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HENRY FORD HEALTH

Henry Ford Health Publication List – September 2022

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health personnel. Searches were conducted in PubMed, Embase, and Web of Science during the month, and then imported into EndNote for formatting. There are 181 unique citations listed this month, with 103 articles, 68 conference abstracts, and 10 book chapters.

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

Click the "Full Text" link to view the articles to which Sladen Library provides access. If the full-text of the article is not available, you may request it through ILLiad by clicking on "Request Article," or calling us at (313) 916-2550. If you would like to be added to the monthly email distribution list to automatically receive a PDF of this bibliography, or you have any questions or comments, please contact smoore31@hfhs.org. If your published work has been missed, please use this form to notify us for inclusion on next month's list. All articles and abstracts listed here are deposited into Scholarly Commons, the Henry Ford Health institutional repository.

Articles

Allergy and Immunology
Anesthesiology
Behavioral Health Services/Psychiatry/Neuropsychology
Cardiology/Cardiovascular Research
Center for Health Policy and Health Services Research
Center for Individualized and Genomic Medicine Research
Dermatology
Diagnostic Radiology
Emergency Medicine
Endocrinology and Metabolism
Gastroenterology
Hematology-Oncology
Hospital Medicine
Hypertension and Vascular Research
Infectious Diseases
Internal Medicine
Neurology
Neurosurgery
Obstetrics, Gynecology and Women's Health Services
Orthopedics/Bone and Joint Center
Otolaryngology – Head and Neck Surgery
Pathology and Laboratory Medicine
Pediatrics
Pharmacy
Podiatry
Public Health Sciences
Pulmonary and Critical Care Medicine
Radiation Oncology
Rheumatology
Sleep Medicine
Surgery
Urology

Conference Abstracts

Cardiology/Cardiovascular Research
Dermatology
Diagnostic Radiology
Hematology-Oncology
Internal Medicine
Pathology and Laboratory Medicine
Public Health Sciences
Pulmonary and Critical Care Medicine
Radiation Oncology
Surgery

Books and Book Chapters

Hematology-Oncology
Neurosurgery
Pathology and Laboratory Medicine
Surgery

Articles

Allergy and Immunology

Washington C, 3rd, Dapas M, Biddanda A, Magnaye KM, Aneas I, Helling BA, Szczesny B, Boorgula MP, Taub MA, Kenny E, Mathias RA, Barnes KC, Khurana Hershey GK, Kercsmar CM, Gereige JD, Makhija M, Gruchalla RS, Gill MA, Liu AH, Rastogi D, Busse W, Gergen PJ, Visness CM, Gold DR, Hartert T, **Johnson CC**, Lemanske RF, Jr., Martinez FD, Miller RL, Ownby D, Seroogy CM, Wright AL, **Zoratti EM**, Bacharier LB, Kattan M, O'Connor GT, Wood RA, Nobrega MA, Altman MC, Jackson DJ, Gern JE, McKennan CG, and Ober C. African-specific alleles modify risk for asthma at the 17q12-q21 locus in African Americans. *Genome Med* 2022; 14(1):112. PMID: 36175932. Full Text

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BACKGROUND: Asthma is the most common chronic disease in children, occurring at higher frequencies and with more severe disease in children with African ancestry. METHODS: We tested for association with haplotypes at the most replicated and significant childhood-onset asthma locus at 17q12-q21 and asthma in European American and African American children. Following this, we used whole-genome

sequencing data from 1060 African American and 100 European American individuals to identify novel variants on a high-risk African American-specific haplotype. We characterized these variants in silico using gene expression and ATAC-seq data from airway epithelial cells, functional annotations from ENCODE, and promoter capture (pc)Hi-C maps in airway epithelial cells. Candidate causal variants were then assessed for correlation with asthma-associated phenotypes in African American children and adults. RESULTS: Our studies revealed nine novel African-specific common variants, enriched on a high-risk asthma haplotype, which regulated the expression of GSDMA in airway epithelial cells and were associated with features of severe asthma. Using ENCODE annotations, ATAC-seq, and pcHi-C, we narrowed the associations to two candidate causal variants that are associated with features of T2 low severe asthma. CONCLUSIONS: Previously unknown genetic variation at the 17q12-21 childhood-onset asthma locus contributes to asthma severity in individuals with African ancestries. We suggest that many other population-specific variants that have not been discovered in GWAS contribute to the genetic risk for asthma and other common diseases.

Anesthesiology
Alhalabi E, Zestos M, Kobayashi D, McKelvey GM, and Taylor RA. Interventions to prevent hypothermia in extremely preterm low-weight infants undergoing cardiac catheterisation. *BMJ Open Qual* 2022; 11(3). PMID: 36122994. Full Text

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BACKGROUND: In January 2019, a new device called the Amplatzer Piccolo Occluder was approved by the US Food and Drug Administration for percutaneous closure of patent ductus arteriosus in infants weighing more than 700 g and of postnatal age more than 3 days. Premature low-weight infants are predisposed to hypothermia when transported outside of the thermo-neutral environment. At our institution, 90% of extremely preterm low-weight infants developed transient moderate hypothermia in the cardiac catheterisation suite. METHODS: We conducted a study testing multiple hypotheses aimed at preventing hypothermia in the cardiac catheterisation suite. Interventions included increasing ambient room temperature, reducing exposure to cold environment and reducing overall time spent in the remote location. The primary outcome was the proportion of patients who developed transient hypothermia at the start of the procedure in the cardiac catheterisation suite. The secondary measures included mean core body temperature at four different instances, as well as anaesthesia time, procedure time and radiation exposure. RESULTS: During the study period, 10 patients were enrolled in each group. The postintervention group saw a reduction in transient hypothermia from 90% to 40% (absolute risk reduction 50%, p=0.02). Data analysis showed an improvement in mean core body temperature (35.4°C vs 36.4°C, p<0.01) as well as a smaller percentage drop in temperature (4% vs 1.3%, p<0.01) between the two groups, both of which were statistically significant. The anaesthesia time, procedure time and radiation exposure reduced between the two groups. CONCLUSION: The application of the interventions reduced hypothermia in this high-risk population. The implementation of a protocol with collaboration of a multidisciplinary team is indispensable in providing optimal care to extremely preterm infants.

Anesthesiology
Fernando RJ, Graulein D, Hamzi RI, Augoustides JG, **Khalil S**, **Sanders J**, **Sibai N**, Hong TS, Kiwakyou LM, and Brodt JL. Buprenorphine and Cardiac Surgery: Navigating the Challenges of Pain Management. *J Cardiothorac Vasc Anesth* 2022; 36(9):3701-3708. PMID: 35667956. Full Text

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Anesthesiology
Nasri BN, **Mitchell JD**, Jackson C, Nakamoto K, Guglielmi C, and Jones DB. Distractions in the operating room: a survey of the healthcare team. *Surg Endosc* 2022; 1-10. Epub ahead of print. PMID: 36070145. Full Text

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BACKGROUND: Distractions during surgical procedures are associated with team inefficiency and medical error. Little is published about the healthcare provider's perception of distraction and its adverse impact in the operating room. We aim to explore the perception of the operating room team on multiple distractions during surgical procedures. METHODS: A 26-question survey was administered to surgeons, anesthesia team members, nurses, and scrub technicians at our institution. Respondents were asked to identify and rank multiple distractions and indicate how each distraction might affect the flow of surgery. RESULTS: There was 160 responders for a response rate of 19.18% (160/834), of which 71 (44.1%) male and 82 (50.9%) female, 48 (29.8%) surgeons, 59 (36.6%) anesthesiologists, Certified Registered Nurse Anesthetists (CRNA), and 53 (32.9%) OR nurses and scrub technicians. Responders were classified into a junior group (< 10 years of experience) and a senior group (≥ 10 years). Auditory distraction followed by equipment were the most distracting factors in the operating room. All potential auditory distractions in this survey were associated with higher percentage of certain level of negative impact on the flow of surgery except for music. The top 5 distractors belonged to equipment and environment categories. Phone calls/ pagers/ beepers and case relevant communications were consistently among the top 5 most common distractors. Case relevant communications, music, teaching, and consultation were the top 4 most perceived positive impact on the flow of surgery. Distractors with higher levels of "bothersome" rating appeared to associate with a higher level of perceived negative impact on the flow of surgery. Vision was the least distracting factor and appeared to cause minimal positive impact on the flow of surgery. CONCLUSIONS: To our knowledge, this is the first survey studying perception of surgery, anesthesia, and OR staff on various distractions in the operating room. Fewer unnecessary distractions might improve the flow of surgery, improve OR teamwork, and potentially improve patient outcomes.

Anesthesiology
Patel N, **Fayed M**, Faldu P, Maroun W, and Chandarana J. Chronic Proton-Pump Inhibitor Therapy and Fracture Risk in Women Aged Between 50 and 65 years: A Retrospective Case-Control Study. *Cureus* 2022. PMID: Not assigned. Full Text

Introduction: Chronic proton-pump inhibitor (PPI) prescription is on the rise in the last decade with an increased prevalence in the elderly population. For most patients, this class of drugs is the primary treatment for various diseases. Even though PPIs are generally safe, long-term use has been associated with multiple adverse effects like bone fractures. The extent of the association between PPI and fracture is still unclear in women aged between 50 and 65 years. Besides, many other variables and risk factors must be accounted for in the analysis of this relation. Methods: This is a retrospective case-control study looking at women 50-65 years of age who presented to Genesys Health for a low-impact fall. Data were extracted from electronic medical records and fracture outcomes; PPI therapy exposure and duration

were determined. Chi-square analysis was performed to determine the association between chronic PPI therapy and fracture outcome and independently analyzed for major risk factors of osteoporosis, including smoking, low body mass index, and cancer. Results: Patients in the chronic PPI therapy group were found to have a decreased fracture outcome overall in each subcategory of risk factors. When adjusting for all risk factors, there was a significant but weak association between chronic PPI therapy and increased fracture outcome. Conclusion: With different results from previous studies, this study sheds new light on this debate. More studies need to be carried out to determine the association between chronic PPI therapy and fracture outcomes in postmenopausal women.

Behavioral Health Services/Psychiatry/Neuropsychology

Kahn GD, **Tam SH**, **Felton JW**, **Westphal J**, Simon GE, Owen-Smith AA, Rossom RC, Beck AL, Lynch FL, Daida YG, Lu CY, Waring S, **Frank CB**, **Akinyemi EO**, and **Ahmedani BK**. Cancer and psychiatric diagnoses in the year preceding suicide. *Cancer Med* 2022; Epub ahead of print. PMID: 36114785. Full Text

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BACKGROUND: Patients with cancer are known to be at increased risk for suicide but little is known about the interaction between cancer and psychiatric diagnoses, another well-documented risk factor. METHODS: Electronic medical records from nine healthcare systems participating in the Mental Health Research Network were aggregated to form a retrospective case-control study, with ICD-9 codes used to identify diagnoses in the 1 year prior to death by suicide for cases (N = 3330) or matching index date for controls (N = 297,034). Conditional logistic regression was used to assess differences in cancer and psychiatric diagnoses between cases and controls, controlling for sex and age. RESULTS: Among patients without concurrent psychiatric diagnoses, cancer at disease sites with lower average 5-year survival rates were associated with significantly greater relative risk, while cancer disease sites with survival rates of >70% conferred no increased risk. Patients with most psychiatric diagnoses were at higher risk, however, there was no additional risk conferred to these patients by a concurrent cancer diagnosis. CONCLUSION: We found no evidence of a synergistic effect between cancer and psychiatric diagnoses. However, cancer patients with a concurrent psychiatric illness remain at the highest relative risk for suicide, regardless of cancer disease site, due to strong independent associations between psychiatric diagnoses and suicide. For patients without a concurrent psychiatric illness, cancer disease sites associated with worse prognoses appeared to confer greater suicide risk.

Cardiology/Cardiovascular Research

Ahlers MJ, Srivastava PK, **Basir MB**, **O'Neill WW**, **Hacala M**, Ammar K, Khalil S, Hollowed J, and Nsair A. Characteristics and outcomes of patients presenting with acute myocardial infarction and cardiogenic shock during COVID-19. *Catheter Cardiovasc Interv* 2022; Epub ahead of print. PMID: 36073018. Full Text

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OBJECTIVES: To evaluate characteristics and outcomes of patients presenting with acute myocardial infarction and cardiogenic shock (AMICS) during the coronavirus disease 2019 (COVID-19) pandemic. BACKGROUND: The COVID-19 pandemic has created challenges in delivering acute cardiovascular care. Quality measures and outcomes of patients presenting with AMICS during COVID-19 in the United States have not been well described. METHODS: We identified 406 patients from the National Cardiogenic Shock Initiative (NCSI) with AMICS and divided them into those presenting before (N = 346, 5/9/2016-2/29/2020) and those presenting during the COVID-19 pandemic (N = 60, 3/1/2020-11/10/2020). We compared baseline clinical data, admission characteristics, and outcomes. RESULTS: The median age of the cohort was 64 years, and 23.7% of the group was female. There were no significant differences in age, sex, and medical comorbidities between the two groups. Patients presenting during the pandemic were less likely to be Black compared to those presenting prior. Median door to balloon (90 vs. 88 min, p = 0.38), door to support (88 vs. 78 min, p = 0.13), and the onset of shock to support (74 vs. 62 min, p = 0.15) times were not significantly different between the two groups. Patients presented with ST-elevation myocardial infarction more often during the COVID-19 period (95.0% vs. 80.0%, p = 0.005). In adjusted logistic regression models, COVID-19 period did not significantly associate with survival to discharge (odds ratio [OR] 1.09, 95% confidence interval [CI] 0.54-2.19, p = 0.81) or with 1-month survival (OR 0.82, 95% CI 0.42-1.61, p = 0.56). CONCLUSIONS: Care of patients presenting with AMICS has remained robust among hospitals participating in the NCSI during the COVID-19 pandemic.

Cardiology/Cardiovascular Research

Bansal A, and **Ananthasubramaniam K**. Cardiovascular positron emission tomography: established and emerging role in cardiovascular diseases. *Heart Fail Rev* 2022; Epub ahead of print. PMID: 36129644. Full Text

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Cardiac positron emission tomography (PET) imaging has established themselves firmly as excellent and reliable functional imaging modalities in assessment of the spectrum of coronary artery disease. With the explosion of technology advances and the dream of flow quantification now a reality, the value of PET is now well realized. Cardiac PET has proved itself as precise imaging modality that provides functional imaging of the heart in addition to anatomical imaging. It has established itself as one of the best available techniques for evaluation of myocardial viability. Hybrid PET/computed tomography provides simultaneous integration of coronary anatomy and function with myocardial perfusion and metabolism, thereby improving characterization of the dysfunctional area and chronic coronary artery disease. The availability of quantitative myocardial blood flow evaluation with PET provides additional prognostic information and increases diagnostic accuracy in the management of patients with coronary artery disease. Hybrid imaging seems to hold immense potential in optimizing management of cardiovascular diseases and furthering clinical research.

Cardiology/Cardiovascular Research

Ehrman JK, Gardner AW, Salisbury D, Lui K, and Treat-Jacobson D. Supervised Exercise Therapy for Symptomatic Peripheral Artery Disease: A REVIEW OF CURRENT EXPERIENCE AND PRACTICE-BASED RECOMMENDATIONS. *J Cardiopulm Rehabil Prev* 2022; Epub ahead of print. PMID: 36114638. Full Text

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan (Dr Ehrman); Physical Medicine and Rehabilitation, Penn State College of Medicine, Hershey, Pennsylvania (Dr Gardner); School of Nursing, Adult and Gerontological Health Cooperative, University of Minnesota, Minneapolis, Minnesota (Drs Salisbury and Treat-Jacobson); and Advocate for Action, Gainesville, Georgia (Ms Lui).

PURPOSE: This review encompasses several practical components of supervised exercise therapy (SET) for patients with claudication including referral, exercise training, and billing issues. Real-life SET session examples are also provided. SET was approved for reimbursement by the Centers for Medicare & Medicaid Services (CMS) in 2017, and there is continual growth of programs offering SET and in participation. The purpose of this review is to provide useful information for the clinical exercise professionals working with these patients. REVIEW METHODS: The 2016 ACC/AHA Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease (PAD) provided a class I (highest level) recommendation for the use of SET in those with symptomatic PAD. Since there has been much growth in the literature about the utility of SET, the literature was reviewed (PubMed) to provide information for this article. Topics reviewed include the benefits of exercise training, exercise prescription, billing, referral and participation, and best practices. SUMMARY: SET should be offered to all patients with symptomatic PAD who are not at risk of acute limb ischemia. For optimal results, SET should be implemented several times per week and in a progressive process to increase exercise intensity as tolerated. For best results, programs should recommend patients supplement SET with home exercise. Considerations for utilizing reimbursed sessions should also be discussed because patients have a maximum of 72 sessions/lifetime. Referral practices need refinement, and participation rates remain extremely low and may be influenced by demographics. Research on best practices and home or hybrid training must continue to address issues related to common enrollment and participation barriers. CONDENSED ABSTRACT: Supervised exercise training (SET) for symptomatic peripheral artery disease is a class IA recommendation and reimbursable by most insurances. Improvements in walking performance can be dramatic. However, referral and participation in SET remain very low and thus SET is vastly underutilized.

Cardiology/Cardiovascular Research

Guichard JL, **Cowger JA**, Chaparro SV, Kiernan MS, Mullens W, Mahr C, Mullin C, Forouzan O, Hiivala NJ, Sauerland A, Leadley K, and Klein L. RATIONALE AND DESIGN OF THE PROACTIVE-HF TRIAL FOR MANAGING NYHA CLASS III HEART FAILURE PATIENTS WITH THE COMBINED CORDELLA(TM) PULMONARY ARTERY SENSOR AND THE CORDELLA(TM) HEART FAILURE SYSTEM. *J Card Fail* 2022; Epub ahead of print. PMID: 36191758. Full Text

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BACKGROUND: Optimizing guideline-directed medical therapy (GDMT) and monitoring congestion in heart failure (HF) patients are key to disease management and preventing hospitalizations. A pulmonary artery pressure (PAP)-guided HF management system providing access to body weight, blood pressure, heart rate, blood oxygen saturation, PAP, and symptoms, may provide new insights into the effects of patient engagement and comprehensive care for remote GDMT titration and congestion management. METHODS: The PROACTIVE-HF study was originally approved in 2018 as a prospective, randomized, controlled, single-blind, multi-center trial to evaluate the safety and effectiveness of the Cordella(TM) PAP Sensor in HF patients with New York Heart Association (NYHA) functional class III symptoms. Since then, robust clinical evidence supporting PAP-guided HF management has emerged, making clinical equipoise

and enrolling patients into a standard-of-care control arm challenging. Therefore, PROACTIVE-HF was changed to a single-arm trial in 2021 with pre-specified safety and effectiveness endpoints to provide evidence for a similar risk-benefit profile as the CardioMEMS(TM) HF System. CONCLUSION: The single-arm PROACTIVE-HF trial is expected to further demonstrate the benefits of PAP-guided HF management in NYHA class III patients. The addition of vital signs, patient engagement and self-reported symptoms may provide new insights into remote GDMT titration and congestion management.

Cardiology/Cardiovascular Research

Jaiswal V, Khan N, Jaiswal A, Dagar M, Joshi A, Huang H, Naz H, Attia AM, **Ghanim M**, Baburaj A, and Song D. Early surgery vs conservative management among asymptomatic aortic stenosis: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc* 2022; 43:101125. PMID: 36176308. Full Text

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INTRODUCTION: Although aortic valve replacement in severe symptomatic Aortic Stenosis (AS) are clearly outlined, the role of surgical intervention in asymptomatic severe AS remains unclear with limited evidence. The aim of our meta-analysis is to evaluate the efficacy and safety of early surgical aortic valve repair compared to conservative management. METHODS: A systematic literature search was performed in PubMed, Scopus, Embase and Cochrane databases for studies comparing the early surgery versus conservative management among asymptomatic aortic stenosis patients. Unadjusted odds ratios (OR) were pooled using a random-effect model, and a p-value of < 0.05 was considered statistically significant. RESULTS: A total of 5 articles (3 observational studies and 2 randomized controlled trials) were included. At a median followup of 4.1 years, here were significantly lower odds of all-cause mortality [OR = 0.30 (95 %CI:0.17-0.53), $p < 0.0001$], cardiovascular mortality [OR = 0.35 (95 %CI:(0.17-0.72), $p = 0.005$], and sudden cardiac death (OR = 0.36 (95 %CI: 0.15-0.89), $p = 0.03$) among early surgery group compared with conservative care. There was no significant difference between incidence of major bleeding, clinical thromboembolic events, hospitalization due to heart failure, stroke and myocardial infarction between the conservative care groups and early surgery. CONCLUSION: Among asymptomatic patients with AS, early surgery shows better outcomes in reducing all-cause mortality and cardiovascular mortality compared with conservative management approaches.

Cardiology/Cardiovascular Research

Kapur NK, Kim RJ, Moses JW, Stone GW, Udelson JE, Ben-Yehuda O, Redfors B, Issever MO, Josephy N, Polak SJ, and **O'Neill WW**. Primary left ventricular unloading with delayed reperfusion in patients with anterior ST-elevation myocardial infarction: Rationale and design of the STEMI-DTU randomized pivotal trial. *Am Heart J* 2022; 254:122-132. PMID: 36058253. Full Text

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BACKGROUND: Despite successful primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI), myocardial salvage is often suboptimal, resulting in large infarct size and increased rates of heart failure and mortality. Unloading of the left ventricle (LV) before primary PCI may reduce infarct size and improve prognosis. STUDY DESIGN AND OBJECTIVES: STEMI-DTU (NCT03947619) is a prospective, randomized, multicenter trial designed to compare mechanical LV unloading with the Impella CP device for 30 minutes prior to primary PCI to primary PCI alone without LV unloading. The trial aims to enroll approximately 668 subjects, with a potential sample size adaptation, with anterior STEMI with a primary end point of infarct size as a percent of LV mass evaluated by cardiac magnetic resonance at 3-5 days after PCI. The key secondary efficacy end point is a hierarchical composite of the 1-year rates of cardiovascular mortality, cardiogenic shock ≥24 hours after PCI, use of a surgical left ventricular assist device or heart transplant, heart failure, intra-cardiac defibrillator or chronic resynchronization therapy placement, and infarct size at 3 to 5 days post-PCI. The key secondary safety end point is Impella CP-related major bleeding or major vascular complications within 30 days. Clinical follow-up is planned for 5 years. CONCLUSIONS: STEMI-DTU is a large-scale, prospective, randomized trial evaluating whether mechanical unloading of the LV by the Impella CP prior to primary PCI reduces infarct size and improves prognosis in patients with STEMI compared to primary PCI alone without LV unloading.

Cardiology/Cardiovascular Research

Kostantinis S, Simsek B, Karacsonyi J, **Alaswad K**, Krestyaninov O, Khelimskii D, Karmpaliotis D, Jaffer FA, Khatri JJ, Poommipanit P, Choi JW, Jaber WA, Rinfret S, Nicholson W, Patel MP, Mahmud E, Dattilo P, Gorgulu S, Koutouzis M, Tsiafoutis I, Elbarouni B, Sheikh AM, Uretsky BF, ElGuindy AM, Jefferson BK, Patel TN, Wollmuth J, Riley RF, Benton SM, Jr., Davies RE, Chandwaney RH, Toma C, Yeh RW, Schimmel DR, Abi Rafeh N, Goktekin O, Kerrigan JL, Mastrodemos OC, Rangan BV, Garcia S, Sandoval Y, Burke MN, and Brilakis E. In-hospital outcomes and temporal trends of percutaneous coronary interventions for chronic total occlusion. *EuroIntervention* 2022; Epub ahead of print. PMID: 36065983.
Request Article

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Cardiology/Cardiovascular Research

Lim DS, Smith RL, Gillam LD, Zahr F, Chadderdon S, Makkar R, Stephan von Bardeleben R, Kipperman RM, Rassi AN, Szerlip M, Goldman S, Inglessis-Azuaje I, Yadav P, Lurz P, Davidson CJ, Mumtaz M, Gada H, Kar S, Kodali SK, Laham R, Hiesinger W, Fam NP, Keßler M, **O'Neill WW**, Whisenant B, Kliger C, Kapadia S, Rudolph V, Choo J, Hermiller J, Morse MA, Schofer N, Gafoor S, Latib A, Koulogiannis K, Marcoff L, and Hausleiter J. Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients. *JACC Cardiovasc Interv* 2022; Epub ahead of print. PMID: 36121247. Full Text

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Northwell-Lenox Hill, New York, NY.
Cleveland Clinic Foundation, Cleveland, OH.
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Ascension Saint Thomas Hospital, Nashville, TN.
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Swedish Medical Center, Seattle, WA.
Montefiore Medical Center, Bronx, NY.
Klinikum der Universität München, Munich, Germany.

BACKGROUND: Severe symptomatic degenerative mitral regurgitation (DMR) has a poor prognosis in the absence of treatment, and new transcatheter options are emerging. OBJECTIVES: The CLASP IID randomized trial (NCT03706833) is the first to evaluate the safety and effectiveness of the PASCAL system compared to the MitraClip system in patients with significant symptomatic DMR. In this report, we present the primary safety and effectiveness endpoints for the trial. METHODS: Patients with 3+ or 4+ DMR at prohibitive surgical risk were assessed by a central screening committee and randomized 2:1 (PASCAL:MitraClip). Study oversight also included an echocardiographic core laboratory and a clinical events committee. The primary safety endpoint was a composite major adverse event (MAE) rate at 30 days. The primary effectiveness endpoint was the proportion of patients with MR ≤2+ at 6 months. RESULTS: A pre-specified interim analysis in 180 patients demonstrated non-inferiority of the PASCAL system vs. MitraClip system for the primary safety and effectiveness endpoints, MAE: 3.4% vs. 4.8%, MR

≤2+: 96.5% vs. 96.8%, respectively. Functional and quality-of-life outcomes significantly improved in both groups (p<0.05). The proportion of patients with MR ≤1+ was durable in the PASCAL group from discharge to 6 months [PASCAL: 87.2% and 83.7% (p=0.317 vs. discharge); MitraClip: 88.5% and 71.2% (p=0.003 vs. discharge), respectively]. CONCLUSIONS: The CLASP IID trial demonstrated safety and effectiveness of the PASCAL system and met non-inferiority endpoints, expanding transcatheter treatment options for prohibitive surgical risk patients with significant symptomatic DMR.

Cardiology/Cardiovascular Research
Megaly M, Buda K, Karacsonyi J, Kostantinis S, Simsek B, **Basir MB**, Mashayekhi K, Rinfret S, McEntegart M, Yamane M, Azzalini L, **Alaswad K**, and Brilakis ES. Extraplaque versus intraplaque tracking in chronic total occlusion percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2022; Epub ahead of print. PMID: 36168859. Full Text

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OBJECTIVE: To compare the clinical outcomes after extraplaque (EP) versus intraplaque (IP) tracking in chronic total occlusion (CTO) percutaneous coronary intervention (PCI). BACKGROUND: The impact of modern dissection and reentry (DR) techniques on the long-term outcomes of CTO PCI remains controversial. METHODS: We performed a systematic review and meta-analysis of studies that compared EP versus IP tracking in CTO PCI. Odds ratios (ORs) with 95% confidence intervals (CIs) are calculated using the Der-Simonian and Laird random-effects method. RESULTS: Our meta-analysis included seven observational studies with 2982 patients. Patients who underwent EP tracking had significantly more complex CTOs with higher J-CTO score, longer lesion length, and more severe calcification and had significantly longer stented segments. During a median follow-up of 12 months (range 9-12 months), EP tracking was associated with a higher risk of major adverse cardiovascular events (MACE) (OR 1.50, 95% CI (1.10-2.06), p = 0.01) and target vessel revascularization (TVR) (OR 1.69, 95% CI (1.15-2.48), p = 0.01) compared with IP tracking. There was no difference in the incidence of all-cause death (OR 1.37, 95% CI (0.67-2.78), p = 0.39), myocardial infarction (MI) (OR 1.48, 95% CI (0.82-2.69), p = 0.20), stent thrombosis (OR 2.09, 95% CI (0.69-6.33), p = 0.19), or cardiac death (OR 1.10, 95% CI (0.39-3.15), p = 0.85) between IP and EP tracking. CONCLUSION: EP tracking is utilized in more complex CTOs and requires more stents. EP tracking is associated with a higher risk of MACE, driven by a higher risk of TVR at 1 year, but without an increased risk of death or MI compared with IP tracking. EP tracking is critically important for contemporary CTO PCI.

Cardiology/Cardiovascular Research
Mehra MR, Goldstein DJ, Cleveland JC, **Cowger JA**, Hall S, Salerno CT, Naka Y, Horstmanshof D, Chuang J, Wang A, and Uriel N. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. *Jama* 2022; 328(12):1233-1242. PMID: 36074476. Full Text

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IMPORTANCE: Although durable left ventricular assist device (LVAD) therapy has emerged as an important treatment option for patients with advanced heart failure refractory to pharmacological support, outcomes, including survival, beyond 2 years remain poorly characterized. OBJECTIVE: To report the composite end point of survival to transplant, recovery, or LVAD support free of debilitating stroke (Modified Rankin Scale score >3) or reoperation to replace the pump 5 years after the implant in participants who received the fully magnetically levitated centrifugal-flow HeartMate 3 or axial-flow HeartMate II LVAD in the MOMENTUM 3 randomized trial and were still receiving LVAD therapy at the 2-year follow-up. DESIGN, SETTING, AND PARTICIPANTS: This observational study was a 5-year follow-up of the MOMENTUM 3 trial, conducted in 69 US centers, that demonstrated superiority of the centrifugal-flow LVAD to the axial-flow pump with respect to survival to transplant, recovery, or LVAD support free of debilitating stroke or reoperation to replace the pump at 2 years. A total of 295 patients were enrolled between June 2019 to April 2021 in the extended-phase study, with 5-year follow-up completed in September 2021. EXPOSURES: Of 1020 patients in the investigational device exemption per-protocol population, 536 were still receiving LVAD support at 2 years, of whom 289 received the centrifugal-flow pump and 247 received the axial-flow pump. MAIN OUTCOMES AND MEASURES: There were 10 end points evaluated at 5 years in the per-protocol population, including a composite of survival to transplant, recovery, or LVAD support free of debilitating stroke or reoperation to replace the pump between the centrifugal-flow and axial-flow pump groups and overall survival between the 2 groups. RESULTS: A total of 477 patients (295 enrolled and 182 provided limited data) of 536 patients still receiving LVAD support at 2 years contributed to the extended-phase analysis (median age, 62 y; 86 [18%] women). The 5-year Kaplan-Meier estimate of survival to transplant, recovery, or LVAD support free of debilitating stroke or reoperation to replace the pump in the centrifugal-flow vs axial-flow group was 54.0% vs 29.7% (hazard ratio, 0.55 [95% CI, 0.45-0.67]; P < .001). Overall Kaplan-Meier survival was 58.4% in the centrifugal-flow group vs 43.7% in the axial-flow group (hazard ratio, 0.72 [95% CI, 0.58-0.89]; P = .003). Serious adverse events of stroke, bleeding, and pump thrombosis were less frequent in the centrifugal-flow pump group. CONCLUSIONS AND RELEVANCE: In this observational follow-up study of patients from the MOMENTUM 3 randomized trial, per-protocol analyses found that receipt of a fully magnetically levitated centrifugal-flow LVAD vs axial-flow LVAD was associated with a better composite outcome and higher likelihood of overall survival at 5 years. These findings support the use of the fully magnetically levitated LVAD. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02224755 and NCT03982979.

