardolillo J**, **Farhat N**, **Kolander S**, and **Thomas E**. Real-world evaluation of insulin requirements after GLP1 agonist or SGLT2 inhibitor initiation and titration. *Am J Health Syst Pharm* 2022; Epub ahead of print. PMID: 35136945. Full Text

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 PURPOSE: To describe insulin adjustments made following initiation of glucagon-like peptide 1 agonist (GLP1a) or sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy in patients within a primary care setting. METHODS: This was a multicenter, retrospective cohort study conducted at an academic health system. Adults with type 2 diabetes mellitus initiated on a GLP1a or SGLT2i while on insulin and managed by an ambulatory care pharmacist were included. The primary endpoint was the percent change in total daily insulin dose at specified time points (2 weeks, 4 weeks, 6 weeks, 3 months, and 6 months) after agent initiation. The secondary endpoints included a glycosylated hemoglobin

(HbA1c) value of less than 8%, change from baseline HbA1c, and safety profiles of GLP1a therapy and SGLT2i therapy. RESULTS: Of the 150 patients included, 123 were initiated on a GLP1a and 27 on an SGLT2i. After 6 months, GLP1a initiation had resulted in a mean 23.5% decrease (P < 0.001) in insulin dosage and SGLT2i resulted in a mean 0.2% increase (P = 0.20). Insulin dosage reduction with GLP1a use was significantly different between baseline and each time point (P < 0.001). About 72% of patients initiated on a GLP1a and 59% of those initiated on an SGLT2i achieved an HbA1c value of less than 8%. The mean absolute change from baseline in HbA1c concentration was -1.7% with GLP1a use and -1.5% with SGLT2i use (P < 0.001 for both comparisons with baseline values). Hypoglycemia occurred in 21% of patients on a GLP1a and 11% of those on an SGLT2i. CONCLUSION: After GLP1a initiation, the mean total daily insulin dose decreased by 23.5%; after SGLT2i initiation, insulin requirements increased by a mean of 0.2%. These results will help guide insulin adjustments after initiation of these medications.

Public Health Sciences

Chung JR, Kim SS, Belongia EA, McLean HQ, King JP, Nowalk MP, Zimmerman RK, Moehling Geffel K, Martin ET, Monto AS, **Lamerato LE**, Gaglani M, Hoffman E, Volz M, Jackson ML, Jackson LA, Patel MM, and Flannery B. Vaccine effectiveness against COVID-19 among symptomatic persons aged ≥12 years with reported contact with COVID-19 cases, February-September 2021. *Influenza Other Respir Viruses* 2022; Epub ahead of print. PMID: 35170231. Full Text

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BACKGROUND: Individuals in contact with persons with COVID-19 are at high risk of developing COVID-19; protection offered by COVID-19 vaccines in the context of known exposure is poorly understood. METHODS: Symptomatic outpatients aged ≥12 years reporting acute onset of COVID-19-like illness and tested for SARS-CoV-2 between February 1 and September 30, 2021 were enrolled. Participants were stratified by self-report of having known contact with a COVID-19 case in the 14 days prior to illness onset. Vaccine effectiveness was evaluated using the test-negative study design and multivariable logistic regression. RESULTS: Among 2229 participants, 283/451 (63%) of those reporting contact and 331/1778 (19%) without known contact tested SARS-CoV-2-positive. Adjusted vaccine effectiveness was 71% (95% confidence interval [CI], 49%-83%) among fully vaccinated participants reporting a known contact versus 80% (95% CI, 72%-86%) among those with no known contact (p-value for interaction = 0.2). CONCLUSIONS: This study contributes to growing evidence of the benefits of vaccinations in preventing COVID-19 and support vaccination recommendations and the importance of efforts to increase vaccination coverage.

Public Health Sciences

Gordon SC, Teshale EH, Spradling PR, Moorman AC, Boscarino JA, Schmidt MA, Daida YG, **Rupp LB**, **Trudeau S**, **Zhang J**, and **Lu M**. Lower rates of emergency visits and hospitalizations among chronic hepatitis C patients with sustained virological response to interferon-free direct-acting antiviral therapy (2014-2018). *Clin Infect Dis* 2022; Epub ahead of print. PMID: 35147184. Full Text

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We compared rates of emergency department (ED) visits and hospitalizations between HCV patients who achieved sustained virological response (SVR) after direct-acting antiviral (DAA) therapy (cases) to matched controls. Among 3049 pairs, cases demonstrated lower rates of liver-related ED visits (P=.01) than controls; all-cause and liver-related hospitalization rates and hospitalized days were also lower in cases (P<.0001).

Public Health Sciences

Herrgott GA, **Asmaro KP**, **Wells M**, **Sabedot TS**, **Malta TM**, **Mosella MS**, **Nelson K**, **Scarpace L**, Barnholtz-Sloan JS, Sloan AE, Selman WR, **deCarvalho AC**, **Poisson LM**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Snyder J**, **Walbert T**, **Rosenblum M**, **Mikkelsen T**, **Bhan A**, **Craig J**, **Kalkanis S**, **Rock J**, **Noushmehr H**, and **Castro AV**. Detection of Tumor-specific DNA Methylation Markers in the Blood of Patients with Pituitary Neuroendocrine Tumors. *Neuro Oncol* 2022; Epub ahead of print. PMID: 35212383. Full Text

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Public Health Sciences

Kim RY, Rendle KA, Mitra N, Saia CA, **Neslund-Dudas C**, Greenlee RT, Burnett-Hartman AN, Honda SA, **Simoff MJ**, Schapira MM, Croswell JM, Meza R, Ritzwoller DP, and Vachani A. Racial Disparities in Adherence to Annual Lung Cancer Screening and Recommended Follow-up Care: A Multicenter Cohort Study. *Ann Am Thorac Soc* 2022; Epub ahead of print. PMID: 35167781. Full Text

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RATIONALE: Black patients receive recommended lung cancer screening (LCS) follow-up care less frequently than White patients, but it is unknown if this racial disparity persists across both decentralized and centralized LCS programs. OBJECTIVES: To determine adherence to American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) recommendations among individuals undergoing LCS at either decentralized or centralized programs, and to evaluate the association of race with LCS adherence. METHODS: We performed a multicenter retrospective cohort study of patients receiving LCS at five heterogeneous U.S. healthcare systems. We calculated adherence to annual LCS among patients with a negative baseline screen (Lung-RADS 1 or 2) and recommended follow-up care among those with a positive baseline screen (Lung-RADS 3, 4A, 4B, or 4X) stratified by type of LCS program and evaluated the association between race and adherence using multivariable modified Poisson regression. RESULTS: Of the 6,134 total individuals receiving LCS, 5,142 (83.8%) had negative baseline screens, and 992 (16.2%) had positive baseline screens. Adherence to both annual LCS (34.8% vs 76.1%; P<0.001) and recommended follow-up care (63.9% vs 74.6%; P<0.001) was lower at decentralized compared to centralized programs. Among individuals with negative baseline screens, a racial disparity in adherence was observed only at decentralized screening programs (interaction term, P<0.001). At decentralized programs, Black race was associated with 27% reduced adherence to annual LCS (adjusted relative risk [aRR], 0.73; 95% CI, 0.63-0.84) while at centralized programs, no effect by race was observed (aRR, 0.98; 95% CI, 0.91-1.05). In contrast, among those with positive baseline screens, there was no significant difference by race for adherence to recommended follow-up care by type of LCS program (decentralized aRR, 0.95; 95% CI, 0.81-1.11; centralized aRR, 0.81; 95% CI, 0.71-0.93; interaction term, P=0.176). CONCLUSIONS: In this large multicenter study of individuals screened for lung cancer, adherence to both annual LCS and recommended follow-up care was greater at centralized screening programs. Black patients were less likely to receive annual LCS compared to White patients at decentralized compared to centralized LCS programs. Our results highlight the need for further study of healthcare system-level mechanisms to optimize longitudinal LCS care.

Public Health Sciences

Kim WR, Telep LE, Jump B, **Lu M**, Ramroth H, Flaherty J, Gaggar A, Chokkalingam AP, and **Gordon SC**. Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States. *Aliment Pharmacol Ther* 2022; Epub ahead of print. PMID: 35137422. Full Text

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BACKGROUND: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are the first-line treatment agents for chronic hepatitis B virus (HBV). Recently, whether the degree to which the risk of hepatocellular carcinoma (HCC) may be reduced by ETV vs TDF has been debated. We compared the incidence of HCC among treatment-naïve patients receiving TDF vs ETV in the United States. METHODS: From a large administrative medical claims database of commercially insured patients, we identified 166,933 adults with a diagnosis of chronic hepatitis B and a minimum of 12 months of prior enrolment, of whom 3934 and 6127 initiated ETV and TDF respectively. Fine-Gray hazard regression models incorporating treatment propensity scores (PS) were used to estimate the risk of HCC incidence associated with TDF vs ETV; variables considered for adjustment included demographic characteristics, concomitant medication use and baseline comorbidities, as well as competing events including liver transplantation and medication changes. RESULTS: After PS weighting, the TDF and ETV groups were well-matched. During the follow-up, 90 patients developed HCC, including 50 receiving ETV and 40 receiving TDF, giving rise to crude incidence rates of 0.62 per 100 person-years (PY) and 0.30 per 100 PY respectively. In PS-weighted, multivariable analysis, TDF was associated with a subdistribution hazard ratio for HCC of 0.58 (95% confidence interval [CI]: 0.38-0.89) compared to ETV. Results were similar when patients ≥40 years and men and women were analysed separately. CONCLUSION: Among commercially insured, treatment-naïve patients with chronic hepatitis B in the United States, treatment with TDF was associated with significantly lower risk of HCC than ETV.

Public Health Sciences

Kitajima T, **Kuno Y**, **Ivanics T**, **Lu M**, **Moonka D**, **Shimada S**, **Shamaa T**, **Abouljoud MS**, and **Nagai S**. Improved Survival With Higher-risk Donor Grafts in Liver Transplant With Acute-on-chronic Liver Failure. *Transplant Direct* 2022; 8(2):e1283. PMID: 35187210. Full Text

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Use of higher-risk grafts in liver transplantation for patients with acute-on-chronic liver failure (ACLF) has been associated with poor outcomes. This study analyzes trends in liver transplantation outcomes for ACLF over time based on the donor risk index (DRI). METHODS: Using the Organ Procurement and Transplantation Network and the United Network for Organ Sharing registry, 17 300 ACLF patients who underwent liver transplantation between 2002 and 2019 were evaluated. Based on DRI, adjusted hazard ratios for 1-y patient death were analyzed in 3 eras: Era 1 (2002-2007, n = 4032), Era 2 (2008-2013, n = 6130), and Era 3 (2014-2019, n = 7138). DRI groups were defined by DRI <1.2, 1.2-1.6, 1.6-2.0, and >2.0. RESULTS: ACLF patients had significantly lower risks of patient death within 1 y in Era 2 (adjusted hazard ratio, 0.69; 95% confidence interval, 0.61-0.78; P < 0.001) and Era 3 (adjusted hazard ratio, 0.48; 95% confidence interval, 0.42-0.55; P < 0.001) than in Era 1. All DRI groups showed lower hazards in Era 3 than in Era 1. Improvement of posttransplant outcomes were found both in ACLF-1/2 and ACLF-3 patients. In ACLF-1/2, DRI 1.2 to 1.6 and >2.0 had lower adjusted risk in Era 3 than in Era 1. In ACLF-3, DRI 1.2 to 2.0 had lower risk in Era 3. In the overall ACLF cohort, the 2 categories with DRI >1.6 had significantly higher adjusted risks of 1-y patient death than DRI <1.2. When analyzing hazards in each era, DRI > 2.0 carried significantly higher adjusted risks in Eras 1 and 3' whereas DRI 1.2 to 2.0 had similar adjusted risks throughout eras. Similar tendency was found in ACLF-1/2. In the non-ACLF cohort, steady improvement of posttransplant outcomes was obtained in all DRI categories. Similar results were obtained when only hepatitis C virus-uninfected ACLF patients were evaluated. CONCLUSIONS: In ACLF

patients, posttransplant outcomes have significantly improved, and outcomes with higher-risk organs have improved in all ACLF grades. These results might encourage the use of higher-risk donors in ACLF patients and provide improved access to transplant.

Public Health Sciences

McCauley KE, Flynn K, DiMassa V, LaMere B, Fadrosh DW, Lynch KV, Gill MA, Pongracic JA, Khurana Hershey GK, Kercsmar CM, Liu AH, **Johnson CC**, **Kim H**, Kattan M, O'Connor GT, Bacharier LB, Teach SJ, Gergen PJ, Wheatley LM, Togias A, LeBeau P, Calatroni A, Presnell S, Boushey HA, Busse WW, Gern JE, Jackson DJ, Altman MC, and Lynch SV. Seasonal Airway Microbiome and Transcriptome Interactions Promote Childhood Asthma Exacerbations. *J Allergy Clin Immunol* 2022; Epub ahead of print. PMID: 35149044. Full Text

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BACKGROUND: Seasonal variation in respiratory illnesses and exacerbations in pediatric populations with asthma is well described, though whether upper airway microbes play season-specific roles in these events is unknown. OBJECTIVE: We hypothesized that nasal microbiota composition is seasonally dynamic and that discrete microbial-host interactions modify risk of asthma exacerbation in a season-specific manner. METHODS: Repeated nasal samples from children with exacerbation-prone asthma collected during periods of respiratory health (Baseline; n=181 samples) or first captured respiratory illness (n=97) across all seasons, underwent bacterial (16S rRNA gene) and fungal (ITS2) biomarker sequencing. Virus detection was performed by multiplex PCR. Paired nasal transcriptome data was examined for seasonal dynamics and integrative analyses. RESULTS: Upper airway bacterial and fungal microbiota and rhinovirus detection exhibited significant seasonal dynamics. In seasonally-adjusted analysis, variation in both baseline and respiratory illness microbiota related to subsequent exacerbation. Specifically in the fall, when respiratory illness and exacerbation events were most frequent, several Moraxella and Haemophilus members were enriched both in viral positive respiratory illnesses and those that progressed to exacerbations. The abundance of two discrete bacterial networks, characteristically comprising either Streptococcus or Staphylococcus exhibited opposing interactions with an exacerbation-associated SMAD3 nasal epithelial transcriptional module to significantly increase odds of subsequent exacerbation [OR=14.7, 95% CI: 1.50-144, P=0.02; OR=39.17, 95% CI: 2.44-626, P=0.008, respectively]. CONCLUSIONS: Upper airway microbiomes co-vary with season and with seasonal trends in respiratory illnesses and asthma exacerbations. Seasonally-adjusted analyses reveal specific bacterial-host interactions that significantly increase risk of asthma exacerbation in these children.