Cardiology/Cardiovascular Research

Pan G, **Roy B**, **Giri S**, **Lanfear DE**, Thandavarayan RA, Guha A, **Ortiz PA**, and **Palaniyandi SS**. Aldehyde Dehydrogenase 2 Activator Augments the Beneficial Effects of Empagliflozin in Mice with Diabetes-Associated HFpEF. *Int J Mol Sci* 2022; 23(18). PMID: 36142350. Full Text

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To ameliorate diabetes mellitus-associated heart failure with preserved ejection fraction (HFpEF), we plan to lower diabetes-mediated oxidative stress-induced 4-hydroxy-2-nonenal (4HNE) accumulation by pharmacological agents that either decrease 4HNE generation or increase its detoxification.A cellular reactive carbonyl species (RCS), 4HNE, was significantly increased in diabetic hearts due to a diabetes-induced decrease in 4HNE detoxification by aldehyde dehydrogenase (ALDH) 2, a cardiac mitochondrial enzyme that metabolizes 4HNE. Therefore, hyperglycemia-induced 4HNE is critical for diabetes-mediated cardiotoxicity and we hypothesize that lowering 4HNE ameliorates diabetes-associated HFpEF. We fed a

high-fat diet to ALDH2*2 mice, which have intrinsically low ALDH2 activity, to induce type-2 diabetes. After 4 months of diabetes, the mice exhibited features of HFpEF along with increased 4HNE adducts, and we treated them with vehicle, empagliflozin (EMP) (3 mg/kg/d) to reduce 4HNE and Alda-1 (10 mg/kg/d), and ALDH2 activator to enhance ALDH2 activity as well as a combination of EMP + Alda-1 (E + A), via subcutaneous osmotic pumps. After 2 months of treatments, cardiac function was assessed by conscious echocardiography before and after exercise stress. EMP + Alda-1 improved exercise tolerance, diastolic and systolic function, 4HNE detoxification and cardiac liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) pathways in ALDH2*2 mice with diabetes-associated HFpEF. This combination was even more effective than EMP alone. Our data indicate that ALDH2 activation along with the treatment of hypoglycemic agents may be a salient strategy to alleviate diabetes-associated HFpEF.

Cardiology/Cardiovascular Research
Raad M, **Miletic K**, **Khan A**, and **Maskoun W**. A hybrid subcutaneous and epicardial biventricular implantable cardiac defibrillator with an abdominal generator. *HeartRhythm Case Rep* 2022; 8(9):655-657. PMID: 36147718. Full Text

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Cardiology/Cardiovascular Research
Sattar Y, **Aronow HD**, and Alam M. Drug-Coated Balloon Failure Following Femoro-Popliteal Intervention: Where to Draw the Line? *J Am Coll Cardiol* 2022; 80(13):1251-1253. PMID: 36137675. Full Text

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Cardiology/Cardiovascular Research
Waack A, Jaggernauth S, and **Sharma S**. Bilateral common iliac vein stent migration. *Radiol Case Rep* 2022; 17(11):4332-4336. PMID: 36132062. Full Text

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Venous stent migration to the heart is considered to be a rare complication of a common procedure. Therefore, many physicians do not include this complication in their differential diagnosis. We explain why this complication is likely more common than currently thought and why it should be considered as a potential diagnosis. This case describes migration of bilateral iliac vein stents into the right ventricular outflow tract and right interlobar pulmonary artery. We provide multiple imaging modalities demonstrating the migrated stents. We believe radiologists should be cognizant of this complication and consider it as a potential diagnosis. Hopefully, this will create a greater awareness of this life-threatening complication of venous stent placement.

Center for Health Policy and Health Services Research
Creech SK, Pearson R, Saenz JJ, **Braciszewski JM**, Riggs SA, and Taft CT. Pilot trial of Strength at Home Parents, a trauma-informed parenting support treatment for veterans. *Couple Family Psychol* 2022; 11(3):205-216. PMID: 36185500. Request Article

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University of North Texas, Denton, TX; and Sam Houston State University, Huntsville, TX.
National Center for PTSD, VA Boston Healthcare System, Boston, MA, USA; and Boston University School of Medicine, Boston, MA.

PTSD is associated with compromised parenting which is not adequately addressed in available evidence-based PTSD treatments. Strength at Home - Parents (SAHP) is a trauma-informed parenting intervention which aims to improve parenting behaviors and overall parent-child functioning. Here we report pilot data obtained in a sample of veterans (N=21) with PTSD and parent-child functioning difficulties. Results support feasibility of study methods, and intervention acceptability, credibility and satisfaction. Movement on primary outcome measures suggested improved overall family functioning, a decrease in the use of dysfunctional parenting practices, an increase in positive parenting practices and a trend towards a reduction in parenting stress. Results should be interpreted with caution because of the small sample size and attrition at follow-up. Limitations withstanding, findings support further study of the intervention, which would provide insights into whether an efficacy trial is indicated.

Center for Health Policy and Health Services Research
Felton JW, Shadur JM, Havewala M, Cassidy J, Lejuez CW, and Chronis-Tuscano A. Specific Pathways from Parental Distress Reactions to Adolescent Depressive Symptoms: The Mediating Role of Youths' Reactions to Negative Life Events. *J Psychopathol Behav Assess* 2022; 44(3):750-762. PMID: 36189339. Full Text

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The current multimethod longitudinal study examines how parents' distress reactions to adolescents' negative emotions may shape youths' own perceptions of negative life events and subsequent increases in depressive symptomology. Ninety adolescents (41 girls, 49 boys, average age = 16.5 years old) and their parents were assessed over three timepoints. We found that greater parent-reported distress reactions to adolescents' emotions predicted subsequent increase in youths' own self-reported negative reactions to stressful experiences over a two-week period, which in turn predicted steeper increases in youth-reported depressive symptoms across this same two-week period. Moreover, youths' negative reactions mediated the relation between parent emotion socialization and increases in adolescent depressive symptoms. These findings support the use of interventions that simultaneously target parent and child distress to prevent the onset of adolescent depression.

Center for Health Policy and Health Services Research
Hoskins K, Linn KA, **Ahmedani BK**, Boggs JM, Johnson C, Heintz J, Marcus SC, Kaminer I, **Zabel C**, Wright L, Quintana L, Buttenheim AM, Daley MF, **Elias ME**, Jager-Hyman S, Lieberman A, Lyons J, **Maye M**, **McArdle B**, Ritzwoller DP, Small DS, **Westphal J**, Wolk CB, **Zhang S**, Shelton RC, and Beidas RS. Equitable implementation of S.A.F.E. Firearm: A multi-method pilot study. *Prev Med* 2022; 107281. Epub ahead of print. PMID: 36191653. Full Text

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Attention to health equity is critical in the implementation of firearm safety efforts. We present our operationalization of equity-oriented recommendations in preparation for launch of a hybrid effectiveness-implementation trial focused on firearm safety promotion in pediatric primary care as a universal suicide prevention strategy. In Step 1 of our process, pre-trial engagement with stakeholders and literature review alerted us that delivery of a firearm safety program may vary by patients' medical complexity, race, and ethnicity. In Step 2, we selected the Health Equity Implementation Framework to inform our understanding of contextual determinants (i.e., barriers and facilitators). In Step 3, we leveraged an implementation pilot across 5 pediatric primary care clinics in 2 health system sites to study signals of inequities. Eligible well-child visits for 694 patients and 47 clinicians were included. Our results suggested that medical complexity was not associated with program delivery. We did see potential signals of inequities by race and ethnicity but must interpret with caution. Though we did not initially plan to examine differences by sex, we discovered that clinicians may be more likely to deliver the program to parents of males than females. Seven qualitative interviews with clinicians provided additional context. In Step 4, we interrogated equity considerations (e.g., why and how do these inequities exist). In Step 5, we will develop a plan to probe potential inequities related to race, ethnicity, and sex in the fully powered trial. Our process highlights that prospective, rigorous, exploratory work is vital for equity-informed implementation trials.

Center for Health Policy and Health Services Research
Kahn GD, **Tam SH**, **Felton JW**, **Westphal J**, Simon GE, Owen-Smith AA, Rossom RC, Beck AL, Lynch FL, Daida YG, Lu CY, Waring S, **Frank CB**, **Akinyemi EO**, and **Ahmedani BK**. Cancer and psychiatric diagnoses in the year preceding suicide. *Cancer Med* 2022; Epub ahead of print. PMID: 36114785. Full Text

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BACKGROUND: Patients with cancer are known to be at increased risk for suicide but little is known about the interaction between cancer and psychiatric diagnoses, another well-documented risk factor. METHODS: Electronic medical records from nine healthcare systems participating in the Mental Health Research Network were aggregated to form a retrospective case-control study, with ICD-9 codes used to identify diagnoses in the 1 year prior to death by suicide for cases (N = 3330) or matching index date for controls (N = 297,034). Conditional logistic regression was used to assess differences in cancer and psychiatric diagnoses between cases and controls, controlling for sex and age. RESULTS: Among patients without concurrent psychiatric diagnoses, cancer at disease sites with lower average 5-year survival rates were associated with significantly greater relative risk, while cancer disease sites with survival rates of >70% conferred no increased risk. Patients with most psychiatric diagnoses were at higher risk, however, there was no additional risk conferred to these patients by a concurrent cancer diagnosis. CONCLUSION: We found no evidence of a synergistic effect between cancer and psychiatric

diagnoses. However, cancer patients with a concurrent psychiatric illness remain at the highest relative risk for suicide, regardless of cancer disease site, due to strong independent associations between psychiatric diagnoses and suicide. For patients without a concurrent psychiatric illness, cancer disease sites associated with worse prognoses appeared to confer greater suicide risk.

Center for Health Policy and Health Services Research

Kamineni A, Doria-Rose VP, Chubak J, Inadomi JM, Corley DA, Haas JS, Kobrin SC, Winer RL, **Lafata JE**, Beaber EF, Yudkin JS, Zheng Y, Skinner CS, Schottinger JE, Ritzwoller DP, Croswell JM, and Burnett-Hartman AN. Evaluation of Harms Reporting in U.S. Cancer Screening Guidelines. *Ann Intern Med* 2022; Epub ahead of print. PMID: 36162112. Full Text

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University of Texas Health Science Center at Houston, Houston, Texas (J.S.Y.).
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BACKGROUND: Cancer screening should be recommended only when the balance between benefits and harms is favorable. This review evaluated how U.S. cancer screening guidelines reported harms, within and across organ-specific processes to screen for cancer. OBJECTIVE: To describe current reporting practices and identify opportunities for improvement. DESIGN: Review of guidelines. SETTING: United States. PATIENTS: Patients eligible for screening for breast, cervical, colorectal, lung, or prostate cancer according to U.S. guidelines. MEASUREMENTS: Information was abstracted on reporting of patient-level harms associated with screening, diagnostic follow-up, and treatment. The authors classified harms reporting as not mentioned, conceptual, qualitative, or quantitative and noted whether literature was cited when harms were described. Frequency of harms reporting was summarized by organ type. RESULTS: Harms reporting was inconsistent across organ types and at each step of the cancer screening process. Guidelines did not report all harms for any specific organ type or for any category of harm across organ types. The most complete harms reporting was for prostate cancer screening guidelines and the least complete for colorectal cancer screening guidelines. Conceptualization of harms and use of quantitative evidence also differed by organ type. LIMITATIONS: This review considers only patient-level harms. The authors did not verify accuracy of harms information presented in the guidelines. CONCLUSION: The review identified opportunities for improving conceptualization, assessment, and reporting of screening process-related harms in guidelines. Future work should consider nuances associated with each organ-specific process to screen for cancer, including which harms are most salient and where evidence gaps exist, and explicitly explore how to optimally weigh available evidence in determining net screening benefit. Improved harms reporting could aid informed decision making, ultimately improving cancer screening delivery. PRIMARY FUNDING SOURCE: National Cancer Institute.

Center for Health Policy and Health Services Research

Patel V, Metz A, **Schultz L**, **Nerenz D**, Park P, **Chang V**, **Schwalb J**, Khalil J, Perez-Cruet M, and Aleem I. Rates and Reasons for Reoperation Within 30 and 90 days Following Cervical Spine Surgery: A Retrospective Cohort Analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Registry. *Spine J* 2022; Epub ahead of print. PMID: 36152774. Full Text

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BACKGROUND CONTEXT: Reoperation following cervical spinal surgery negatively impacts patient outcomes and increases healthcare system burden. To date, most studies have evaluated reoperations within 30 days after spine surgery and have been limited in scope and focus. Evaluation within the 90-day period, however, allows a more comprehensive assessment of factors associated with reoperation. PURPOSE: The purpose of this study is to assess the rates and reasons for reoperations after cervical spine surgery within 30 and 90 days. DESIGN: We performed a retrospective analysis of a state-wide prospective, multi-center, spine-specific database of patients surgically treated for degenerative disease. PATIENT SAMPLE: Patients 18 years of age or older who underwent cervical spine surgery for degenerative pathologies from February 2014 to May 2019. Operative criteria included all degenerative cervical spine procedures, including those with cervical fusions with contiguous extension down to T3. OUTCOME MEASURES: We determined causes for reoperation and independent surgical and demographic risk factors impacting reoperation. METHODS: Patient-specific and surgery-specific data was extracted from the registry using ICD-10-DM codes. Reoperations data was obtained through abstraction of medical records through 90 days. Univariate analysis was done using chi-square tests for categorical variables, t-tests for normally distributed variables, and Wilcoxon rank-sum tests for variables with skewed distributions. Odds ratios for return to the operating room (OR) were evaluated in multivariate analysis. RESULTS: A total of 13435 and 13440 patients underwent cervical spine surgery and were included in the 30 and 90-day analysis, respectively. The overall reoperation rate was 1.24% and 3.30% within 30 and 90 days, respectively. Multivariate analysis showed within 30 days, procedures involving four or more levels, posterior only approach, and longer length of stay had increased odds of returning to the OR ($p < 0.05$), whereas private insurance had a decreased odds of return to OR ($p < 0.05$). Within 90 days, male sex, coronary artery disease (CAD), previous spine surgery, procedures with 4 or more levels, and longer length of stay had significantly increased odds of returning to the OR ($p < 0.05$). Non-white race, independent ambulatory status pre-operatively, and having private insurance had decreased odds of return to the OR ($p < 0.05$). The most common specified reasons for return to the OR within 30 days was hematoma (19%), infection (17%), and wound dehiscence (11%). Within 90 days, reoperation reasons were pain (10%), infection (9%), and hematoma (8%). CONCLUSION: Reoperation rates after elective cervical spine surgery are 1.24% and 3.30% within 30 and 90 days, respectively. Within 30 days, four or more levels, posterior approach, and longer length of stay were risk factors for reoperation. Within 90 days, male sex, CAD, four or more levels, and longer length of hospital stay were risk factors for reoperation. Non-white demographic and independent preoperative ambulatory status were associated with decreased reoperation rates.

Center for Individualized and Genomic Medicine Research

Herrera-Luis E, Mak ACY, Perez-Garcia J, Martin-Gonzalez E, Eng C, Beckman KB, Huntsman S, Hu D, González-Pérez R, Hernández-Pérez JM, Mederos-Luis E, Sio YY, Poza-Guedes P, Sardón O, Corcuera P, Sánchez-Machín I, Korta-Murua J, Martínez-Rivera C, Mullol J, Muñoz X, Valero A, Sastre J, Garcia-Aymerich J, Llop S, Torrent M, Casas M, Rodríguez-Santana JR, Villar J, Del Pozo V, Lorenzo-Diaz F, **Williams LK**, Melén E, Chew FT, Borrell LN, Burchard EG, and Pino-Yanes M. Admixture mapping of severe asthma exacerbations in Hispanic/Latino children and youth. *Thorax* 2022; Epub ahead of print. PMID: 36180068. Full Text

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BACKGROUND: In the USA, genetically admixed populations have the highest asthma prevalence and severe asthma exacerbations rates. This could be explained not only by environmental factors but also by genetic variants that exert ethnic-specific effects. However, no admixture mapping has been performed for severe asthma exacerbations. OBJECTIVE: We sought to identify genetic variants associated with severe asthma exacerbations in Hispanic/Latino subgroups by means of admixture mapping analyses and fine mapping, and to assess their transferability to other populations and potential functional roles. METHODS: We performed an admixture mapping in 1124 Puerto Rican and 625 Mexican American children with asthma. Fine-mapping of the significant peaks was performed via allelic testing of common and rare variants. We performed replication across Hispanic/Latino subgroups, and the transferability to non-Hispanic/Latino populations was assessed in 1001 African Americans, 1250 Singaporeans and 941 Europeans with asthma. The effects of the variants on gene expression and DNA methylation from whole blood were also evaluated in participants with asthma and in silico with data obtained through public databases. RESULTS: Genomewide significant associations of Indigenous American ancestry with severe asthma exacerbations were found at 5q32 in Mexican Americans as well as at 13q13-q13.2 and 3p13 in Puerto Ricans. The single nucleotide polymorphism (SNP) rs1144986 (C5orf46) showed consistent effects for severe asthma exacerbations across Hispanic/Latino subgroups, but it was not validated in non-Hispanics/Latinos. This SNP was associated with DPYSL3 DNA methylation and

SCGB3A2 gene expression levels. CONCLUSIONS: Admixture mapping study of asthma exacerbations revealed a novel locus that exhibited Hispanic/Latino-specific effects and regulated DPYSL3 and SCGB3A2.

Center for Individualized and Genomic Medicine Research
Williams LK. The time to PREPARE is over; the time to improve diversity in asthma studies is now. *J Allergy Clin Immunol* 2022; Epub ahead of print. PMID: 36154847. Full Text

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Dermatology
Almukhtar R, Wood E, Goldman M, Fabi SG, and Boen M. The Efficacy and Safety of Radiofrequency Microneedling Versus a Nonablative Fractional 1,550-nm Erbium:Glass Laser for the Rejuvenation of the Neck. *Dermatol Surg* 2022; 48(9):937-942. PMID: 36054046. Full Text

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BACKGROUND: Radiofrequency microneedling (RFMN) and nonablative fractional 1,550-nm erbium:glass lasers (NAFLs) have been reported to be used with success in neck rejuvenation. There are no head-to-head trials to compare these modalities. OBJECTIVE: The purpose of the study was to compare the efficacy and safety of radiofrequency microneedling and nonablative fractional 1,550-nm erbium:glass lasers for the rejuvenation of the neck. METHODS: This was a single-center, randomized, investigator-blinded clinical trial. A total of 21 subjects were randomized into 2 groups, NAFL and RFMN; subjects received 3 treatments 4 weeks apart and were followed up 12 weeks after last treatment. RESULTS: Subjects in NAFL and RFMN groups showed 42.1% and 8.6% improvement in the Fitzpatrick-Goldman Wrinkling Score, respectively, 41.3% and 16.3% improvement in the elastosis score, respectively. Subjects in the NAFL 1,550-nm erbium:glass group showed significantly better blinded investigator Fitzpatrick-Goldman Wrinkling and Elastosis scores; subjects in the RFMN groups showed a more significant reduction in the Horizontal Neck Wrinkle Severity Score. There was a trend for higher patient satisfaction with the NAFL. CONCLUSION: This study showed that both treatments resulted in significant improvement in wrinkling and elastosis scores; the NAFL treatment was associated with significantly better blinded investigator Fitzpatrick-Goldman Wrinkling and Elastosis scores and better subject satisfaction.

Dermatology
Almukhtar RM, and Goldman MP. Large Varicose Vein Closure: A Comprehensive Review. *Dermatol Surg* 2022; 48(9):967-971. PMID: 36054051. Full Text

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BACKGROUND: Treatment of chronic venous disease and varicose veins has significant psychosocial and economic impact. The great saphenous vein is a common vein to develop incompetence and reflux and, therefore, been the focus of therapy for many years. OBJECTIVE: To review the published medical literature relating to large varicose vein closure and provide a guide for closure techniques' efficacy and safety. METHODS: A comprehensive search of the English language literature was performed up to and including December 2021. All references pertaining to large varicose vein closure were reviewed. RESULTS: There are multiple safe and effective minimally invasive methods to achieve occlusion of incompetent great saphenous vein, the most widely used of which is endovenous thermal ablation. Other nonthermal, tumescent, and nontumescent methods can also be used. CONCLUSION: Proper knowledge of vein anatomy, ultrasound, and vein closure procedures is needed to ensure safe and effective outcomes.

Dermatology
Baldwin H, Alexis A, Andriessen A, Berson D, Harper J, Lain E, Marchbein S, and **Stein Gold L**. Supplement Article: Skin Barrier Deficiency in Rosacea: An Algorithm Integrating OTC Skincare Products Into Treatment Regimens. *J Drugs Dermatol* 2022; 21(9):Sf3595563-sf35955610. PMID: 36074516. Request Article

INTRODUCTION: Rosacea is a chronic condition involving inflammation leading to a diminished skin barrier function in sebaceous gland-rich facial skin. The current algorithm represents part II of a series investigating similar topics associated with preventing, treating, and maintaining rosacea, including ceramides-containing skincare. METHODS: The consensus process consisted of a modified Delphi technique. A previously published review by the US Cutaneous Rosacea Outcomes (USCRO) group on skin barrier deficiency in rosacea and the integration of over-the-counter (OTC) products and skincare recommended for rosacea treatment and maintenance informed the development of the current algorithm. The selected information from the literature searches, coupled with the USCRO group's opinion and experience, was used to develop, discuss, and reach a consensus on an evidence-based clinical treatment and maintenance algorithm focusing on rosacea phenotypes. RESULTS: The algorithm includes foundational measures to be taken by all patients with rosacea and rosacea-prone skin. These measures include education, behavioral modifications, avoidance of triggers and skin irritants, preventative skincare, and sun avoidance and sunscreen use. The algorithm further describes how assessment of skin condition and grading of cutaneous rosacea should take place during treatment and maintenance while the preventative measures continue. CONCLUSIONS: Prescription medications combined with gentle cleansers, moisturizers, and sunscreen support a successful rosacea therapy. J Drugs Dermatol. 2022;21:9(Suppl 1):s3-10.

Dermatology
Blum FR, Miles JA, Farag SW, Johnson EF, Davis M, **Hamzavi IH**, **Lyons AB**, Sayed CJ, and Googe PB. Characterizing the immune checkpoint marker profiles of cutaneous squamous cell carcinomas in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2022; Epub ahead of print. PMID: 36151986. Full Text

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Dermatology
Freeman EE, Casas CG, Prasad S, Fuller C, Peebles K, Rosenbach M, Fox L, McMahon DE, Strahan A, Lubov J, Chen G, Nguyen CV, McMillen A, **Lim HW**, Stratigos AJ, Kaufmann MD, Hruza GJ, and French L. The American Academy of Dermatology & International League of Dermatological Societies Monkeypox Registry: Expanding the COVID-19 Registry to Emerging Infections. *J Am Acad Dermatol* 2022; Epub ahead of print. PMID: 36075281. Full Text

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Dermatology
Lebwohl MG, Kircik LH, Moore AY, **Stein Gold L**, Draelos ZD, Gooderham MJ, Papp KA, Bagel J, Bhatia N, Del Rosso JQ, Ferris LK, Green LJ, Hebert AA, Jones T, Kempers SE, Pariser DM, Yamauchi PS, Zirwas M, Albrecht L, Devani AR, Lomaga M, Feng A, Snyder S, Burnett P, Higham RC, and Berk DR. Effect of Roflumilast Cream vs Vehicle Cream on Chronic Plaque Psoriasis: The DERMIS-1 and DERMIS-2 Randomized Clinical Trials. *Jama* 2022; 328(11):1073-1084. PMID: 36125472. Full Text

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Advanced Dermatology and Cosmetic Surgery, Maitland, Florida.
University of Pittsburgh Clinical and Translational Science Institute, Pittsburgh, Pennsylvania.
George Washington University School of Medicine, Rockville, Maryland.
UT Health McGovern Medical School, Houston, Texas.
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IMPORTANCE: Once-daily roflumilast cream, 0.3%, a potent phosphodiesterase 4 inhibitor, demonstrated efficacy and was well tolerated in a phase 2b trial of patients with psoriasis. OBJECTIVE: To evaluate the efficacy of roflumilast cream, 0.3%, applied once daily for 8 weeks in 2 trials of patients with plaque psoriasis. DESIGN, SETTING, AND PARTICIPANTS: Two phase 3, randomized, double-blind, controlled, multicenter trials (DERMIS-1 [trial 1; n = 439] and DERMIS-2 [trial 2; n = 442]) were conducted at 40 centers (trial 1) and 39 centers (trial 2) in the US and Canada between December 9, 2019, and November 16, 2020, and between December 9, 2019, and November 23, 2020, respectively. Patients aged 2 years or older with plaque psoriasis involving 2% to 20% of body surface area were enrolled. The dates of final follow-up were November 20, 2020, and November 23, 2020, for trial 1 and trial 2, respectively. INTERVENTIONS: Patients were randomized 2:1 to receive roflumilast cream, 0.3% (trial 1: n = 286; trial 2: n = 290), or vehicle cream (trial 1: n = 153; trial 2: n = 152) once daily for 8 weeks. MAIN OUTCOMES AND MEASURES: The primary efficacy end point was Investigator Global Assessment (IGA) success (clear or almost clear status plus ≥2-grade improvement from baseline [score range, 0-4]) at week 8, analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline IGA score, and intertriginous involvement. There were 9 secondary outcomes, including intertriginous IGA success, 75% reduction in Psoriasis Area and Severity Index (PASI) score, and Worst Itch Numeric Rating Scale score of 4 or higher at baseline achieving 4-point reduction (WI-NRS success) at week 8 (scale: 0 [no itch] to 10 [worst imaginable itch]; minimum clinically important difference, 4 points). RESULTS: Among 881 participants (mean age, 47.5 years; 320 [36.3%] female), mean IGA scores in trial 1 were 2.9 [SD, 0.52] for roflumilast and 2.9 [SD, 0.45] for vehicle and in trial 2 were 2.9 [SD, 0.48] for roflumilast and 2.9 [SD, 0.47]) for vehicle. Statistically significantly greater percentages of roflumilast-treated patients than vehicle-treated patients had IGA success at week 8 (trial 1: 42.4% vs 6.1%; difference, 39.6% [95% CI, 32.3%-46.9%]; trial 2: 37.5% vs 6.9%; difference, 28.9% [95% CI, 20.8%-36.9%]; P < .001 for both). Of 9 secondary end points, statistically significant differences favoring roflumilast vs vehicle were observed for 8 in trial 1 and 9 in trial 2, including intertriginous IGA success (71.2% vs 13.8%; difference, 66.5% [95% CI, 47.1%-85.8%] and 68.1% vs 18.5%; difference, 51.6% [95% CI, 29.3%-73.8%]; P < .001 for both), 75% reduction in PASI score (41.6% vs 7.6%; difference, 36.1% [95% CI, 28.5%-43.8%] and 39.0% vs 5.3%; difference, 32.4% [95% CI, 24.9%-39.8%]; P < .001 for both), WI-NRS success (67.5% vs 26.8%; difference, 42.6% [95% CI, 31.3%-53.8%] and 69.4% vs 35.6%; difference, 30.2% [95% CI, 18.2%-42.2%]; P < .001 for both). The incidence of treatment-emergent adverse events was 25.2% with roflumilast vs 23.5% with vehicle in trial 1 and 25.9% with roflumilast vs 18.4% with vehicle in trial 2. The incidence of serious adverse events was 0.7% with roflumilast vs 0.7% with vehicle in trial 1 and 0% with roflumilast vs 0.7% with vehicle in trial 2. CONCLUSIONS AND RELEVANCE: Among patients with chronic plaque psoriasis, treatment with roflumilast cream, 0.3%, compared with vehicle cream resulted in better clinical status at 8 weeks. Further research is needed to assess efficacy compared with other active treatments and to assess longer-term efficacy and safety. TRIAL REGISTRATION: ClinicalTrials.gov Identifiers: NCT04211363, NCT04211389.

Dermatology

Liu T, **Toor JS**, **Subedi K**, **Wang J**, **Yi Q**, **Loveless I**, **Zhou L**, and **Mi QS**. Cbf-β is required for the development, differentiation, and function of murine mucosal-associated invariant T cells. *Cell Mol Immunol* 2022; Epub ahead of print. PMID: 36068293. Request Article

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Dermatology

Yao Y, **Subedi K**, **Liu T**, **Khalasawi N**, Pretto-Kernahan CD, Wotring JW, **Wang J**, **Yin C**, **Jiang A**, **Fu C**, **Dimitrion P**, **Li J**, **Veenstra J**, **Yi Q**, **McKinnon K**, **McKinnon JE**, Sexton JZ, **Zhou L**, and **Mi QS**. Surface translocation of ACE2 and TMPRSS2 upon TLR4/7/8 activation is required for SARS-CoV-2 infection in circulating monocytes. *Cell Discov* 2022; 8(1):89. PMID: 36085197. Full Text

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Infection of human peripheral blood cells by SARS-CoV-2 has been debated because immune cells lack mRNA expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease type 2 (TMPRSS2). Herein we demonstrate that resting primary monocytes harbor abundant cytoplasmic ACE2 and TMPRSS2 protein and that circulating exosomes contain significant ACE2 protein. Upon ex

vivo TLR4/7/8 stimulation, cytoplasmic ACE2 was quickly translocated to the monocyte cell surface independently of ACE2 transcription, while TMPRSS2 surface translocation occurred in conjunction with elevated mRNA expression. The rapid translocation of ACE2 to the monocyte cell surface was blocked by the endosomal trafficking inhibitor endosidin 2, suggesting that endosomal ACE2 could be derived from circulating ACE2-containing exosomes. TLR-stimulated monocytes concurrently expressing ACE2 and TMPRSS2 on the cell surface were efficiently infected by SARS-CoV-2, which was significantly mitigated by remdesivir, TMPRSS2 inhibitor camostat, and anti-ACE2 antibody. Mass cytometry showed that ACE2 surface translocation in peripheral myeloid cells from patients with severe COVID-19 correlated with its hyperactivation and PD-L1 expression. Collectively, TLR4/7/8-induced ACE2 translocation with TMPRSS2 expression makes circulating monocytes permissive to SARS-CoV-2 infection.

Dermatology

Zhou L, **Jiang A**, **Veenstra J**, **Ozog DM**, and **Mi QS**. The Roles of Skin Langerhans Cells in Immune Tolerance and Cancer Immunity. *Vaccines (Basel)* 2022; 10(9). PMID: 36146458. Full Text

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Langerhans cells (LC) are a unique population of tissue-resident macrophages with dendritic cell (DC) functionality that form a network of cells across the epidermis of the skin. Their location at the skin barrier suggests an important role for LC as immune sentinels at the skin surface. The classification of LC as DC over the past few decades has driven the scientific community to extensively study how LC function as DC-like cells that prime T cell immunity. However, LC are a unique type of tissue-resident macrophages, and recent evidence also supports an immunoregulatory role of LC at steady state and during specific inflammatory conditions, highlighting the impact of cutaneous environment in shaping LC functionality. In this mini review, we discuss the recent literature on the immune tolerance function of LC in homeostasis and disease conditions, including malignant transformation and progression; as well as LC functional plasticity for adaption to microenvironmental cues and the potential connection between LC population heterogeneity and functional diversity. Future investigation into the molecular mechanisms that LC use to integrate different microenvironment cues and adapt immunological responses for controlling LC functional plasticity is needed for future breakthroughs in tumor immunology, vaccine development, and treatments for inflammatory skin diseases.

Diagnostic Radiology

Harmon QE, Patchel SA, Denslow S, LaPorte F, **Cooper T**, Wise LA, **Wegienka G**, and Baird DD. Vitamin D and uterine fibroid growth, incidence, and loss: a prospective ultrasound study. *Fertil Steril* 2022; Epub ahead of print. PMID: 36150919. Full Text

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OBJECTIVE: Fibroid treatments that have few side-effects and can preserve fertility are a clinical priority. We studied the association between serum vitamin D and uterine fibroid growth, incidence, and loss. DESIGN: A prospective community cohort study (enrollment 2010-2012) with 4 study visits over 5 years to conduct standardized ultrasounds, measure 25-hydroxyvitamin D (25(OH)D), and update covariates. SETTING: Detroit, Michigan area. PATIENTS: Self-identified African American or Black women aged 23-

35 at enrollment without previous clinical diagnosis of fibroids. INTERVENTION(S): Serum 25(OH)D measured using immunoassay or liquid chromatography-tandem mass spectrometry. MAIN OUTCOME MEASURE(S): The primary outcomes were fibroid growth, as measured by change in log volume per 18 months, and fibroid incidence (first detection of fibroid in previously fibroid-free uterus). Adjusted growth estimates from linear mixed models were converted to estimated difference in volume for high vs. low 25(OH)D. Incidence differences were estimated as hazard ratios from age-specific Cox regression. A secondary outcome fibroid loss (reduction in fibroid number between visits), was modeled using Poisson regression. Covariates (reproductive and hormonal variables, demographics, body mass index, current smoking) and 25(OH)D were modeled as time-varying factors. RESULT(S): At enrollment among 1,610 participants with ≥1 follow-up ultrasound, mean age was 29.2 years, 73% had deficient vitamin D (<20ng/mL), and only 7% had sufficient vitamin D (≥30ng/mL). Serum 25(OH)D ≥20ng/mL compared with <20ng/mL was associated with an estimated 9.7% reduction in fibroid growth (95% confidence interval [CI]: -17.3%, -1.3%), similar to the minimally adjusted estimate -8.4% (95% CI: -16.4, 0.3). Serum 25(OH)D ≥30ng/mL compared with <30ng/mL was associated with an imprecise 22% reduction in incidence (adjusted hazard ratio=0.78; 95% CI: 0.47, 1.30), similar to the unadjusted estimate of 0.84 (95% CI: 0.51, 1.39). The >30ng/mL group also had a 32% increase in fibroid loss (adjusted risk ratio=1.32; 95% CI: 0.95, 1.83). CONCLUSION(S): Our data support the hypothesis that high concentrations of vitamin D decrease fibroid development but are limited by the few participants with serum 25(OH)D ≥30ng/mL. Interventional trials that raise and maintain 25(OH)D concentrations >30ng/mL and then prospectively monitor fibroid development are needed to further assess supplemental vitamin D efficacy and determine optimal treatment protocols.

Emergency Medicine

Bunch CM, Berquist M, Ansari A, McCoy ML, Langford JH, Brenner TJ, Aboukhaled M, Thomas SJ, Peck E, Patel S, Cancel E, Al-Fadhl MD, Zackariya N, Thomas AV, Aversa JG, Greene RB, Seder CW, Speybroeck J, **Miller JB**, Kwaan HC, and Walsh MM. The Choice between Plasma-Based Common Coagulation Tests and Cell-Based Viscoelastic Tests in Monitoring Hemostatic Competence: Not an either-or Proposition. *Semin Thromb Hemost* 2022; Epub ahead of print. PMID: 36174601. Request Article

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There has been a significant interest in the last decade in the use of viscoelastic tests (VETs) to determine the hemostatic competence of bleeding patients. Previously, common coagulation tests (CCTs) such as the prothrombin time (PT) and partial thromboplastin time (PTT) were used to assist in the guidance of blood component and hemostatic adjunctive therapy for these patients. However, the experience of decades of VET use in liver failure with transplantation, cardiac surgery, and trauma has now spread to obstetrical hemorrhage and congenital and acquired coagulopathies. Since CCTs measure only 5 to 10% of the lifespan of a clot, these assays have been found to be of limited use for acute surgical and medical conditions, whereby rapid results are required. However, there are medical indications for the PT/PTT that cannot be supplanted by VETs. Therefore, the choice of whether to use a CCT or a VET to guide blood component therapy or hemostatic adjunctive therapy may often require consideration of both methodologies. In this review, we provide examples of the relative indications for CCTs and VETs in monitoring hemostatic competence of bleeding patients.

Emergency Medicine

Davuluri K, **Goyal N**, Gomez Acevedo H, **Folt J**, **Jayaprakash N**, **Slezak M**, and **Caldwell MT**. Patient perspectives of the climate of diversity, equity, and inclusion in the emergency department. *J Am Coll Emerg Physicians Open* 2022; 3(5):e12798. PMID: 36176501. Full Text

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OBJECTIVE: Assessing the diversity, equity, and inclusion (DEI) climate of emergency departments (EDs) can inform organizational change to provide equitable, inclusive, and high-quality care to their diverse patient populations. The purpose of this project was to investigate patient perspectives on the climate of DEI in an urban ED. METHODS: This was a cross-sectional survey study conducted in a large-volume, urban ED in Detroit, MI, from November 2018 to January 2019. The survey was developed by an experienced ED DEI committee via an iterative process and broad consensus. RESULTS: During their care in the ED, 849 patients completed an anonymous survey about their perspectives and experiences of DEI in that ED. Overall, the responses were favorable as most respondents reported that the ED staff treated patients from all races equally (75.8%) and made patients feel accepted (86%). However, some respondents felt that the ED staff's treatment of populations with greater complexity, such as patients who are mentally ill (16.8%) or lower income (14.3%), needs the most improvement. CONCLUSIONS: This DEI climate assessment survey of ED patients' perspectives revealed important insights that could guide strategic initiatives to advance DEI in the ED. This assessment may serve as a model for continuous evaluation of DEI over time and in multiple healthcare settings to help guide organizational change efforts.

Emergency Medicine

Grobbelaar LM, Kruger A, Venter C, Burger EM, Laubscher GJ, Maponga TG, Kotze MJ, Kwaan HC, **Miller JB**, Fulkerson D, Huff W, Chang E, Wiarda G, **Bunch CM**, Walsh MM, Raza S, Zamlut M, Moore HB, Moore EE, Neal MD, Kell DB, and Pretorius E. Relative Hypercoagulopathy of the SARS-CoV-2 Beta and Delta Variants when Compared to the Less Severe Omicron Variants Is Related to TEG Parameters, the Extent of Fibrin Amyloid Microclots, and the Severity of Clinical Illness. *Semin Thromb Hemost* 2022; Epub ahead of print. PMID: 36174604. Full Text

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Earlier variants of SARS-CoV-2 have been associated with plasma hypercoagulability (as judged by thromboelastography) and an extensive formation of fibrin amyloid microclots, which are considered to contribute to the pathology of the coronavirus 2019 disease (COVID-19). The newer Omicron variants appear to be far more transmissible, but less virulent, even when taking immunity acquired from previous infections or vaccination into account. We here show that while the clotting parameters associated with Omicron variants are significantly raised over those of healthy, matched controls, they are only raised to levels significantly lower than those seen with more severe variants such as beta and delta. We also observed that individuals infected with omicron variants manifested less extensive microclot formation in platelet-poor plasma compared with those harboring the more virulent variants. The measurement of clotting effects between the different variants acts as a kind of "internal control" that demonstrates the relationship between the extent of coagulopathies and the virulence of the variant of interest. This adds to the evidence that microclots may play an important role in reflecting the severity of symptoms observed in COVID-19.

Emergency Medicine

Miranian D, Schwartz A, Jiang C, Kue Ndukwe J, **Caldwell M**, Lim C, and Marsh EE. Emergency Department Utilization for Adnexal Torsion: An Analysis of the Nationwide Emergency Department Sample from 2006 to 2018. *J Minim Invasive Gynecol* 2022; 29(9):1068-1074. PMID: 35649480. Full Text

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STUDY OBJECTIVE: To characterize emergency department (ED) utilization for adnexal torsion (AT) among adult patients in the United States. DESIGN: Retrospective analysis to identify primary AT diagnoses and ED utilization. Other variables analyzed included primary payer type, income quartile by ZIP code, hospital teaching status, and urban vs rural location. Secondary analyses identified diagnosis codes associated with a primary diagnosis of AT. SETTING: Healthcare Cost and Utilization Project Nationwide Emergency Sample database. PATIENTS: Women aged 18 to 65 years presenting to the ED with AT from 2006 to 2018. INTERVENTIONS: Not applicable. MEASUREMENTS AND MAIN RESULTS: From 2006 to 2018, the annual number of ED visits for AT among women aged 18 to 65 years increased from 2791 to 5243. Hospital admission rates for AT declined over the study period from 76% to 37%. Patients with AT were less likely to be admitted if they had private insurance, but admission rates for AT were similar regardless of income quartile and hospital teaching status. Average ED charges for AT nearly quadrupled over the study period compared with ED charges overall, which doubled. The average charge for AT patients in 2006 was $5212 and in 2018 was $20 213-an average annual increase of 24.0%, compared with 14.3% for all other diagnoses in age-matched women. CONCLUSION: Although admission rates for AT decreased by 50% from 2006 to 2018, ED utilization nearly doubled, and the average associated charges quadrupled, summing to an annual weighted charge of over $500 million by 2018. The data suggest that women are evaluated similarly for AT regardless of income or insurance status.

Emergency Medicine

Punches BE, Stolz U, Freiermuth CE, Ancona RM, McLean SA, House SL, Beaudoin FL, An X, Stevens JS, Zeng D, Neylan TC, Clifford GD, Jovanovic T, Linnstaedt SD, Germine LT, Bollen KA, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Musey PI, Jr., Hendry PL, Sheikh S, Jones CW, Kurz MC, Gentile NT, McGrath ME, Hudak LA, Pascual JL, Seamon MJ, Harris E, Chang AM, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, O'Neil BJ, Sanchez LD, Bruce SE, Pietrzak RH, Joormann J, Barch DM, Pizzagalli DA, Smoller JW, Luna B, Harte SE, Elliott JM, Kessler RC, Ressler KJ, Koenen KC, and Lyons MS. Predicting at-risk opioid use three months after ed visit for trauma: Results from the AURORA study. *PLoS One* 2022; 17(9):e0273378. PMID: 36149896. Full Text

OBJECTIVE: Whether short-term, low-potency opioid prescriptions for acute pain lead to future at-risk opioid use remains controversial and inadequately characterized. Our objective was to measure the association between emergency department (ED) opioid analgesic exposure after a physical, trauma-related event and subsequent opioid use. We hypothesized ED opioid analgesic exposure is associated with subsequent at-risk opioid use. METHODS: Participants were enrolled in AURORA, a prospective cohort study of adult patients in 29 U.S., urban EDs receiving care for a traumatic event. Exclusion criteria were hospital admission, persons reporting any non-medical opioid use (e.g., opioids without prescription or taking more than prescribed for euphoria) in the 30 days before enrollment, and missing or incomplete data regarding opioid exposure or pain. We used multivariable logistic regression to assess the relationship between ED opioid exposure and at-risk opioid use, defined as any self-reported non-medical opioid use after initial ED encounter or prescription opioid use at 3-months. RESULTS: Of 1441 subjects completing 3-month follow-up, 872 participants were included for analysis. At-risk opioid use occurred within 3 months in 33/620 (5.3%, CI: 3.7,7.4) participants without ED opioid analgesic exposure; 4/16 (25.0%, CI: 8.3, 52.6) with ED opioid prescription only; 17/146 (11.6%, CI: 7.1, 18.3) with ED opioid administration only; 12/90 (13.3%, CI: 7.4, 22.5) with both. Controlling for clinical factors, adjusted odds ratios (aORs) for at-risk opioid use after ED opioid exposure were: ED prescription only: 4.9 (95% CI 1.4, 17.4); ED administration for analgesia only: 2.0 (CI 1.0, 3.8); both: 2.8 (CI 1.2, 6.5). CONCLUSIONS: ED opioids were associated with subsequent at-risk opioid use within three months in a geographically diverse cohort of adult trauma patients. This supports need for prospective studies focused on the long-term consequences of ED opioid analgesic exposure to estimate individual risk and guide therapeutic decision-making.

Endocrinology and Metabolism

Hinnen D, **Kruger D**, and Magwire M. Type 2 diabetes and cardiovascular disease: risk reduction and early intervention. *Postgrad Med* 2022; Epub ahead of print. PMID: 36154802. Request Article

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People with type 2 diabetes (T2D) have a higher risk of cardiovascular disease (CVD) than those without. This increased risk begins with pre-diabetes, potentially 7-10 years before T2D is diagnosed. Selecting medication for patients with T2D should focus on reducing the risk of CVD and established CVD. Within the last decade, several antihyperglycemic agents with proven cardiovascular (CV) benefit have been approved for the treatment of hyperglycemia and for the prevention of primary and secondary CV events, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors. T2D treatment guidelines recommend that an antihyperglycemic agent with proven CV benefit should be used after metformin in patients with high risk of or established CVD, regardless of glycated hemoglobin levels. Despite the availability of antihyperglycemic agents with proven CV benefit, and guidelines on when to use them, less than one in four patients with T2D and CVD receive this type of therapy. These findings suggest a potential gap between current recommendations and clinical practice. This article reviews the approved agents with CV indications, with a focus on injectable GLP-1RAs, and their place in the T2D treatment paradigm according to current guidelines. We aim to provide primary healthcare providers with in-depth information on subsets of patients who would benefit from this type of therapy and when it should be initiated, taking into consideration safety and tolerability and other disease

factors. An individualized treatment approach is increasingly recommended in the management of T2D, employing a shared decision-making strategy between patients and healthcare professionals.

Endocrinology and Metabolism

Russell SJ, Beck RW, Damiano ER, El-Khatib FH, Ruedy KJ, Balliro CA, Li Z, Calhoun P, Wadwa RP, Buckingham B, Zhou K, Daniels M, Raskin P, White PC, Lynch J, Pettus J, Hirsch IB, Goland R, Buse JB, **Kruger D**, Mauras N, Muir A, McGill JB, Cogen F, Weissberg-Benchell J, Sherwood JS, Castellanos LE, Hillard MA, Tuffaha M, Putman MS, Sands MY, Forlenza G, Slover R, Messer LH, Cobry E, Shah VN, Polsky S, Lal R, Ekhlaspour L, Hughes MS, Basina M, Hatipoglu B, Olansky L, Bhangoo A, Forghani N, Kashmiri H, Sutton F, Choudhary A, Penn J, Jafri R, Rayas M, Escaname E, Kerr C, Favela-Prezas R, Boeder S, Trikudanathan S, Williams KM, Leibel N, Kirkman MS, Bergamo K, Klein KR, Dostou JM, Machineni S, Young LA, Diner JC, **Bhan A**, **Jones JK**, Benson M, Bird K, Englert K, Permuy J, Cossen K, Felner E, Salam M, Silverstein JM, Adamson S, Cedeno A, Meighan S, and Dauber A. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. *N Engl J Med* 2022; 387(13):1161-1172. PMID: 36170500. Full Text

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BACKGROUND: Currently available semiautomated insulin-delivery systems require individualized insulin regimens for the initialization of therapy and meal doses based on carbohydrate counting for routine operation. In contrast, the bionic pancreas is initialized only on the basis of body weight, makes all dose decisions and delivers insulin autonomously, and uses meal announcements without carbohydrate counting. METHODS: In this 13-week, multicenter, randomized trial, we randomly assigned in a 2:1 ratio persons at least 6 years of age with type 1 diabetes either to receive bionic pancreas treatment with insulin aspart or insulin lispro or to receive standard care (defined as any insulin-delivery method with unblinded, real-time continuous glucose monitoring). The primary outcome was the glycated hemoglobin level at 13 weeks. The key secondary outcome was the percentage of time that the glucose level as assessed by continuous glucose monitoring was below 54 mg per deciliter; the prespecified noninferiority limit for this outcome was 1 percentage point. Safety was also assessed. RESULTS: A total of 219 participants 6 to 79 years of age were assigned to the bionic-pancreas group, and 107 to the standard-care group. The glycated hemoglobin level decreased from 7.9% to 7.3% in the bionic-pancreas group and did not change (was at 7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, -0.5 percentage points; 95% confidence interval [CI], -0.6 to -0.3; P<0.001). The percentage of time that the glucose level as assessed by continuous glucose monitoring was below 54 mg per deciliter did not differ significantly between the two groups (13-week adjusted difference, 0.0 percentage points; 95% CI, -0.1 to 0.04; P<0.001 for noninferiority). The rate of severe hypoglycemia was 17.7 events per 100 participant-years in the bionic-pancreas group and 10.8 events per 100 participant-years in the standard-care group (P = 0.39). No episodes of diabetic ketoacidosis occurred in either group. CONCLUSIONS: In this 13-week, randomized trial involving adults and children with type 1 diabetes, use of a bionic pancreas was associated with a greater reduction than standard care in the

glycated hemoglobin level. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov number, NCT04200313.).

Gastroenterology
Hartgerink C, **Nimri FM**, **Zuchelli T**, **Jafri SM**, and **Piraka C**. Band Ligation Can Be Used to Treat Barrett's Esophagus and Concurrent Esophageal Varices: A Case Series. *Dig Dis Sci* 2022; Epub ahead of print. PMID: 36131048. Request Article

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BACKGROUND: Patients with Barrett's esophagus (BE) and esophageal varices present a unique management dilemma. Endoscopic ablation and endoscopic resection are not suitable treatment options due to bleeding risk. Data are limited on successful eradication of BE and esophageal varices utilizing band ligation. AIMS: To assess the outcomes of patients with BE and esophageal varices treated with banding. METHODS: Retrospective analysis of patients with BE and esophageal varices who were treated with band ligation. RESULTS: A total of eight patients were included in the case series. In all eight cases, BE and esophageal varices were successfully treated with band ligation alone. There were no bleeding, perforation or infectious complications in any patients undergoing banding for treatment of BE. Four patients had biopsy-proven dysplasia prior to treatment with band ligation. After band ligation, the 2 of 4 dysplastic cases that had repeat biopsies showed histologic resolution of the dysplasia. All patients who received banding for BE were followed at least yearly except for one patient lost to follow up. No interval esophageal cancers were reported in any patients with BE that were banded. CONCLUSIONS: Band ligation was used to treat BE pathology in eight patients with esophageal varices. Treatment of dysplasia through this method yielded negative biopsies both for dysplasia and BE on repeat endoscopy. This case series highlights the value of utilizing band ligation to address the management dilemma of BE in the context of esophageal varices.

Gastroenterology
Nagai S, **Ivanics T**, **Kitajima T**, **Shimada S**, **Shamaa TM**, **Collins K**, **Rizzari M**, **Yoshida A**, **Moonka D**, and **Abouljoud M**. Disparities in the Effects of Acuity Circle-based Liver Allocation on Waitlist and Transplant Practice Between Centers. *Transplant Direct* 2022; 8(10):e1356. PMID: 36176726. Full Text

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Liver allocation in the United States was updated on February 4, 2020, by introducing the acuity circle (AC)-based model. This study evaluated the early effects of the AC-based allocation on waitlist outcomes. METHODS: Adult liver transplant (LT) candidates listed between January 1, 2019, and September 30, 2021, were assessed. Two periods were defined according to listing date (pre- and post-AC), and 90-d waitlist outcomes were compared. Median transplant Model for End-stage Liver Disease (MELD) score of each transplant center was calculated, with centers categorized as low- (<25 percentile), mid- (25-75 percentile), and high-MELD (>75 percentile) centers. RESULTS: A total of 12 421 and 17 078 LT candidates in the pre- and post-AC eras were identified. Overall, the post-AC era was associated with higher cause-specific 90-d hazards of transplant (csHR, 1.32; 95% confidence interval [CI], 1.27-1.38; P < 0.001) and waitlist mortality (cause-specific hazard ratio [csHR], 1.20; 95% CI, 1.09-1.32; P < 0.001). The latter effect was primarily driven by high-MELD centers. Low-MELD centers had a higher proportion of donations after circulatory death (DCDs) used. Compared with low-MELD centers, mid-MELD and high-MELD centers had significantly lower cause-specific hazards of DCD-LT in both eras (mid-MELD: csHR, 0.47; 95% CI, 0.38-0.59 in pre-AC and csHR, 0.56; 95% CI, 0.46-0.67 in post-AC and high-MELD: csHR, 0.11; 95% CI, 0.07-0.17 in pre-AC and csHR, 0.14; 95% CI, 0.10-0.20 in post-AC; all P < 0.001). Using a structural Bayesian time-series model, the AC policy was associated with an increase in the actual monthly DCD-LTs in low-, mid-, and high-MELD centers (actual/predicted: low-MELD: 19/16; mid-MELD: 21/14; high-MELD: 4/3), whereas the increase in monthly donation after brain death-LTs were only

present in mid- and high-MELD centers. CONCLUSIONS: Although AC-based allocation may improve waitlist outcomes, regional variation exists in the drivers of such outcomes between centers.

Hematology-Oncology

Martini R, Delpe P, Chu TR, Arora K, Lord B, Verma A, Bedi D, Karanam B, Elhussin I, **Chen Y**, Gebregzabher E, Oppong JK, Adjei EK, Jibril Suleiman A, Awuah B, Muleta MB, Abebe E, Kyei I, Aitpillah FS, Adinku MO, Ankomah K, Osei-Bonsu EB, **Chitale DA**, **Bensenhaver JM**, **Nathanson DS**, **Jackson L**, **Petersen LF**, Proctor E, Stonaker B, Gyan KK, Gibbs LD, Manojlovic Z, Kittles RA, White J, Yates CC, Manne U, Gardner K, Mongan N, Cheng E, Ginter P, Hoda S, Elemento O, Robine N, Sboner A, Carpten JD, Newman L, and Davis MB. African Ancestry Associated Gene Expression Profiles in Triple Negative Breast Cancer Underlie Altered Tumor Biology and Clinical Outcome in Women of African Descent. *Cancer Discov* 2022; Epub ahead of print. PMID: 36121736. Full Text

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Women of sub-Saharan African descent have disproportionately higher incidence of Triple Negative Breast Cancer (TNBC), and TNBC-specific mortality. Population comparative studies show racial differences in TNBC biology, including higher prevalence of basal-like and Quadruple-Negative subtypes in African Americans (AA). However, previous investigations relied on self-reported race (SRR) of primarily United States (US) populations. Due to heterogenous genetic admixture, and biological consequences of social determinants, the true association of African ancestry with TNBC biology is unclear. To address this, we conducted RNAseq on an international cohort of AAs, west and east Africans with TNBC. Using comprehensive genetic ancestry estimation in this African-enriched cohort, we found expression of 613 genes associated with African ancestry and 2000+ associated with regional African ancestry. A subset of African-associated genes also showed differences in normal breast tissue. Pathway enrichment and deconvolution of tumor cellular composition revealed tumor-associated immunological profiles are distinct in patients of African descent.

Hematology-Oncology

Mello AM, Ngodup T, Lee Y, Donahue KL, Li J, Rao A, Carpenter ES, **Crawford HC**, Pasca di Magliano M, and Lee KE. Hypoxia promotes an inflammatory phenotype of fibroblasts in pancreatic cancer. *Oncogenesis* 2022; 11(1):56. PMID: 36109493. Full Text

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Pancreatic ductal adenocarcinoma (PDAC) is characterized by an extensive fibroinflammatory stroma and often experiences conditions of insufficient oxygen availability or hypoxia. Cancer-associated fibroblasts (CAF) are a predominant and heterogeneous population of stromal cells within the pancreatic tumor microenvironment. Here, we uncover a previously unrecognized role for hypoxia in driving an inflammatory phenotype in PDAC CAFs. We identify hypoxia as a strong inducer of tumor IL1α expression, which is required for inflammatory CAF (iCAF) formation. Notably, iCAFs preferentially reside in hypoxic regions of PDAC. Our data implicate hypoxia as a critical regulator of CAF heterogeneity in PDAC.

Hematology-Oncology

Uddin MH, Al-Hallak MN, **Philip PA**, Chen H, El-Rayes B, and Azmi AS. Aberrant transcription factors in the cancers of the pancreas. *Semin Cancer Biol* 2022; 86(Pt 2):28-45. PMID: 36058426. Full Text

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Transcription factors (TFs) are essential for proper activation of gene during the process of organogenesis, differentiation, lineage specificity. Reactivation or dysregulation of TFs regulatory networks could lead to deformation of organs, diseases including various malignancies. Currently, understanding the mechanism of oncogenesis became a necessity for the development of targeted therapeutic strategy for different cancer types. It is evident that many TFs go awry in cancers of the pancreas such as pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine neoplasms (PanNENs). These mutated or dysregulated TFs abnormally controls various signaling pathways in PDAC and PanNENs including RTK, PI3K-PTEN-AKT-mTOR, JNK, TGF-β/SMAD, WNT/β-catenin, SHH,

NOTCH and VEGF which in turn regulate different hallmarks of cancer. Aberrant regulation of such pathways have been linked to the initiation, progression, metastasis, and resistance in pancreatic cancer. As of today, a number of TFs has been identified as crucial regulators of pancreatic cancer and a handful of them shown to have potential as therapeutic targets in pre-clinical and clinical settings. In this review, we have summarized the current knowledge on the role and therapeutic usefulness of TFs in PDAC and PanNENs.

Hematology-Oncology

Wagner MJ, Hennessy C, Beeghly A, French B, Shah DP, Croessmann S, Vilar-Compte D, Ruiz-Garcia E, Ingham M, Schwartz GK, Painter CA, Chugh R, Fecher L, Park C, Zamulko O, Trent JC, Subbiah V, Khaki AR, Tachiki L, Nakasone ES, Loggers ET, Labaki C, Saliby RM, McKay RR, Ajmera A, Griffiths EA, Puzanov I, Tap WD, **Hwang C**, **Tejwani S**, Jhawar SR, Hayes-Lattin B, Wulff-Burchfield E, Kasi A, Reuben DY, Nagaraj G, Joshi M, Polimera H, Kulkarni AA, Esfahani K, Kwon DH, Paoluzzi L, Bilen MA, Durbin EB, Grivas P, Warner JL, and Davis EJ. Demographics, Outcomes, and Risk Factors for Patients with Sarcoma and COVID-19: A CCC19-Registry Based Retrospective Cohort Study. *Cancers (Basel)* 2022; 14(17). PMID: 36077869. Full Text

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BACKGROUND: Patients with sarcoma often require individualized treatment strategies and are likely to receive aggressive immunosuppressive therapies, which may place them at higher risk for severe COVID-19. We aimed to describe demographics, risk factors, and outcomes for patients with sarcoma and COVID-19. METHODS: We performed a retrospective cohort study of patients with sarcoma and COVID-19 reported to the COVID-19 and Cancer Consortium (CCC19) registry (NCT04354701) from 17 March 2020 to 30 September 2021. Demographics, sarcoma histologic type, treatments, and COVID-19 outcomes were analyzed. RESULTS: of 281 patients, 49% (n = 139) were hospitalized, 33% (n = 93) received supplemental oxygen, 11% (n = 31) were admitted to the ICU, and 6% (n = 16) received mechanical ventilation. A total of 23 (8%) died within 30 days of COVID-19 diagnosis and 44 (16%) died overall at the time of analysis. When evaluated by sarcoma subtype, patients with bone sarcoma and COVID-19 had a higher mortality rate than patients from a matched SEER cohort (13.5% vs 4.4%). Older age, poor performance status, recent systemic anti-cancer therapy, and lung metastases all contributed to higher COVID-19 severity. CONCLUSIONS: Patients with sarcoma have high rates of severe COVID-19 and those with bone sarcoma may have the greatest risk of death.

Hospital Medicine

Schaefer JK, Errickson J, Gu X, Alexandris-Souphis T, Ali MA, Haymart B, **Kaatz S**, Kline-Rogers E, Kozlowski JH, **Krol GD**, **Shah V**, Sood SL, Froehlich JB, and Barnes GD. Assessment of an Intervention to Reduce Aspirin Prescribing for Patients Receiving Warfarin for Anticoagulation. *JAMA Netw Open* 2022; 5(9):e2231973. PMID: 36121653. Full Text

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IMPORTANCE: For some patients receiving warfarin, adding aspirin (acetylsalicylic acid) increases bleeding risk with unclear treatment benefit. Reducing excess aspirin use could be associated with improved clinical outcomes. OBJECTIVE: To assess changes in aspirin use, bleeding, and thrombosis event rates among patients treated with warfarin. DESIGN, SETTING, AND PARTICIPANTS: This pre-post observational quality improvement study was conducted from January 1, 2010, to December 31, 2019, at a 6-center quality improvement collaborative in Michigan among 6738 adults taking warfarin for atrial fibrillation and/or venous thromboembolism without an apparent indication for concomitant aspirin. Statistical analysis was conducted from November 26, 2020, to June 14, 2021. INTERVENTION: Primary care professionals for patients taking aspirin were asked whether an ongoing combination aspirin and warfarin treatment was indicated. If not, then aspirin was discontinued with the approval of the managing clinician. MAIN OUTCOMES AND MEASURES: Outcomes were assessed before and after intervention for the primary analysis and before and after 24 months before the intervention (when rates of aspirin use first began to decrease) for the secondary analysis. Outcomes included the rate of aspirin use, bleeding, and thrombotic outcomes. An interrupted time series analysis assessed cumulative monthly event rates over time. RESULTS: A total of 6738 patients treated with warfarin (3160 men [46.9%]; mean [SD] age, 62.8 [16.2] years) were followed up for a median of 6.7 months (IQR, 3.2-19.3 months). Aspirin use decreased slightly from a baseline mean use of 29.4% (95% CI, 28.9%-29.9%) to 27.1% (95% CI, 26.1%-28.0%) during the 24 months before the intervention ($P < .001$ for slope before and after 24 months before the intervention) with an accelerated decrease after the intervention (mean aspirin use, 15.7%; 95% CI, 14.8%-16.8%; $P = .001$ for slope before and after intervention). In the primary analysis, the intervention

was associated with a significant decrease in major bleeding events per month (preintervention, 0.31%; 95% CI, 0.27%-0.34%; postintervention, 0.21%; 95% CI, 0.14%-0.28%; P = .03 for difference in slope before and after intervention). No change was observed in mean percentage of patients having a thrombotic event from before to after the intervention (0.21% vs 0.24%; P = .34 for difference in slope). In the secondary analysis, reducing aspirin use (starting 24 months before the intervention) was associated with decreases in mean percentage of patients having any bleeding event (2.3% vs 1.5%; P = .02 for change in slope before and after 24 months before the intervention), mean percentage of patients having a major bleeding event (0.31% vs 0.25%; P = .001 for change in slope before and after 24 months before the intervention), and mean percentage of patients with an emergency department visit for bleeding (0.99% vs 0.67%; P = .04 for change in slope before and after 24 months before the intervention), with no change in mean percentage of patients with a thrombotic event (0.20% vs 0.23%; P = .36 for change in slope before and after 24 months before the intervention). CONCLUSIONS AND RELEVANCE: This quality improvement intervention was associated with an acceleration of a preexisting decrease in aspirin use among patients taking warfarin for atrial fibrillation and/or venous thromboembolism without a clear indication for aspirin therapy. Reductions in aspirin use were associated with reduced bleeding. This study suggests that an anticoagulation clinic-based aspirin deimplementation intervention can improve guideline-concordant aspirin use.