Public Health Sciences

McCord J, **Gibbs J**, **Hudson M**, **Moyer M**, **Jacobsen G**, Murtagh G, and **Nowak R**. Machine Learning to Assess for Acute Myocardial Infarction within 30 Minutes. *Crit Pathw Cardiol* 2022; Epub ahead of print. PMID: 35190507. Full Text

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Variations in high-sensitivity cardiac troponin I (hs-cTnI) by age and sex along with various sampling times can make the evaluation for acute myocardial infarction (AMI) challenging. Machine learning integrates these variables to allow a more accurate evaluation for possible AMI. The goal was to test the diagnostic and prognostic utility of a machine learning algorithm in the evaluation of possible AMI. We applied a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, sex, and hs-cTnI levels at time 0 and 30 minutes in 529 patients evaluated for possible AMI in a single urban emergency department. MI3 generates an index value from 0-100 reflecting the likelihood of AMI. Patients were followed at 30-45 days for major adverse cardiac events (MACE). There were 42 (7.9%) patients that had an AMI. Patients were divided into 3 groups by the MI3 score: low-risk (≤ 3.13), intermediate-risk (> 3.13-51.0), and high-risk (> 51.0). The sensitivity for AMI was 100% with a MI3 value ≤ 3.13 and 353 (67%) ruled-out for AMI at 30 minutes. At 30-45 days there were 2 (0.6%) MACEs (2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 AMIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 AMIs, 2 cardiac deaths). The MI3 algorithm had 100% sensitivity for AMI at 30 minutes and identified a low-risk cohort who may be considered for early discharge.

Public Health Sciences

Powell M, Wilder F, Obafemi O, Mohan N, Higgins R, **Tang X**, and **Okereke I**. Trends in Diversity in Integrated Cardiothoracic Surgery Residencies. *Ann Thorac Surg* 2022; Epub ahead of print. PMID: 35183505. Full Text

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BACKGROUND: Integrated cardiothoracic surgery residencies were begun in 2006 to address workforce shortages in cardiothoracic surgery. As more attention has been given to racial and gender disparities, our goal was to examine trends in diversity among integrated cardiothoracic residents. METHODS: All United States accredited integrated cardiothoracic programs which had accepted residents through 2020 were included. A resident list was collected through online websites and direct institutional contact. Gender, race and year of entry were recorded. Linear regression models were used to evaluate racial and gender trends over time. RESULTS: From 2006 through 2020, 321 residents were accepted into integrated cardiothoracic training programs. Males comprised 72 percent (232/321) of the cohort. The racial distribution was 66.4 percent Caucasian (213/321), 26.2 percent Asian (84/321), 5.3 percent Hispanic (17/321) and 2.2 percent African American (7/321). Over the study period the time slope for Caucasians was -2.95 ($p < 0.01$), indicating an approximately 3 percent decrease each year. The time slope for Asians was 1.60 ($p < 0.01$). The time slope did not change significantly for African Americans (0.10, $p = 0.94$) or Hispanics (0.13, $p = 0.91$). Adjusting for number of integrated programs each year as a covariate did not change trends for any race. The time slope did not change significantly over the time period for males (-0.25, $p = 0.71$). CONCLUSIONS: Gender and racial diversity have not improved over time in integrated cardiothoracic residencies. Institutions should strive to recruit medical students from underrepresented backgrounds and increase their focus on gender diversity.

Public Health Sciences

Schuchard J, Blackwell CK, Ganiban JM, Giardino AP, McGrath M, Sherlock P, Dabelea DM, Deoni SCL, Karr C, McEvoy CT, Patterson B, **Santarossa S**, Sathyanarayana S, Tung I, and Forrest CB. Influences of chronic physical and mental health conditions on child and adolescent positive health. *Acad Pediatr* 2022; Epub ahead of print. PMID: 35121190. Full Text

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OBJECTIVE: Pediatric positive health refers to children's assessments of their well-being. The purpose of this study was to contrast positive health for children aged 8 to 17 years with and without chronic physical and mental health conditions. METHODS: Data were drawn from the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) research program. Participants included 1,764 children ages 8 to 17 years from 13 ECHO cohorts. We measured positive health using the PROMIS Pediatric Global Health and Life Satisfaction patient-reported outcome (PRO) measures. We used multiple regression to examine cross-sectional associations between the PROs and parent-reported health conditions and sociodemographic variables. We defined a meaningful difference in average scores as a PROMIS T-score difference of >3. RESULTS: The sample included 45% 13-17 year-olds, 50% females, 8% Latinx, and 23% Black/African-American. 54% had a chronic health condition. Of the 16 chronic conditions included in the study, only chronic pain (β = -3.5; 95% CI: -5.2 to -1.9) and depression (β = -6.6; 95% CI: -8.5 to -4.6) were associated with scoring >3 points lower on global health. Only depression was associated with >3 points lower on life satisfaction (β = -6.2; 95% CI: -8.1 to -4.3). Among those with depression, 95% also had another chronic condition. CONCLUSION: Many children with chronic conditions have similar levels of positive health as counterparts without chronic conditions. The study results suggest that negative associations between chronic conditions and positive health may be primarily attributable to presence or co-occurrence of depression.

Public Health Sciences

Shimada S, **Ivanics T**, **Kitajima T**, **Shamaa T**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, **Moonka D**, **Zhang J**, **Lu M**, and **Nagai S**. Improvements in liver transplant outcomes in patients with HCV/HIV coinfection after the introduction of direct-acting antiviral therapies. *Transpl Infect Dis* 2022;13808. Epub ahead of print. PMID: 35157334. Full Text

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BACKGROUND: In recipients with HCV/HIV coinfection, the impact that the wider use of direct-acting antivirals (DAAs) has had on post-liver transplant (LT) outcomes has not been evaluated. We investigated the impact of DAAs introduction on post-LT outcome in patients with HCV/HIV coinfection. METHODS: Using Organ Procurement and Transplant Network/United Network for Organ Sharing data, we compared post-LT outcomes in patients with HCV and/or HIV pre- and post-DAAs introduction. We categorized these patients into two eras: pre-DAA (2008-2012 [pre-DAA era]) and post-DAA (2014-2019 [post-DAA era]). To study the impact of DAAs introduction, inverse probability of treatment weighting was used to adjust patient characteristics. RESULTS: A total of 17 215 LT recipients were eligible for this study (HCV/HIV [n = 160]; HIV mono-infection [n = 188]; HCV mono-infection [n = 16 867]). HCV/HIV coinfection and HCV mono-infection had a significantly lower hazard of 1- and 3-year graft loss post-DAA, compared pre-DAA (1-year: adjusted hazard ratio [aHR] 0.29, 95% confidence interval (CI) 0.16-0.53 in HIV/HCV, aHR 0.58, 95% CI 0.54-0.63, respectively; 3-year: aHR 0.30, 95% CI 0.14-0.61, aHR 0.64, 95% CI 0.58-0.70, respectively). The hazards of 1- and 3-year graft loss post-DAA in HIV mono-infection were comparable to those in pre-DAA. HCV/HIV coinfection had significantly lower patient mortality post-DAA, compared to pre-DAA (1-year: aHR 0.30, 95% CI 0.17-0.55; 3-year: aHR 0.31, 95% CI 0.15-0.63). CONCLUSIONS: Post-LT outcomes in patients with coinfection significantly improved and became comparable to those with HCV mono-infection after introducing DAA therapy. The introduction of DAAs supports the use of LT in the setting of HCV/HIV coinfection.

Public Health Sciences

Shipp GM, Weatherspoon LJ, Comstock SS, Norman GS, **Alexander GL**, Gardiner JC, and Kerver JM. Breastfeeding Self-Efficacy as a Predictor of Breastfeeding Intensity Among African American Women in the Mama Bear Feasibility Trial. *Breastfeed Med* 2022; Epub ahead of print. PMID: 35166571. Full Text

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Background: Improving breastfeeding rates among African American (AA) families is an important public health goal. Breastfeeding self-efficacy, a known predictor of breastfeeding behavior, has seldom been assessed among AAs, in relation to breastfeeding intensity (% breastfeeding relative to total feeding) or as a protective factor in combating the historical breastfeeding challenges faced by people of color. We aimed to test the association between breastfeeding self-efficacy assessed during pregnancy and breastfeeding intensity assessed in the early postpartum period. Methods: This was a secondary data analysis of a randomized controlled feasibility trial of breastfeeding support and postpartum weight management. AA women were recruited during pregnancy from a prenatal clinic in Detroit, MI. Data presented, in this study, were collected at enrollment (n = 50) and ~6 weeks postpartum (n = 31). Linear regression models were used, adjusting for potential confounders. Results: There were no differences in breastfeeding intensity by study arm; data are from all women with complete data on targeted variables. Age ranged from 18 to 43 years, 52% were Women, Infant's, and Children program enrollees, and 62% had ≥ some college. Breastfeeding self-efficacy during pregnancy was a significant predictor of breastfeeding intensity in the early postpartum period ($\beta = 0.125$, $p < 0.05$) with only slight attenuation in the fully adjusted model ($\beta = 0.123$, $p < 0.05$). Implications for Practice: Our results confirm that self-efficacy is an important predictor of breastfeeding practice. Furthermore, the simple act of assessing

breastfeeding self-efficacy permits an opportunity for women to reflect on breastfeeding possibilities, and can inform individualized confidence-building interventions to improve the disproportionately low breastfeeding rates among AAs. Clinical Trial Registration number NCT03480048.

Public Health Sciences

Wise LA, Thomas L, Anderson S, Baird DD, Anchan RM, Terry KL, Marsh EE, **Wegienka G**, Nicholson WK, Wallace K, Bigelow R, Spies J, Maxwell GL, Jacoby V, Myers ER, and Stewart EA. Route of myomectomy and fertility: a prospective cohort study. *Fertil Steril* 2022; Epub ahead of print. PMID: 35216832. Full Text

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OBJECTIVE: To assess prospectively the association between the myomectomy route and fertility. DESIGN: Prospective cohort study. SETTING: The Comparing Treatments Options for Uterine Fibroids (COMPARE-UF) Study is a multisite national registry of eight clinic centers across the United States. PATIENT(S): Reproductive-aged women undergoing surgery for symptomatic uterine fibroids. INTERVENTION(S): Not applicable. MAIN OUTCOME MEASURE(S): We used life-table methods to estimate cumulative probabilities and 95% confidence intervals (CI) of pregnancy and live birth by the myomectomy route during 12, 24, and 36 months of follow-up (2015-2019). We also conducted 12-month interval-based analyses that used logistic regression to estimate odds ratios and 95% CIs for associations of interest. In all analyses, we used propensity score weighting to adjust for differences across surgical routes. RESULT(S): Among 1,095 women who underwent myomectomy (abdominal = 388, hysteroscopic = 273, and laparoscopic = 434), 202 reported pregnancy and 91 reported live birth during 36 months of follow-up. There was little difference in the 12-month probability of pregnancy or live birth by route of myomectomy overall or among women intending pregnancy. In interval-based analyses, adjusted ORs for pregnancy were 1.28 (95% CI, 0.76-2.14) for hysteroscopic myomectomy and 1.19 (95% CI, 0.76-1.85) for laparoscopic myomectomy compared with abdominal myomectomy. Among women intending pregnancy, adjusted ORs were 1.27 (95% CI, 0.72-2.23) for hysteroscopic myomectomy and 1.26 (95% CI, 0.77-2.04) for laparoscopic myomectomy compared with abdominal myomectomy. Associations were slightly stronger but less precise for live birth. CONCLUSION(S): The probability of conception or live birth did not differ appreciably by the myomectomy route among women observed for 36 months postoperatively. CLINICAL TRIALS REGISTRATION NUMBER: (NCT02260752, clinicaltrials.gov).

Pulmonary and Critical Care Medicine

Davis SP, Stover CF, and Willhaus JK. Simulation Use in Entry-Into-Practice Respiratory Care Programs. *Respir Care* 2022; Epub ahead of print. PMID: 35169065. Full Text

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BACKGROUND: Teaching and learning using simulation-based methods is increasing in health professions education; however, the prevalence of simulation use in respiratory care programs to date has not been explored. METHODS: All 412 Commission on Accreditation for Respiratory Care (CoARC)-accredited entry-into-practice respiratory care programs were e-mailed a survey inquiring about simulation use as an educational tool in their programs. RESULTS: Of the initial 412 programs contacted, 124 returned the survey, for a 30% response rate. More than three-quarters of programs reported using simulation including 87% of associate degree programs, 75% of bachelor's degree programs, and 100% of master's degree programs. Simulation modalities differed by course and program as did length of simulation activities and debriefings. Simulation hours may not be substituted for learner's clinical time under CoARC guidelines, and 69% of respondents agreed with this stance; however, 66% of responding programs have mandatory simulation learning activities, and 68% believe the amount of simulation should be increased. The survey also revealed respiratory care faculty have limited training in the use of simulation. CONCLUSIONS: Simulation-based teaching and learning is widespread and varied, but there is a lack of faculty development in its use among respiratory care programs.

Pulmonary and Critical Care Medicine

Kim RY, Rendle KA, Mitra N, Saia CA, **Neslund-Dudas C**, Greenlee RT, Burnett-Hartman AN, Honda SA, **Simoff MJ**, Schapira MM, Croswell JM, Meza R, Ritzwoller DP, and Vachani A. Racial Disparities in Adherence to Annual Lung Cancer Screening and Recommended Follow-up Care: A Multicenter Cohort Study. *Ann Am Thorac Soc* 2022; Epub ahead of print. PMID: 35167781. Full Text

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RATIONALE: Black patients receive recommended lung cancer screening (LCS) follow-up care less frequently than White patients, but it is unknown if this racial disparity persists across both decentralized and centralized LCS programs. OBJECTIVES: To determine adherence to American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) recommendations among individuals undergoing LCS at either decentralized or centralized programs, and to evaluate the association of race with LCS adherence. METHODS: We performed a multicenter retrospective cohort study of patients receiving LCS at five heterogeneous U.S. healthcare systems. We calculated adherence to annual LCS among patients with a negative baseline screen (Lung-RADS 1 or 2) and recommended follow-up care among those with a positive baseline screen (Lung-RADS 3, 4A, 4B, or 4X) stratified by type of LCS program and evaluated the association between race and adherence using multivariable modified Poisson regression. RESULTS: Of the 6,134 total individuals receiving LCS, 5,142 (83.8%) had negative

baseline screens, and 992 (16.2%) had positive baseline screens. Adherence to both annual LCS (34.8% vs 76.1%; P<0.001) and recommended follow-up care (63.9% vs 74.6%; P<0.001) was lower at decentralized compared to centralized programs. Among individuals with negative baseline screens, a racial disparity in adherence was observed only at decentralized screening programs (interaction term, P<0.001). At decentralized programs, Black race was associated with 27% reduced adherence to annual LCS (adjusted relative risk [aRR], 0.73; 95% CI, 0.63-0.84) while at centralized programs, no effect by race was observed (aRR, 0.98; 95% CI, 0.91-1.05). In contrast, among those with positive baseline screens, there was no significant difference by race for adherence to recommended follow-up care by type of LCS program (decentralized aRR, 0.95; 95% CI, 0.81-1.11; centralized aRR, 0.81; 95% CI, 0.71-0.93; interaction term, P=0.176). CONCLUSIONS: In this large multicenter study of individuals screened for lung cancer, adherence to both annual LCS and recommended follow-up care was greater at centralized screening programs. Black patients were less likely to receive annual LCS compared to White patients at decentralized compared to centralized LCS programs. Our results highlight the need for further study of healthcare system-level mechanisms to optimize longitudinal LCS care.

Radiation Oncology

Dilworth JT, Griffith KA, Pierce LJ, Jagsi R, Quinn TJ, **Walker EM**, Radawski JD, Dominello MM, Gustafson GS, Moran JM, Hayman JA, and Vicini FA. The impact of chemotherapy on toxicity and cosmetic outcome in patients receiving whole breast irradiation: an analysis within a state-wide quality consortium. *Int J Radiat Oncol Biol Phys* 2022; Epub ahead of print. PMID: 35157997. Full Text

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PURPOSE: We investigated whether the use of chemotherapy prior to whole breast irradiation (WBI) using either conventional fractionation (CWBI) or hypofractionation (HWBI) is associated with increased toxicity or worse cosmetic outcome compared to WBI alone. METHODS AND MATERIALS: We identified 6,754 patients who received WBI alone (without a third field covering the superior axillary and supraclavicular nodal regions) with data prospectively collected in a state-wide consortium. We reported rates of four toxicity outcomes: physician-reported acute moist desquamation, patient-reported acute moderate/severe breast pain, a composite acute toxicity measure (including moist desquamation and either patient-reported or physician-reported moderate/significant breast pain), and physician-reported impaired cosmetic outcome at one year following WBI. Successive multivariable models were constructed to estimate the impact of chemotherapy on these outcomes. RESULTS: Rates of moist desquamation, patient-reported pain, composite acute toxicity, and impaired cosmetic outcome were 23%, 34%, 42%, and 10% for 2,859 patients receiving CWBI and 13%, 28%, 31%, and 11% for 3,895 patients receiving HWBI. Receipt of chemotherapy prior to CWBI was not associated with higher rates of patient-reported pain, composite acute toxicity, or impaired cosmetic outcome compared to CWBI without chemotherapy but was associated with more moist desquamation (OR=1.32 [1.07-1.63], p=0.01). Receipt of chemotherapy prior to HWBI was not associated with higher rates of any of the four toxicity outcomes compared to HWBI alone. CONCLUSIONS: In this cohort, use of chemotherapy prior to WBI was generally well tolerated. CWBI with chemotherapy, but not to HWBI with chemotherapy, was associated with higher rates of moist desquamation. Rates of acute breast pain and impaired cosmetic outcome at one year were comparable in patients receiving chemotherapy prior to either CWBI or HWBI. These data support the use of HWBI following chemotherapy.

Radiation Oncology

Ghanen AI, Woody NM, **Schymick MA**, Joshi NP, Geiger JL, Jillian Tsai C, Dunlap NE, Liu HY, Burkey BB, Lamarre ED, Ku JA, Scharpf J, Caudell JJ, S VP, Lee NY, Adelstein DJ, Koyfman SA, and **Siddiqui F**. Influence of Treatment Package Time on outcomes in High-Risk Oral Cavity Carcinoma in patients receiving Adjuvant Radiation and Concurrent Systemic Therapy: A Multi-Institutional Oral Cavity Collaborative study. *Oral Oncol* 2022; 126:105781. PMID: 35183910. Full Text

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OBJECTIVES: To explore the influence of treatment package time(TPT) in high-risk oral cavity squamous cell carcinoma(OCSCC) receiving adjuvant radiotherapy with concurrent chemotherapy(CRT). MATERIALS AND METHODS: We queried our multi-institutional OCSCC collaborative database for cases diagnosed between 2005 and 2015 who underwent surgery followed by adjuvant CRT. All patients had high-risk features: extranodal extension(ENE) and/or positive surgical margin(PM). TPT was days between surgery to last radiotherapy fraction. Kaplan-Meier curves, log-rank p-values and multivariate analysis(MVA) were used to investigate the impact of TPT on overall(OS), disease-free(DFS), locoregional failure-free(LRFS) and distant metastases-free(DMFS) survival. RESULTS: We identified 187 cases: median age 58 (range, 24-87 years), males 66%, and ever smokers 69%. ENE and PM were detected in 85% and 32%, and oral tongue and floor of the mouth constituted 49% and 18%, respectively. Median radiotherapy and cisplatin doses received were 66 Gy and 200 mg/m2. Overall, median TPT was

98 (range, 63-162 days). OS was worse for TPT > 90-days (n = 134) than TPT ≤ 90 (n = 53) at two-(65% vs. 71%) and five-years (45% vs. 62%); p = 0.05, with similar results for DFS. No influence on LRFS or DMFS was noted. More lymph nodes(LN) dissected(P = 0.039), T3-4 disease(P = 0.017), and unplanned reoperations(P = 0.037) occurred with TPT > 90-days. On MVA, TPT in 10-day increments was independently detrimental for OS (Hazard Ratio: 1.14; 95 %Confidence Interval [1-1.28]; P = 0.043), perineural invasion, age and positive LN (p < 0.05 for all). CONCLUSION: In one of the largest multi-institutional cohorts, TPT > 90-days predicted worse OS for high-risk OCSCC receiving adjuvant CRT. All efforts are needed to optimize perioperative care and baseline conditions for favorable outcomes.

Radiation Oncology

Herr DJ, Hochstedler KA, Yin H, Dess RT, Matuszak M, Grubb M, Dominello M, **Movsas B**, Kestin LL, Bergsma D, Dragovic AF, Grills IS, Hayman JA, Paximadis P, Schipper M, and Jolly S. Effect of education and standardization of cardiac dose constraints on heart dose in lung cancer patients receiving definitive radiation therapy across a statewide consortium. *Pract Radiat Oncol* 2022; Epub ahead of print. PMID: 35121192. Full Text

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PURPOSE/OBJECTIVES: Cardiac radiation exposure is associated with an increased rate of adverse cardiac events in patients receiving radiation therapy for locally advanced non-small cell lung carcinoma (NSCLC). Previous analysis of practice patterns within XXXX revealed 1 in 4 patients received a mean heart dose >20 Gy and significant heterogeneity existed among treatment centers in using cardiac dose constraints. The purpose of this study is to analyze the effect of education and initiation of standardized cardiac dose constraints on heart dose across a statewide consortium. MATERIALS/METHODS: From 2012 to 2020, 1681 patients from 27 academic and community centers who received radiation therapy for locally advanced NSCLC were included in this analysis. Dosimetric endpoints including mean heart dose (MHD), mean lung dose, and mean esophagus dose were calculated using data from dose-volume histograms. These dose metrics were grouped by year of treatment initiation for all patients. Education regarding data for cardiac dose constraints first occurred in small lung cancer working group meetings and then consortium-wide starting in 2016. In 2018, a quality metric requiring mean heart dose <20 Gy while maintaining dose coverage (D95) to the target was implemented. Dose metrics were compared before (2012-2016) versus after (2017-2020) initiation of interventions targeting cardiac constraints. Statistical analysis was performed using the Wilcoxon Rank Sum test. RESULTS: Following education and implementation of the heart dose performance metric, mean MHD declined from an average of 12.2 Gy pre-intervention to 10.4 Gy post-intervention (p < 0.0001), and the percentage of patients receiving MHD >20 Gy reduced from 21.1% to 10.3% (p < 0.0001). Mean lung dose and mean esophagus dose did not increase, and target coverage remained unchanged. CONCLUSIONS: Education and implementation of a standardized cardiac dose quality measure across a statewide consortium was associated with a reduction of mean heart dose in patients receiving radiation therapy for locally advanced NSCLC. These dose reductions were achieved without sacrificing target coverage, increasing mean lung dose, or increasing mean esophagus dose. Analysis of the clinical ramifications of the reduction in cardiac doses is ongoing.

Radiation Oncology

Laucis AMB, Hochstedler KA, Schipper MJ, Paximadis PA, Boike TP, Bergsma DP, **Movsas B**, **Kretzler A**, Spratt DE, Dess RT, Mietzel MA, Dominello MM, Matuszak MM, Jagsi R, Hayman JA, Pierce LJ, and Jolly S. Racial Differences in Treatments and Toxicity in Patients With Non-Small-Cell Lung Cancer Treated With Thoracic Radiation Therapy. *JCO Oncol Pract* 2022; Epub ahead of print. PMID: 35167337. Full Text

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PURPOSE: Historical racial disparities in lung cancer surgery rates resulted in lower survival in Black patients. Our objective was to examine racial differences in thoracic radiation treatments and toxicities in patients with non-small-cell lung cancer. METHODS AND MATERIALS: A large institutional review board-approved statewide patient-level database of patients with stage II-III non-small-cell lung cancer who received definitive thoracic radiation from March 2012 to November 2019 was analyzed to assess associations between race and other variables. Race (White or Black) was defined by patient self-report. Provider-reported toxicity was defined by Common Terminology Criteria for Adverse Events version 4.0. Patient-reported toxicity was determined by the Functional Assessment of Cancer Therapy-Lung quality-of-life instrument. Univariable and multivariable regression models were fitted to assess relationships between race and variables of interest. Spearman rank-correlation coefficients were calculated between provider-reported toxicity and similar patient-reported outcomes. RESULTS: One thousand four hundred forty-one patients from 24 institutions with mean age 68 years (range, 38-94 years) were evaluated. Race was not significantly associated with radiation or chemotherapy approach. There was significantly increased patient-reported general pain in Black patients at the preradiation and end-of-radiation time points. Black patients were significantly less likely to have provider-reported grade 2+ pneumonitis (odds ratio 0.36, P = .03), even after controlling for known patient and treatment factors. Correlation coefficients between provider- and patient-reported toxicities were generally similar across race groups except for a stronger correlation between patient- and provider-reported esophagitis in White patients. CONCLUSION: In this large multi-institutional study, we found no evidence of racial differences in radiation treatment or chemotherapy approaches. We did, however, unexpectedly find that Black race was associated with lower odds of provider-reported grade 2+ radiation pneumonitis. The stronger correlation between patient- and provider-reported esophagitis and swallowing symptoms for White patients also suggests possible under-recognition of symptoms in Black patients. Further research is needed to study the implications for Black patients.