Hospital Medicine

Vaughn VM, Ratz D, McLaughlin ES, Horowitz JK, Flanders SA, Middleton EA, Grant PJ, **Kaatz S**, and Barnes GD. Eligibility for Posthospitalization Venous Thromboembolism Prophylaxis in Hospitalized Patients With COVID-19: A Retrospective Cohort Study. *J Am Heart Assoc* 2022; e025914. Epub ahead of print. PMID: 36073649. Full Text

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Background A recent randomized trial, the MICHELLE trial, demonstrated improved posthospital outcomes with a 35-day course of prophylactic rivaroxaban for patients hospitalized with COVID-19 at high risk of venous thromboembolism. We explored how often these findings may apply to an unselected clinical population of patients hospitalized with COVID-19. Methods and Results Using a 35-hospital retrospective cohort of patients hospitalized between March 7, 2020, and January 23, 2021, with COVID-19 (MI-COVID19 database), we quantified the percentage of hospitalized patients with COVID-19 who would be eligible for rivaroxaban at discharge per MICHELLE trial criteria and report clinical event rates. The main clinical outcome was derived from the MICHELLE trial and included a composite of symptomatic venous thromboembolism, pulmonary embolus-related death, nonhemorrhagic stroke, and cardiovascular death at 35 days. Multiple sensitivity analyses tested different eligibility and exclusion criteria definitions to determine the effect on eligibility for postdischarge anticoagulation prophylaxis. Of 2016 patients hospitalized with COVID-19 who survived to discharge and did not have another indication for anticoagulation, 25.9% (n=523) would be eligible for postdischarge thromboprophylaxis per the MICHELLE trial criteria (range, 2.9%-39.4% on sensitivity analysis). Of the 416 who had discharge anticoagulant data collected, only 13.2% (55/416) were actually prescribed a new anticoagulant at discharge. Of patients eligible for rivaroxaban per the MICHELLE trial, the composite clinical outcome occurred in 1.2% (6/519); similar outcome rates were 5.7% and 0.63% in the MICHELLE trial's control (no anticoagulation) and intervention (rivaroxaban) groups, respectively. Symptomatic venous thromboembolism events and all-cause mortality were 6.2% (32/519) and 5.66% in the MI-COVID19 and MICHELLE trial control cohorts, respectively. Conclusions Across 35 hospitals in Michigan, ≈1 in 4 patients hospitalized with COVID-19 would qualify for posthospital thromboprophylaxis. With only 13% of

patients actually receiving postdischarge prophylaxis, there is a potential opportunity for improvement in care.

Hypertension and Vascular Research
Neupane R, Cieslik KA, Youker K, **Palaniyandi SS**, Guha A, and Thandavarayan RA. 3'UTR shortening of profibrotic genes and reversibility of fibrosis in patients with end-stage right ventricular failure. *Clin Transl Med* 2022; 12(9):e1017. PMID: 36082691. Full Text

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Hypertension and Vascular Research
Pan G, **Roy B**, **Giri S**, **Lanfear DE**, Thandavarayan RA, Guha A, **Ortiz PA**, and **Palaniyandi SS**. Aldehyde Dehydrogenase 2 Activator Augments the Beneficial Effects of Empagliflozin in Mice with Diabetes-Associated HFpEF. *Int J Mol Sci* 2022; 23(18). PMID: 36142350. Full Text

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To ameliorate diabetes mellitus-associated heart failure with preserved ejection fraction (HFpEF), we plan to lower diabetes-mediated oxidative stress-induced 4-hydroxy-2-nonenal (4HNE) accumulation by pharmacological agents that either decrease 4HNE generation or increase its detoxification.A cellular reactive carbonyl species (RCS), 4HNE, was significantly increased in diabetic hearts due to a diabetes-induced decrease in 4HNE detoxification by aldehyde dehydrogenase (ALDH) 2, a cardiac mitochondrial enzyme that metabolizes 4HNE. Therefore, hyperglycemia-induced 4HNE is critical for diabetes-mediated cardiotoxicity and we hypothesize that lowering 4HNE ameliorates diabetes-associated HFpEF. We fed a high-fat diet to ALDH2*2 mice, which have intrinsically low ALDH2 activity, to induce type-2 diabetes. After 4 months of diabetes, the mice exhibited features of HFpEF along with increased 4HNE adducts, and we treated them with vehicle, empagliflozin (EMP) (3 mg/kg/d) to reduce 4HNE and Alda-1 (10 mg/kg/d), and ALDH2 activator to enhance ALDH2 activity as well as a combination of EMP + Alda-1 (E + A), via subcutaneous osmotic pumps. After 2 months of treatments, cardiac function was assessed by conscious echocardiography before and after exercise stress. EMP + Alda-1 improved exercise tolerance, diastolic and systolic function, 4HNE detoxification and cardiac liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) pathways in ALDH2*2 mice with diabetes-associated HFpEF. This combination was even more effective than EMP alone. Our data indicate that ALDH2 activation along with the treatment of hypoglycemic agents may be a salient strategy to alleviate diabetes-associated HFpEF.

Hypertension and Vascular Research
Roy B, and Runa SA. SARS-CoV-2 infection and diabetes: Pathophysiological mechanism of multi-system organ failure. *World J Virol* 2022; 11(5):252-274. PMID: 36188734. Full Text

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Since the discovery of the coronavirus disease 2019 outbreak, a vast majority of studies have been carried out that confirmed the worst outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with preexisting health conditions, including diabetes, obesity, hypertension, cancer, and cardiovascular diseases. Likewise, diabetes itself is one of the leading causes of global public health concerns that impose a heavy global burden on public health as well as socio-economic development. Both diabetes and SARS-CoV-2 infection have their independent ability to induce the pathogenesis and severity of multi-system organ failure, while the co-existence of these two culprits can accelerate the rate of disease progression and magnify the severity of the disease. However, the exact pathophysiology of multi-system organ failure in diabetic patients after SARS-CoV-2 infection is still obscure. This review summarized the organ-specific possible molecular mechanisms of SARS-CoV-2 and diabetes-induced pathophysiology of several diseases of multiple organs, including the lungs, heart, kidneys, brain, eyes, gastrointestinal system, and bones, and sub-sequent manifestation of multi-system organ failure.

Infectious Diseases

Fana M, **Werner L**, **Williams J**, and **Zaman I**. Multiple Strokes in a Patient With Systemic Lupus Erythematosus in the Absence of Common Underlying Syndromes. *Prim Care Companion CNS Disord* 2022; 24(5). PMID: 36084642. Request Article

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Infectious Diseases

Shrestha R, Luterbach CL, Dai W, Komarow L, Earley M, Weston G, **Herc E**, Jacob JT, Salata R, Wong D, Anderson D, Rydell KB, Arias CA, Chen L, and van Duin D. Characteristics of community-acquired carbapenem-resistant Enterobacterales. *J Antimicrob Chemother* 2022; 77(10):2763-2771. PMID: 36179278. Full Text

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BACKGROUND: Community-acquired carbapenem-resistant Enterobacterales (CA-CRE) are an important threat. METHODS: In CRACKLE-2, we defined patients with CA-CRE as admitted from home, without pre-existing conditions, and a positive culture within 48 h of admission. Healthcare-associated CRE (HA-CRE) were those with the lowest likelihood of community acquisition, not admitted from home

and cultured >48 h after admission. Specific genetic markers in carbapenemase-producing Klebsiella pneumoniae were evaluated through random forest modelling. RESULTS: CA-CRE and HA-CRE were detected in 83 (10%) and 208 (26%) of 807 patients. No significant differences were observed in bacterial species or strain type distribution. K. pneumoniae (204/291, 70%) was the most common CRE species, of these 184/204 (90%) were carbapenemase producers (CPKP). The top three genetic markers in random forest models were kpi_SA15, fimE, and kpfC. Of these, kpi_SA15 (which encodes a chaperone/usher system) was positively associated (OR 3.14, 95% CI 1.13-8.87, P=0.026), and kpfC negatively associated (OR 0.21, 95% CI 0.05-0.72, P=0.015) with CA-CPKP. CONCLUSIONS: Ten percent of CDC-defined CRE were CA. The true proportion of CA-CRE in hospitalized patients is likely lower as patients may have had unrecorded prior healthcare exposure. The kpi_SA15 operon was associated with the CA phenotype.

Infectious Diseases

Yao Y, **Subedi K**, **Liu T**, **Khalasawi N**, Pretto-Kernahan CD, Wotring JW, **Wang J**, **Yin C**, **Jiang A**, **Fu C**, **Dimitrion P**, **Li J**, **Veenstra J**, **Yi Q**, **McKinnon K**, **McKinnon JE**, Sexton JZ, **Zhou L**, and **Mi QS**. Surface translocation of ACE2 and TMPRSS2 upon TLR4/7/8 activation is required for SARS-CoV-2 infection in circulating monocytes. *Cell Discov* 2022; 8(1):89. PMID: 36085197. Full Text

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Infection of human peripheral blood cells by SARS-CoV-2 has been debated because immune cells lack mRNA expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease type 2 (TMPRSS2). Herein we demonstrate that resting primary monocytes harbor abundant cytoplasmic

ACE2 and TMPRSS2 protein and that circulating exosomes contain significant ACE2 protein. Upon ex vivo TLR4/7/8 stimulation, cytoplasmic ACE2 was quickly translocated to the monocyte cell surface independently of ACE2 transcription, while TMPRSS2 surface translocation occurred in conjunction with elevated mRNA expression. The rapid translocation of ACE2 to the monocyte cell surface was blocked by the endosomal trafficking inhibitor endosidin 2, suggesting that endosomal ACE2 could be derived from circulating ACE2-containing exosomes. TLR-stimulated monocytes concurrently expressing ACE2 and TMPRSS2 on the cell surface were efficiently infected by SARS-CoV-2, which was significantly mitigated by remdesivir, TMPRSS2 inhibitor camostat, and anti-ACE2 antibody. Mass cytometry showed that ACE2 surface translocation in peripheral myeloid cells from patients with severe COVID-19 correlated with its hyperactivation and PD-L1 expression. Collectively, TLR4/7/8-induced ACE2 translocation with TMPRSS2 expression makes circulating monocytes permissive to SARS-CoV-2 infection.

Internal Medicine

Affas Z, Affas S, and **Tabbaa K**. Continuous positive airway pressure reduces the incidence of atrial fibrillation in patients with obstructive sleep apnea: A Meta-Analysis and Systematic Review. *Spartan Med Res J* 2022; 7(2):34521. PMID: 36128027. Full Text

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INTRODUCTION: Obstructive sleep apnea (OSA) and atrial fibrillation (AF) are disorders that have increased in the United States during recent years. Earlier investigations have shown that underlying undiagnosed and unmanaged OSA plays a significant role in high rates and also as a trigger for newly diagnosed AF. Since the introduction of continuous positive airway pressure (CPAP) as a main therapy for OSA, more studies have evaluated the effect of CPAP on the development or recurrence of AF in OSA patients. However, sample sizes in a limited number of studies have been too small to conclude whether CPAP therapy has a significant effect on the development of AF in patients with OSA. The authors report results of their systematic review and meta-analysis summarizing what is currently known about the efficacy of CPAP for mitigating AF in patients with OSA. METHOD: The authors systematically reviewed the published reports on CPAP use and the incidence of AF from PubMed, Google Scholar, EMBASE, Web of Science, meeting abstracts, and Cochrane databases published between January 2015 and November 2021. Study data were extracted by two reviewers and a random-effects meta-analysis was performed using RevMan version 5.4. RESULTS: A total of 17 studies that met inclusion criteria were identified Studies included a total of 6,523 patients, 3,248 (49.8%) who used CPAP and 3,275 (50.2%) who did not use CPAP. In a random effects model, patients treated with CPAP showed a decrease in the incidence of AF (OR, 0.51; 95% CI; 0.27; 0.97, p = 0.04). High heterogeneity among the included studies was also observed (I2 = 97%). CONCLUSION: Our results add to the increasing evidence that CPAP therapy may reduce the incidence of development of AF in patients with OSA. Prospective future studies and clinical trials are needed to refine our understanding of the relationship between OSA and AF and how CPAP may reduce cardiovascular disease development.

Internal Medicine

Mikesell L, **Rea S**, Cuddihy C, Perry M, and Allison B. Exploring the Connectivity Paradox: How the Sociophysical Environment of Telehealth Shapes Adolescent Patients' and Parents' Perceptions of the Patient-Clinician Relationship. *Health Commun* 2022; 1-11. Epub ahead of print. PMID: 36102361. Request Article

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Even before the widespread transition to telehealth as a result of COVID-19, there was a considerable amount of research exploring its value and impact. However, telehealth research with adolescent patients is somewhat limited, with most work focusing on access, feasibility, and acceptability but reporting far less frequently on relationship building and rapport. This study examines qualitative interviews with adolescent patients (n = 14) and parents (n = 20) from a larger convergent parallel mixed methods study to explore

how they understand telehealth to have altered the sociophysical environment of primary care clinic encounters and whether they perceive these changes to influence adolescents' relationships with clinicians. We show that participants perceived the sociophysical environment of telehealth to be both less institutional (e.g. more relaxed and less rushed) and more instrumental (e.g. more focused on the chief complaint), which shaped interactions with clinicians in ways that were experienced as paradoxically less personal (e.g. lacking social connection) and more person-centered (e.g. more attentive to the individual patient). We discuss theoretical and practical implications of these findings and what they mean for defining person-centered communication for adolescent care.

Internal Medicine

Ohikere K, **Veracruz N**, and Wong RJ. Cognitive Impairment and Cirrhosis in Older Patients: A Systematic Review. *Gerontol Geriatr Med* 2022; 8:23337214221122520. PMID: 36105374. Full Text

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Prevalence of cirrhosis and hepatic encephalopathy (HE) in older patients receiving care in long-term care settings is unknown. This systematic review aimed to identify potential factors associated with HE and cognitive impairment in older patients with cirrhosis. A PubMed search of English-language articles published between January 1, 2000, and November 3, 2021, was conducted to identify studies in adults with cirrhosis relevant to cognitive impairment and/or HE (e.g., fall, frailty, and sarcopenia). Of 2,879 English-language publications, 24 were included. In patients with cirrhosis, falls were increased in the presence of HE and were associated with increased injury risk. Frailty was associated with HE development and cognitive impairment in patients with cirrhosis. Further, cognitive impairment and frailty were predictive of HE-related hospitalizations. Sarcopenia increased the risk of developing HE. Furthermore, specific medications increased the risk of developing HE. Risk reduction and management of patients with HE are critical to prevent negative outcomes.

Internal Medicine

Schaefer JK, Errickson J, Gu X, Alexandris-Souphis T, Ali MA, Haymart B, **Kaatz S**, Kline-Rogers E, Kozlowski JH, **Krol GD**, **Shah V**, Sood SL, Froehlich JB, and Barnes GD. Assessment of an Intervention to Reduce Aspirin Prescribing for Patients Receiving Warfarin for Anticoagulation. *JAMA Netw Open* 2022; 5(9):e2231973. PMID: 36121653. Full Text

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IMPORTANCE: For some patients receiving warfarin, adding aspirin (acetylsalicylic acid) increases bleeding risk with unclear treatment benefit. Reducing excess aspirin use could be associated with improved clinical outcomes. OBJECTIVE: To assess changes in aspirin use, bleeding, and thrombosis event rates among patients treated with warfarin. DESIGN, SETTING, AND PARTICIPANTS: This pre-post observational quality improvement study was conducted from January 1, 2010, to December 31, 2019, at a 6-center quality improvement collaborative in Michigan among 6738 adults taking warfarin for atrial fibrillation and/or venous thromboembolism without an apparent indication for concomitant aspirin. Statistical analysis was conducted from November 26, 2020, to June 14, 2021. INTERVENTION: Primary care professionals for patients taking aspirin were asked whether an ongoing combination aspirin and warfarin treatment was indicated. If not, then aspirin was discontinued with the approval of the managing clinician. MAIN OUTCOMES AND MEASURES: Outcomes were assessed before and after intervention for the primary analysis and before and after 24 months before the intervention (when rates of aspirin use

first began to decrease) for the secondary analysis. Outcomes included the rate of aspirin use, bleeding, and thrombotic outcomes. An interrupted time series analysis assessed cumulative monthly event rates over time. RESULTS: A total of 6738 patients treated with warfarin (3160 men [46.9%]; mean [SD] age, 62.8 [16.2] years) were followed up for a median of 6.7 months (IQR, 3.2-19.3 months). Aspirin use decreased slightly from a baseline mean use of 29.4% (95% CI, 28.9%-29.9%) to 27.1% (95% CI, 26.1%-28.0%) during the 24 months before the intervention (P < .001 for slope before and after 24 months before the intervention) with an accelerated decrease after the intervention (mean aspirin use, 15.7%; 95% CI, 14.8%-16.8%; P = .001 for slope before and after intervention). In the primary analysis, the intervention was associated with a significant decrease in major bleeding events per month (preintervention, 0.31%; 95% CI, 0.27%-0.34%; postintervention, 0.21%; 95% CI, 0.14%-0.28%; P = .03 for difference in slope before and after intervention). No change was observed in mean percentage of patients having a thrombotic event from before to after the intervention (0.21% vs 0.24%; P = .34 for difference in slope). In the secondary analysis, reducing aspirin use (starting 24 months before the intervention) was associated with decreases in mean percentage of patients having any bleeding event (2.3% vs 1.5%; P = .02 for change in slope before and after 24 months before the intervention), mean percentage of patients having a major bleeding event (0.31% vs 0.25%; P = .001 for change in slope before and after 24 months before the intervention), and mean percentage of patients with an emergency department visit for bleeding (0.99% vs 0.67%; P = .04 for change in slope before and after 24 months before the intervention), with no change in mean percentage of patients with a thrombotic event (0.20% vs 0.23%; P = .36 for change in slope before and after 24 months before the intervention). CONCLUSIONS AND RELEVANCE: This quality improvement intervention was associated with an acceleration of a preexisting decrease in aspirin use among patients taking warfarin for atrial fibrillation and/or venous thromboembolism without a clear indication for aspirin therapy. Reductions in aspirin use were associated with reduced bleeding. This study suggests that an anticoagulation clinic-based aspirin deimplementation intervention can improve guideline-concordant aspirin use.

Neurology

Bonner K, **Aboul Nour H**, and **Memon AB**. Overlapping Autoimmune Neurological Syndrome: A Case Report of Triple-Positive Antibody. *Cureus* 2022; 14(9):e29379. PMID: 36168655. Full Text

Neurology, Wayne State University School of Medicine, Detroit, USA.
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The presentation of several autoimmune neurological disorders in a single patient is rare and often debilitating. However, early diagnosis and efficacious treatment can lead to a significant recovery. Here, we present an interesting case of a triple antibody-positive autoimmune neurological syndrome patient who manifested the clinical features of neuromyelitis optica (NMO) spectrum disorder (NMOSD), N-methyl-D-aspartate (NMDA) receptor (NMDAR) encephalitis, and myasthenia gravis (MG). Hence, the patient manifested both central and peripheral nervous system immune-mediated neurological syndromes. A middle-aged female with a history of seropositive aquaporin-4 (AQP4) NMOSD on mycophenolate 1 g twice daily presented with severe fatigue and right eye ptosis (three months since NMOSD diagnosis) and tested positive for acetylcholine receptor (AchR) binding antibody, consistent with MG. Six months after the patient's NMOSD diagnosis, she began to experience subacute progressive cognitive decline, behavioral changes, imbalance, anxiety/panic attacks, and paranoid delusions. NMDAR encephalitis was suspected, and she tested positive for cerebrospinal fluid NMDAR antibodies. After treatment with steroids failed, she was given two doses of rituximab 1 g, two weeks apart, and reported improvement in her symptoms shortly after the second dose.

Neurology

Fana M, **Werner L**, **Williams J**, and **Zaman I**. Multiple Strokes in a Patient With Systemic Lupus Erythematosus in the Absence of Common Underlying Syndromes. *Prim Care Companion CNS Disord* 2022; 24(5). PMID: 36084642. Request Article

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Wayne State University, School of Medicine, Detroit, Michigan.
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Neurology
Feit H, **Solway J**, and **Chedid MK**. Neurogenic Unilateral Leg Edema. *JAMA Neurol* 2022; Epub ahead of print. PMID: 36156066. Full Text

Neurology, Henry Ford Hospital, West Bloomfield, Michigan.
Podiatry, Henry Ford Hospital, West Bloomfield, Michigan.
Neurosurgery, Henry Ford Hospital, West Bloomfield, Michigan.

This case report describes neurogenic unilateral leg edema that was a consequence of chronic regional pain syndrome induced by an S1 radiculopathy.

Neurology
Jumah A, Aboul Nour H, **Intikhab O**, **Choudhury O**, Gagi K, **Fana M**, Alhajala H, **Alkhoujah M**, **Alsrouji OK**, Eltous L, **Schultz L**, **Latack K**, **Brady M**, **Chebl A**, **Marin H**, and **Miller D**. Non-stenosing carotid artery plaques in embolic stroke of undetermined source: a retrospective analysis. *Neurol Sci* 2022; Epub ahead of print. PMID: 36166175. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI, USA. ajumah1@hfhs.org.
Department of Vascular Neurology, Emory University School of Medicine, Atlanta, GA, USA.
Department of Neuroradiology, Henry Ford Hospital, Detroit, MI, USA.
Department of Neurology, Henry Ford Hospital, Detroit, MI, USA.
Department of Neurology, Sparrow Hospital, Lansing, MI, USA.
Department of Vascular Neurology, University of Toledo, Toledo, OH, USA.
Jordan University of Science and Technology, Amman, Jordan.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: We aim to identify the association between high-risk carotid plaques and their laterality to stroke in ESUS patient population. We also discuss recurrent stroke events and their laterality to the index stroke. METHODS: This was a retrospective study. We reviewed data for patients with ESUS between June 20, 2016, and June 20, 2021. Using computed tomography angiography, we analyzed plaque features that are associated with ESUS, and then, we identified the recurrent stroke events and characterized lateralization to the index stroke. RESULTS: Out of 1779 patients with cryptogenic ischemic stroke, we included 152 patients who met the criteria for ESUS. High-risk plaque features were found more often ipsilateral to the stroke side when compared contralaterally: plaque ulceration (19.08% vs 5.26%, $p < .0001$), plaque thickness > 3 mm (19.08% vs 7.24%, $p = 0.001$), and plaque length > 1 cm (13.16% vs 5.92%, $p = 0.0218$). There was also a significant difference in plaque component in which both components (soft and calcified) and only soft plaques were more prevalent ipsilaterally (42.76% vs 23.68% and 17.76% vs 9.21%, respectively, $p < .0001$). Of the 152 patients, 17 patients were found to have a recurrent stroke event, and 47% (n = 8) had an ipsilateral stroke to the index event. Moreover, stroke was bilateral in 41% of the patients (n = 7), and contralateral in 12% (n = 2). CONCLUSION: High-risk plaque features studied here were more prevalent ipsilaterally to the stroke side in ESUS than contralaterally. Multicenter studies are needed to form precise prediction models and scoring systems to help guide treatment, i.e., choice of medical therapy and/or revascularization.

Neurology
Pan G, **Roy B**, **Giri S**, **Lanfear DE**, Thandavarayan RA, Guha A, **Ortiz PA**, and **Palaniyandi SS**. Aldehyde Dehydrogenase 2 Activator Augments the Beneficial Effects of Empagliflozin in Mice with Diabetes-Associated HFpEF. *Int J Mol Sci* 2022; 23(18). PMID: 36142350. Full Text

Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, MI 48202, USA.
Department of Physiology, Wayne State University, Detroit, MI 48202, USA.
Department of Neurology, Henry Ford Health System, Detroit, MI 48202, USA.

Heart and Vascular Institute, Henry Ford Hospital, Detroit, MI 48202, USA.
Center for Health Policy and Health Services Research, Henry Ford Hospital, Detroit, MI 48202, USA.
Department of Cardiovascular Sciences, Houston Methodist Research Institute, Houston, TX 77030, USA.

To ameliorate diabetes mellitus-associated heart failure with preserved ejection fraction (HFpEF), we plan to lower diabetes-mediated oxidative stress-induced 4-hydroxy-2-nonenal (4HNE) accumulation by pharmacological agents that either decrease 4HNE generation or increase its detoxification.A cellular reactive carbonyl species (RCS), 4HNE, was significantly increased in diabetic hearts due to a diabetes-induced decrease in 4HNE detoxification by aldehyde dehydrogenase (ALDH) 2, a cardiac mitochondrial enzyme that metabolizes 4HNE. Therefore, hyperglycemia-induced 4HNE is critical for diabetes-mediated cardiotoxicity and we hypothesize that lowering 4HNE ameliorates diabetes-associated HFpEF. We fed a high-fat diet to ALDH2*2 mice, which have intrinsically low ALDH2 activity, to induce type-2 diabetes. After 4 months of diabetes, the mice exhibited features of HFpEF along with increased 4HNE adducts, and we treated them with vehicle, empagliflozin (EMP) (3 mg/kg/d) to reduce 4HNE and Alda-1 (10 mg/kg/d), and ALDH2 activator to enhance ALDH2 activity as well as a combination of EMP + Alda-1 (E + A), via subcutaneous osmotic pumps. After 2 months of treatments, cardiac function was assessed by conscious echocardiography before and after exercise stress. EMP + Alda-1 improved exercise tolerance, diastolic and systolic function, 4HNE detoxification and cardiac liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) pathways in ALDH2*2 mice with diabetes-associated HFpEF. This combination was even more effective than EMP alone. Our data indicate that ALDH2 activation along with the treatment of hypoglycemic agents may be a salient strategy to alleviate diabetes-associated HFpEF.

Neurology

Sharma HS, **Chopp M**, Chen L, Sarnowska A, Xue M, Ao Q, Siniscalco D, Chen L, Hawamdeh Z, and Huang H. The 2021 yearbook of neurorestoratology. *J Neurorestoratology* 2022; 10(3). PMID: Not assigned. Full Text

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Breakthroughs with rapid changes are the themes of the development in Neurorestoratology this year. Given the very difficult circumstances of the persistent COVID-19 pandemic, most of the colleagues in Neurorestoratology have conducted meaningful research and obtained encouraging results, as described in the 2020 Yearbook of Neurorestoratology. Neurorestorative progress during 2021 depicts recent findings on the pathogenesis of neurological diseases, neurorestorative mechanisms and clinical therapeutic achievements. The pathogenesis and risk factors of Alzheimer's disease were parts of the most prominent hot research topics. Yet, it remains controversial whether β-amyloid accumulation and tau protein deposition are the results of, or the reasons for the neurodegenerative processes. Neurogenesis is an important neurorestorative mechanism, however, it is questionable whether neural stem cells are present in the adult humans brain. Thus, neurogenesis may not derive from endogenous neural stem cells in the adult humans. Neurorestorative treatments were important areas of the 2021 research efforts and these therapies are improving the quality of life in patients with neurological diseases. There was major exploration of cell-based therapies for neurological disease and injury. However, unfortunately several multi-center, double-blind or observing-blind, placebo controlled, randomized clinical trials of mesenchymal stromal cells or products of mesenchymal stem cells failed to show positive results in ischemic stroke when employed in the sub-acute or recovery phases as there were no appreciable differences in the quality of life as compared with controls. Excitingly, increased numbers of clinical investigations of brain–computer interface (BCI) were reported that showed benefits for patients with neurological deficits. In pharmaceutical neurorestorative therapies, Aducanumab (Aduhelm) and Sodium Oligomannate are approved respectively by the United States Food and Drug Administration (USFDA) and the China National Medical Products Administration (NMPA) to treat patients with mild-to-moderate Alzheimer's disease. Although, the decisions to approve these drugs are highly contentious in the medical and scientific community because of the contradictory findings or other problems associated with the drug usage. We believe that repeating low-level evidence studies that showed negative results or scanty evidences in randomized control trials is of little significance. However, we strongly recommend

conducting multi-center, double-blind, placebo controlled, randomized clinical trials for promising innovative therapeutic methods to facilitate their possible clinical translation.

Neurology
Zhang L, Schwartz-Byrne R, Gertz S, McGuire M, Woodhouse C, **Powell B**, **Wei M**, **Li C**, Billing CB, Verdoorn TA, Lam L, Parry TJ, Buller B, **Zhang ZG**, Poulsen D, and **Chopp M**. Pharmacological Characterization of a Novel Neuroactive Steroid Prodrug, NTS-104, and Its Neuroprotective Activity in Experimental Stroke Models. *Stroke* 2022; Epub ahead of print. PMID: 36168130. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI (L.Z., B.P., M.W., C.L., Z.G.Z., M.C.).
Department of Neurosurgery, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY (R.S.-B., S.G., M.M., C.W., D.P.).
NeuroTrauma Sciences, Alpharetta, GA (C.B.B., T.A.V., L.L., T.J.P., B.B.).
Department of Physics, Oakland University, Rochester, MI (M.C.).

BACKGROUND: Ischemic stroke affects about 700 000 patients per year in the United States, and to date, there are no effective pharmacological agents that promote recovery. Here, we studied the pharmacokinetics, pharmacodynamics, and efficacy of NTS-105, a novel neuroactive steroid, and NTS-104, a prodrug of NTS-105, in 2 models of ischemic stroke. METHODS: The pharmacodynamics and pharmacokinetics of NTS-104/105 were investigated in naive and stroke rats, and models of embolic and transient middle cerebral artery occlusion were used to investigate the dose-related effects of NTS-104. All rats were randomly assigned into the experimental groups, and all outcome measurements were performed blindly. RESULTS: Blood plasma and brain pharmacokinetic analysis revealed that NTS-104 rapidly converted to NTS-105, which reached peak concentration at ≈1 hour after dosing and distributed similarly to normal and ischemic brains. NTS-104 administration 4 hours after embolic middle cerebral artery occlusion led to a dose-dependent improvement of neurological outcomes and a dose-dependent reduction of infarct volumes relative to vehicle-treated animals. A single dose level study confirmed that NTS-104 administered 4 hours after transient middle cerebral artery occlusion was also neuroprotective. Quantitative ELISA revealed that NTS-104 treatment resulted in time- and dose-dependent changes in AKT activation and cytokine levels within the ischemic brain, which included reductions of IL-6, VEGF, ICAM-1, IL-1β, MCP-1, RAGE, and GM-CSF. Time- and dose-dependent reductions in IL-6 and GM-CSF were also observed in the plasma along with an elevation of galectin-1. CONCLUSIONS: NTS-104 is a novel prodrug that converts to a novel neuroactive steroid, NTS-105, which improves functional outcomes in experimental ischemic stroke models.