Radiation Oncology

Mao W, **Riess J**, **Kim J**, **Vance S**, **Chetty IJ**, **Movsas B**, and **Kretzler A**. Evaluation of auto-contouring and dose distributions for online adaptive radiation therapy of patients with locally advanced lung cancers. *Pract Radiat Oncol* 2022; Epub ahead of print. PMID: 35219879. Full Text

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PURPOSE: Retrospective studies were performed to evaluate the accuracy of automatically mapped structures and dosimetric consequences of daily online adaptive radiation therapy (ART) for lung cancer treatments. METHODS: Ten locally advanced lung cancer patients (prescription=2Gyx30) with 297 fractions of treatment were selected for this retrospective study on a research emulator (Ethos™, Varian

Medical Systems). All adaptive treatments were simulated twice: Automatic-ART (A-ART) - automatic contours were utilized without modification, and Supervised-ART (S-ART) - automatic contours were modified manually by physicians and physicists. Dosimetric results were analyzed by relating supervised scheduled (S-SCH) dose (initial baseline reference (REF) plan delivered on daily anatomy and supervised contour correction without any adaptation), A-ART and S-ART to the REF dose. RESULTS: Two hundred ninety (of 297) fractions were analyzed. Comparing target volumes between A-ART and S-ART, Dice similarity coefficient was 0.93±0.05, mean contour distance was 1.5±1.2 mm, and Hausdorff distance was 4.0±2.3 mm. Analysis of daily results over 290 fractions of treatment showed that average target coverage improved from 0.96±0.04 (S-SCH) to 1.00±0.02 (A-ART) and 1.02±0.04 (S-ART); average upper dose constraint was reduced from 1.01±0.11 (S-SCH) to 0.94±0.10 (A-ART) and 0.93±0.12 (S-ART). A-ART and S-ART improved PTV minimum doses by 4.85±3.03 Gy (p=0.049) and 4.46±8.99 Gy (p=0.058), respectively. Statistical analysis shows that A-ART and S-ART significantly improved cumulative target dose by 0.033 ± 0.087 (p = 0.002) and 0.032 ± 0.086 (p = 0.003) and reduced upper constraints by 0.033 ± 0.072 (p <0.001) and 0.032 ± 0.072 (p <0.001) relative to S-SCH dose results, respectively. CONCLUSION: Accuracy of Ethos automatic contouring for lung cancer is considered clinically acceptable. The online adaptive radiation therapy improves target coverage and spares organs-at-risk significantly.

Research Administration

Inman KS, Liu Y, Scotti Buzhardt ML, Leitges M, Krishna M, **Crawford HC**, Fields AP, and Murray NR. Prkci Regulates Autophagy and Pancreatic Tumorigenesis in Mice. *Cancers (Basel)* 2022; 14(3). PMID: 35159064. Full Text

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Protein kinase C iota (PKCι) functions as a bonafide human oncogene in lung and ovarian cancer and is required for Kras(G12D)-mediated lung cancer initiation and progression. PKCι expression is required for pancreatic cancer cell growth and maintenance of the transformed phenotype; however, nothing is known about the role of PKCι in pancreas development or pancreatic tumorigenesis. In this study, we investigated the effect of pancreas-specific ablation of PKCι expression on pancreatic cellular homeostasis, susceptibility to pancreatitis, and Kras(G12D)-mediated pancreatic cancer development. Knockout of pancreatic Prkci significantly increased pancreatic immune cell infiltration, acinar cell DNA damage, and apoptosis, but reduced sensitivity to caerulein-induced pancreatitis. Prkci-ablated pancreatic acinar cells exhibited P62 aggregation and a loss of autophagic vesicles. Loss of pancreatic Prkci promoted Kras(G12D)-mediated pancreatic intraepithelial neoplasia formation but blocked progression to adenocarcinoma, consistent with disruption of autophagy. Our results reveal a novel promotive role for PKCι in pancreatic epithelial cell autophagy and pancreatic cancer progression.

Research Administration

Salmanpour MR, Shamsaei M, Hajianfar G, **Soltanian-Zadeh H**, and Rahmim A. Longitudinal clustering analysis and prediction of Parkinson's disease progression using radiomics and hybrid machine learning. *Quant Imaging Med Surg* 2022; 12(2):906-919. PMID: 35111593. Full Text

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BACKGROUND: We employed machine learning approaches to (I) determine distinct progression trajectories in Parkinson's disease (PD) (unsupervised clustering task), and (II) predict progression trajectories (supervised prediction task), from early (years 0 and 1) data, making use of clinical and imaging features. METHODS: We studied PD-subjects derived from longitudinal datasets (years 0, 1, 2 & 4; Parkinson's Progressive Marker Initiative). We extracted and analyzed 981 features, including motor, non-motor, and radiomics features extracted for each region-of-interest (ROIs: left/right caudate and putamen) using our standardized standardized environment for radiomics analysis (SERA) radiomics software. Segmentation of ROIs on dopamine transposer - single photon emission computed tomography (DAT SPECT) images were performed via magnetic resonance images (MRI). After performing cross-sectional clustering on 885 subjects (original dataset) to identify disease subtypes, we identified optimal longitudinal trajectories using hybrid machine learning systems (HMLS), including principal component analysis (PCA) + K-Means algorithms (KMA) followed by Bayesian information criterion (BIC), Calinski-Harabatz criterion (CHC), and elbow criterion (EC). Subsequently, prediction of the identified trajectories from early year data was performed using multiple HMLSs including 16 Dimension Reduction Algorithms (DRA) and 10 classification algorithms. RESULTS: We identified 3 distinct progression trajectories. Hotelling's t squared test (HTST) showed that the identified trajectories were distinct. The trajectories included those with (I, II) disease escalation (2 trajectories, 27% and 38% of patients) and (III) stable disease (1 trajectory, 35% of patients). For trajectory prediction from early year data, HMLSs including the stochastic neighbor embedding algorithm (SNEA, as a DRA) as well as locally linear embedding algorithm (LLEA, as a DRA), linked with the new probabilistic neural network classifier (NPNNC, as a classifier), resulted in accuracies of 78.4% and 79.2% respectively, while other HMLSs such as SNEA + Lib_SVM (library for support vector machines) and t_SNE (t-distributed stochastic neighbor embedding) + NPNNC resulted in 76.5% and 76.1% respectively. CONCLUSIONS: This study moves beyond cross-sectional PD subtyping to clustering of longitudinal disease trajectories. We conclude that combining medical information with SPECT-based radiomics features, and optimal utilization of HMLSs, can identify distinct disease trajectories in PD patients, and enable effective prediction of disease trajectories from early year data.

Sleep Medicine

Kalmbach DA. The emerging role of prenatal insomnia therapy in the prevention of perinatal depression and anxiety. *Sleep* 2022; Epub ahead of print. PMID: 35150286. Full Text

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Sleep Medicine

Roth T, Rosenberg R, Morin CM, Yardley J, Pinner K, Perdomo C, Atkins N, Jr., Pappadopulos E, Malhotra M, and Moline M. Impact of lemborexant treatment on insomnia severity: analyses from a 12-month study of adults with insomnia disorder. *Sleep Med* 2022; 90:249-257. PMID: 35220140. Full Text

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OBJECTIVE/BACKGROUND: Evaluate changes in insomnia severity in subjects with moderate to severe insomnia (Insomnia Severity Index [ISI] score ≥15) treated for 12 months nightly with lemborexant. PATIENTS/METHODS: This phase 3 randomized study comprised two 6-month treatment periods. In Period 1, 949 subjects were randomized to placebo, lemborexant 5 mg (LEM5) or 10 mg (LEM10). In Period 2, placebo subjects were rerandomized to LEM5 or LEM10; subjects initially randomized to lemborexant continued their assigned treatment. Insomnia severity was assessed using baseline ISI and 1-, 3-, 6-, 9-, and 12-month post-treatment scores. RESULTS: Mean ISI scores improved significantly

across treatment groups and disease severities, with greater decreases from baseline in the LEM5 and LEM10 versus placebo groups at months 1 (-7.1, -7.2, -5.2, respectively), 3 (-8.6, -8.9, -6.1, respectively), and 6 (-9.9, -9.8, -7.2 respectively); ISI score improvements were maintained with LEM5 and LEM10 at months 9 (-11.1 and -11.2, respectively) and 12 (-11.5 and -11.2, respectively). At months 1, 3, and 6, significantly more treatment responders (≥7-point ISI score decrease from baseline) were observed with LEM5 (44%-57%) and LEM10 (44%-52%) versus placebo (30%-41%). At months 1, 3, and 6, more remitters (ISI total score <10 and < 8) were observed with LEM5 (30%-44% and 22%-34%, respectively) and LEM10 (31%-41% and 22%-31%, respectively) versus placebo (18%-28% and 11%-21%, respectively). CONCLUSIONS: Lemborexant significantly reduced insomnia severity for 12 months and increased clinically meaningful response and remission rates versus placebo. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT02952820; ClinicalTrialsRegister.eu, EudraCT Number 2015-001463-39.

Surgery

Choi WJ, Williams PJ, Claasen M, **Ivanics T**, Englesakis M, Gallinger S, Hansen B, and Sapisochin G. Systematic Review and Meta-Analysis of Prognostic Factors for Early Recurrence in Intrahepatic Cholangiocarcinoma After Curative-Intent Resection. *Ann Surg Oncol* 2022; Epub ahead of print. PMID: 35181812. Full Text

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BACKGROUND: Recurrence rates of intrahepatic cholangiocarcinoma (iCCA) after curative hepatectomy are as high as 50% to 70%, and about half of these recurrences occur within 2 years. This systematic review aims to define prognostic factors (PFs) for early recurrence (ER, within 24 months) and 24-month disease-free survival (DFS) after curative-intent iCCA resections. METHODS: Systematic searching was performed from database inception to 14 January 2021. Duplicate independent review and data extraction were performed. Data on 13 predefined PFs were collected. Meta-analysis was performed on PFs for ER and summarized using forest plots. The Quality in Prognostic Factor Studies tool was used for risk-of-bias assessment. RESULTS: The study enrolled 10 studies comprising 4158 patients during an accrual period ranging from 1990 to 2016. In the risk-of-bias assessment of patients who experienced ER after curative-intent iCCA resection, six studies were rated as low risk and four as moderate risk (49.6%; 95% confidence interval [CI], 49.2-50.0). Nine studies were pooled for meta-analysis. Of the postoperative PFs, multiple tumors, microvascular invasion, macrovascular invasion, lymph node metastasis, and R1 resection were associated with an increased hazard for ER or a reduced 24-month DFS, and the opposite was observed for receipt of adjuvant chemo/radiation therapy. Of the preoperative factors, cirrhosis, sex, HBV status were not associated with ER or 24-month DFS. CONCLUSION: The findings from this systematic review could allow for improved surveillance, prognostication, and treatment decision-making for patients with resectable iCCAs. Further well-designed prospective studies are needed to explore prognostic factors for iCCA ER with a focus on preoperative variables.

Surgery

Ferguson R, and **Popoff AM**. Improving Esophagectomy Outcomes in France: Petit a Petit. *Ann Surg Oncol* 2022; Epub ahead of print. PMID: 35171403. Full Text

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Surgery

Ivanics T, Murillo Perez CF, Claasen MP, Patel MS, Morgenshtern G, Erdman L, Shwaartz C, Rajendran L, O'Kane GM, Hansen BE, Cleary SP, and Sapisochin G. Dynamic risk profiling of hepatocellular carcinoma recurrence after curative intent liver resection. *Hepatology* 2022; Epub ahead of print. PMID: 35178739. Full Text

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BACKGROUND AND AIMS: Following liver resection(LR) for hepatocellular carcinoma(HCC), the likelihood of survival is dynamic, in that multiple recurrences and/or metastases are possible, each having variable impact on outcomes. We sought to evaluate the natural progression, pattern, and timing of various disease states after LR for HCC using multistate modeling and to create a practical calculator to provide prognostic information for patients and clinicians. APPROACH AND RESULTS: Adult patients undergoing LR for HCC between Jan-2000 and Dec-2018 were retrospectively identified at a single center. Multistate analysis modeled post-LR tumour progression by describing transitions between distinct disease states. In this model, the states included surgery, intra-hepatic recurrence(1(st) ,2(nd) ,3(rd) ,4(th) ,5(th)), distant metastasis with or without intra-hepatic recurrence, and death. Of the 486 patients included,169(34.8%) remained recurrence-free,205(42.2%) developed intra-hepatic recurrence, 80(16.5%) developed distant metastasis, and 32(7%) died. For an average patient having undergone LR,there was a 33.1% chance of remaining disease-free,31.0% of at least one intra-hepatic recurrence,16.3% of distant metastasis, and 19.8% of death within the first 60-months post-LR. The transition probability from surgery to first intra-hepatic recurrence, without a subsequent state transition, increased from 3%(3-months),to 17.4%(30-months),and 17.2%(60-months). Factors that could modify these probabilities included tumour size, satellite lesions, and microvascular invasion. CONCLUSIONS: In contrast to standard single time-to-event estimates, multistate modeling provides more realistic prognostication of outcomes after LR for HCC by taking into account many postoperative disease states and transitions between them. Our multistate modeling calculator can provide meaningful data to guide the management of patients undergoing postoperative surveillance and therapy.

Surgery

Jesse MT, **Gartrelle K**, **Bruschwein H**, **Hug G**, **LeTarte B**, **Lerret S**, and **Dew MA**. Non-pharmacological interventions engaging organ transplant caregivers: A systematic review. *Clin Transplant* 2022; e14611. Epub ahead of print. PMID: 35143701. Full Text

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INTRODUCTION: Lay-caregivers in organ transplantation (to candidates, recipients, and donors) are essential to pre- and postoperative care, but report significant caregiving-related stressors. This review aims to summarize studies testing nonpharmacological interventions aimed at improving organ transplant caregiver-reported outcomes. METHODS: In accordance with PRISMA, we conducted a systematic review (searched PubMed, Embase, Cochrane Central, PsycInfo, and CINAHL, no start-date restriction through 7/1/2021). Quality of comparative studies assessed by ROBS-2 or ROBINS. RESULTS: Twelve studies met inclusion. Study designs, interventions, and outcomes varied. Sample sizes were small across caregivers to adults (nine studies, five with caregiver samples ns≤50) and pediatric patients (three studies, caregiver samples ns≤16). Study designs included seven single-arm interventions, two prepost with comparison cohorts, and three randomized-controlled trials. Eight studies included transplant-specific education as the intervention, an interventional component, or as the comparison group. Outcomes included transplant specific knowledge, mental health, and intervention acceptability. Of the nine prepost caregiver assessments and/or comparison groups, four studies demonstrated no statistically significant intervention effects. CONCLUSION: Few interventions addressing the needs of organ transplant caregivers have been empirically evaluated. Existing interventions were well-received by caregivers. Given complexities of care in transplantation, research is needed evaluating interventions using rigorous trial methodology with adequate samples.

Surgery

Julin MJ, Ochoa S, Cooper D, and Dabney B. Using the Oncology Care Model to Manage Cancer Pain at an Outpatient Oncology Clinic. *Clin J Oncol Nurs* 2022; 26(1):E7-e13. PMID: 35073299. Full Text

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BACKGROUND: Cancer prevalence and the incidence of cancer pain are increasing. Although individualized care plans have been proposed to help manage cancer pain, minimal research has evaluated their effectiveness. OBJECTIVES: This quality improvement project assessed whether an education session on pain management guidelines from the Centers for Medicare and Medicaid Services Oncology Care Model (OCM) increased provider use of care plans and pain management options and patient satisfaction. METHODS: A pre-/postintervention analysis was performed in an outpatient oncology clinic with patients reporting cancer pain. Staff received an education session on the OCM. Quizzes documented staff knowledge, and chart reviews documented use of care plans and pain management options. Patients' pain management satisfaction was assessed via survey. FINDINGS: There was no significant increase in provider use of pain management care plans, and patients' pain scores increased in the postintervention period. These findings likely were affected by the COVID-19 pandemic. However, patients' pain management satisfaction scores and provider use of nonpharmacologic treatment options increased postintervention.

Surgery

Kitajima T, **Kuno Y**, **Ivanics T**, **Lu M**, **Moonka D**, **Shimada S**, **Shamaa T**, **Abouljoud MS**, and **Nagai S**. Improved Survival With Higher-risk Donor Grafts in Liver Transplant With Acute-on-chronic Liver Failure. *Transplant Direct* 2022; 8(2):e1283. PMID: 35187210. Full Text

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Use of higher-risk grafts in liver transplantation for patients with acute-on-chronic liver failure (ACLF) has been associated with poor outcomes. This study analyzes trends in liver transplantation outcomes for ACLF over time based on the donor risk index (DRI). METHODS: Using the Organ Procurement and Transplantation Network and the United Network for Organ Sharing registry, 17 300 ACLF patients who

underwent liver transplantation between 2002 and 2019 were evaluated. Based on DRI, adjusted hazard ratios for 1-y patient death were analyzed in 3 eras: Era 1 (2002-2007, n = 4032), Era 2 (2008-2013, n = 6130), and Era 3 (2014-2019, n = 7138). DRI groups were defined by DRI <1.2, 1.2-1.6, 1.6-2.0, and >2.0. RESULTS: ACLF patients had significantly lower risks of patient death within 1 y in Era 2 (adjusted hazard ratio, 0.69; 95% confidence interval, 0.61-0.78; P < 0.001) and Era 3 (adjusted hazard ratio, 0.48; 95% confidence interval, 0.42-0.55; P < 0.001) than in Era 1. All DRI groups showed lower hazards in Era 3 than in Era 1. Improvement of posttransplant outcomes were found both in ACLF-1/2 and ACLF-3 patients. In ACLF-1/2, DRI 1.2 to 1.6 and >2.0 had lower adjusted risk in Era 3 than in Era 1. In ACLF-3, DRI 1.2 to 2.0 had lower risk in Era 3. In the overall ACLF cohort, the 2 categories with DRI >1.6 had significantly higher adjusted risks of 1-y patient death than DRI <1.2. When analyzing hazards in each era, DRI > 2.0 carried significantly higher adjusted risks in Eras 1 and 3' whereas DRI 1.2 to 2.0 had similar adjusted risks throughout eras. Similar tendency was found in ACLF-1/2. In the non-ACLF cohort, steady improvement of posttransplant outcomes was obtained in all DRI categories. Similar results were obtained when only hepatitis C virus-uninfected ACLF patients were evaluated. CONCLUSIONS: In ACLF patients, posttransplant outcomes have significantly improved, and outcomes with higher-risk organs have improved in all ACLF grades. These results might encourage the use of higher-risk donors in ACLF patients and provide improved access to transplant.

Surgery

Larrabee KA, Kao AS, **Barbetta BT**, and **Jones LR**. Midface Including Le Fort Level Injuries. *Facial Plast Surg Clin North Am* 2022; 30(1):63-70. PMID: 34809887. Full Text

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Le Fort fractures occur at uniform weak areas in the midface often due to blunt impact to the face. Sporting injuries are a common cause of facial trauma; however, use of protective equipment has reduced the number of sports-related injuries. All patients with traumatic injuries should be evaluated using Advanced Trauma Life Support protocol. Le Fort fractures can contribute to airway obstruction, and urgent intubation may be indicated. Surgery is indicated for most displaced Le Fort fractures to restore function and facial harmony. To facilitate reduction, the original occlusive relationship should be restored by placing the patient in MMF.

Surgery

Nagai S, Nallabasannagari AR, **Moonka D**, Reddiboina M, **Yeddula S**, **Kitajima T**, **Francis I**, and **Abouljoud M**. Use of Neural Network Models to Predict Liver Transplant Waitlist Mortality. *Liver Transpl* 2022; Epub ahead of print. PMID: 35224855. Full Text

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Current liver transplant (LT) organ allocation relies on MELD-Na scores to predict mortality in patients awaiting LT. This study aims to develop Neural Network (NN) models that more accurately predict LT waitlist mortality. The study evaluates patients listed for LT between February 27(th) , 2002 and June 30(th) , 2021 using the OPTN/UNOS registry. We excluded patients listed with MELD exception scores and those listed for multi-organ transplant, except for liver-kidney transplant. Subset of data from the waitlist was used to create a mortality prediction model at 90 days after listing with 105,140 patients. A total of 28 variables were selected for model creation. The data was split using random sampling into training, validation, and test datasets in a 60:20:20 ratio. The performance of the model was

assessed using Area Under Receiver Operating Curve (AUC-ROC) and Area Under Precision-Recall curve (PR-AUC). AUC-ROC for 90-Day mortality was 0.936 (0.934-0.937, 95% CI), and PR-AUC was 0.758 (0.754-0.762, 95% CI). The NN 90-Day Mortality model outperformed MELD-based models for both AUC-ROC and PR-AUC. The 90-Day Mortality model specifically identified more waitlist deaths with a higher Recall (Sensitivity) of 0.807 (0.803-0.811, 95% CI) vs 0.413 (0.409 - 0.418, 95% CI) (P<0.001). The performance metrics were compared by breaking the test dataset into multiple patient subsets by Ethnicity, Gender, Region, Age, Diagnosis Group, and Year of listing. The NN 90-Day Mortality model outperformed MELD-based models across all subsets in predicting mortality. In conclusion, organ allocation based on NN modeling has the potential to decrease waitlist mortality and lead to more equitable allocation systems in LT.

Surgery

Powell M, Wilder F, Obafemi O, Mohan N, Higgins R, **Tang X**, and **Okereke I**. Trends in Diversity in Integrated Cardiothoracic Surgery Residencies. *Ann Thorac Surg* 2022; Epub ahead of print. PMID: 35183505. Full Text

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BACKGROUND: Integrated cardiothoracic surgery residencies were begun in 2006 to address workforce shortages in cardiothoracic surgery. As more attention has been given to racial and gender disparities, our goal was to examine trends in diversity among integrated cardiothoracic residents. METHODS: All United States accredited integrated cardiothoracic programs which had accepted residents through 2020 were included. A resident list was collected through online websites and direct institutional contact. Gender, race and year of entry were recorded. Linear regression models were used to evaluate racial and gender trends over time. RESULTS: From 2006 through 2020, 321 residents were accepted into integrated cardiothoracic training programs. Males comprised 72 percent (232/321) of the cohort. The racial distribution was 66.4 percent Caucasian (213/321), 26.2 percent Asian (84/321), 5.3 percent Hispanic (17/321) and 2.2 percent African American (7/321). Over the study period the time slope for Caucasians was -2.95 ($p < 0.01$), indicating an approximately 3 percent decrease each year. The time slope for Asians was 1.60 ($p < 0.01$). The time slope did not change significantly for African Americans (0.10, $p = 0.94$) or Hispanics (0.13, $p = 0.91$). Adjusting for number of integrated programs each year as a covariate did not change trends for any race. The time slope did not change significantly over the time period for males (-0.25, $p = 0.71$). CONCLUSIONS: Gender and racial diversity have not improved over time in integrated cardiothoracic residencies. Institutions should strive to recruit medical students from underrepresented backgrounds and increase their focus on gender diversity.

Surgery

Saifi O, **Chahrour MA**, Li Z, Hoballah J, Panoff J, Vallow LA, and Zeidan YH. Is breast conservation superior to mastectomy in early stage triple negative breast cancer? *Breast* 2022; 62:144-151. PMID: 35182994. Full Text

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PURPOSE: Compare overall survival (OS) and breast cancer-specific survival (BCSS) outcomes of breast conservative therapy (BCT) and mastectomy in a large cohort of patients with early-stage triple negative breast cancer (TNBC), using a propensity score-based matching approach. METHODS: Surveillance, Epidemiology, and End Results (SEER) database was used to study the role of RT in early stage TNBC. Primary end points were OS and BCSS. Cox proportional hazard regression models and Kaplan-Meier plots were used to generate the desired outcomes. Propensity score matching was done to minimize bias. RESULTS: 12,761 patients with T1-2N0M0 TNBC as their first malignancy were retrieved. Of these 7237 had lumpectomy with RT, and 5524 had mastectomy only. Age, race, marital status, tumor laterality, grade and stage, and receipt of chemotherapy were prognostic variables for OS and BCSS. Among 4848 matched subjects, the 5-year OS was significantly higher in patients with lumpectomy and RT (89%) compared to mastectomy alone (84.5%) (p-value <0.001). Similarly, BCSS was significantly higher in patients with lumpectomy and RT (93%) compared to mastectomy alone (91%) (p-value <0.001). On subgroup analysis, patients who are younger than 40 had similar survival outcomes after either mastectomy alone or lumpectomy with RT. However, those who are older than 60, have any grade or T stage had better survival outcomes with lumpectomy and RT. CONCLUSIONS: Overall, lumpectomy followed by RT is associated with better OS and BCSS compared to mastectomy in T1-2N0M0 TNBC patients. Further research is needed to determine the optimal treatment strategy for specific patient subgroups.

Surgery

Shimada S, **Ivanics T**, **Kitajima T**, **Shamaa T**, **Rizzari M**, **Collins K**, **Yoshida A**, **Abouljoud M**, **Moonka D**, **Zhang J**, **Lu M**, and **Nagai S**. Improvements in liver transplant outcomes in patients with HCV/HIV coinfection after the introduction of direct-acting antiviral therapies. *Transpl Infect Dis* 2022; e13808. Epub ahead of print. PMID: 35157334. Full Text

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BACKGROUND: In recipients with HCV/HIV coinfection, the impact that the wider use of direct-acting antivirals (DAAs) has had on post-liver transplant (LT) outcomes has not been evaluated. We investigated the impact of DAAs introduction on post-LT outcome in patients with HCV/HIV coinfection. METHODS: Using Organ Procurement and Transplant Network/United Network for Organ Sharing data, we compared post-LT outcomes in patients with HCV and/or HIV pre- and post-DAAs introduction. We categorized these patients into two eras: pre-DAA (2008-2012 [pre-DAA era]) and post-DAA (2014-2019 [post-DAA era]). To study the impact of DAAs introduction, inverse probability of treatment weighting was used to adjust patient characteristics. RESULTS: A total of 17 215 LT recipients were eligible for this study (HCV/HIV [n = 160]; HIV mono-infection [n = 188]; HCV mono-infection [n = 16 867]). HCV/HIV coinfection and HCV mono-infection had a significantly lower hazard of 1- and 3-year graft loss post-DAA, compared pre-DAA (1-year: adjusted hazard ratio [aHR] 0.29, 95% confidence interval (CI) 0.16-0.53 in HIV/HCV, aHR 0.58, 95% CI 0.54-0.63, respectively; 3-year: aHR 0.30, 95% CI 0.14-0.61, aHR 0.64, 95% CI 0.58-0.70, respectively). The hazards of 1- and 3-year graft loss post-DAA in HIV mono-infection were comparable to those in pre-DAA. HCV/HIV coinfection had significantly lower patient mortality post-DAA, compared to pre-DAA (1-year: aHR 0.30, 95% CI 0.17-0.55; 3-year: aHR 0.31, 95% CI 0.15-0.63). CONCLUSIONS: Post-LT outcomes in patients with coinfection significantly improved and became comparable to those with HCV mono-infection after introducing DAA therapy. The introduction of DAAs supports the use of LT in the setting of HCV/HIV coinfection.