Neurosurgery
Feit H, **Solway J**, and **Chedid MK**. Neurogenic Unilateral Leg Edema. *JAMA Neurol* 2022; Epub ahead of print. PMID: 36156066. Full Text

Neurology, Henry Ford Hospital, West Bloomfield, Michigan.
Podiatry, Henry Ford Hospital, West Bloomfield, Michigan.
Neurosurgery, Henry Ford Hospital, West Bloomfield, Michigan.

This case report describes neurogenic unilateral leg edema that was a consequence of chronic regional pain syndrome induced by an S1 radiculopathy.
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Neurosurgery
Hamilton T, Hadi M, Simo L, and **Chang V**. Commentary: Sacroiliac Joint Fusion Using Robotic Navigation: Technical Note and Case Series. *Oper Neurosurg (Hagerstown)* 2022; 23(3):e209-e210. PMID: 35972120. Full Text

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College of Human Medicine, Michigan State University, Grand Rapids, Michigan, USA.
Wayne State University School of Medicine, Detroit, Michigan, USA.

Neurosurgery

Patel V, Metz A, **Schultz L**, **Nerenz D**, Park P, **Chang V**, **Schwalb J**, Khalil J, Perez-Cruet M, and Aleem I. Rates and Reasons for Reoperation Within 30 and 90 days Following Cervical Spine Surgery: A Retrospective Cohort Analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Registry. *Spine J* 2022; Epub ahead of print. PMID: 36152774. Full Text

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BACKGROUND CONTEXT: Reoperation following cervical spinal surgery negatively impacts patient outcomes and increases healthcare system burden. To date, most studies have evaluated reoperations within 30 days after spine surgery and have been limited in scope and focus. Evaluation within the 90-day period, however, allows a more comprehensive assessment of factors associated with reoperation. PURPOSE: The purpose of this study is to assess the rates and reasons for reoperations after cervical spine surgery within 30 and 90 days. DESIGN: We performed a retrospective analysis of a state-wide prospective, multi-center, spine-specific database of patients surgically treated for degenerative disease. PATIENT SAMPLE: Patients 18 years of age or older who underwent cervical spine surgery for degenerative pathologies from February 2014 to May 2019. Operative criteria included all degenerative cervical spine procedures, including those with cervical fusions with contiguous extension down to T3. OUTCOME MEASURES: We determined causes for reoperation and independent surgical and demographic risk factors impacting reoperation. METHODS: Patient-specific and surgery-specific data was extracted from the registry using ICD-10-DM codes. Reoperations data was obtained through abstraction of medical records through 90 days. Univariate analysis was done using chi-square tests for categorical variables, t-tests for normally distributed variables, and Wilcoxon rank-sum tests for variables with skewed distributions. Odds ratios for return to the operating room (OR) were evaluated in multivariate analysis. RESULTS: A total of 13435 and 13440 patients underwent cervical spine surgery and were included in the 30 and 90-day analysis, respectively. The overall reoperation rate was 1.24% and 3.30% within 30 and 90 days, respectively. Multivariate analysis showed within 30 days, procedures involving four or more levels, posterior only approach, and longer length of stay had increased odds of returning to the OR ($p < 0.05$), whereas private insurance had a decreased odds of return to OR ($p < 0.05$). Within 90 days, male sex, coronary artery disease (CAD), previous spine surgery, procedures with 4 or more levels, and longer length of stay had significantly increased odds of returning to the OR ($p < 0.05$). Non-white race, independent ambulatory status pre-operatively, and having private insurance had decreased odds of return to the OR ($p < 0.05$). The most common specified reasons for return to the OR within 30 days was hematoma (19%), infection (17%), and wound dehiscence (11%). Within 90 days, reoperation reasons were pain (10%), infection (9%), and hematoma (8%). CONCLUSION: Reoperation rates after elective cervical spine surgery are 1.24% and 3.30% within 30 and 90 days, respectively. Within 30 days, four or more levels, posterior approach, and longer length of stay were risk factors for reoperation. Within 90 days, male sex, CAD, four or more levels, and longer length of hospital stay were risk factors for reoperation. Non-white demographic and independent preoperative ambulatory status were associated with decreased reoperation rates.

Obstetrics, Gynecology and Women's Health Services

Ayyash M, **Keerthy M**, **Roberson J**, and **Shaman M**. Recurrence Rate for Isolated Elevated Maternal Serum Alpha-Fetoprotein Levels and Pregnancy Outcomes. *Genet Test Mol Biomarkers* 2022; 26(9):443-448. PMID: 36166740. Full Text

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Objective: To examine the rate of recurrence for elevated isolated maternal serum alpha-fetoprotein (MSAFP) and its associated adverse outcomes during a subsequent pregnancy. Materials and Methods: A retrospective cohort study of pregnant multiparous women who had elevated MSAFP levels during an initial and a subsequent pregnancy between 1994 and 2020. Results: Twenty-seven out of 344 (7.8%) women with elevated MSAFP had recurrent elevated MSAFP in a subsequent pregnancy. Four women were excluded due to missing data. Of the 23 women included, 5 (22%) had fetal growth restriction (FGR), 2 (9%) had pre-eclampsia, 9 (35%) had preterm births, and 2 (9%) had fetal death/miscarriage in their subsequent pregnancy. Looking at individual outcomes, 60% of women had recurrence of preterm labor, 33% had recurrence of fetal death, and 25% had recurrence of FGR. Conclusion: Women with elevated MSAFP levels during an initial pregnancy should be informed during preconception counseling about their risk of recurring elevated MSAFP and its associated adverse outcomes risks.

Orthopedics/Bone and Joint Center

Ali SA, and Bowden JL. Editorial: Implementation of physical, psychosocial, and mind-body approaches for the management of osteoarthritis. *Front Rehabil Sci* 2022; 3:1023931. PMID: 36189024. Full Text

Bone and Joint Center, Department of Orthopaedic Surgery, Henry Ford Health, Detroit, MI, United States.
Center for Molecular Medicine and Genetics, School of Medicine, Wayne State University, Detroit, MI, United States.
Department of Physiology, College of Human Medicine, Michigan State University, East Lansing, MI, United States.
Sydney Musculoskeletal Health, Kolling Institute, The University of Sydney, Sydney, NSW, Australia.
Department of Rheumatology, Royal North Shore Hospital, Sydney, NSW, Australia.

Orthopedics/Bone and Joint Center

Cross AG, **Khalil LS**, **Swantek AJ**, **Lizzio VA**, **Ziedas AC**, Camp CL, Chalmers PN, Smith K, **Chaides SE**, **Rexroth JD**, and **Makhni EC**. Athletes Perceive Weighted Baseballs to Carry a Notable Injury Risk, yet Still Use Them Frequently: A Multicenter Survey Study. *J Am Acad Orthop Surg Glob Res Rev* 2022; 6(9). PMID: 36083831. Full Text

From the Henry Ford Hospital (Dr. Cross, Dr. Khalil, Dr. Swantek, Dr. Lizzio, Dr. Ziedas, Ms. Chaides, Mr. Rexroth, and Dr. Makhni), Department of Orthopaedic Surgery, Detroit, MI; the Department of Orthopedic Surgery and Sports Medicine (Dr. Camp), Mayo Clinic, Rochester, NY; and the Department of Orthopedic Surgery (Dr. Chalmers and Smith), University of Utah, Salt Lake City, UT.

INTRODUCTION: Weighted baseball use in throwing programs is widespread; however, their use remains controversial. Prior research shows that weighted baseball programs can increase ball velocity but potentially increase throwing arm injuries. This study aims to ascertain perceptions of weighted baseballs among elite baseball players. METHODS: A created online survey questioned common practices, throwing regimens, injury risk factors, and weighted baseball program use. The questions were modeled to ascertain the perceptions of elite baseball players to understand their experience with weighted baseballs. Descriptive statistical analysis was conducted. RESULTS: Three hundred seventy-six baseball players with a mean age of 20 ± 2 years completed the survey; 64% of the players (239/376) were pitchers. 71% (267/376) reported the use of weighted baseballs. Of those, 75% (199/267) thought it made them a better player. Overall, 73% (275/377) thought weighted baseballs are a risk for injury. 17% (46/267) attributed their injury to using weighted baseballs. Overall, participants reported a mean 72% ± 30% likelihood of future weighted baseball use. CONCLUSION: Most of the participating elite adult baseball players reported prior weighted baseball use with a corresponding improvement in pitching performance despite a perceived increased injury risk. Nearly 20% of the players attributed pain or injury to weighted baseball use. Moreover, the players surveyed intend to continue using weighted baseballs because of the perceived performance benefit.

Orthopedics/Bone and Joint Center

Khalil LS, and **Lynch TS**. Editorial Commentary: Surgeons Planning Hip Labral Arthroscopic Repair Should Have a Backup Plan of Labral Reconstruction or Augmentation Based on Intraoperative Labral Degeneration, Hypoplasia, or Ossification. *Arthroscopy* 2022; 38(9):2669-2671. PMID: 36064279. Full Text

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The arena of hip arthroscopy has seen leaps in practices over the past decade, evolving from surgical debridement of the labrum to improvements in techniques which now allow repair, augmentation, and circumferential reconstruction. But as the operating theater continues to change its act, so too must the preoperative choreography. Recent advancements in the understanding of preoperative risk factors for failure of primary labral repair have identified the diminutive or hypoplastic labra on prescreening magnetic resonance imaging as a negative predictor of success. While this quantitative assessment predicts the anatomical coverage of the labrum, we are still limited in our ability to qualify the latter's tissue substance preoperatively. Ossified or degenerative labra may not have the inherent functional capacity to restore the suction seal of the hip in a primary repair setting. If the applause from the audience fails to reach a significant threshold, we must rethink our act, and that begins with the choreography. The next step in hip arthroscopy is determining if a primary augmentation or reconstruction, in lieu of primary repair, warrants further consideration. Until we develop reliable methods of quantifying and qualifying the labral tissue, both preoperatively and optimally, we should establish backup for surprises encountered while on the "stage."

Orthopedics/Bone and Joint Center

Khan AZ, Best MJ, Fedorka CJ, Belniak RM, Haas DA, Zhang X, Armstrong AD, Jawa A, O'Donnell EA, Simon JE, Wagner ER, Malik M, Gottschalk MB, Updegrove GF, **Makhni EC**, Warner JJ, Srikumaran U, and Abboud JA. Impact of the COVID-19 Pandemic on Shoulder Arthroplasty: Surgical Trends and Post-Operative Care Pathway Analysis. *J Shoulder Elbow Surg* 2022; Epub ahead of print. PMID: 36075547. Full Text

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INTRODUCTION: COVID-19 triggered disruption in the conventional care pathways for many orthopedic procedures. The current study aims to quantify the impact of the COVID-19 pandemic on shoulder arthroplasty hospital surgical volume, trends in surgical case distribution, length of hospitalization, post-hospital disposition, and 30-day readmission rates. METHODS: This study queried all Medicare (100% sample) fee-for-service beneficiaries who underwent a shoulder arthroplasty procedure (DRG 483, CPT 23472) from January 1, 2019 to December 18, 2020. Fracture cases were separated from non-fracture

cases, which were further subdivided into anatomic or reverse arthroplasty. Volume per 1000 Medicare beneficiaries was calculated from April to December 2020 and compared to the same months in 2019. Length of stay (LOS), discharged-home rate, and 30-day readmission for the same period were obtained. The yearly difference adjusted for age, sex, race (white vs. non-white), CMS-Hierarchical Condition Categories (HCC) risk score, month fixed effects, and Core-based Statistical Area (CBSA) fixed effects, with standard errors clustered at the provider level was calculated using a multivariate analysis ($p < 0.05$). RESULTS: 49,412 and 41,554 TSA cases were observed April through December for 2019 and 2020, respectively. There was an overall decrease in shoulder arthroplasty volume per 1000 Medicare beneficiaries by 14% (19% reduction in anatomic TSA, 13% reduction in RTSA, and 3% reduction in fracture cases). LOS for all shoulder arthroplasty cases decreased by 16% (-0.27 days, $p< 0.001$) when adjusted for confounders. There was a 5% increase in the discharge-home rate (88.0% to 92.7%, $p<0.001$); most prominent in fracture cases with a 20% increase in discharged-home cases (65.0% to 73.4%, $p<0.001$). There was no significant change in 30-day hospital readmission rates overall ($p = 0.20$) or when broken down by individual procedures. CONCLUSIONS: There was an overall decrease in shoulder arthroplasty volume per 1000 Medicare beneficiaries by 14% during the COVID-19 pandemic. A decrease in LOS and increase in the discharged-home rates was also observed with no significant change in 30-day hospital readmission, indicating that a shift towards an outpatient surgical model can be performed safely, efficiently and has potential to provide value.

Orthopedics/Bone and Joint Center

Popkin CA, Fortney TA, Padaki AS, Rogers AJ, Trofa DP, **Lynch TS**, Tuominen M, and Stuart MJ. Injuries to Ice Hockey Referees and Linesmen: A Survey of International Ice Hockey Federation Officials. *Orthop J Sports Med* 2022; 10(9):23259671221117504. PMID: 36105655. Full Text

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BACKGROUND: Ice hockey referees and linesmen are at risk for musculoskeletal injuries because of the lack of protective equipment and contact with players, sticks, pucks, the ice surface and boards. PURPOSE: To quantify and analyze injuries reported by officials of the International Ice Hockey Federation (IIHF). STUDY DESIGN: Descriptive epidemiology study. METHODS: A 61-question survey tool was designed by an interdisciplinary team to evaluate musculoskeletal injuries experienced by ice hockey officials. This survey was administered to 600 active IIHF referees and linesmen. Only completed survey responses were included in the statistical analysis. Continuous variables were analyzed using unpaired t-tests, while categorical data were assessed utilizing chi-square tests. RESULTS: Of the 600 surveys administered, 264 surveys were completed by officials from 45 countries (44% response rate). Of the respondents, 72% were male, and 28% were female, with a mean age of 31.1 ± 5.8 years. Officiating experience averaged 11.4 ± 6.0 years (6.3 ± 4.5 years with the IIHF). A total of 295 injuries were reported by 55% of the officials. Injuries occurred more frequently during games compared with training, and officials who worked year-round had more total injuries than those who took time off ($P = .03$). The most common injuries involved the wrist and hand (n = 64 [22%]), head and face (n = 58 [20%]), and the knee (n = 47 [16%]). Wrist and hand trauma included 23 fractures. Knee and shoulder injuries were most likely to require surgery compared with other body areas ($P < .001$); 30 officials underwent surgery because of an acute knee injury (10%). Injury prevention activities were effective at reducing injuries ($P = .04$). CONCLUSION: Most ice hockey officials experienced musculoskeletal injuries during their career. The risk of trauma to the wrist and hand can possibly be reduced via equipment modifications including protective gloves. A greater emphasis should be placed on injury prevention programs and time away from officiating competitions.

Orthopedics/Bone and Joint Center

Rocha FA, and **Ali SA**. Soluble Biomarkers in Osteoarthritis in 2022: Year in review. *Osteoarthritis Cartilage* 2022; Epub ahead of print. PMID: 36179981. Full Text

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OBJECTIVE: To review articles reporting on the development of soluble biomarkers in osteoarthritis (OA) over the past year. DESIGN: Two literature searches were conducted using the PubMed database for articles published between April 1, 2021 and March 31, 2022. Two searches were done, one on soluble biomarkers and another on circulating non-coding RNAs in OA. Additional articles were hand-picked to highlight emerging biomarker trends in OA. RESULTS: Of 348 publications retrieved, we included 20 articles with 3 that were hand-picked for the narrative synthesis. We review recent data on soluble biomarkers and circulating non-coding microRNAs in OA using the BIPED classification system. We highlight studies using proteomics to show that cartilage acidic protein 1 (CRTAC1) is a promising biomarker, helping diagnose and estimate severity in hand, hip, and knee OA. Subtle changes in the structure of glycosaminoglycans from the extracellular cartilage matrix were shown to discriminate OA from non-OA cartilage. C-reactive protein metabolite (CRPM) and collagen metabolites may help discriminate subsets of OA patients as well as disease progression. Additionally, physical activity may impact determination of biomarkers. We also report on circulating microRNAs, lncRNAs, and circRNAs in OA and their predictive accuracy in diagnosis and prognosis. CONCLUSIONS: Biomarkers for routine use are still an unmet need in the OA clinical scenario. Emerging data and novel classes of biomarkers (i.e., non-coding RNAs) show promise. Although still requiring validation in multiple independent cohorts, the past year brought advances towards a ready-to-use, reproducible, cost-effective biomarker, namely CRTAC1, to better manage the OA patient.

Orthopedics/Bone and Joint Center

Tang CT, Sookochoff M, Rhea L, **Carrier J**, Prather H, and Guan L. An audit of structure-based medical acupuncture by a single provider in patients with musculoskeletal pain using PROMIS scores as the outcome. *Acupunct Med* 2022; Epub ahead of print. PMID: 36112861. Full Text

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BACKGROUND: To assess whether structure-based medical acupuncture (SMA) can improve Patient-Reported Outcomes Measurement Information System (PROMIS) scores in patients presenting with musculoskeletal pain. METHODS: An audit was conducted of all patients presenting with musculoskeletal pain treated by a single provider with SMA in 2017. Inclusion criteria included a pre-treatment and at least one post-treatment PROMIS score. Patient demographics and previous treatments tried were recorded. Documented events other than acupuncture that were thought to interfere with PROMIS scores were recorded, and no further scores were used after these events. A maximum of nine visits after the initial visit were used. The PROMIS domains assessed included anxiety, depression, pain interference and physical function. RESULTS: Seventy-two patients who had been treated with SMA met the inclusion criteria. Sixty-five of the patients (90%) had chronic pain. For their presenting complaint, 59 (82%) had previously sought treatment from another non-operative provider, 60 (83%) had tried physical therapy, and 20 (28%) had even had surgery. Despite this, SMA appeared to be able to significantly improve PROMIS anxiety at visits 1-3 and PROMIS depression at visit 3. After just one treatment, minimal clinically important differences (MCID) were reached in 32%-44% of patients for PROMIS anxiety, 17%-36% for PROMIS depression, 28%-29% for PROMIS physical function, and 21%-36% for PROMIS pain interference, based on low and high cut-offs of a range of quoted MCID values. CONCLUSION: In a difficult patient population with musculoskeletal pain, SMA is a technique that can likely be used to

improve PROMIS anxiety and depression, although no firm conclusions can be drawn from this uncontrolled clinical audit. Of note, MCIDs were sometimes obtained even after just one treatment.

Orthopedics/Bone and Joint Center

Yeni YN, **Dix MR**, **Xiao A**, and **Oravec DJ**. Uniaxial compressive properties of human lumbar 1 vertebrae loaded beyond compaction and their relationship to cortical and cancellous microstructure, size and density properties. *J Mech Behav Biomed Mater* 2022; 133:105334. PMID: 35793605. Request Article

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Lumbar 1 vertebrae are among those most commonly fracture due to osteoporosis. The strength of human vertebrae and its structural, microstructural and material determinants have been the subject of numerous studies. However, a comprehensive evaluation of properties beyond maximum load to fracture has not been available for the L1 vertebrae. The objective of this study was to document these properties in association with each other and with the geometric, density and cancellous and cortical structure properties for human L1 vertebrae. Bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular separation (Tb.Sp), connectivity density (Conn.Dn), degree of anisotropy (DA), structure model index (SMI) and fractal dimension (FD) of the cancellous microstructure, tissue mineral density (TMD), and thickness of the cortical shell (Sh.Th) and superior and inferior endplates thicknesses (EP.Th.S and EP.Th.I) were measured using microcomputed tomography for 27 cadaveric L1 vertebrae. Volumetric cancellous, shell and integral bone mineral densities (vBMD, shBMD and iBMD) as well as vertebral volume (V), height and width were measured using high resolution CT. Areal whole vertebral body and regional BMDs were measured using dual energy x-ray absorptiometry (DXA) in coronal and lateral views. Specimens were then uniaxially compressed to 15% of their height to obtain vertebral stiffness (K) and strength (F(max)) as well as displacement (D), force (F) and energy (W) properties at characteristic points of the load-displacement curve including yield (y), fracture (f), compaction (c), final displacement (t) and residual after unload (r). Correlation and principal component analyses suggested displacements to failure (D(f)), collapse (D(c)) and recovery (D(r)) contain information distinct from strength and stiffness. Bone size (V) was present, independently, in multiple regression models of K, F(y), W(y), F(max), D(f), W(t), W(fc) and D(r) ($p < 0.05$ to $p < 0.0001$), areal BMD in models of D(y), W(y), F(max), W(f), F(c), W(t), W(yf) and W(ct) ($p < 0.04$ to $p < 0.0001$), Sh.Th in models of D(f), F(c) and ε(r) ($p < 0.02$ to $p < 0.002$), EP.Th.S in models of F(c) and W(ct) ($p < 0.004$ to $p < 0.0006$), EP.Th.I in the model of W(ct) ($p < 0.02$), FD in models of F(y), D(y) and F(max) ($p < 0.03$ to $p < 0.004$), Tb.Sp in models of K and D(y) ($p < 0.002$ to $p < 0.0004$), Conn.Dn in the model of D(f) ($p < 0.0009$), and SMI in the model of W(t) ($p < 0.02$). R(2)(adj) varied from 0.12 (D(r)) to 0.80 (W(t)) for the multiple regression models for all significant variables. In conclusion, there is distinct information in forces and displacements associated with characteristic events occurring during uniaxial compression and recovery, specifically in displacements associated with compaction and recovery. Though there are common factors such as bone mass for some, distinct cancellous and cortical features likely contribute to these events in L1. The descriptive data reported here are expected to provide reference values for comparative and model building efforts, and the relationships found are expected to provide insight into mechanical functions of an L1 vertebra.

Otolaryngology – Head and Neck Surgery

Chang JL, Goldberg AN, Alt JA, Ashbrook L, Auckley D, Ayappa I, Bakhtiar H, Barrera JE, Bartley BL, Billings ME, Boon MS, Bosschieter P, Braverman I, Brodie K, Cabrera-Muffly C, Caesar R, Cahali MB, Cai Y, Cao M, Capasso R, Caples SM, Chahine LM, Chang CP, Chang KW, Chaudhary N, Cheong CSJ, Chowdhuri S, Cistulli PA, Claman D, Collen J, Coughlin K, Creamer J, Davis EM, Dupuy-McCauley KL, Durr ML, Dutt M, Ali ME, Elkassabany NM, Epstein LJ, Fiala JA, Freedman N, Gill K, Gillespie MB, Golisch L, Gooneratne N, Gottlieb DJ, Green KK, Gulati A, Gurubhagavatula I, Hayward N, Hoff PT, Hoffmann OMG, Holfinger SJ, Hsia J, Huntley C, Huoh KC, Huyett P, Inala S, Ishman S, Jella TK, Jobanputra AM, Johnson AP, Junna MR, Kado JT, Kaffenberger TM, Kapur VK, Kezirian EJ, Khan M, Kirsch DB, Kominsky A, Kryger M, Krystal AD, Kushida CA, Kuzniar TJ, Lam DJ, Lettieri CJ, Lim DC, Lin HC, Liu SYC, MacKay SG, Magalang UJ, Malhotra A, Maurer JT, May AM, Mitchell RB, Mokhlesi B,

Mullins AE, Nada EM, Naik S, Nokes B, Olson MD, Pack AI, Pang EB, Pang KP, Patil SP, de Perck EV, Piccirillo JF, Pien GW, Piper AJ, **Plawecki A**, Quigg M, Ravesloot MJL, Redline S, Rotenberg BW, Ryden A, Sarmiento KF, Sbeih F, Schell AE, Schmickl CN, Schotland HM, Schwab RJ, Seo J, Shah N, Shelgikar AV, Shochat I, Soose RJ, Steele TO, Stephens E, Stepnowsky C, Strohl KP, Sutherland K, Suurna MV, Thaler E, Thapa S, Vanderveken OM, de Vries N, Weaver EM, Weir ID, Wolfe LF, Woodson BT, Won CHJ, Xu J, Yalamanchi P, **Yaremchuk K**, Yeghiazarians Y, Yu JL, Zeidler M, and Rosen IM. International consensus statement on obstructive sleep apnea. *Int Forum Allergy Rhinol* 2022; Epub ahead of print. PMID: 36068685. Full Text

BACKGROUND: Evaluation and interpretation of the literature on obstructive sleep apnea is needed to consolidate and summarize key factors important for clinical management of the OSA adult patient. Toward this goal, an international collaborative of multidisciplinary experts in sleep apnea evaluation and treatment have produced the International Consensus statement on Obstructive Sleep Apnea (ICS:OSA). METHODS: Using previously defined methodology, focal topics in OSA were assigned as literature review (LR), evidence-based review (EBR), or evidence-based review with recommendations (EBR-R) formats. Each topic incorporated the available and relevant evidence which was summarized and graded on study quality. Each topic and section underwent iterative review and the ICS:OSA was created and reviewed by all authors for consensus. RESULTS: The ICS:OSA addresses OSA syndrome definitions, pathophysiology, epidemiology, risk factors for disease, screening methods, diagnostic testing types, multiple treatment modalities, and effects of OSA and treatment on the multiple comorbidities. Specific focus on outcomes with positive airway pressure (PAP) and surgical treatments were evaluated. CONCLUSION: This review of the literature in OSA consolidates the available knowledge and identifies the limitations of the current evidence. This effort aims to highlight the basis of OSA evidence-based practice and identify future research needs. Knowledge gaps and opportunities for improvement include improving the metrics of OSA disease, determining the optimal OSA screening paradigms, developing strategies for PAP adherence and longitudinal care, enhancing selection of PAP alternatives and surgery, understanding health risk outcomes, and translating evidence into individualized approaches to therapy.

Otolaryngology – Head and Neck Surgery

Kahn GD, **Tam SH**, **Felton JW**, **Westphal J**, Simon GE, Owen-Smith AA, Rossom RC, Beck AL, Lynch FL, Daida YG, Lu CY, Waring S, **Frank CB**, **Akinyemi EO**, and **Ahmedani BK**. Cancer and psychiatric diagnoses in the year preceding suicide. *Cancer Med* 2022; Epub ahead of print. PMID: 36114785. Full Text

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BACKGROUND: Patients with cancer are known to be at increased risk for suicide but little is known about the interaction between cancer and psychiatric diagnoses, another well-documented risk factor. METHODS: Electronic medical records from nine healthcare systems participating in the Mental Health Research Network were aggregated to form a retrospective case-control study, with ICD-9 codes used to identify diagnoses in the 1 year prior to death by suicide for cases (N = 3330) or matching index date for controls (N = 297,034). Conditional logistic regression was used to assess differences in cancer and psychiatric diagnoses between cases and controls, controlling for sex and age. RESULTS: Among

patients without concurrent psychiatric diagnoses, cancer at disease sites with lower average 5-year survival rates were associated with significantly greater relative risk, while cancer disease sites with survival rates of >70% conferred no increased risk. Patients with most psychiatric diagnoses were at higher risk, however, there was no additional risk conferred to these patients by a concurrent cancer diagnosis. CONCLUSION: We found no evidence of a synergistic effect between cancer and psychiatric diagnoses. However, cancer patients with a concurrent psychiatric illness remain at the highest relative risk for suicide, regardless of cancer disease site, due to strong independent associations between psychiatric diagnoses and suicide. For patients without a concurrent psychiatric illness, cancer disease sites associated with worse prognoses appeared to confer greater suicide risk.

Otolaryngology – Head and Neck Surgery

Tiu RAY, Meyer TK, **Mayerhoff RM**, Ray JC, Kritek PA, Merati AL, and Sardesai MG. Tracheotomy care simulation training program for inpatient providers. *Laryngoscope Investig Otolaryngol* 2022; Epub ahead of print. PMID: Not assigned. Request Article

Objectives: Tracheotomy complications can be life-threatening. Many of these complications may be avoided with proper education of health care providers. Unfortunately, access to high-quality tracheotomy care curricula is limited. We developed a program to address this gap in tracheotomy care education for inpatient providers. This study aimed to assess the efficacy of this training program in improving trainee knowledge and comfort with tracheotomy care. Methods: The curriculum includes asynchronous online modules coupled with a self-directed hands-on simulation activity using a low-cost tracheotomy care task trainer. The program was offered to inpatient providers including medical students, residents, medical assistants, nurses, and respiratory therapists. Efficacy of the training was assessed using pre-training and post-training surveys of learner comfort, knowledge, and qualitative feedback. Results: Data was collected on 41 participants. After completing the program, participants exhibited significantly improved comfort in performing tracheotomy care activities and 15% improvement in knowledge scores, with large effect sizes respectively and greater gains among those with little prior tracheotomy care experience. Conclusion: This study has demonstrated that completion of this integrated online and hands-on tracheotomy simulation curriculum training increases comfort and knowledge, especially for less-experienced learners. This training addresses an important gap in tracheotomy care education among health care professionals with low levels of tracheotomy care experience and ultimately aims to improve patient safety and quality of care. This curriculum is easily transferrable as it requires only access to the online modules and low-cost simulation materials and could be used in other hospitals, long-term care facilities, outpatient clinics, and home settings.

Pathology and Laboratory Medicine

Martini R, Delpe P, Chu TR, Arora K, Lord B, Verma A, Bedi D, Karanam B, Elhussin I, **Chen Y**, Gebregzabher E, Oppong JK, Adjei EK, Jibril Suleiman A, Awuah B, Muleta MB, Abebe E, Kyei I, Aitpillah FS, Adinku MO, Ankomah K, Osei-Bonsu EB, **Chitale DA**, **Bensenhaver JM**, **Nathanson DS**, **Jackson L**, **Petersen LF**, Proctor E, Stonaker B, Gyan KK, Gibbs LD, Manojlovic Z, Kittles RA, White J, Yates CC, Manne U, Gardner K, Mongan N, Cheng E, Ginter P, Hoda S, Elemento O, Robine N, Sboner A, Carpten JD, Newman L, and Davis MB. African Ancestry Associated Gene Expression Profiles in Triple Negative Breast Cancer Underlie Altered Tumor Biology and Clinical Outcome in Women of African Descent. *Cancer Discov* 2022; Epub ahead of print. PMID: 36121736. Full Text

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Women of sub-Saharan African descent have disproportionately higher incidence of Triple Negative Breast Cancer (TNBC), and TNBC-specific mortality. Population comparative studies show racial differences in TNBC biology, including higher prevalence of basal-like and Quadruple-Negative subtypes in African Americans (AA). However, previous investigations relied on self-reported race (SRR) of primarily United States (US) populations. Due to heterogenous genetic admixture, and biological consequences of social determinants, the true association of African ancestry with TNBC biology is unclear. To address this, we conducted RNAseq on an international cohort of AAs, west and east Africans with TNBC. Using comprehensive genetic ancestry estimation in this African-enriched cohort, we found expression of 613 genes associated with African ancestry and 2000+ associated with regional African ancestry. A subset of African-associated genes also showed differences in normal breast tissue. Pathway enrichment and deconvolution of tumor cellular composition revealed tumor-associated immunological profiles are distinct in patients of African descent.

Pathology and Laboratory Medicine
Vijayanarayanan A, and Menon MP. Cholesterol Pericarditis. *N Engl J Med* 2022; 387(11):1021. PMID: 36094842. Full Text

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Pathology and Laboratory Medicine
Xu Z, and **Otrock ZK**. Extracorporeal photopheresis: A case of graft-versus-host-disease and hemophagocytic lymphohistiocytosis following liver transplantation. *Transfusion* 2022; Epub ahead of print. PMID: 36082758. Full Text

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BACKGROUND: Graft-versus-host-disease (GVHD) is one of the rare complications following liver transplantation. We report on the efficacy and safety of extracorporeal photopheresis (ECP) in managing GVHD and hemophagocytic lymphohistiocytosis (HLH) after liver transplantation. CASE REPORT: The patient is a 63-year-old male with hepatitis B cirrhosis who underwent liver transplantation. Three weeks after transplant, he presented with fever, diarrhea, and poor appetite. The patient also had bilateral blanchable erythematous patches on his palms, biopsy of which was suggestive of GVHD. The patient continued to have high-grade fever with altered mental status. CBC showed pancytopenia. Liver function examination was normal. Patient was started on methylprednisolone. Additional laboratory analysis showed high ferritin (>15000 ug/L), triglycerides (280 mg/dl), and low fibrinogen (80 mg/dl). Chimerism analysis using short tandem repeat (STR) PCR confirmed the diagnosis of GVHD. Marrow biopsy showed hemophagocytosis. The patient fulfilled the HLH-2004 diagnostic criteria. He was kept on tacrolimus and

steroids and was started on etanercept and ECP. After the first two cycles of ECP (one cycle defined as the weekly two procedures of ECP), the patient reported improvement of symptoms. He tolerated ECP well. His labs improved during the course of treatment, until his peripheral blood STR showed 100% recipient DNA. He was discharged after the fourth cycle of ECP to receive the remaining treatments as outpatient. At one year follow-up, the patient is asymptomatic with no evidence of GVHD or HLH. DISCUSSION: ECP in combination with immunosuppressive therapy and etanercept was safe and efficient in managing GVHD and HLH following liver transplantation.

Pediatrics

Hoskins K, Linn KA, **Ahmedani BK**, Boggs JM, Johnson C, Heintz J, Marcus SC, Kaminer I, **Zabel C**, Wright L, Quintana L, Buttenheim AM, Daley MF, **Elias ME**, Jager-Hyman S, Lieberman A, Lyons J, **Maye M**, **McArdle B**, Ritzwoller DP, Small DS, **Westphal J**, Wolk CB, **Zhang S**, Shelton RC, and Beidas RS. Equitable implementation of S.A.F.E. Firearm: A multi-method pilot study. *Prev Med* 2022; Epub ahead of print. PMID: 36191653. Full Text

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Attention to health equity is critical in the implementation of firearm safety efforts. We present our operationalization of equity-oriented recommendations in preparation for launch of a hybrid effectiveness-implementation trial focused on firearm safety promotion in pediatric primary care as a universal suicide prevention strategy. In Step 1 of our process, pre-trial engagement with stakeholders and literature review alerted us that delivery of a firearm safety program may vary by patients' medical complexity, race, and ethnicity. In Step 2, we selected the Health Equity Implementation Framework to inform our understanding of contextual determinants (i.e., barriers and facilitators). In Step 3, we leveraged an implementation pilot across 5 pediatric primary care clinics in 2 health system sites to study signals of inequities. Eligible well-child visits for 694 patients and 47 clinicians were included. Our results suggested that medical complexity was not associated with program delivery. We did see potential signals of inequities by race and ethnicity but must interpret with caution. Though we did not initially plan to examine differences by sex, we discovered that clinicians may be more likely to deliver the program to parents of males than females. Seven qualitative interviews with clinicians provided additional context. In Step 4, we interrogated equity considerations (e.g., why and how do these inequities exist). In Step 5, we will develop a plan to probe potential inequities related to race, ethnicity, and sex in the fully powered trial. Our process highlights that prospective, rigorous, exploratory work is vital for equity-informed implementation trials.

Pharmacy

Corrigan M, **MacDonald NC**, Musselman M, Pinto J, Skildum M, and Smith AP. ASHP Statement on the Role of the Pharmacy Workforce in Emergency Preparedness. *Am J Health Syst Pharm* 2022; Epub ahead of print. PMID: 36099081. Full Text

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Pharmacy
Crawford R, 3rd, **Perkins NB, 3rd**, Hobbs DA, and Hobbs ALV. Time to Defervescence Evaluation for Extended- vs. Standard-Infusion Cefepime in Patients with Acute Leukemia and Febrile Neutropenia. *Pharmacotherapy* 2022; Epub ahead of print. PMID: 36106434. Full Text

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BACKGROUND/OBJECTIVES: Febrile neutropenia (FN) occurs in up to 80% of patients with hematologic malignancies. Evidence suggests using extended infusions (EI) of beta-lactams can improve outcomes in some populations, but there is limited clinical literature comparing cefepime standard infusion (SI) vs EI for FN. The FDA-approved regimen for FN was used at a large community teaching hospital for patients with FN until a hospital-wide EI beta-lactam protocol was introduced that allowed for EI cefepime in FN at the physicians' discretion. We sought to compare outcomes between patients with FN who received SI and EI cefepime. METHODS: Patients with acute myeloid or lymphocytic leukemia who developed FN between April 2014-January 2021 were included in this single-center, retrospective study. The primary outcome was to compare mean time to defervescence after initiation of cefepime SI or EI regimens. SI regimens consisted of IV cefepime 2G q8h/0.5h, and EI regimens as IV cefepime 1G q8h/4h. Secondary outcomes included 30-day all-cause mortality, hospital length of stay (LOS), duration of cefepime, and need to escalate therapy. RESULTS: Overall, 193 patients were included. Baseline characteristics were similar between groups. Time to defervescence was significantly shorter with EI compared to the SI group (median 48h [48-100.5] vs. 70h [48-113], p=0.005). Cefepime duration of therapy was significantly shorter in the EI compared to the SI group (median 6.0 days vs. 8.0 days, p=0.002). There was no difference between other secondary outcomes including LOS, mortality, and antibiotic escalation. CONCLUSION: Despite reduced total daily dose of cefepime, EI cefepime administered as a 1G/0.5h LD followed 2 hours later by 1G q8h/4h for FN acutely achieves more rapid defervescence than the FDA-approved SI regimen and ultimately attains comparable patient outcomes.

Pharmacy
Garzio K, McElroy K, Grossman S, Holdhoff M, Ozer B, and **Yankulina O**. Safety of temozolomide use in adult patients with renal dysfunction. *J Neurooncol* 2022; 159(3):591-596. PMID: 36001203. Full Text

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PURPOSE: Temozolomide (TMZ), a cytotoxic DNA alkylating agent, is the main chemotherapy used for the treatment of high grade astrocytomas. The active alkylator, methylhydrazine, is not recovered in urine and thus renal function is not expected to affect clearance. Prescribing information for TMZ states pharmacokinetics have not been studied in adults with poor renal function, eGFR < 36 mL/min/1.73 m(2). We reviewed our clinical experience with TMZ in patients with impaired renal function to evaluate safety of administering full dose TMZ. METHODS: The primary endpoint was to characterize the incidence and severity of thrombocytopenia in patients with eGFR < 60 mL/min/1.73 m(2) who received TMZ for treatment of high grade gliomas (HGG) or primary CNS lymphoma (PCNSL). Secondary endpoints included incidence and severity of neutropenia, lymphopenia hepatotoxicity, and number of TMZ cycles administered. Medical records of patients with HGG or PCNSL treated with TMZ from October 1, 2016-

September 30, 2019 were accessed to identify cases for this study. RESULTS: Thirty-two patients were eligible for this study. Of the seven patients with eGFR < 36 mL/min/1.73m(2), 38/39 cycles (97%) were completed without grade 3-4 thrombocytopenia. No patients experienced grade 3-4 neutropenia, and grade 3-4 lymphopenia occurred in 5 cycles (15%). One patient discontinued TMZ 7 days prior to completion of radiation due to thrombocytopenia. CONCLUSION: Hematologic toxicity in patients with severe renal dysfunction, eGFR < 36 mL/min/1.73m(2), is similar to that of patients with normal renal function. Severe renal impairment does not preclude use of temozolomide, but cautious monitoring of blood counts is warranted.

Pharmacy

Holger DJ, Rebold NS, Alosaimy S, Morrisette T, Lagnf A, Belza AC, Coyne AJK, El Ghali A, **Veve MP**, and Rybak MJ. Impact of Ceftolozane-Tazobactam vs. Best Alternative Therapy on Clinical Outcomes in Patients with Multidrug-Resistant and Extensively Drug-Resistant Pseudomonas aeruginosa Lower Respiratory Tract Infections. *Infect Dis Ther* 2022; Epub ahead of print. PMID: 36048335. Full Text

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INTRODUCTION: Infections caused by multidrug-resistant (MDR), extensively drug-resistant (XDR), and difficult-to-treat (DTR) Pseudomonas aeruginosa are increasingly challenging to combat. Ceftolozane-tazobactam (C/T) is a novel β-lactam-β-lactamase inhibitor combination now commonly used to treat MDR and XDR P. aeruginosa. Lower respiratory tract infections (LRTIs) remain the most common source of infection caused by MDR/XDR P. aeruginosa. Comparative effectiveness studies to date have been limited by the type of comparator agents (i.e., aminoglycosides and polymyxins) and the inclusion of multiple infection sources (i.e., urinary tract, abdominal, skin and soft tissue, etc.). METHODS: We performed a multicenter, retrospective analysis of adults with LRTI caused by MDR or XDR P. aeruginosa admitted from January 2014 to December 2019. We aimed to compare clinical outcomes between patients who received C/T (n = 118) versus best alternative therapy (n = 88). The primary outcome was clinical failure, defined as 30-day mortality and/or an adverse drug reaction on antibiotic therapy. RESULTS: Two hundred and six patients met inclusion criteria. The C/T group had a significantly higher proportion of XDR P. aeruginosa and ventilator-associated bacterial pneumonia (VABP). After multivariable logistic regression, C/T treatment was independently associated with a 73.3% reduction in clinical failure compared to those who received best alternative therapy (P < 0.001). The number needed to harm with best alternative therapy was 3. CONCLUSION: Our results suggest that C/T is a safe and effective therapeutic regimen for patients with MDR and XDR P. aeruginosa LRTI.

Podiatry

Feit H, **Solway J**, and **Chedid MK**. Neurogenic Unilateral Leg Edema. *JAMA Neurol* 2022; Epub ahead of print. PMID: 36156066. Full Text

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This case report describes neurogenic unilateral leg edema that was a consequence of chronic regional pain syndrome induced by an S1 radiculopathy.

Public Health Sciences

Adjei Boakye E, Fedorovich Y, White M, Vohra S, Volle M, Osazuwa-Peters N, and Gerend MA. Rural-Urban Disparities in HPV Vaccination Coverage Among Adolescents in the Central Part of the State of Illinois, USA. *J Community Health* 2022; Epub ahead of print. PMID: 36066667. Full Text

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Human Papillomavirus (HPV) is associated with six cancers and widespread immunization with HPV vaccine could reduce the number of these cancers. Although HPV vaccination rates are available for the state of Illinois and the city of Chicago, data are limited for specific areas. We assessed rates of HPV vaccine initiation and completion among adolescents in central Illinois and identified factors associated with initiation and completion. This was a retrospective study of adolescents (aged 11-17) who receive care at the Southern Illinois University Medicine Department of Pediatrics. The outcome variables were HPV vaccination initiation (receipt of ≥ 1 dose) and completion (receipt of ≥ 2 or 3 doses, depending on age of initiation). Multivariable logistic regressions were used to identify factors associated with HPV vaccine uptake. A total of 9,351 adolescents were included in the study. Overall, HPV vaccine initiation was 46.2% and completion was 24.7%. In adjusted analyses, adolescents residing in rural areas were 38% and 24% less likely to initiate (aOR = 0.62; 95 CI: 0.54-0.72) and complete (aOR = 0.76; 95 CI: 0.65-0.88) the HPV vaccine compared with those residing in urban areas. Similarly, adolescents were less likely to initiate and complete the HPV vaccine if they were not update to date on the hepatitis A, meningococcal, or Tdap vaccinations. HPV vaccination rates in central Illinois were low, and far below the national average and the Illinois state average. Future directions should include interventions to increase HPV vaccine uptake, particularly in rural areas.

Public Health Sciences

Brodowsky EC, **Sood A**, **Butaney M**, **Majdalany SE**, **Stephens A**, **Corsi N**, **Piontkowski AJ**, **Rakic I**, **Jamil M**, **Dalela D**, **Peabody JO**, **Rogers CG**, and **Abdollah F**. Time to second biochemical recurrence as a prognostic indicator in postprostatectomy patients who undergo salvage radiation therapy: An RTOG 9601 based post hoc analysis. *Prostate* 2022; Epub ahead of print. PMID: 36120850. Full Text

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INTRODUCTION AND OBJECTIVE: The prognostic significance of a "second" biochemical recurrence (sBCR) after salvage radiation therapy (sRT) with/without hormonal therapy following primary radical prostatectomy in men with prostate cancer has not been examined. We hypothesized that a shorter time to sBCR will be associated with worse cancer control outcomes. METHODS: The RTOG 9601 study included 760 patients with tumor stage pT2/T3, pN0, who had either persistently elevated prostate-specific antigen (PSA) postradical prostatectomy or developed subsequent biochemical recurrence with PSA levels between 0.2 and 4.0 ng/ml. All patients received sRT (with or without 2 years of Bicalutamide) from 1998 to 2015. For our study, we focused on 421 patients who had sBCR after sRT-which was defined as a PSA increase of at least 0.3 ng/ml over the first nadir. Patients were divided into two categories: early sBCR (n = 210) and late sBCR (n = 211) using median time to sBCR (3.51 years). All patients who experienced sBCR received salvage hormonal therapy. Competing-risk analysis was used to examine the impact of early versus late sBCR on prostate cancer specific mortality (CSM), after accounting for available covariates. RESULTS: The majority of patients were age 60 years or older (75.8%), had pT3 disease (74.8%), and Gleason score 7 (75.2%). Overall, 13.8% had persistent PSA initially after surgery. At 10 years, starting at the time of sBCR, CSM rate was 31.3% in the early sBCR group versus 20.0% in the late sBCR group. In competing-risk analysis, time to sBCR was an independent predictor of CSM, where patients with early sBCR had 1.7-fold higher CSM risk (p = 0.026) than their counterparts with late sBCR. CONCLUSIONS: Time to sBCR after sRT (with or without concomitant Bicalutamide) is a significant predictor of CSM following initial radical prostatectomy. This information can be used to guide subsequent treatments, and to counsel patients.

Public Health Sciences

Du EY, **Adjei Boakye E**, Taylor DB, Kuziez D, Rohde RL, Pannu JS, Simpson MC, Patterson RH, Varvares MA, and Osazuwa-Peters N. Medical students' knowledge of HPV, HPV vaccine, and HPV-associated head and neck cancer. *Hum Vaccin Immunother* 2022; 2109892. Epub ahead of print. PMID: 36070503. Full Text

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On the basis of their training, medical students are considered "the best case scenario" among university students in knowledge of the human papillomavirus (HPV). We evaluated differences in knowledge of HPV, HPV vaccine, and head and neck cancer (HNC) among medical students. A previously validated questionnaire was completed by 247 medical students at a Midwestern university. Outcomes of interest were knowledge score for HPV and HPV vaccine, and HNC, derived from combining questionnaire items to form HPV knowledge and HNC scores, and analyzed using multivariate linear regression. Mean scores for HPV knowledge were 19.4 out of 26, and 7.2 out of 12 for HNC knowledge. In the final multivariate linear regression model, sex, race, and year of study were independently associated with HPV and HPV vaccine knowledge. Males had significantly lower HPV vaccine knowledge than females (β = -1.53; 95% CI: -2.53, -0.52), as did nonwhite students (β = -1.05; 95% CI: -2.07, -0.03). There was a gradient in HPV

vaccine knowledge based on the year of study, highest among fourth year students (β = 6.75; 95% CI: 5.17, 8.33). Results were similar for factors associated with HNC knowledge, except for sex. HNC knowledge similarly increased based on year of study, highest for fourth year students (β = 2.50; 95% CI: 1.72, 3.29). Among medical students, gaps remain in knowledge of HPV, HPV vaccine, and HPV-linked HNC. Male medical students have significantly lower knowledge of HPV. This highlights the need to increase medical student knowledge of HPV and HPV-linked HNC.

Public Health Sciences

Geller RJ, Wesselink AK, Upson K, Claus Henn B, Schildroth S, Wright R, Coleman CM, Willis MD, Bethea TN, Williams PL, Harmon QE, Baird DD, **Wegienka G**, and Wise LA. Correlates of whole blood metal concentrations among reproductive-aged Black women. *J Expo Sci Environ Epidemiol* 2022; Epub ahead of print. PMID: 36104525. Request Article

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BACKGROUND: Metals may influence reproductive health, but few studies have investigated correlates of metal body burden among reproductive-aged women outside of pregnancy. Furthermore, while there is evidence of racial disparities in exposure to metals among U.S. women, there is limited research about correlates of metal body burden among Black women. OBJECTIVE: To identify correlates of whole blood metal concentrations among reproductive-aged Black women. METHODS: We analyzed cross-sectional data from a cohort of 1664 Black women aged 23-35 years in Detroit, Michigan, 2010-2012. We collected blood samples and questionnaire data. We measured concentrations of 17 metals in whole blood using inductively-coupled plasma-mass spectrometer-triple quadrupole and total mercury using Direct Mercury Analyzer-80. We used multivariable linear regression models to identify sociodemographic, environmental, reproductive, and dietary correlates of individual metal concentrations. RESULTS: In adjusted models, age was positively associated with multiple metals, including arsenic, cadmium, and mercury. Education and income were inversely associated with cadmium and lead. Current smoking was strongly, positively associated with cadmium and lead. Alcohol intake in the past year was positively associated with arsenic, barium, copper, lead, mercury, vanadium, and zinc. Having pumped gasoline in the past 24 h was positively associated with cadmium, chromium, and molybdenum. Having lived in an urban area for the majority of residence in Michigan was positively associated with arsenic, lead, and nickel. Higher water intake in the past year was positively associated with several metals, including lead. Fish intake in the past year was positively associated with arsenic, cesium, and mercury. We also observed associations with body mass index, season, and other environmental, reproductive, and dietary factors. SIGNIFICANCE: We identified potential sources of exposure to metals among reproductive-aged Black women. Our findings improve understanding of exposures to metals among non-pregnant reproductive-aged women, and can inform policies in support of reducing disparities in exposures. IMPACT STATEMENT: There are racial disparities in exposures to metals. We analyzed correlates of blood metal concentrations among reproductive-aged Black women in the Detroit, Michigan metropolitan area. We identified sociodemographic, anthropometric, lifestyle, environmental, reproductive, and dietary correlates of metal body burden. Age was positively associated with several metals. Education and

income were inversely associated with cadmium and lead, indicating socioeconomic disparities. We identified potential exposure sources of metals among reproductive-aged Black women, including smoking, environmental tobacco smoke, pumping gasoline, living in an urban area, and intake of alcohol, water, fish, and rice.

Public Health Sciences

Harmon QE, Patchel SA, Denslow S, LaPorte F, **Cooper T**, Wise LA, **Wegienka G**, and Baird DD. Vitamin D and uterine fibroid growth, incidence, and loss: a prospective ultrasound study. *Fertil Steril* 2022; Epub ahead of print. PMID: 36150919. Full Text

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OBJECTIVE: Fibroid treatments that have few side-effects and can preserve fertility are a clinical priority. We studied the association between serum vitamin D and uterine fibroid growth, incidence, and loss. DESIGN: A prospective community cohort study (enrollment 2010-2012) with 4 study visits over 5 years to conduct standardized ultrasounds, measure 25-hydroxyvitamin D (25(OH)D), and update covariates. SETTING: Detroit, Michigan area. PATIENTS: Self-identified African American or Black women aged 23-35 at enrollment without previous clinical diagnosis of fibroids. INTERVENTION(S): Serum 25(OH)D measured using immunoassay or liquid chromatography-tandem mass spectrometry. MAIN OUTCOME MEASURE(S): The primary outcomes were fibroid growth, as measured by change in log volume per 18 months, and fibroid incidence (first detection of fibroid in previously fibroid-free uterus). Adjusted growth estimates from linear mixed models were converted to estimated difference in volume for high vs. low 25(OH)D. Incidence differences were estimated as hazard ratios from age-specific Cox regression. A secondary outcome fibroid loss (reduction in fibroid number between visits), was modeled using Poisson regression. Covariates (reproductive and hormonal variables, demographics, body mass index, current smoking) and 25(OH)D were modeled as time-varying factors. RESULT(S): At enrollment among 1,610 participants with ≥1 follow-up ultrasound, mean age was 29.2 years, 73% had deficient vitamin D (<20ng/mL), and only 7% had sufficient vitamin D (≥30ng/mL). Serum 25(OH)D ≥20ng/mL compared with <20ng/mL was associated with an estimated 9.7% reduction in fibroid growth (95% confidence interval [CI]: -17.3%, -1.3%), similar to the minimally adjusted estimate -8.4% (95% CI: -16.4, 0.3). Serum 25(OH)D ≥30ng/mL compared with <30ng/mL was associated with an imprecise 22% reduction in incidence (adjusted hazard ratio=0.78; 95% CI: 0.47, 1.30), similar to the unadjusted estimate of 0.84 (95% CI: 0.51, 1.39). The >30ng/mL group also had a 32% increase in fibroid loss (adjusted risk ratio=1.32; 95% CI: 0.95, 1.83). CONCLUSION(S): Our data support the hypothesis that high concentrations of vitamin D decrease fibroid development but are limited by the few participants with serum 25(OH)D ≥30ng/mL. Interventional trials that raise and maintain 25(OH)D concentrations >30ng/mL and then prospectively monitor fibroid development are needed to further assess supplemental vitamin D efficacy and determine optimal treatment protocols.

Public Health Sciences

Jumah A, Aboul Nour H, **Intikhab O**, **Choudhury O**, Gagi K, **Fana M**, Alhajala H, **Alkhoujah M**, **Alsrouji OK**, Eltous L, **Schultz L**, **Latack K**, **Brady M**, **Chebl A**, **Marin H**, and **Miller D**. Non-stenosing carotid artery plaques in embolic stroke of undetermined source: a retrospective analysis. *Neurol Sci* 2022; Epub ahead of print. PMID: 36166175. Full Text

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BACKGROUND: We aim to identify the association between high-risk carotid plaques and their laterality to stroke in ESUS patient population. We also discuss recurrent stroke events and their laterality to the index stroke. METHODS: This was a retrospective study. We reviewed data for patients with ESUS between June 20, 2016, and June 20, 2021. Using computed tomography angiography, we analyzed plaque features that are associated with ESUS, and then, we identified the recurrent stroke events and characterized lateralization to the index stroke. RESULTS: Out of 1779 patients with cryptogenic ischemic stroke, we included 152 patients who met the criteria for ESUS. High-risk plaque features were found more often ipsilateral to the stroke side when compared contralaterally: plaque ulceration (19.08% vs 5.26%, $p < .0001$), plaque thickness > 3 mm (19.08% vs 7.24%, $p = 0.001$), and plaque length > 1 cm (13.16% vs 5.92%, $p = 0.0218$). There was also a significant difference in plaque component in which both components (soft and calcified) and only soft plaques were more prevalent ipsilaterally (42.76% vs 23.68% and 17.76% vs 9.21%, respectively, $p < .0001$). Of the 152 patients, 17 patients were found to have a recurrent stroke event, and 47% (n = 8) had an ipsilateral stroke to the index event. Moreover, stroke was bilateral in 41% of the patients (n = 7), and contralateral in 12% (n = 2). CONCLUSION: High-risk plaque features studied here were more prevalent ipsilaterally to the stroke side in ESUS than contralaterally. Multicenter studies are needed to form precise prediction models and scoring systems to help guide treatment, i.e., choice of medical therapy and/or revascularization.

Public Health Sciences

Li P, Lee Y, Jehangir Q, Lin CH, Krishnamoorthy G, Sule AA, Halabi AR, Patel K, **Poisson L**, and Nair GB. SARS-COV-ATE risk assessment model for arterial thromboembolism in COVID-19. *Sci Rep* 2022; 12(1):16176. PMID: 36171201. Full Text

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Patients with SARS-CoV-2 infection are at an increased risk of cardiovascular and thrombotic complications conferring an extremely poor prognosis. COVID-19 infection is known to be an independent risk factor for acute ischemic stroke and myocardial infarction (MI). We developed a risk assessment model (RAM) to stratify hospitalized COVID-19 patients for arterial thromboembolism (ATE). This multicenter, retrospective study included adult COVID-19 patients admitted between 3/1/2020 and 9/5/2021. Among 3531 patients from the training cohort, 15.5% developed acute in-hospital ATE, including stroke, MI, and other ATE, compared to 13.4% in the validation cohort. The 16-item final score was named SARS-COV-ATE (Sex: male = 1, Age [40-59 = 2, > 60 = 4], Race: non-African American = 1, Smoking = 1 and Systolic blood pressure elevation = 1, Creatinine elevation = 1; Over the range: leukocytes/lactate dehydrogenase/interleukin-6, B-type natriuretic peptide = 1, Vascular disease (cardiovascular/cerebrovascular = 1), Aspartate aminotransferase = 1, Troponin-I [> 0.04 ng/mL = 1, troponin-I > 0.09 ng/mL = 3], Electrolytes derangement [magnesium/potassium = 1]). RAM had a good discrimination (training AUC 0.777, 0.756-0.797; validation AUC 0.766, 0.741-0.790). The validation cohort was stratified as low-risk (score 0-8), intermediate-risk (score 9-13), and high-risk groups (score ≥ 14), with the incidence of ATE 2.4%, 12.8%, and 33.8%, respectively. Our novel prediction model based on 16 standardized, commonly available parameters showed good performance in identifying COVID-19 patients at risk for ATE on admission.

Public Health Sciences

Partha DB, **Cassidy-Bushrow AE**, and Huang Y. Global preterm births attributable to BTEX (benzene, toluene, ethylbenzene, and xylene) exposure. *Sci Total Environ* 2022; 838(Pt 4):156390. PMID: 35654176. Request Article

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Epidemiological studies have shown that long-term exposure to toxic volatile organic compounds, such as benzene, toluene, ethylbenzene, and xylene (BTEX), is associated with preterm births (PTB). However, global PTB attributable to long-term BTEX exposure has not been reported in the literature yet. In this study, we employed a global chemical transport model, GEOS-Chem (Goddard Earth Observing System coupled with chemistry), in conjunction with an epidemiological model, to quantify the global country-specific PTB associated with long-term BTEX exposure at the horizontal resolution of 1 km × 1 km for the year 2015. Model simulated surface annual mean BTEX concentrations in GEOS-Chem have been thoroughly evaluated against global in-situ observations, which demonstrated that model simulated BTEX concentrations fairly agreed with observations but tended to be underestimated in India. Our study found that the global annual total PTB attributable to BTEX was 2.01 million [95% confidence interval (95CI): 1.16-2.70 million] in 2015, with largest contributions from India (28.3%), followed by China (27.5%), Pakistan (6.2%), Indonesia (4.2%), Bangladesh (3.7%) and United States (2.3%). The global annual total PTB due to BTEX exposure accounted for 19.6% (95CI: 11.3-26.4%) relative to the global annual total all-cause PTB (10.24 million) in 2015. Our study has significant implications on air pollution mitigation policy associated with country-specific anthropogenic BTEX emission reductions to achieve the benefit of human health.

Public Health Sciences

Patel V, Metz A, **Schultz L**, **Nerenz D**, Park P, **Chang V**, **Schwalb J**, Khalil J, Perez-Cruet M, and Aleem I. Rates and Reasons for Reoperation Within 30 and 90 days Following Cervical Spine Surgery: A Retrospective Cohort Analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Registry. *Spine J* 2022; Epub ahead of print. PMID: 36152774. Full Text

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BACKGROUND CONTEXT: Reoperation following cervical spinal surgery negatively impacts patient outcomes and increases healthcare system burden. To date, most studies have evaluated reoperations within 30 days after spine surgery and have been limited in scope and focus. Evaluation within the 90-day period, however, allows a more comprehensive assessment of factors associated with reoperation. PURPOSE: The purpose of this study is to assess the rates and reasons for reoperations after cervical spine surgery within 30 and 90 days. DESIGN: We performed a retrospective analysis of a state-wide prospective, multi-center, spine-specific database of patients surgically treated for degenerative disease. PATIENT SAMPLE: Patients 18 years of age or older who underwent cervical spine surgery for degenerative pathologies from February 2014 to May 2019. Operative criteria included all degenerative cervical spine procedures, including those with cervical fusions with contiguous extension down to T3. OUTCOME MEASURES: We determined causes for reoperation and independent surgical and demographic risk factors impacting reoperation. METHODS: Patient-specific and surgery-specific data was extracted from the registry using ICD-10-DM codes. Reoperations data was obtained through abstraction of medical records through 90 days. Univariate analysis was done using chi-square tests for categorical variables, t-tests for normally distributed variables, and Wilcoxon rank-sum tests for variables with skewed distributions. Odds ratios for return to the operating room (OR) were evaluated in multivariate

analysis. RESULTS: A total of 13435 and 13440 patients underwent cervical spine surgery and were included in the 30 and 90-day analysis, respectively. The overall reoperation rate was 1.24% and 3.30% within 30 and 90 days, respectively. Multivariate analysis showed within 30 days, procedures involving four or more levels, posterior only approach, and longer length of stay had increased odds of returning to the OR ($p < 0.05$), whereas private insurance had a decreased odds of return to OR ($p < 0.05$). Within 90 days, male sex, coronary artery disease (CAD), previous spine surgery, procedures with 4 or more levels, and longer length of stay had significantly increased odds of returning to the OR ($p < 0.05$). Non-white race, independent ambulatory status pre-operatively, and having private insurance had decreased odds of return to the OR ($p < 0.05$). The most common specified reasons for return to the OR within 30 days was hematoma (19%), infection (17%), and wound dehiscence (11%). Within 90 days, reoperation reasons were pain (10%), infection (9%), and hematoma (8%). CONCLUSION: Reoperation rates after elective cervical spine surgery are 1.24% and 3.30% within 30 and 90 days, respectively. Within 30 days, four or more levels, posterior approach, and longer length of stay were risk factors for reoperation. Within 90 days, male sex, CAD, four or more levels, and longer length of hospital stay were risk factors for reoperation. Non-white demographic and independent preoperative ambulatory status were associated with decreased reoperation rates.