Surgery

Shimada S, **Kitajima T**, **Suzuki Y**, **Kuno Y**, **Shamaa T**, **Ivanics T**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, **Moonka D**, and **Nagai S**. Impact on Waitlist Outcomes from Changes in the Medical Eligibility of Candidates for Simultaneous Liver-Kidney Transplantation Following Implementation of the 2017 Organ Procurement and Transplantation Network/United Network for Organ Sharing Policy in the United States. *Ann Transplant* 2022; 27. PMID: 35177580. Full Text

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BACKGROUND The new simultaneous liver-kidney transplantation (SLK) listing criteria in the United States was implemented in 2017. We aimed to investigate the impact on waitlist and post-transplantation outcomes from changes in the medical eligibility of candidates for SLK after policy implementation in the United States. MATERIAL AND METHODS We analyzed adult primary SLK candidates between January 2015 and March 2019 using the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) registry. We compared waitlist practice, post-transplantation outcomes, and final transplant graft type in SLK candidates before and after the policy. RESULTS A total of 4641 patients were eligible, with 2975 and 1666 registered before and after the 2017 policy, respectively. The daily number of SLK candidates was lower after the 2017 policy (3.25 vs 2.89, P=0.01); 1956 received SLK and 95 received liver transplant alone (LTA). The proportion of patients who eventually received LTA was higher after the 2017 policy (7.9% vs 3.0%; P<0.001). The 1-year graft survival rate was worse in patients with LTA than in those with SLK (80.5% vs 90.4%; P=0.003). The adjusted risk of 1-year graft failure in patients with LTA was 2.01 (95% confidence interval 1.13-3.58, P=0.01) compared with patients with SLK among the SLK candidates. CONCLUSIONS Although the number of registrations for SLK increased, the number of SLK transplants decreased, and the number of liver transplants increased. LTA in this patient cohort was associated with worse post-transplantation outcomes.

Urology

Alanee S, **Deebajah M**, **Dabaja A**, **Peabody J**, and **Menon M**. Utilizing lesion diameter and prostate specific antigen density to decide on magnetic resonance imaging guided confirmatory biopsy of prostate imaging reporting and data system score three lesions in African American prostate cancer patients managed with active surveillance. *Int Urol Nephrol* 2022; Epub ahead of print. PMID: 35138582. Full Text

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OBJECTIVE: The objective of the study is to identify the rate of significant prostate cancer (PCa) detection in PI-RADS3 lesions in AA patients stratified by PSAD threshold of < 0.15 vs. ≥ 0.15 ng/ml(2) and lesion diameter of < 1 cm vs ≥ 1 cm. METHODS: We analyzed our institutional database of MRI-TB to identify the rate of significant prostate cancer (PCa) detection in PI-RADS3 lesions in AA patients stratified by PSAD threshold of < 0.15 vs. ≥ 0.15 ng/ml(2) and lesion diameter of < 1 cm vs ≥ 1 cm. Significant prostate cancer was defined as Gleason grade group 2 or higher on MRI-TB of the PI-RADS 3 lesion. RESULTS: Of 768 patients included in the database, 211 (27.5%) patients identified themselves as AAs. Mean age of AA patients was 63 years and mean PSAD was 0.21. Sixty nine (32.7%) AA patients were found to have PI-RADS 3 lesions. Mean PSAD of AA patients with PI-RADS 3 lesions was 0.21 ng/ml(2) as well. Fifty percent of AA patients with PI-RADS 3 lesions had PSAD ≥ 0.15 ng/ml(2). Significant PCa detection rate for AA patients with PI-RADS 3 lesions was 9% for PSAD of ≥ 0.15 vs. 0.03% percent for AA patients with PSAD < 0.15 ng/ml(2) (OR 7.056, CI 1.017-167.9, P = 0.04). Stratification by lesion diameter (< 1 cm vs. > 1 cm) resulted in missing 0% of significant PCa when only AA patients with PSAD ≥ 0.15 ng/ml(2) and lesion diameter ≥ 1 cm received MRI-TB. CONCLUSIONS: We report on the performance of a reported PSAD density threshold in detecting significant PCa in one of the largest series of AA patients receiving MRI-TB of the prostate. Our results have direct clinical implications when counseling AA patients with PI-RADS 3 lesion on whether they should undergo MRI-TB of such lesions.

Urology
Prebay ZJ, **Patel A**, Johnson A, Kim T, Fonshell C, Raman JD, Ginzburg S, Uzzo RG, **Rogers CG**, and Lane BR. Perspectives on the Role of Biopsy for Management of T1 Renal Masses: Survey Results from Two Regional Quality Improvement Collaboratives. *Urology* 2022; Epub ahead of print. PMID: 35143851.
Full Text

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OBJECTIVES: To understand perspectives on RMB, a survey was distributed to urologists in the Michigan Urological Surgery Improvement Collaborative (MUSIC) and Pennsylvania Urologic Regional Collaborative (PURC). Renal mass biopsy (RMB) may reduce treatment of benign renal neoplasms; however, utilization varies widely. METHODS: MUSIC and PURC are two quality improvement collaboratives that include a "real-world" collection of urologists from academic- and community-based settings. A 12-item survey assessing current RMB utilization, patient- and tumor-specific factors, adverse events, impact on management, and simulated patient scenarios was distributed. Responses are reported using descriptive statistics. RESULTS: Many responders (n=54) indicated using RMB in <25% of cT1a (59%) and cT1b (85%) tumors. The most important patient-specific factors on decision to recommend RMB were possible metastasis to kidney (94%), patient comorbidity as a risk factor for active treatment (89%), and patient age (81%). The most important tumor-specific factors were presence of bilateral tumors (81%), tumor size (70%) and perceived potential of performing nephron-sparing surgery (67%). Ten (19%) noted barriers to RMB in their practice, 23 (43%) recalled experiences with complications or poor outcomes; without asking severity, and 43 (80%) reported experiences where the results of RMB altered management. When presented with simulated patients, few urologists (9-20%) recommended RMB in younger patients with any sized mass. Recommendations varied based on patient age, comorbidity, and tumor size. CONCLUSIONS: Understanding perspectives on RMB usage is essential prior to implementing quality improvement efforts. Most urologists participating in two statewide collaboratives infrequently recommend RMB. Optimizing RMB utilization may help reduce unnecessary treatments.

Conference Abstracts

Allergy and Immunology
Afshan T, Kulkarni A, Blackshere T, Smith J, Tesson E, Hartert T, Rivera-Spoljaric K, **Zoratti E**, **Joseph C**, Gern J, and Singh AM. Childhood Allergy and the NeOnatal Environment (CANOE) Research Protocol and Recruitment Redesign during the COVID-19 Pandemic. *J Allergy Clin Immunol* 2022; 149(2):AB7. Full Text

Rationale: Recruitment for research studies is a challenging endeavor that has been further complicated by the COVID-19 pandemic. While clinical research was temporarily halted due to the pandemic, it was hypothesized that study and recruitment restructuring would enable brisk enrollment when research resumed. Methods: A new NIH/ECHO-supported multi-center birth cohort, “Childhood Allergy and the NeOnatal Environment” (CANOE) was launched in January 2019 across four sites to determine how pre-, peri-, and post-natal factors influence development of recurrent wheezing and atopic dermatitis. Study recruitment was halted for nine months due to the COVID-19 pandemic, during which recruitment and study procedures were redesigned. Results: Recruitment strategies were modified to limit in-person contact, shifting toward alternative HIPAA-compliant methods like clinician referrals, institutional social media, and telemedicine consenting. Protocol changes included reducing frequency of in-person visits, leveraging clinical care visits to collect bio-samples, expanded self-collection of samples at home, and posting study materials online. Recruitment rates range from 3-12 families per month per site. In-clinic recruitment with modifications for social distancing has been successful across all sites. Other successful strategies have included targeted social media posts, mailed letters, and email. Rates of consent have been similar across recruitment strategies and the implementation of multiple recruitment strategies has yielded the highest rates of ongoing consent and enrollment of mother-infant dyads. Conclusions: Study procedures that prioritize health and safety measures such as social distancing, study participant convenience, and diversification of recruitment strategies enable continued birth cohort recruitment and data collection while adhering to public health restrictions during the pandemic.

Allergy and Immunology
Altman M, Bacharier L, Villarreal M, Gill M, Liu A, Gruchalla R, O G, Robison R, Hershey GK, Sherenian M, Rivera-Spoljaric K, Stokes J, **Zoratti E**, Teach S, Kattan M, Lovinsky-Desir S, Visness C, Becker P, Gergen P, Gern J, Sorkness C, Busse W, and Jackson D. Distinct Airway Inflammatory Pathways Associated with Asthma Exacerbations are Modulated by Mepolizumab Therapy in Children. *J Allergy Clin Immunol* 2022; 149(2):AB146. Full Text

Rationale: Identification of specific airway inflammatory pathways can lead to effective personalized treatment with biologics in asthma and insights to mechanisms of action. Methods: 290 urban children with exacerbation-prone asthma and ≥150/mm3 blood eosinophils were randomized (1:1) to placebo or mepolizumab added to guideline-based care. Nasal lavage samples were collected at randomization and during treatment for RNA-sequencing, and analyzed by cell-deconvolution modular analysis to assess genome-wide expression patterns associated with exacerbation number and effect of treatment. Results: Mepolizumab significantly reduced the frequency of exacerbations compared to placebo. At randomization, there were no differences in expression between treatment groups; multiple modules were subsequently differentially expressed during mepolizumab but not placebo treatment. Furthermore, expression levels of multiple modules were associated with the exacerbation number during the study, with distinct relationships observed in the placebo and/or mepolizumab groups. Notably, higher expression at randomization of an eosinophil-associated module enriched for Type-2 genes including IL4, IL5, and IL13, was associated with increased exacerbations in placebo ($\beta=0.19$, $p<0.001$), but not mepolizumab-treated children (interaction $p<0.01$). Furthermore, mepolizumab treatment reduced expression of this module (Fold-change=0.62, $p<0.001$). In contrast, higher expression at randomization of an eosinophil-associated module enriched for eosinophil activation (e.g. CD9) and mucus hypersecretion (e.g. MUC5AC) genes was associated with exacerbation number in both groups throughout the study ($\beta=0.18$, $p<0.01$) and was unaltered by mepolizumab therapy. Conclusions: Multiple distinct airway inflammation patterns were identified associated with exacerbation frequency. These findings identify inflammatory endotypes and indicate likelihood and potential mechanisms of a beneficial clinical response to mepolizumab therapy to prevent exacerbations.

Allergy and Immunology

Eapen A, Kottyan L, Parameswaran S, Forney C, Edsall L, Miller D, Donmez O, Weirauch M, Dunn K, Lu X, Granitto M, Rowden H, Magier A, Pujato M, Chen X, Bernstein D, Devonshire A, and Rothenberg M. Epigenetic and Transcriptional Dysregulation in T cells of Patients with Atopic Dermatitis. *J Allergy Clin Immunol* 2022; 149(2):AB5. Full Text

Rationale: Atopic dermatitis (AD) is linked to genetic and environmental risk factors. The effect of these factors on molecular and transcriptional events is not well understood. Immunologically, AD involves skin barrier defects and CD4+ T cells that produce inflammatory cytokines and amplify epidermal dysfunction Our objective was to investigate epigenetic mechanisms that may account for genetic susceptibility in CD4+ T cells. Methods: We measured chromatin accessibility (ATAC-seq), NFKB1 binding (ChIP-seq), and gene expression (RNA-seq) in anti-CD3/CD28 stimulated CD4+ T cells from 6 subjects with active moderate-to-severe AD and 6 age-matched non-allergic controls. Results: AD genetic risk loci were enriched for open chromatin regions in stimulated CD4+ T cells. The majority of ATAC-seq peaks were shared between matched AD-control pairs, consistent with those sections of chromatin being equally available. In contrast, NFKB DNA binding motifs were enriched in AD-dependent open chromatin. NFKB1 ChIP-seq identified genomic regions that were more strongly bound in AD cases, more strongly bound in controls, or shared between cases and controls. Chromatin that was strongly accessible and bound by NFKB1 in AD was enriched for AD genetic risk variants. Using whole genome sequencing data, we identified genotype-dependent accessible chromatin at AD risk loci corresponding to 32 genes with genotype-dependent expression in stimulated CD4+ T cells. Conclusions: The response of CD4+ T cells to stimulation is AD-specific and results in differential chromatin accessibility and transcription factor binding. These differences in transcriptional regulation result in epigenetic and transcriptional dysregulation in CD4+ T cells of patients with AD.

Allergy and Immunology

Jackson D, Bacharier L, Gergen P, Gagalis L, Villarreal M, Gill M, Liu A, Gruchalla R, Cohen R, Makhija M, Hershey GK, Sherenian M, Rivera-Spoljaric K, Stokes J, **Zoratti E**, Teach S, Kattan M, Visness C, Becker P, Gern J, Sorkness C, Busse W, and Altman M. Phenotype-directed Therapy with Mepolizumab for Urban Children with Exacerbation-Prone Asthma. *J Allergy Clin Immunol* 2022; 149(2):AB146. Full Text

Rationale: Asthma exacerbations are common in urban children and have significant short- and long-term consequences. Elevated peripheral blood and airway eosinophils have been identified as risk factors for exacerbations, and therapies targeting these biomarkers reduce exacerbations in adults; however, data on anti-eosinophil treatment in children and adolescents are limited. The primary objective of this study is to determine if phenotype-directed use of mepolizumab reduces the rate of asthma exacerbations in urban children. Methods: Urban children 6-17 years of age (n=290) with exacerbation-prone asthma (2+ exacerbations in previous year) and blood eosinophils ≥150/mm3 were randomized 1:1 to mepolizumab (6-11 years: 40 mg; 12-17 years: 100 mg) or placebo every 4 weeks added to guideline-based care for 1 year. The primary outcome was the number of asthma exacerbations treated with systemic corticosteroids; a comparison of the two treatment groups was evaluated using a negative-binomial model. Results: Mepolizumab significantly reduced peripheral blood eosinophils ($p<0.01$) and nasal eosinophils ($p<0.01$). The rate of asthma exacerbations was significantly lower in mepolizumab (0.96 exacerbations/year) vs. placebo (1.30 exacerbations/year) treated participants [relative risk 0.73 (95% confidence interval 0.56-0.96), $p=0.027$]. There were no significant differences in secondary outcomes, including time to first exacerbation, lung function, quality of life, or composite asthma severity index (CASI). Post hoc, the time to second asthma exacerbation increased significantly with mepolizumab ($p=0.02$). Adverse events were similar between groups. Conclusions: Phenotype-directed therapy with mepolizumab in urban children and adolescents with exacerbation-prone eosinophilic asthma significantly reduced recurrent exacerbations and was well tolerated, but did not impact other asthma outcomes.