Public Health Sciences

Paul EN, Grey JA, Carpenter TJ, Madaj ZB, Lau KH, Givan SA, Burns GW, Chandler RL, **Wegienka GR**, Shen H, and Teixeira JM. Transcriptome and DNA methylome analyses reveal underlying mechanisms for the racial disparity in uterine fibroids. *JCI Insight* 2022; Epub ahead of print. PMID: 36066972. Full Text

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Uterine fibroids (leiomyomas) affect Black women disproportionately in terms of prevalence, incidence, and severity of symptoms. The causes of this racial disparity are essentially unknown. We hypothesized that myometria of Black women are more susceptible to developing fibroids and examined the transcriptomic and DNA methylation profiles of myometria and fibroids from Black and White women for comparison. Myometrial samples cluster by race in both their transcriptome and DNA methylation profiles, whereas fibroid samples only cluster by race in the latter. More differentially expressed genes (DEGs) were detected in the Black and White myometrial sample comparison than in the fibroid comparison. Leiomyoma gene set expression analysis identified four clusters of DEGs, including a cluster of 24 genes with higher expression in myometrial samples from Black women. One of the DEGs in this group, VWF, was significantly hypomethylated at two CpG probes that are near a putative enhancer site in myometrial samples from Black women and in all fibroids and that correlate with VWF expression levels. These results suggest that the molecular basis for the disparity in fibroid disease between Black and White women could be found in the myometria before fibroid development and not in the fibroids themselves.

Public Health Sciences

Washington C, 3rd, Dapas M, Biddanda A, Magnaye KM, Aneas I, Helling BA, Szczesny B, Boorgula MP, Taub MA, Kenny E, Mathias RA, Barnes KC, Khurana Hershey GK, Kercsmar CM, Gereige JD, Makhija M, Gruchalla RS, Gill MA, Liu AH, Rastogi D, Busse W, Gergen PJ, Visness CM, Gold DR, Hartert T, **Johnson CC**, Lemanske RF, Jr., Martinez FD, Miller RL, Ownby D, Seroogy CM, Wright AL, **Zoratti EM**, Bacharier LB, Kattan M, O'Connor GT, Wood RA, Nobrega MA, Altman MC, Jackson DJ, Gern JE, McKennan CG, and Ober C. African-specific alleles modify risk for asthma at the 17q12-q21 locus in African Americans. *Genome Med* 2022; 14(1):112. PMID: 36175932. Full Text

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BACKGROUND: Asthma is the most common chronic disease in children, occurring at higher frequencies and with more severe disease in children with African ancestry. METHODS: We tested for association with haplotypes at the most replicated and significant childhood-onset asthma locus at 17q12-q21 and asthma in European American and African American children. Following this, we used whole-genome sequencing data from 1060 African American and 100 European American individuals to identify novel variants on a high-risk African American-specific haplotype. We characterized these variants in silico using gene expression and ATAC-seq data from airway epithelial cells, functional annotations from ENCODE, and promoter capture (pc)Hi-C maps in airway epithelial cells. Candidate causal variants were then assessed for correlation with asthma-associated phenotypes in African American children and adults. RESULTS: Our studies revealed nine novel African-specific common variants, enriched on a high-risk asthma haplotype, which regulated the expression of GSDMA in airway epithelial cells and were associated with features of severe asthma. Using ENCODE annotations, ATAC-seq, and pcHi-C, we narrowed the associations to two candidate causal variants that are associated with features of T2 low severe asthma. CONCLUSIONS: Previously unknown genetic variation at the 17q12-21 childhood-onset asthma locus contributes to asthma severity in individuals with African ancestries. We suggest that many other population-specific variants that have not been discovered in GWAS contribute to the genetic risk for asthma and other common diseases.

Public Health Sciences

Yao Y, **Subedi K**, **Liu T**, **Khalasawi N**, Pretto-Kernahan CD, Wotring JW, **Wang J**, **Yin C**, **Jiang A**, **Fu C**, **Dimitrion P**, **Li J**, **Veenstra J**, **Yi Q**, **McKinnon K**, **McKinnon JE**, Sexton JZ, **Zhou L**, and **Mi QS**. Surface translocation of ACE2 and TMPRSS2 upon TLR4/7/8 activation is required for SARS-CoV-2 infection in circulating monocytes. *Cell Discov* 2022; 8(1):89. PMID: 36085197. Full Text

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Infection of human peripheral blood cells by SARS-CoV-2 has been debated because immune cells lack mRNA expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease type 2 (TMPRSS2). Herein we demonstrate that resting primary monocytes harbor abundant cytoplasmic ACE2 and TMPRSS2 protein and that circulating exosomes contain significant ACE2 protein. Upon ex vivo TLR4/7/8 stimulation, cytoplasmic ACE2 was quickly translocated to the monocyte cell surface independently of ACE2 transcription, while TMPRSS2 surface translocation occurred in conjunction with elevated mRNA expression. The rapid translocation of ACE2 to the monocyte cell surface was blocked by the endosomal trafficking inhibitor endosidin 2, suggesting that endosomal ACE2 could be derived from circulating ACE2-containing exosomes. TLR-stimulated monocytes concurrently expressing ACE2 and TMPRSS2 on the cell surface were efficiently infected by SARS-CoV-2, which was significantly mitigated by remdesivir, TMPRSS2 inhibitor camostat, and anti-ACE2 antibody. Mass cytometry showed that ACE2 surface translocation in peripheral myeloid cells from patients with severe COVID-19 correlated with its hyperactivation and PD-L1 expression. Collectively, TLR4/7/8-induced ACE2 translocation with TMPRSS2 expression makes circulating monocytes permissive to SARS-CoV-2 infection.

Pulmonary and Critical Care Medicine

Awdish R. Artist's Statement: Sanitized. *Acad Med* 2022; 97(9):1317. PMID: 36098779. Full Text

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Radiation Oncology

Babier A, Mahmood R, Zhang B, Alves VGL, Barragán-Montero AM, Beaudry J, Cardenas CE, Chang Y, Chen Z, Chun J, Diaz K, David Eraso H, Faustmann E, Gaj S, Gay S, Gronberg M, Guo B, He J, Heilemann G, Hira S, Huang Y, Ji F, Jiang D, Carlo Jimenez Giraldo J, Lee H, Lian J, Liu S, Liu KC, Marrugo J, Miki K, Nakamura K, Netherton T, Nguyen D, Nourzadeh H, Osman AFI, Peng Z, Darío Quinto Muñoz J, Ramsl C, Joo Rhee D, David Rodriguez J, Shan H, Siebers JV, Soomro MH, Sun K, Usuga Hoyos A, Valderrama C, Verbeek R, Wang E, Willems S, Wu Q, Xu X, Yang S, Yuan L, **Zhu S**, Zimmermann L, Moore KL, Purdie TG, McNiven AL, and Chan TCY. OpenKBP-Opt: an international and reproducible evaluation of 76 knowledge-based planning pipelines. *Phys Med Biol* 2022; 67(18). PMID: 36093921. Full Text

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Objective.To establish an open framework for developing plan optimization models for knowledge-based planning (KBP).Approach.Our framework includes radiotherapy treatment data (i.e. reference plans) for 100 patients with head-and-neck cancer who were treated with intensity-modulated radiotherapy. That data also includes high-quality dose predictions from 19 KBP models that were developed by different research groups using out-of-sample data during the OpenKBP Grand Challenge. The dose predictions were input to four fluence-based dose mimicking models to form 76 unique KBP pipelines that generated 7600 plans (76 pipelines × 100 patients). The predictions and KBP-generated plans were compared to the reference plans via: the dose score, which is the average mean absolute voxel-by-voxel difference in dose; the deviation in dose-volume histogram (DVH) points; and the frequency of clinical planning criteria satisfaction. We also performed a theoretical investigation to justify our dose mimicking models.Main results.The range in rank order correlation of the dose score between predictions and their KBP pipelines was 0.50-0.62, which indicates that the quality of the predictions was generally positively correlated with the quality of the plans. Additionally, compared to the input predictions, the KBP-generated plans performed significantly better ($P < 0.05$; one-sided Wilcoxon test) on 18 of 23 DVH points. Similarly, each optimization model generated plans that satisfied a higher percentage of criteria than the reference plans, which satisfied 3.5% more criteria than the set of all dose predictions. Lastly, our theoretical investigation demonstrated that the dose mimicking models generated plans that are also optimal for an inverse planning model.Significance.This was the largest international effort to date for evaluating the combination of KBP prediction and optimization models. We found that the best performing models significantly outperformed the reference dose and dose predictions. In the interest of reproducibility, our data and code is freely available.

Radiation Oncology
Chapman WC, Jr., **Parikh P**, and Hunt S. Reply. *Dis Colon Rectum* 2022; 65(9):e920. PMID: 35671247. Full Text

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Radiation Oncology
Li X, **Bagher-Ebadian H**, **Gardner S**, **Kim J**, **Elshaikh M**, **Movsas B**, Zhu D, and **Chetty IJ**. An uncertainty-aware deep learning architecture with outlier mitigation for prostate gland segmentation in radiotherapy treatment planning. *Med Phys* 2022; Epub ahead of print. PMID: 36112996. Full Text

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PURPOSE: Task automation is essential for efficient and consistent image segmentation in radiation oncology. We report on a deep learning architecture, comprising a U-Net and a variational autoencoder (VAE) for automatic contouring of the prostate gland incorporating interobserver variation for radiotherapy treatment planning. The U-Net/VAE generates an ensemble set of segmentations for each image CT slice. A novel outlier mitigation (OM) technique was implemented to enhance the model segmentation accuracy. METHODS: The primary source dataset (source_prim) consisted of 19 200 CT slices (from 300 patient planning CT image datasets) with manually contoured prostate glands. A smaller secondary source dataset (source_sec) comprised 640 CT slices (from 10 patient CT datasets), where prostate glands were segmented by 5 independent physicians on each dataset to account for interobserver variability. Data augmentation via random rotation (<5 degrees), cropping, and horizontal flipping was applied to each dataset to increase sample size by a factor of 100. A probabilistic hierarchical U-Net with VAE was implemented and pretrained using the augmented source_prim dataset for 30 epochs. Model parameters of the U-Net/VAE were fine-tuned using the augmented source_sec dataset for 100 epochs. After the first round of training, outlier contours in the training dataset were automatically detected and replaced by the most accurate contours (based on Dice similarity coefficient, DSC) generated by the model. The U-Net/OM-VAE was retrained using the revised training dataset. Metrics for comparison included DSC, Hausdorff distance (HD, mm), normalized cross-correlation (NCC) coefficient, and center-of-mass (COM) distance (mm). RESULTS: Results for U-Net/OM-VAE with outliers replaced in the training dataset versus U-Net/VAE without OM were as follows: DSC = 0.82 ± 0.01 versus 0.80 ± 0.02 ($p = 0.019$), HD = 9.18 ± 1.22 versus 10.18 ± 1.35 mm ($p = 0.043$), NCC = 0.59 ± 0.07 versus 0.62 ± 0.06, and COM = 3.36 ± 0.81 versus 4.77 ± 0.96 mm over the average of 15 contours. For the average of 15 highest accuracy contours, values were as follows: DSC = 0.90 ± 0.02 versus 0.85 ± 0.02, HD = 5.47 ± 0.02 versus 7.54 ± 1.36 mm, and COM = 1.03 ± 0.58 versus 1.46 ± 0.68 mm ($p < 0.03$ for all metrics). Results for the U-Net/OM-VAE with outliers removed were as follows: DSC = 0.78 ± 0.01, HD = 10.65 ± 1.95 mm, NCC = 0.46 ± 0.10, COM = 4.17 ± 0.79 mm for the average of 15 contours, and DSC = 0.88 ± 0.02, HD = 7.00 ± 1.17 mm, COM = 1.58 ± 0.63 mm for the average of 15 highest accuracy contours. All metrics for U-Net/VAE trained on the source_prim and source_sec datasets via pretraining, followed by fine-tuning, show statistically significant improvement over that trained on the source_sec dataset only. Finally, all metrics for U-Net/VAE with or without OM showed statistically significant improvement over those for the standard U-Net. CONCLUSIONS: A VAE combined with a hierarchical U-Net and an OM strategy (U-Net/OM-VAE) demonstrates promise toward capturing interobserver variability and produces accurate prostate auto-contours for radiotherapy planning. The availability of multiple contours for each CT slice enables clinicians to determine trade-offs in selecting the "best fitting" contour on each CT slice. Mitigation of outlier contours in the training dataset improves prediction accuracy, but one must be wary of reduction in variability in the training dataset.

Radiation Oncology
Mao JJ, Ismaila N, Bao T, Barton D, Ben-Arye E, Garland EL, Greenlee H, Leblanc T, Lee RT, Lopez AM, Loprinzi C, Lyman GH, MacLeod J, Master VA, Ramchandran K, Wagner LI, **Walker EM**, Bruner DW, Witt CM, and Bruera E. Integrative Medicine for Pain Management in Oncology: Society for Integrative Oncology-ASCO Guideline. *J Clin Oncol* 2022; Epub ahead of print. PMID: 36122322. Full Text

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Duke University School of Medicine Durham, NC.
City of Hope Comprehensive Cancer Center, Duarte, CA.
Thomas Jefferson. Sidney Kimmel Cancer Center, Philadelphia, PA.
Mayo Clinic, Rochester, MN.
Patient Representative, Memorial Sloan Kettering Integrative Medicine Service, New York, NY.

Winship Cancer Institute of Emory University, Atlanta, GA.
Stanford University, Palo Alto, CA.
Wake Forest School of Medicine, Winston-Salem, NC.
Henry Ford Hospital, Detroit, MI.
University Hospital Zurich, Zurich, Switzerland.
MD Anderson Cancer Center, Houston, TX.

PURPOSE: The aim of this joint guideline is to provide evidence-based recommendations to practicing physicians and other health care providers on integrative approaches to managing pain in patients with cancer. METHODS: The Society for Integrative Oncology and ASCO convened an expert panel of integrative oncology, medical oncology, radiation oncology, surgical oncology, palliative oncology, social sciences, mind-body medicine, nursing, and patient advocacy representatives. The literature search included systematic reviews, meta-analyses, and randomized controlled trials published from 1990 through 2021. Outcomes of interest included pain intensity, symptom relief, and adverse events. Expert panel members used this evidence and informal consensus to develop evidence-based guideline recommendations. RESULTS: The literature search identified 227 relevant studies to inform the evidence base for this guideline. RECOMMENDATIONS: Among adult patients, acupuncture should be recommended for aromatase inhibitor-related joint pain. Acupuncture or reflexology or acupressure may be recommended for general cancer pain or musculoskeletal pain. Hypnosis may be recommended to patients who experience procedural pain. Massage may be recommended to patients experiencing pain during palliative or hospice care. These recommendations are based on an intermediate level of evidence, benefit outweighing risk, and with moderate strength of recommendation. The quality of evidence for other mind-body interventions or natural products for pain is either low or inconclusive. There is insufficient or inconclusive evidence to make recommendations for pediatric patients. More research is needed to better characterize the role of integrative medicine interventions in the care of patients with cancer.Additional information is available at https://integrativeonc.org/practice-guidelines/guidelines and www.asco.org/survivorship-guidelines.

Radiation Oncology

Wang P, **Chapman D**, and **Siddiqui F**. A Rare Cardiac Cavernous Hemangioma Treated with Radiotherapy. *Case Rep Vasc Med* 2022; 2022:5698475. PMID: 36105488. Full Text

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BACKGROUND: Although cardiac hemangiomas, as rare benign cardiac tumors, have been described in previous case reports, the role of radiation therapy in an unresectable cardiac hemangioma in adult has not been reported. We present a case report of a rare unresectable cardiac cavernous hemangioma treated with radiotherapy. Case Presentation. A 45-year-old female with new onset of coughing and worsening shortness of breath was found to have a biopsy proven cardiac cavernous hemangioma. Surgery was aborted due to excessive bleeding, and she was then treated with radiotherapy. A total dose of 30 Gy in 15 fractions was given using intensity-modulated radiation therapy (IMRT) to the mass with a modified 1 cm margin. Complete clinical symptomatic relief was achieved with reduction of the mass posttreatment. Ten-year follow-up revealed a stable, reduced hemangioma with no recurrence of symptoms. CONCLUSIONS: This is a rare example of cardiac hemangioma that developed in the right ventricle and compressed several major vessels. Radiotherapy may be safely used for treatment of unresectable cardiac hemangioma.

Rheumatology

Yao Y, **Subedi K**, **Liu T**, **Khalasawi N**, Pretto-Kernahan CD, Wotring JW, **Wang J**, **Yin C**, **Jiang A**, **Fu C**, **Dimitrion P**, **Li J**, **Veenstra J**, **Yi Q**, **McKinnon K**, **McKinnon JE**, Sexton JZ, **Zhou L**, and **Mi QS**. Surface translocation of ACE2 and TMPRSS2 upon TLR4/7/8 activation is required for SARS-CoV-2 infection in circulating monocytes. *Cell Discov* 2022; 8(1):89. PMID: 36085197. Full Text

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Infection of human peripheral blood cells by SARS-CoV-2 has been debated because immune cells lack mRNA expression of both angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease type 2 (TMPRSS2). Herein we demonstrate that resting primary monocytes harbor abundant cytoplasmic ACE2 and TMPRSS2 protein and that circulating exosomes contain significant ACE2 protein. Upon ex vivo TLR4/7/8 stimulation, cytoplasmic ACE2 was quickly translocated to the monocyte cell surface independently of ACE2 transcription, while TMPRSS2 surface translocation occurred in conjunction with elevated mRNA expression. The rapid translocation of ACE2 to the monocyte cell surface was blocked by the endosomal trafficking inhibitor endosidin 2, suggesting that endosomal ACE2 could be derived from circulating ACE2-containing exosomes. TLR-stimulated monocytes concurrently expressing ACE2 and TMPRSS2 on the cell surface were efficiently infected by SARS-CoV-2, which was significantly mitigated by remdesivir, TMPRSS2 inhibitor camostat, and anti-ACE2 antibody. Mass cytometry showed that ACE2 surface translocation in peripheral myeloid cells from patients with severe COVID-19 correlated with its hyperactivation and PD-L1 expression. Collectively, TLR4/7/8-induced ACE2 translocation with TMPRSS2 expression makes circulating monocytes permissive to SARS-CoV-2 infection.

Sleep Medicine

Hadid R, and **Skiba V**. Board Review: Not so fast! Home sleep apnea testing. *J Clin Sleep Med* 2022; Epub ahead of print. PMID: 36148626. Full Text

Department of Sleep Disorders, Henry Ford Hospital, Detroit, MI.

Surgery

Choi WJ, **Ivanics T**, Claasen M, Gallinger S, Hansen B, and Sapisochin G. Is it safe to administer neoadjuvant chemotherapy to patients undergoing hepatectomy for intrahepatic cholangiocarcinoma? ACS-NSQIP propensity-matched analysis. *HPB (Oxford)* 2022; 24(9):1535-1542. PMID: 35474005. Full Text

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BACKGROUND: The use of neoadjuvant chemotherapy (NAC) in patients with intrahepatic cholangiocarcinoma (iCCA) is increasing. The objective of this study was to compare the 30-day post-operative complications and length-of-stay (LOS) between patients undergoing hepatectomy for iCCA with and without NAC. METHODS: A retrospective study was conducted using the ACS-NSQIP database queried from 2014 to 2018. Patients with NAC receipt were propensity-score matched into 1:3 ratio with controls using the greedy-matching algorithm and a caliper of 0.2. Logistic and Poisson regression models were used to estimate the effect sizes. RESULTS: A total of 1508 patients who underwent hepatectomy for iCCA were included. 706 patients remained after matching and balance were achieved. The NAC group had 110 (60.1%) complications vs. 289 (55.3%) complications in the non-NAC group ($p = 0.29$). NAC was not associated with worse 30-day postoperative complications [OR 1.24, 95% CI: 0.87-1.76; $p = 0.24$]. Post-operative LOS in the NAC group was 8.56 days (mean, SD 7.4) vs. non-NAC group 9.27 days (mean, SD 8.41, $p = 0.32$). NAC was not associated with longer post-operative LOS [RR 0.93, 95% CI:0.80, 1.08; $p = 0.32$]. CONCLUSION: NAC may be safely administered without increasing the risk of 30-day complications or post-operative hospital LOS.

Surgery

Jesse MT, and Haver DB. Current recommendations regarding evaluation of cognitive functioning in organ transplant candidates. *Curr Opin Organ Transplant* 2022; Epub ahead of print. PMID: 36094545. Full Text

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PURPOSE OF REVIEW: Cognitive impairment is associated with negative effects on solid organ transplant candidates, recipients, and their care partners. However, because of the heterogeneity of mechanisms, presentations, and assessment measures, research suggests a wide array of impairments, patterns of impairments, and unclear trajectories posttransplant. This review provides an abbreviated synthesis of recent research on cognitive impairments observed in organ-eligible candidates and potential trajectories through posttransplant, current clinical recommendations regarding integration of assessment into routine clinical transplant practice, as well as recommendations for future research. RECENT FINDINGS: Transplantation may resolve certain disease-contributing factors to cognitive impairments but also introduces new potential neurocognitive assaults. Recent studies in kidney and lung recipients document continued impairments in subsets of patients, particularly those identified as frail. For liver candidates, new assessment measures of hepatic encephalopathy have been developed and preliminarily tested with potential for translation into routine clinical care. Clinical implications, as well as ethical considerations are discussed. SUMMARY: Although guidelines agree that cognitive assessment is an important part of the organ transplantation process, many questions remain of how to best assess

cognition and intervene when cognitive impairment is identified in transplant populations. Further research should focus on prospective, longitudinal assessments in transplant-eligible populations through posttransplant.

Surgery

Martini R, Delpe P, Chu TR, Arora K, Lord B, Verma A, Bedi D, Karanam B, Elhussin I, **Chen Y**, Gebregzabher E, Oppong JK, Adjei EK, Jibril Suleiman A, Awuah B, Muleta MB, Abebe E, Kyei I, Aitpillah FS, Adinku MO, Ankomah K, Osei-Bonsu EB, **Chitale DA**, **Bensenhaver JM**, **Nathanson DS**, **Jackson L**, **Petersen LF**, Proctor E, Stonaker B, Gyan KK, Gibbs LD, Manojlovic Z, Kittles RA, White J, Yates CC, Manne U, Gardner K, Mongan N, Cheng E, Ginter P, Hoda S, Elemento O, Robine N, Sboner A, Carpten JD, Newman L, and Davis MB. African Ancestry Associated Gene Expression Profiles in Triple Negative Breast Cancer Underlie Altered Tumor Biology and Clinical Outcome in Women of African Descent. *Cancer Discov* 2022; Epub ahead of print. PMID: 36121736. Full Text

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Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.
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Women of sub-Saharan African descent have disproportionately higher incidence of Triple Negative Breast Cancer (TNBC), and TNBC-specific mortality. Population comparative studies show racial differences in TNBC biology, including higher prevalence of basal-like and Quadruple-Negative subtypes in African Americans (AA). However, previous investigations relied on self-reported race (SRR) of primarily United States (US) populations. Due to heterogenous genetic admixture, and biological consequences of social determinants, the true association of African ancestry with TNBC biology is unclear. To address this, we conducted RNAseq on an international cohort of AAs, west and east Africans with TNBC. Using comprehensive genetic ancestry estimation in this African-enriched cohort, we found expression of 613 genes associated with African ancestry and 2000+ associated with regional African ancestry. A subset of African-associated genes also showed differences in normal breast tissue. Pathway enrichment and deconvolution of tumor cellular composition revealed tumor-associated immunological profiles are distinct in patients of African descent.

Surgery

Nagai S, **Ivanics T**, **Kitajima T**, **Shimada S**, **Shamaa TM**, **Collins K**, **Rizzari M**, **Yoshida A**, **Moonka D**, and **Abouljoud M**. Disparities in the Effects of Acuity Circle-based Liver Allocation on Waitlist and Transplant Practice Between Centers. *Transplant Direct* 2022; 8(10):e1356. PMID: 36176726. Full Text

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Liver allocation in the United States was updated on February 4, 2020, by introducing the acuity circle (AC)-based model. This study evaluated the early effects of the AC-based allocation on waitlist outcomes. METHODS: Adult liver transplant (LT) candidates listed between January 1, 2019, and September 30, 2021, were assessed. Two periods were defined according to listing date (pre- and post-AC), and 90-d waitlist outcomes were compared. Median transplant Model for End-stage Liver Disease (MELD) score of each transplant center was calculated, with centers categorized as low- (<25 percentile), mid- (25-75 percentile), and high-MELD (>75 percentile) centers. RESULTS: A total of 12 421 and 17 078 LT candidates in the pre- and post-AC eras were identified. Overall, the post-AC era was associated with higher cause-specific 90-d hazards of transplant (csHR, 1.32; 95% confidence interval [CI], 1.27-1.38; P < 0.001) and waitlist mortality (cause-specific hazard ratio [csHR], 1.20; 95% CI, 1.09-1.32; P < 0.001). The latter effect was primarily driven by high-MELD centers. Low-MELD centers had a higher proportion of donations after circulatory death (DCDs) used. Compared with low-MELD centers, mid-MELD and high-MELD centers had significantly lower cause-specific hazards of DCD-LT in both eras (mid-MELD: csHR, 0.47; 95% CI, 0.38-0.59 in pre-AC and csHR, 0.56; 95% CI, 0.46-0.67 in post-AC and high-MELD: csHR, 0.11; 95% CI, 0.07-0.17 in pre-AC and csHR, 0.14; 95% CI, 0.10-0.20 in post-AC; all P < 0.001). Using a structural Bayesian time-series model, the AC policy was associated with an increase in the actual monthly DCD-LTs in low-, mid-, and high-MELD centers (actual/predicted: low-MELD: 19/16; mid-MELD: 21/14; high-MELD: 4/3), whereas the increase in monthly donation after brain death-LTs were only present in mid- and high-MELD centers. CONCLUSIONS: Although AC-based allocation may improve waitlist outcomes, regional variation exists in the drivers of such outcomes between centers.

Surgery

Natour AK, **Shepard A**, **Nypaver T**, **Weaver M**, **Peshkepija A**, **Kafri O**, and **Kabbani L**. Socioeconomic status is not associated with unfavorable outcomes in patients with acute limb ischemia. *Vascular* 2022; Epub ahead of print. PMID: 36117451. Full Text

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OBJECTIVE: Whether socioeconomic status (SES) is associated with health outcomes in patients with acute limb ischemia (ALI) is largely unknown. We aimed to determine whether SES is associated with worse presentations and outcomes for patients with ALI. METHODS: We performed a retrospective medical record review of patients who presented with ALI between April 2016 and October 2020 at a single tertiary care center. SES was quantified using individual variables (median household income, level of education, and employment) and a composite endpoint, the neighborhood deprivation index (NDI). The NDI is a standardized and reproducible index that uses census tract data (higher number indicates lower SES status). The NDI summarizes 8 domains of socioeconomic deprivation. ALI severity was categorized using the Rutherford classification. The association between SES and the severity of ALI at presentation and between SES and other health outcomes were analyzed using bivariate analysis of variance, independent t test, and multivariate logistic regression. RESULTS: During the study period, 278 patients were treated for ALI, of whom 211 had complete SES data available. The mean age was 64 years, 55% were men, and 57% were White. The Rutherford classification of disease severity was grade 1, 2a, 2b, and 3 for 6%, 54%, 32%, and 8% of patients, respectively. Patients with a low SES status per the NDI were more likely to have a history of peripheral arterial disease and chronic kidney disease at presentation. The ALI etiology (thrombotic vs embolic) was not associated with SES. No significant differences were seen between SES and the severity of ALI at presentation (p = 0.96) or the treatment modality (p = 0.80). No associations between SES and 30-day or 1-year mortality were observed (mean NDI, 0.15 vs 0.26, p = 0.58, and 0.20 vs 0.26, p = 0.71, respectively) or between SES and 30-day or 1-year limb loss (mean NDI, 0.06 vs 0.30, p = 0.18, and 0.1 vs 0.32, p = 0.17, respectively). Lower SES

(higher NDI) was associated with increased 30-day readmission (mean NDI, 0.49 vs 0.15, p = 0.021). However, this association was not significant on multivariate analysis (odds ratio 1.4, 95% CI 0.9-2.1, p = 0.06). CONCLUSIONS: SES was not associated with the severity of ALI at patient presentation. Although SES was associated with the presence of peripheral arterial disease and chronic kidney disease at presentation, SES was not a predictor of short-term or 1-year limb loss and mortality. Overall, ALI presentation and treatment outcomes were independent of SES.

Surgery

Pina L, Dove J, Wood GC, Parker DM, Still C, Petrick A, and **Daouadi M**. Stratified Preoperative A1c is not Significantly Associated With Clavien-Dindo Major Complications Following Bariatric Surgery in the MBSAQIP Database. *Am Surg* 2022; Epub ahead of print. PMID: 36069148. Full Text

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BACKGROUND: Type 2 Diabetes Mellitus (T2DM) is highly prevalent comorbidity in patients with morbid obesity. It is still unclear whether a cutoff value of preoperative A1c represents an increased risk for major postoperative complications following Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG). METHODS: Retrospective MBSAQIP Participant Use File cohort for both years 2017 and 2018 were analyzed to evaluate the relationship between HbA1c in patients with morbid obesity and T2DM undergoing bariatric surgery, and the 30 days postoperative major complications by Clavien-Dindo classification (III/IV). We used an HbA1c cutoff of <7, > =7, and stratified by 1% increment for a total of 11 groups. We used univariate and multivariate logistic regression to analyze the outcome of the complications. Predicted probabilities were calculated for major complications. All statistical tests were two-sided with a P-value of less than .05 considered as a cut-off for statistical significance. RESULTS: Of 42,181 patients that met inclusion criteria, there were 20,955 identified with HbA1c <7%, and 21,226 patients with HbA1c >7%. Utilizing HbA1c <7% as a cutoff, we found no consistent statistical significance in the major postoperative complication in patients with HbA1c >7%, and when stratified with 1% increment between groups. We also found no significance between groups with risk adjustment. CONCLUSIONS: Extensive analysis of the large MBSAQIP cohort didn't result in a clinically significant association between stratified HbA1c and 30-day Clavien-Dindo major complications (III/IV) following Roux-en-Y Gastric Bypass (RYGB) and (SG).