Allergy and Immunology

Seibold M, Moore C, Everman J, Williams B, Nolin J, Fairbanks-Mahnke A, Plender E, Patel B, Arbes S, Bacharier L, Bendixsen C, Calatroni A, Camargo C, Dupont W, Furuta G, Gebretsadik T, Gruchalla R, Gupta R, Hershey GK, Murrison L, Jackson D, **Johnson C**, Kattan M, Liu A, Lussier S, O'Connor G, River-Spoljaric K, Phipatanakul W, Rothenberg M, Seroogy C, Teach S, **Zoratti E**, Togias A, Fulkerson P, and Hartert T. SARS-CoV-2 surveillance in households with and without asthmatic/allergic children: The Human Epidemiology and Response to SARS-CoV-2 study (HEROS). *J Allergy Clin Immunol* 2022; 149(2):AB325. Full Text

Rationale: Whether children and people with asthma and allergic diseases are at increased risk for SARS-CoV-2 infection is not known. Neither is their role in household transmission. Methods: Biweekly nasal sample collections and weekly surveys were conducted to identify incident SARS-CoV-2 infections among children (<13 years) and teenagers (13-21 years) enrolled in asthma/allergic disease focused cohorts, and their household members, from May 2020-February 2021. Probability of subject/household infections and household transmissions were calculated using time-to-event analyses, and factors associated with infection and transmission risk using regression analyses. Results: Household (N=1,394) and subject (N=4,142) SARS-CoV-2 infection probability was 25.8% and 14.0%, respectively, and was similar for children (14.0%,CI:8.0-19.6%), teenagers (12.1%,CI:8.2-15.9%), and adults (14.0%,CI:9.5-18.4%). Infections were symptomatic in 24.5% of children, 41.2% of teenagers, and 62.5% of adults. Exposure to both symptomatic (aHR=87.39,CI:58.02-131.63) and asymptomatic (aHR=27.80,CI:17.16–45.03) infected household members was a risk factor for infection. Food allergy was associated with decreased infection risk (aHR=0.50,CI:0.32-0.81), but asthma was not (aHR=1.04,CI:0.73-1.46). Household infection risk was associated with attending in-person school (aHR=1.67,CI:1.09-2.57). Household secondary attack rate was 57.7%. Decreased risk of household transmission was associated with teen age, lower BMI, and lower viral load. Conclusions: Asthma does not increase risk of SARS-CoV-2 infection, while food allergy is protective. SARS-CoV-2 infection risk in children is similar to that of teenagers and adults. SARS-CoV-2 transmission risk and secondary attack rate is much higher than previously estimated in households with children, likely driven by the high frequency of asymptomatic childhood infections.

Dermatology

Gold LS, Green LJ, Dhawan S, Kirsch A, Selmer J, and Praestegaard M. Rapid and clinically meaningful improvement of plaque psoriasis-associated itch after treatment with calcipotriol and betamethasone dipropionate cream. *J Dtsch Dermatol Ges* 2022; 20:32-32. Full Text

[Gold, Linda Stein] Henry Ford Hlth Syst, Dermatol Clin Res, Detroit, MI USA. [Green, Lawrence J.] George Washington Univ, Sch Med, Washington, DC USA. [Dhawan, Sunil] Ctr Dermatol Clin Res, Fremont, CA USA. [Dhawan, Sunil] Stanford Univ, Sch Med, Fremont, CA USA. [Kirsch, Astrid] Almirall Hermal GmbH, Reinbek, Germany. [Selmer, Johan; Praestegaard, Morten] MC2 Therapeut, Horsholm, Denmark.

Dermatology

Wurzer E, **Gold LS**, Jalili A, Thoning H, and Calzavara-Pinton P. Proactive Management with Cal/BD Foam in Patients with Plaque Psoriasis prolongs Time with improved health-related Quality of Life when compared with reactive Management. *J Dtsch Dermatol Ges* 2022; 20:35-35. Full Text

[Wurzer, Elisabeth] LEO Pharma GmbH, New Isenburg, Germany. [Gold, Linda Stein] Henry Ford Hosp, Dept Dermatol, Detroit, MI 48202 USA. [Jalili, Ahmad] Burgenstock Med Ctr, Dermatol & Skin Care, Obburgen, Switzerland. [Thoning, Henrik] LEO Pharma AS, Ballerup, Denmark. [Calzavara-Pinton, Piergiacomo] Univ Brescia, Dept Dermatol, Brescia, Italy.

Hematology-Oncology
Bekaii-Saab TS, Spira AI, Yaeger R, Buchschacher GL, McRee AJ, Sabari JK, Johnson ML, Barve MA, Hafez N, Velastegui K, Christensen JG, Kheoh T, DerTorossian H, and **Rybkin II**. KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRAS mutation. *J Clin Oncol* 2022; 40(4 SUPPL). Full Text

T.S. Bekaii-Saab

Background: KRAS, the most frequently mutated oncogene in cancer, is a key mediator of the RAS/MAPK signaling cascade that promotes cellular growth and proliferation. KRAS mutations occur in approximately 90% of pancreatic cancer, and approximately 2% of these are KRASG12C mutations. Adagrasib, an investigational agent, is a KRASG12Cinhibitor that irreversibly and selectively binds KRASG12C, locking it in its inactive state; adagrasib has been optimized for favorable pharmacokinetic (PK) properties, including long half-life (24 h), extensive tissue distribution, dose-dependent PK, as well as CNS penetration. Methods: KRYSTAL-1 (NCT03785249) is a multicohort Phase 1/2 study evaluating adagrasib as monotherapy or in combinations in pts with advanced solid tumors harboring a KRAS mutation. Here we report preliminary data from pts enrolled in a Phase 2 cohort evaluating single-agent adagrasib administered orally at 600 mg BID in previously treated pts with unresectable or metastatic solid tumors (excluding NSCLC and CRC), including pancreatic and other GI cancers. Study endpoints include clinical activity, safety, and PK. Results: The data cutoff was 10 September 2021. A total of 42 pts were enrolled in this cohort (median age 63.5 years, range 21-89; 52% female; 71% white; 29%/71% ECOG PS 0/1; median 2 prior lines of therapy, range 1-7; median follow-up 6.3 months), of whom 30 pts had KRASG12C-mutant GI tumors (12 PDAC, 8 biliary tract, 5 appendiceal, 2 gastro-esophageal junction, 2 small bowel, and 1 esophageal). In a preliminary analysis, 27 pts with GI tumors were evaluable for clinical activity; partial responses (PRs) were seen in 41% (11/27, including 3 unconfirmed PRs); the disease control rate (DCR) was 100% (27/27). Of the 12 pts with PDAC (median 3 prior lines of therapy; median follow-up 8.1 months), 10 were evaluable for clinical activity; PRs were seen in 50% (5/10, including 1 unconfirmed PR); the DCR was 100% (10/10). Median progression-free survival (PFS) was 6.6 months (95% CI 1.0-9.7), and treatment was ongoing in 50% of pts with PDAC. Among the 17 evaluable pts with other GI tumors, 6 achieved PR (35%; 2 unconfirmed) with a DCR of 100% (17/17); 11 pts were still receiving treatment. In the overall cohort, treatmentrelated adverse events of any grade occurred in 91% (38/42), the most frequent being nausea (48%), diarrhea (43%), vomiting (43%), and fatigue (29%); grade 3/4 events occurred in 21% of pts, with no grade 5 events. Conclusions: Adagrasib monotherapy is well tolerated and demonstrates encouraging clinical activity in pretreated pts with PDAC and other GI tumors harboring a KRASG12Cmutation. Further exploration of adagrasib is ongoing in this pt population (NCT03785249).

Hematology-Oncology
Saad M, **Clark J**, **Shah RA**, **Siddiqui F**, **Parikh P**, **Gartrelle K**, **Natour AK**, **Khan G**, and **Kwon DS**. A single-center analysis of 30- and 90-day post-pancreatectomy complications in patients undergoing neoadjuvant radiation with EBRT versus MRI-guided SBRT. *J Clin Oncol* 2022; 40(4 SUPPL). Full Text

M. Saad

Background: Stereotactic MRI -guided adaptive radiation therapy (SMART) is being investigated for enhanced efficacy in locally advanced, borderline resectable and medically inoperable pancreatic cancer. Traditionally, conventionally fractioned chemoradiation (EBRT) has been used for operable patients. We sought to evaluate whether there would be differences in surgical complications and outcomes in the 30- and 90- day postoperative period in patients who received either neoadjuvant EBRT or SMART followed by definitive surgery. Methods: A retrospective single-center analysis of patients with either resectable, borderline resectable or locally advanced tumors of the pancreas or duodenum, treated with neoadjuvant radiation and surgical management between 2014 and 2021 was performed. Patient demographics and postsurgical complications were collected and stratified according to both treatment arms. The International Study Group of Pancreatic Surgery (ISGPS) classifications were used to define and grade postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatectomy

hemorrhage (PPH). A univariate analysis was done followed by a multivariate analysis. Results: Among the 65 patients (mean age 62.6 years, 46% female) who underwent definitive surgical intervention, 44 (67.7%) received EBRT, and 21 (32.3%) received SMART. Baseline characteristics including age, sex, race, ASA, and Charlson comorbidity index (CCI) scores were found to be similar. Onunivariate analysis, PPH was significantly higher in SMART (OR, 6.6; 95% CI, 1.2 to 37.3; p = 0.034). After adjusting for confounders on multivariate analysis, it appears there is a trend towards higher PPH in the SMART cohort (p = 0.052). Conclusions: Neoadjuvant SMART followed by definitive surgery is not associated with worse outcomes in the 30- and 90- day postoperative period vs. neoadjuvant EBRT. Although there was a trend towards PPH on multivariate analysis, further discussion is warranted involving vascular resection, vascular stents and anticoagulation.

Nephrology

Provenzano M, Toto RD, Vart P, **Umanath K**, Luis Górriz J, Mark PB, Mann JFE, Chertow GM, McMurray JJV, Correa-Rotter R, Rossing P, Langkilde AM, Stefánsson BV, Wheeler DC, and Lambers Heerspink H. POS-255 EFFECT OF DAPAGLIFLOZIN ON BLOOD PRESSURE IN PATIENTS WITH CKD: A PRE-SPECIFIED ANALYSIS FROM DAPA-CKD. *Kidney Int Rep* 2022; 7(2):S112. Full Text

Introduction: Hypertension is common in patients with chronic kidney disease (CKD). Sodium-glucose cotransporter 2 inhibitors decrease blood pressure in patients with type 2 diabetes, but the consistency and magnitude of blood pressure lowering with dapagliflozin in patients with CKD is unknown. We performed a pre-specified analysis of the DAPA-CKD trial to investigate the effect of dapagliflozin on systolic blood pressure in patients with CKD, with and without type 2 diabetes. Methods: We randomized 4,304 adults with baseline eGFR 25–75 mL/min/1.73m2and urinary albumin-to-creatinine ratio (UACR) 200–5,000 mg/g to either dapagliflozin 10 mg or placebo once daily; median follow-up was 2.4 years. The primary outcome was a composite of sustained ≥50% eGFR decline, end-stage kidney disease, or death from a kidney or cardiovascular cause. Change in systolic blood pressure was a pre-specified endpoint. Subgroup analyses were performed according to baseline type 2 diabetes status. Results: Baseline mean (SD) systolic blood pressure was 137.1 mmHg (17.4); in participants with and without type 2 diabetes 139.2 mmHg (17.3) and 132.6 mmHg (16.7), respectively. By week 2, dapagliflozin compared to placebo reduced systolic blood pressure by 3.6 mmHg (95%CI 2.8, 4.4; p<0.001), an effect maintained over the duration of the trial, with similar reductions in patients with and without type 2 diabetes (Table). The reduction in systolic blood pressure with dapagliflozin explained 7.6% (95%CI 1.8, 20.9) of the effect on the primary composite outcome, with similar proportions explained in patients with and without type 2 diabetes. [Formula presented] Conclusions: In participants with CKD, dapagliflozin lowered systolic blood pressure with a consistent effect in participants with and without type 2 diabetes. The modest reduction in blood pressure explained a small proportion of the benefit of dapagliflozin on the primary outcome. Conflict of interest Potential conflict of interest: HLH received grant funding and honoraria for consultancy as a member of the steering committee of the DAPA-CKD trial from AstraZeneca. Honoraria for steering committee membership paid to his institution from Janssen, Gilead, Bayer, Chinook, CSL Pharma honoraria for consultancy paid to his institution from Abbvie, Boehringer Ingleheim, Retrophin, Novo Nordisk honoraria for advisory board participation paid to his institution from Janssen, Merck, Mitsubishi Tanabe and Munipharma lecture fees received from AstraZeneca and Mitsubishi Tanabe and grant support received from Boehringer Ingelheim.

Public Health Sciences

Afshan T, Kulkarni A, Blackshere T, Smith J, Tesson E, Hartert T, Rivera-Spoljaric K, **Zoratti E**, **Joseph C**, Gern J, and Singh AM. Childhood Allergy and the NeOnatal Environment (CANOE) Research Protocol and Recruitment Redesign during the COVID-19 Pandemic. *J Allergy Clin Immunol* 2022; 149(2):AB7. Full Text

Rationale: Recruitment for research studies is a challenging endeavor that has been further complicated by the COVID-19 pandemic. While clinical research was temporarily halted due to the pandemic, it was hypothesized that study and recruitment restructuring would enable brisk enrollment when research resumed. Methods: A new NIH/ECHO-supported multi-center birth cohort, “Childhood Allergy and the NeOnatal Environment” (CANOE) was launched in January 2019 across four sites to determine how pre-, peri-, and post-natal factors influence development of recurrent wheezing and atopic dermatitis. Study

recruitment was halted for nine months due to the COVID-19 pandemic, during which recruitment and study procedures were redesigned. Results: Recruitment strategies were modified to limit in-person contact, shifting toward alternative HIPAA-compliant methods like clinician referrals, institutional social media, and telemedicine consenting. Protocol changes included reducing frequency of in-person visits, leveraging clinical care visits to collect bio-samples, expanded self-collection of samples at home, and posting study materials online. Recruitment rates range from 3-12 families per month per site. In-clinic recruitment with modifications for social distancing has been successful across all sites. Other successful strategies have included targeted social media posts, mailed letters, and email. Rates of consent have been similar across recruitment strategies and the implementation of multiple recruitment strategies has yielded the highest rates of ongoing consent and enrollment of mother-infant dyads. Conclusions: Study procedures that prioritize health and safety measures such as social distancing, study participant convenience, and diversification of recruitment strategies enable continued birth cohort recruitment and data collection while adhering to public health restrictions during the pandemic.

Public Health Sciences

Seibold M, Moore C, Everman J, Williams B, Nolin J, Fairbanks-Mahnke A, Plender E, Patel B, Arbes S, Bacharier L, Bendixsen C, Calatroni A, Camargo C, Dupont W, Furuta G, Gebretsadik T, Gruchalla R, Gupta R, Hershey GK, Murrison L, Jackson D, **Johnson C**, Kattan M, Liu A, Lussier S, O'Connor G, River-Spoljaric K, Phipatanakul W, Rothenberg M, Seroogy C, Teach S, **Zoratti E**, Togias A, Fulkerson P, and Hartert T. SARS-CoV-2 surveillance in households with and without asthmatic/allergic children: The Human Epidemiology and Response to SARS-CoV-2 study (HEROS). *J Allergy Clin Immunol* 2022; 149(2):AB325. Full Text

Rationale: Whether children and people with asthma and allergic diseases are at increased risk for SARS-CoV-2 infection is not known. Neither is their role in household transmission. Methods: Biweekly nasal sample collections and weekly surveys were conducted to identify incident SARS-CoV-2 infections among children (<13 years) and teenagers (13-21 years) enrolled in asthma/allergic disease focused cohorts, and their household members, from May 2020-February 2021. Probability of subject/household infections and household transmissions were calculated using time-to-event analyses, and factors associated with infection and transmission risk using regression analyses. Results: Household (N=1,394) and subject (N=4,142) SARS-CoV-2 infection probability was 25.8% and 14.0%, respectively, and was similar for children (14.0%,CI:8.0-19.6%), teenagers (12.1%,CI:8.2-15.9%), and adults (14.0%,CI:9.5-18.4%). Infections were symptomatic in 24.5% of children, 41.2% of teenagers, and 62.5% of adults. Exposure to both symptomatic (aHR=87.39,CI:58.02-131.63) and asymptomatic (aHR=27.80,CI:17.16–45.03) infected household members was a risk factor for infection. Food allergy was associated with decreased infection risk (aHR=0.50,CI:0.32-0.81), but asthma was not (aHR=1.04,CI:0.73-1.46). Household infection risk was associated with attending in-person school (aHR=1.67,CI:1.09-2.57). Household secondary attack rate was 57.7%. Decreased risk of household transmission was associated with teen age, lower BMI, and lower viral load. Conclusions: Asthma does not increase risk of SARS-CoV-2 infection, while food allergy is protective. SARS-CoV-2 infection risk in children is similar to that of teenagers and adults. SARS-CoV-2 transmission risk and secondary attack rate is much higher than previously estimated in households with children, likely driven by the high frequency of asymptomatic childhood infections.

Radiation Oncology

Saad M, **Clark J**, **Shah RA**, **Siddiqui F**, **Parikh P**, **Gartrelle K**, **Natour AK**, **Khan G**, and **Kwon DS**. A single-center analysis of 30- and 90-day post-pancreatectomy complications in patients undergoing neoadjuvant radiation with EBRT versus MRI-guided SBRT. *J Clin Oncol* 2022; 40(4 SUPPL). Full Text

M. Saad

Background: Stereotactic MRI -guided adaptive radiation therapy (SMART) is being investigated for enhanced efficacy in locally advanced, borderline resectable and medically inoperable pancreatic cancer. Traditionally, conventionally fractioned chemoradiation (EBRT) has been used for operable patients. We sought to evaluate whether there would be differences in surgical complications and outcomes in the 30- and 90- day postoperative period in patients who received either neoadjuvant EBRT or SMART followed

by definitive surgery. Methods: A retrospective single-center analysis of patients with either resectable, borderline resectable or locally advanced tumors of the pancreas or duodenum, treated with neoadjuvant radiation and surgical management between 2014 and 2021 was performed. Patient demographics and postsurgical complications were collected and stratified according to both treatment arms. The International Study Group of Pancreatic Surgery (ISGPS) classifications were used to define and grade postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatectomy hemorrhage (PPH). A univariate analysis was done followed by a multivariate analysis. Results: Among the 65 patients (mean age 62.6 years, 46% female) who underwent definitive surgical intervention, 44 (67.7%) received EBRT, and 21 (32.3%) received SMART. Baseline characteristics including age, sex, race, ASA, and Charlson comorbidity index (CCI) scores were found to be similar. Onunivariate analysis, PPH was significantly higher in SMART (OR, 6.6; 95% CI, 1.2 to 37.3; p = 0.034). After adjusting for confounders on multivariate analysis, it appears there is a trend towards higher PPH in the SMART cohort (p = 0.052). Conclusions: Neoadjuvant SMART followed by definitive surgery is not associated with worse outcomes in the 30- and 90- day postoperative period vs. neoadjuvant EBRT. Although there was a trend towards PPH on multivariate analysis, further discussion is warranted involving vascular resection, vascular stents and anticoagulation.

Surgery
Saad M, **Clark J**, **Shah RA**, **Siddiqui F**, **Parikh P**, **Gartrelle K**, **Natour AK**, **Khan G**, and **Kwon DS**. A single-center analysis of 30- and 90-day post-pancreatectomy complications in patients undergoing neoadjuvant radiation with EBRT versus MRI-guided SBRT. *J Clin Oncol* 2022; 40(4 SUPPL). Full Text

M. Saad

Background: Stereotactic MRI -guided adaptive radiation therapy (SMART) is being investigated for enhanced efficacy in locally advanced, borderline resectable and medically inoperable pancreatic cancer. Traditionally, conventionally fractioned chemoradiation (EBRT) has been used for operable patients. We sought to evaluate whether there would be differences in surgical complications and outcomes in the 30- and 90- day postoperative period in patients who received either neoadjuvant EBRT or SMART followed by definitive surgery. Methods: A retrospective single-center analysis of patients with either resectable, borderline resectable or locally advanced tumors of the pancreas or duodenum, treated with neoadjuvant radiation and surgical management between 2014 and 2021 was performed. Patient demographics and postsurgical complications were collected and stratified according to both treatment arms. The International Study Group of Pancreatic Surgery (ISGPS) classifications were used to define and grade postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatectomy hemorrhage (PPH). A univariate analysis was done followed by a multivariate analysis. Results: Among the 65 patients (mean age 62.6 years, 46% female) who underwent definitive surgical intervention, 44 (67.7%) received EBRT, and 21 (32.3%) received SMART. Baseline characteristics including age, sex, race, ASA, and Charlson comorbidity index (CCI) scores were found to be similar. Onunivariate analysis, PPH was significantly higher in SMART (OR, 6.6; 95% CI, 1.2 to 37.3; p = 0.034). After adjusting for confounders on multivariate analysis, it appears there is a trend towards higher PPH in the SMART cohort (p = 0.052). Conclusions: Neoadjuvant SMART followed by definitive surgery is not associated with worse outcomes in the 30- and 90- day postoperative period vs. neoadjuvant EBRT. Although there was a trend towards PPH on multivariate analysis, further discussion is warranted involving vascular resection, vascular stents and anticoagulation.

HFHS Publications on COVID-19

Allergy and Immunology

Afshan T, Kulkarni A, Blackshere T, Smith J, Tesson E, Hartert T, Rivera-Spoljaric K, **Zoratti E**, **Joseph C**, Gern J, and Singh AM. Childhood Allergy and the NeOnatal Environment (CANOE) Research Protocol and Recruitment Redesign during the COVID-19 Pandemic. *J Allergy Clin Immunol* 2022; 149(2):AB7. Conference Abstract. Full Text

Gastroenterology

Rehana RW, **Fahad H**, **Sadiq O**, and **Schairer J**. Outcomes of Gastrointestinal Bleeding During the COVID-19 Pandemic. *Gastro Hep Adv* 2022; Epub ahead of print. PMID: 35174367. Full Text

Hematology-Oncology

Elkrief A, Hennessy C, Kuderer NM, Rubinstein SM, Wulff-Burchfield E, Rosovsky RP, Vega-Luna K, Thompson MA, Panagiotou OA, Desai A, Rivera DR, Khaki AR, Tachiki L, Lynch RC, Stratton C, Elias R, Batist G, Kasi A, Shah DP, Bakouny Z, Cabal A, Clement J, Crowell J, Dixon B, Friese CR, Fry SL, Grover P, Gulati S, Gupta S, **Hwang C**, Khan H, Kim SJ, Klein EJ, Labaki C, McKay RR, Nizam A, Pennell NA, Puc M, Schmidt AL, Shahrokni A, Shaya JA, Su CT, Wall S, Williams N, Wise-Draper TM, Mishra S, Grivas P, French B, Warner JL, and Wildes TM. Geriatric risk factors for serious COVID-19 outcomes among older adults with cancer: a cohort study from the COVID-19 and Cancer Consortium. *Lancet Healthy Longev* 2022; Epub ahead of print. PMID: 35187516. Full Text

Hematology-Oncology

Satyanarayana G, Enriquez KT, Sun T, Klein EJ, Abidi M, Advani SM, Awosika J, Bakouny Z, Bashir B, Berg S, Bernardes M, Egan PC, Elkrief A, Feldman LE, Friese CR, Goel S, Gomez CG, Grant KL, Griffiths EA, Gulati S, Gupta S, **Hwang C**, Jain J, Jani C, Kaltsas A, Kasi A, Khan H, Knox N, Koshkin VS, Kwon DH, Labaki C, Lyman GH, McKay RR, McNair C, Nagaraj G, Nakasone ES, Nguyen R, Nonato TK, Olszewski AJ, Panagiotou OA, Puc M, Razavi P, Robilotti EV, Santos-Dutra M, Schmidt AL, Shah DP, Shah SA, Vieira K, Weissmann LB, Wise-Draper TM, Wu U, Wu JT, Choueiri TK, Mishra S, Warner JL, French B, and Farmakiotis D. Coinfections in Patients With Cancer and COVID-19: A COVID-19 and Cancer Consortium (CCC19) Study. *Open Forum Infect Dis* 2022; 9(3). PMID: 35198648. Full Text

Hospital Medicine

Angelini DE, **Kaatz S**, Rosovsky RP, Zon RL, **Pillai S**, Robertson WE, Elavalakanar P, Patell R, and Khorana A. COVID-19 and venous thromboembolism: A narrative review. *Res Pract Thromb Haemost* 2022; 6(2):e12666. PMID: 35224417. Full Text

Infectious Diseases

Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, Brown SM, Knowlton KU, Self WH, Files DC, Jain MK, Benfield T, Bowdish ME, Leshnower BG, Baker JV, Jensen JU, Gardner EM, Ginde AA, Harris ES, Johansen IS, **Markowitz N**, Matthay MA, Østergaard L, Chang CC, Goodman AL, Chang W, Dewar RL, Gerry NP, Higgs ES, Highbarger H, Murray DD, Murray TA, Natarajan V, Paredes R, Parmar MKB, Phillips AN, Reilly C, Rupert AW, Sharma S, Shaw-Saliba K, Sherman BT, Teitelbaum M, Wentworth D, Cao H, Klekotka P, Babiker AG, Davey VJ, Gelijns AC, Kan VL, Polizzotto MN, Thompson BT, Lane HC, and Neaton JD. Responses to a Neutralizing Monoclonal Antibody for Hospitalized Patients With COVID-19 According to Baseline Antibody and Antigen Levels : A Randomized Controlled Trial. *Ann Intern Med* 2022; 175(2):234-243. PMID: 34928698. Full Text

Public Health Sciences

Chung JR, Kim SS, Belongia EA, McLean HQ, King JP, Nowalk MP, Zimmerman RK, Moehling Geffel K, Martin ET, Monto AS, **Lamerato LE**, Gaglani M, Hoffman E, Volz M, Jackson ML, Jackson LA, Patel MM, and Flannery B. Vaccine effectiveness against COVID-19 among symptomatic persons aged ≥12 years with reported contact with COVID-19 cases, February-September 2021. *Influenza Other Respir Viruses* 2022; Epub ahead of print. PMID: 35170231. Full Text