Urology

Agarwal A, Cannarella R, Saleh R, Harraz AM, Kandil H, Salvio G, Boitrelle F, Kuroda S, Farkouh A, **Rambhatla A**, Zini A, Colpi G, Gül M, Kavoussi P, Hamoda TAA, Ko E, Calik G, Toprak T, Pinggera GM, Park HJ, Ghayda RA, Minhas S, Busetto GM, Bakırcıoğlu ME, Kadioglu A, Chung E, Russo GI, Calogero AE, Ambar RF, Jayasena CN, and Shah R. Impact of Antioxidant Therapy on Natural Pregnancy Outcomes and Semen Parameters in Infertile Men: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *World J Mens Health* 2022; Epub ahead of print. PMID: 36102104. Full Text

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PURPOSE: Seminal oxidative stress (OS) is a recognized factor potentially associated with male infertility, but the efficacy of antioxidant (AOX) therapy is controversial and there is no consensus on its utility. Primary outcomes of this study were to investigate the effect of AOX on spontaneous clinical pregnancy, live birth and miscarriage rates in male infertile patients. Secondary outcomes were conventional semen parameters, sperm DNA fragmentation (SDF) and seminal OS. MATERIALS AND METHODS: Literature search was performed using Scopus, PubMed, Ovid, Embase, and Cochrane databases. Only randomized controlled trials (RCTs) were included and the meta-analysis was conducted according to PRISMA guidelines. RESULTS: We assessed for eligibility 1,307 abstracts, and 45 RCTs were finally included, for a total of 4,332 infertile patients. We found a significantly higher pregnancy rate in patients treated with AOX compared to placebo-treated or untreated controls, without significant inter-study heterogeneity. No effects on live-birth or miscarriage rates were observed in four studies. A significantly higher sperm concentration, sperm progressive motility, sperm total motility, and normal sperm morphology was found in patients compared to controls. We found no effect on SDF in analysis of three eligible studies. Seminal levels of total antioxidant capacity were significantly higher, while seminal malondialdehyde acid was significantly lower in patients than controls. These results did not change after exclusion of studies performed following varicocele repair. CONCLUSIONS: The present analysis upgrades the level of evidence favoring a recommendation for using AOX in male infertility to improve the spontaneous pregnancy rate and the conventional sperm parameters. The failure to demonstrate an increase in live-birth rate, despite an increase in pregnancy rates, is due to the very few RCTs specifically assessing the impact of AOX on live-birth rate. Therefore, further RCTs assessing the impact of AOX on live-birth rate and miscarriage rate, and SDF will be helpful.

Urology

Agochukwu-Mmonu N, Qi J, Dunn RL, Montie J, Wittmann D, Miller D, Martin R, Kim T, Johnston WK, and **Peabody J**. Re: Patient- and Surgeon-Level Variation in Patient-Reported Sexual Function Outcomes following Radical Prostatectomy over 2 Years: Results from a Statewide Surgical Improvement Collaborative. *J Urol* 2022; 208(3):725-726. PMID: Not assigned. Full Text

Urology

Brodowsky EC, **Sood A**, **Butaney M**, **Majdalany SE**, **Stephens A**, **Corsi N**, **Piontkowski AJ**, **Rakic I**, **Jamil M**, **Dalela D**, **Peabody JO**, **Rogers CG**, and **Abdollah F**. Time to second biochemical recurrence as a prognostic indicator in postprostatectomy patients who undergo salvage radiation therapy: An RTOG 9601 based post hoc analysis. *Prostate* 2022; Epub ahead of print. PMID: 36120850. Full Text

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INTRODUCTION AND OBJECTIVE: The prognostic significance of a "second" biochemical recurrence (sBCR) after salvage radiation therapy (sRT) with/without hormonal therapy following primary radical prostatectomy in men with prostate cancer has not been examined. We hypothesized that a shorter time to sBCR will be associated with worse cancer control outcomes. METHODS: The RTOG 9601 study included 760 patients with tumor stage pT2/T3, pN0, who had either persistently elevated prostate-specific antigen (PSA) postradical prostatectomy or developed subsequent biochemical recurrence with PSA levels between 0.2 and 4.0 ng/ml. All patients received sRT (with or without 2 years of Bicalutamide) from 1998 to 2015. For our study, we focused on 421 patients who had sBCR after sRT-which was defined as a PSA increase of at least 0.3 ng/ml over the first nadir. Patients were divided into two categories: early sBCR (n = 210) and late sBCR (n = 211) using median time to sBCR (3.51 years). All patients who experienced sBCR received salvage hormonal therapy. Competing-risk analysis was used to examine the impact of early versus late sBCR on prostate cancer specific mortality (CSM), after accounting for available covariates. RESULTS: The majority of patients were age 60 years or older (75.8%), had pT3 disease (74.8%), and Gleason score 7 (75.2%). Overall, 13.8% had persistent PSA initially after surgery. At 10 years, starting at the time of sBCR, CSM rate was 31.3% in the early sBCR group versus 20.0% in the late sBCR group. In competing-risk analysis, time to sBCR was an independent predictor of CSM, where patients with early sBCR had 1.7-fold higher CSM risk (p = 0.026) than their counterparts with late sBCR. CONCLUSIONS: Time to sBCR after sRT (with or without concomitant Bicalutamide) is a significant predictor of CSM following initial radical prostatectomy. This information can be used to guide subsequent treatments, and to counsel patients.

Urology

Sharma G, Shah M, Ahluwalia P, Dasgupta P, Challacombe BJ, Bhandari M, Ahlawat R, Rawal S, Buffi NM, Sivaraman A, Porter JR, **Rogers C**, Mottrie A, Abaza R, Rha KH, Moon D, Yuvaraja TB, Parekh DJ, Capitanio U, Maes KK, Porpiglia F, Turkeri L, and Gautam G. Development and Validation of a Nomogram Predicting Intraoperative Adverse Events During Robot-assisted Partial Nephrectomy. *Eur Urol Focus* 2022; Epub ahead of print. PMID: 36153228. Full Text

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BACKGROUND: Ability to predict the risk of intraoperative adverse events (IOAEs) for patients undergoing partial nephrectomy (PN) can be of great clinical significance. OBJECTIVE: To develop and internally validate a preoperative nomogram predicting IOAEs for robot-assisted PN (RAPN). DESIGN, SETTING, AND PARTICIPANTS: In this observational study, data for demographic, preoperative, and postoperative variables for patients who underwent RAPN were extracted from the Vattikuti Collective Quality Initiative (VCQI) database. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: IOAEs were defined as the occurrence of intraoperative surgical complications, blood transfusion, or conversion to open surgery/radical nephrectomy. Backward stepwise logistic regression analysis was used to identify predictors of IOAEs. The nomogram was validated using bootstrapping, the area under the receiver operating characteristic curve (AUC), and the goodness of fit. Decision curve analysis (DCA) was used to determine the clinical utility of the model. RESULTS AND LIMITATIONS: Among the 2114 patients in the study cohort, IOAEs were noted in 158 (7.5%). Multivariable analysis identified five variables as independent predictors of IOAEs: RENAL nephrometry score (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.02-1.25); clinical tumor size (OR 1.01, 95% CI 1.001-1.024); PN indication as absolute versus elective (OR 3.9, 95% CI 2.6-5.7) and relative versus elective (OR 4.2, 95% CI 2.2-8); Charlson comorbidity index (OR 1.17, 95% CI 1.05-1.30); and multifocal tumors (OR 8.8, 95% CI 5.4-14.1). A nomogram was developed using these five variables. The model was internally valid on bootstrapping and goodness of fit. The AUC estimated was 0.76 (95% CI 0.72-0.80). DCA revealed that the model was clinically useful at threshold probabilities >5%. Limitations include the lack of external validation and selection bias. CONCLUSIONS: We developed and internally validated a nomogram predicting IOAEs during RAPN. PATIENT SUMMARY: We developed a preoperative model than can predict complications that might occur during robotic surgery for partial removal of a kidney. Tests showed that our model is fairly accurate and it could be useful in identifying patients with kidney cancer for whom this type of surgery is suitable.

Conference Abstracts

Cardiology/Cardiovascular Research

Alrayes H, **Alsaadi A**, **Alkhatib A**, **Patel D**, **Alqarqaz M**, **Frisoli T**, **Fuller B**, **Khandelwal A**, **Koenig G**, **O'Neill B**, **Villablanca P**, **Zaidan M**, **O'Neill W**, **Alaswad K**, and **Basir M**. TCT-175 Safety and Complications Associated With the Use of Protamine in Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B71. Full Text

Background: There is a paucity of data on the use of protamine after percutaneous coronary intervention (PCI). Methods: We conducted a retrospective analysis of 168 patients who underwent PCI from 2015 to 2021. All patients received protamine intra- or immediately after index PCI. We evaluated baseline characteristics, intraprocedural characteristics including heparin dosing and protamine dosing, and complications such as acute stent thrombosis (ST), dissection, perforation, and access-site bleeding. The primary outcome was the incidence of acute ST, subacute ST, and other thrombotic complications. Secondary outcomes included mortality within 24 hours and within 28 days of the index procedure. Results: One hundred sixty-eight patients were included. The mean age of patients was 72 ± 12.1 years, and 36% were women. The majority of patients received antiplatelet therapy prior to the index procedure (90%), and the average ejection fraction (EF) was 50% ± 14.3%. Of the 33 insulin-dependent patients (20%), only 1 (0.5%) used neutral protamine Hagedorn insulin. One hundred fifteen of the procedures (68%) were elective, and the average procedure time was 3 hours 21 minutes (SD 1 hour 43 minutes). Fifty-nine patients underwent rotational, orbital, or laser atherectomy (27, 23, and 9 patients, respectively). An average of 2.59 ± 1.38 stents were deployed, and intravascular ultrasound was used in 96 patients (57%). An average protamine dose of 32 mg was administered. Seventy-three patients (43%) had coronary perforations, and 19 (11%) had pericardial effusions requiring pericardiocentesis. Twenty-one patients (13%) had coronary dissections following PCI, and 6 (4%) had access-site bleeding requiring transfusion. Three patients (2%) underwent urgent cardiac surgery. Eight (5%) died within 24 hours of PCI, and 6 (3.5%) died within 28 days of PCI. Four patients (2%) had acute ST, no patients experienced subacute ST, and 1 patient (0.5%) developed arterial thrombosis (common femoral artery). Conclusions: Use protamine in PCI typically occurred because of intraprocedural complications. In our series, protamine was tolerated well in the majority of patients, but 3% of patients experienced coronary or arterial thrombosis, warranting caution when using protamine in these challenging scenarios. Categories: CORONARY: Stents: Drug-Eluting

Cardiology/Cardiovascular Research

Alsaadi A, **Ghandour A**, **Ignatius A**, **Martin A**, **Lee J**, **Rabbani B**, **Zweig B**, **Parikh S**, **Villablanca P**, **Wilson C**, **Frisoli T**, **O'Neill B**, **O'Neill W**, and **Wang DD**. TCT-374 Structural Heart Intraprocedural Versus Nonprocedural Transesophageal Echocardiography: A Quantitative Analysis of Complexity. *J Am Coll Cardiol* 2022; 80(12):B150-B151. Full Text

Background: Transesophageal echocardiography (TEE) is an essential tool in many structural heart procedures, such as transcatheter mitral valve edge-to-edge repair (TEER). Interventional procedural TEE requires a unique skill set. This study aims to evaluate the complexity of interventional structural heart TEE used to guide TEER compared with standard of care (SOC) TEE studies performed at a single center. Methods: A retrospective case-control analysis was performed of 200 patients who underwent TEE in the Henry Ford Health System. One hundred cases of interventional TEE-guided TEER were compared with 100 controls of SOC TEE. Complexity was quantified by the total duration of the procedure, the total number of images, and the number of 3-dimensional clips captured. The mean, median, and SD were compared between these 2 groups. Wilcoxon rank sum tests were used to evaluate statistical significance. Results: One hundred intraprocedural TEE studies to guide TEER and 100 SOC TEE studies were analyzed. The mean duration of TEE procedures, the number of images, and the number of 3-dimensional clips were all significantly higher in the TEER group ($P < 0.0001$) (Table 1). [Formula presented] Conclusion: Interventional TEE guidance for TEER is significantly more complex and more time-consuming than SOC TEE. This is the first large-scale study demonstrating objective differences between interventional and SOC TEE. This conclusion implicates the necessity of dedicated training programs for interventional imaging, in addition to the necessity of reviewing the current

reimbursement codes to account for such a difference. Categories: STRUCTURAL: Valvular Disease: Mitral

Cardiology/Cardiovascular Research
Armario X, Carron J, Abdel-Wahab M, Tchetche D, Bleiziffer S, Lefevre T, Modine T, Wolf A, Pilgrim T, **Villablanca P**, Cunnington M, Van Mieghem N, Hengstenberg C, Sondergaard L, Swaans M, Prendergast B, Barbanti M, Webb J, Uren N, Resar J, Chen M, Hildick-Smith D, Spence M, Zweiker D, Bagur R, de Cruz H, Ribichini F, Park DW, Codner P, Wykrzykowska J, Bunc M, Estevez-Loureiro R, Poon K, Götberg M, Ince H, Latib A, Packer E, Angelillis M, Kobari Y, Nombela-Franco L, Guo Y, Savontaus M, Arafat AA, Kliger C, Roy D, Merkely B, Silva M, White J, Yamamoto M, Ferreira PC, Toggweiler S, Ohno Y, Rodrigues I, Ojeda S, Voudris V, Grygier M, Almerri K, Cruz-Gonzalez I, Fridrich V, De la Torre Hernandez J, Piazza N, Noble S, Arzamendi D, İbrahim halil K, Bosmans J, Erglis M, Casserly I, Sawaya F, Bhindi R, Kefer J, Yin WH, Rosseel L, Kim HS, O'Connor S, Hellig F, Sztejfman M, Mendiz O, Xuereb R, Brito F, Bajoras V, Balghith M, Kang-Yin Lee M, Eid-Lidt G, Vandeloo B, Vaz V, Alasnag M, Ussia GP, Mayol J, Sardella G, Buddhari W, Kao HL, Dager A, Tzikas A, Edris A, Gutierrez L, Arias E, Erturk M, Conde Vela CN, Boljevic D, Guadagnoli AF, ElGuindy A, Santos L, Perez L, Maluenda G, Akyüz AR, Alhaddad I, Amin H, Yu SC, Alnooryani A, Albistur J, Nguyen Q, and Mylotte D. TCT-549 Impact of COVID-19 Pandemic on TAVR Activity: A Worldwide Registry. *J Am Coll Cardiol* 2022; 80(12):B225-B226. Full Text

Background: The COVID-19 pandemic had a considerable impact on the provision of structural heart intervention worldwide. Our objectives were: 1) to assess the impact of the COVID-19 pandemic on transcatheter aortic valve replacement (TAVR) activity globally; and 2) to determine the differences in the impact according to geographic region and the demographic, development, and economic status of diverse international health care systems. Methods: We developed a multinational registry of global TAVR activity and invited individual TAVR sites to submit TAVR implant data before and during the COVID-19 pandemic. Specifically, the number of TAVR procedures performed monthly from January 2019 to December 2021 was collected. The adaptive measures to maintain TAVR activity by each site were recorded, as was a variety of indices relating to type of health care system and national economic indices. The primary subject of interest was the impact on TAVR activity during each of the pandemic waves (2020 and 2021) compared with the same period pre–COVID-19 (2019). Results: Data were received from 130 centers from 61 countries, with 14 subcontinents and 5 continents participating in the study. Overall, TAVR activity increased by 16.7% (2,337 procedures) between 2018 and 2019 (ie, before the pandemic), but between 2019 and 2020 (ie, first year of the pandemic), there was no significant growth (–0.1%; –10 procedures). In contrast, activity again increased by 18.9% (3,085 procedures) between 2020 and 2021 (ie, second year of the pandemic). During the first pandemic wave, there was a reduction of 18.9% (945 procedures) in TAVR activity among participating sites, while during the second and third waves, there was an increase of 6.7% (489 procedures) and 15.9% (1,042 procedures), respectively. Further analysis and results of this study are ongoing and will be available at the time of the congress. Conclusion: The COVID-19 pandemic initially led to a reduction in the number of patients undergoing TAVR worldwide, although health care systems subsequently adapted, and the number of TAVR recipients continued to grow in subsequent COVID-19 pandemic waves. Categories: STRUCTURAL: Valvular Disease: Aortic

Cardiology/Cardiovascular Research
Basir M, **Lemor A**, Li Y, Redfors B, Truesdell A, Bharadwaj A, Kaki A, Wohns D, Meraj P, Daggubati R, Grines C, **O'Neill W**, and Moses J. TCT-70 Clinical Predictors of Patients Requiring Prolonged Mechanical Circulatory Support After High-Risk PCI. *J Am Coll Cardiol* 2022; 80(12):B28-B29. Full Text

Background: There are limited data on predicative parameters to guide weaning after high-risk percutaneous coronary intervention (HRPCI) requiring mechanical circulatory support (MCS). Methods: Patients enrolled into the prospective, multicenter, adjudicated, PROTECT III study who underwent HRPCI with Impella MCS were evaluated. Patients who required prolonged MCS, defined as requiring ongoing MCS beyond the index PCI, were compared to those in whom MCS was successfully weaned and explanted after index PCI. Results: 1,196 patients were treated at 46 sites between 2017 and 2020. 207 patients (17%) required prolonged support with a mean duration of support of 27.3 ± 34.2 compared

to 1.8 ± 5.8 hours for those not requiring prolonged support. Age, gender, and baseline comorbidities were similar between groups. Patients requiring prolonged support had a lower left ventricular ejection fraction (27.3 vs 31.8, P = 0.02), lower blood pressure (BP) pre-PCI (120 vs 126, P < 0.01) and during PCI (121 vs 131, P < 0.01), and higher heart rate pre-PCI (80 vs 76, P < 0.01) and during PCI (82 vs 76, P < 0.01). Patients requiring prolonged support were more likely to undergo urgent PCI (62 vs 49%, P < 0.01), present with acute coronary syndrome (ACS) (44.9 vs 29.7%, P < 0.01) and were more likely to experience intra-procedural complication (9.1 vs 3.9%, P < 0.01). Patients requiring prolonged support were also more likely to die during the hospitalization (10.6% vs 2.8%, P < 0.01) and experience major adverse cardiac and cerebral events (MACCE) at 90 days (23.4 vs 13.9%, P < 0.01). The need for prolonged hemodynamic support was significantly associated with cardiovascular death using logistic regression (OR 2.49, P = 0.04). Conclusion: Patients requiring prolonged support after HRPCI present with more urgent indications for PCI (ie, acute coronary syndrome) and are more likely to have intraprocedural complication. These patients have lower baseline ejection fractions, lower blood pressure, and are more likely to experience in-hospital death and 90-day MACCE. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Bharadwaj A, Abu-Much A, Redfors B, Li Y, Moses J, Grines C, Yeh R, Mallow P, Patel M, Waggoner T, Faraz H, Pinto D, Batchelor W, Truesdell A, Baron S, **Basir M**, and **O'Neill W**. TCT-99 Short- and Long-Term Outcomes of Patients With Chronic Kidney Disease Undergoing Protected High-Risk Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B40. Full Text

Background: Patients with chronic kidney disease (CKD) and concomitant multivessel coronary artery disease (CAD) with or without left ventricular dysfunction often have high surgical risk and are declined for coronary artery bypass grafting. There is little data regarding clinical outcomes in these patients undergoing high-risk PCI (HRPCI) using Impella. Methods: We analyzed patients from the PROTECT III Study who underwent Impella-supported HRPCI and stratified them into 3 groups by kidney function status based on history: 1) normal kidney function, 2) CKD without dialysis, and 3) CKD with dialysis. We compared the composite incidence of major adverse cardiac and cerebrovascular events (MACCE) rate, defined as all-cause death, myocardial infarction (MI), stroke/transient ischemic attack (TIA), and repeat revascularization at 30 and 90 days. Results: We included 1,223 patients, aged 71 ± 11 years; 73% (893) were men, 68% (834) had normal kidney function (serum creatinine [Cr] 1.1 mg/dL, IQR 0.9-1.2), 23% (278) had CKD without dialysis (Cr 1.7 mg/dL, IQR 1.3-1.9), and 9% (111) were on dialysis. Patients on dialysis were younger with more comorbidities such as diabetes, heart failure, anemia, PVD and prior stroke. HRPCI status (urgent or elective), proportion of acute MI, and mean SYNTAX scores were similar. No significant differences in MACCE were shown between groups at 30 days or 90 days (Table). Patients with normal kidney function had comparable risks of 30-day and 90-day MACCE compared with CKD patients without dialysis with Cox proportional hazards analysis, and lower risk of 90-day MACCE compared to CKD patients with dialysis. Notably, CKD patients with or without dialysis also had similar 90-day MACCE risk (Table). [Formula presented] Conclusion: Patients with CKD and dialysis undergoing HRPCI exhibit higher risk for 90-day MACCE compared to patients with normal kidney function. CKD patients without dialysis also had higher risk of MI at 90 days. Further research is needed. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Bharadwaj A, Li Y, Moses J, Redfors B, Abu-Much A, Mallow P, Patel M, Grines C, Faraz H, Yeh R, Waggoner T, Pinto D, Batchelor W, Truesdell A, **O'Neill W**, **Basir M**, and Baron S. TCT-545 Angiographic Features, Lesion, and Procedural Characteristics in Patients With Chronic Kidney Disease Undergoing Protected High-Risk Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B223-B224. Full Text

Background: Patients with chronic kidney disease (CKD) are at risk for accelerated atherosclerosis. There is a paucity of data regarding coronary lesion characteristics and procedural details of CKD patients, especially those on dialysis, undergoing high-risk percutaneous coronary intervention (HRPCI) with left ventricular support. Methods: We analyzed patients from the PROTECT III study who underwent Impella-supported HRPCI, stratified into 3 groups according to kidney function status based on history: 1) normal

kidney function; 2) CKD not on dialysis; and 3) CKD on dialysis. Baseline characteristics, angiographic features, and procedural details were assessed. Results: The study population included 3,702 treated lesions in 1,223 patients with a mean age of 71 ± 11 years; 73% (893) were male, 68% (834) had normal kidney function (serum creatinine = 1 mg/dL [IQR: 0.9-1.2]), 23% (278) had CKD not on dialysis (serum creatinine = 1.6 mg/dL [IQR: 1.3-1.9]), and 9% (111) were on dialysis. Patients on dialysis were significantly younger and had more comorbidities, as well as a greater incidence of acute myocardial infarction as an indication for HRPCI compared with the other 2 groups (45.0 [dialysis] vs 30.1 [CKD not on dialysis] vs 36.0 [normal kidney function]; P = 0.03). There was no difference between groups in prevalence of 3-vessel disease (P = 0.63). Patients on dialysis had greater prevalence of severely calcified lesions and higher use of rotational and orbital atherectomy with greater number of passes (Table 1). Despite this, no significant differences were observed in post-PCI Thrombolysis In Myocardial Infarction flow, incidence of no-reflow, or dissection/perforation. [Formula presented] Conclusion: In contrast to patients with normal kidney function, patients with CKD with or without dialysis treated with Impella had more comorbidities, higher prevalence of severely calcified lesions, and greater use of atherectomy with more passes. Despite the complexity of PCI, no significant differences in complications were observed. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Ghandour A, **Alsaadi A**, **Ignatius A**, **Martin A**, **Lee J**, **Rabbani B**, **Zweig B**, **Parikh S**, **Villablanca P**, **Wilson C**, **Frisoli T**, **O'Neill B**, **O'Neill W**, and **Wang DD**. TCT-378 Not Every TEE Is a "Standard of Care" TEE. *J Am Coll Cardiol* 2022; 80(12):B152. Full Text

Background: Intraprocedural structural heart imaging is more challenging and has unique differences from standard of care (SOC) imaging. However, the variations in time and complexity of different types of SOC transesophageal echocardiographs (TEEs) versus interventional TEEs is not well studied. In this study, we aim to compare the complexity of SOC nonvalvular indication TEE with SOC valvular TEE studies and interventional TEEs performed in the guidance of transcatheter edge-to-edge repair (TEER) MitraClip (Abbott Vascular) procedures. Methods: A retrospective case-control analysis was performed on 200 patients who underwent TEE in the Henry Ford Health System. One hundred cases of interventional TEE-guided TEER were compared with 73 nonvalvular (endocarditis and stroke evaluation) SOC TEEs and 27 valvular (preprocedural mitral, aortic, and tricuspid valve evaluations) SOC TEEs. Complexity was quantified by the total procedure duration, the total number of images, and the number of 3-dimensional (3D) clips captured. The mean, median, and SD were compared between these groups. The Kruskal-Wallis test was used to evaluate statistical significance. Results: The mean duration of TEE procedures, the number of images, and the number of 3D clips were all significantly higher in the interventional imaging TEER group compared with the noninterventional groups (P < 0.0001) (Table 1). The duration and number of images were also significantly higher among valvular compared with nonvalvular SOC TEE groups (P < 0.0002) as well as number of 3D clips (P < 0.0012). [Formula presented] Conclusion: Interventional TEE was more complicated and time-consuming compared with SOC TEE performed for both nonvalvular and valvular indications. The latter was also more complex than SOC nonvalvular TEE. This is the first study of its kind demonstrating objective differences between interventional and 2 SOC TEE groups. These results emphasize the need of dedicated training for intraprocedural imaging as well as restructuring of reimbursement codes. Categories: STRUCTURAL: Valvular Disease: Mitral

Cardiology/Cardiovascular Research

Gregerson S, **Mahmood S**, Brooks C, **Gonzalez PE**, **Villablanca P**, **Frisoli T**, **Lee J**, **Wang DD**, **O'Neill W**, and **O'Neill B**. TCT-353 Clinical Characteristics and Outcomes of Alcohol Septal Ablation in the Era of Transcatheter Valve Interventions. *J Am Coll Cardiol* 2022; 80(12):B143. Full Text

Background: Alcohol septal ablation (ASA) is an alternative to surgical myectomy for left ventricular outflow tract (LVOT) obstruction in HCM and pre-emptive before transcatheter mitral valve replacement (TMVR) to prevent LVOT obstruction. This study aimed to evaluate the procedural characteristics and outcomes of ASA in contemporary practice. Methods: This was a single-center retrospective study of 137 patients undergoing ASA for HCM and TMVR at Henry Ford Hospital from January 2010 to August 2021. Patient/procedure characteristics and outcomes were assessed. The primary endpoint was an adverse

composite of new pacemaker requirement (PPM), stroke, sustained ventricular tachycardia, resuscitated cardiac arrest, and all-cause mortality within 30 days. Results: Eighty-six cases were performed for HCM, and 51 cases were performed for TMVR. Of the entire cohort, 27.7% cases met the primary endpoint with common adverse events being PPM (21%), cardiac arrest (6.5%), and mortality (4.3%). The HCM subgroup had a PPM of 18.7% and mortality of 1.1%. The TMVR subgroup had a PPM of 25.4% and mortality of 9.8%. The LVOT gradient decreased by a mean of 43 mm Hg for the entire cohort, 51.75 mm Hg in the HCM group, and 19.03 mm Hg in the TMVR group. Residual LVOT gradients above 30 mm Hg were noted in the HCM group (41.8%) and the TMVR group (13.7%). [Formula presented] Conclusion: This is the largest study including patients who underwent ASA for pre-emptive TMVR in addition to HCM. Most primary endpoint events consisted of a new pacemaker requirement. The mortality rate in the HCM reflects prior studies, suggesting a mortality of 1% to 2%. The mortality rate in pre-emptive TMVR was higher than previously reported by our group (6.7%). Categories: STRUCTURAL: Alcohol Septal Ablation/HOCM

Cardiology/Cardiovascular Research

Iannaccone M, Franchin L, Hanson I, Boccuzzi G, **Basir M**, Truesdell A, and **O'Neill W**. TCT-66 Door to Impella Placement in Acute Coronary Syndrome Complicated by Cardiogenic Shock: An Updated Meta-analysis. *J Am Coll Cardiol* 2022; 80(12):B27. Full Text

Background: The impact of time to hemodynamic support in acute myocardial infarction complicated by cardiogenic shock (AMICS) has yet to be defined. The aim of this meta-analysis was to evaluate the impact of timing of mechanical circulatory support (MCS) with Impella. Methods: a systematic literature review and meta-analysis was conducted using PubMed and Cochrane databases. All studies reporting short-term mortality rates and timing of Impella insertion, pre vs during/post PCI, were included. Primary end point was short-term mortality (≤30 days), while secondary end pointswere midterm mortality, device-related bleeding and limb ischemia. Results: Of 1,289 studies identified, 13 studies (6,810 patients; 2,970 patients identified as receiving Impella before PCI and 3,840 patients receiving Impella during/after PCI) were included in this analysis. Median age was 63.8 years (IQR 63-65.7 years), 76% of patients were male, and a high prevalence of cardiovascular risk factors was noted across the entire population. Short-term mortality was significantly reduced in those receiving pre-PCI Impella support, 37.2% vs 53.6% (RR 0.7; CI 0.56-0.88). Midterm mortality was also lower in the pre-PCI group, 47.9% vs 73% (RR 0.81; CI 0.68-0.97). The rates of device-related bleeding (RR 1.05; CI 0.47-2.33) and limb ischemia (RR 1.6; CI 0.63-2.15) were similar between the two groups. Conclusion: This analysis suggests that MCS placement with Impella prior to PCI in AMICS may have a positive impact on short- and midterm mortality compared with post-PCI placement, with similar outcome in terms of safety. Categories: CORONARY: Hemodynamic Support and Cardiogenic Shock

Cardiology/Cardiovascular Research

Kapur N, Moses J, Faraz H, George Z, Iyer V, Karas R, Kimmelstiel C, **Koenig G**, Madder R, Meraj P, Kim R, Schreiber T, Wohns D, Udelson J, Stone G, and **O'Neill W**. TCT-34 Reduction of Infarct Size in Anterior ST-Segment Elevation Myocardial Infarction (STEMI) With LAD Occlusion and LV Unloading Using a Micro-axial Pump for 30 Minutes Before PCI: Per-Protocol Analysis of the STEMI Door to Unload (DTU) Pilot Study. *J Am Coll Cardiol* 2022; 80(12):B14-B15. Full Text

Background: The STEMI-DTU pilot trial identified that LV unloading before PCI is safe and feasible in anterior STEMI without shock. We now report findings from patients who met all protocol inclusion and exclusion criteria. Methods: In a multicenter, randomized safety and feasibility trial, 50 patients with anterior STEMI were unloaded using the Impella CP followed by immediate (U-IR) or delayed PCI after 30 minutes of unloading (U-DR). Cardiac magnetic resonance (CMR) imaging assessed infarct size 3-5 days after PCI. Patients without CMR at 3-5 days (n = 10; 5/arm), without PCI of a culprit LAD lesion (n = 2; 1/arm) and without STEMI (n = 5; 4 U-IR, 1 U-DR) were not per protocol and thus excluded. Results: 33 patients met all inclusion and exclusion criteria (U-IR n = 15, U-DR n = 18) with respective door-to-balloon times of 75 ± 26 and 89 ± 23 minutes (P = 0.10) and mean unload-to-balloon times of 10 ± 5 and 34 ± 3 (P < 0.01). In the total cohort 2-5 day IS was significantly associated with microvascular obstruction (MVO), 30-day IS normalized to total LV mass, 90 day LVEF, and 90 day LV end systolic volume with or without delayed reperfusion (Table) (R > 0.5, P < 0.005 for all). Despite longer symptom to balloon times

in the U-DR arm (174 ± 59 vs 228 ± 78, P < 0.01) IS/AAR was lower in the U-DR arm (62 ± 16 vs 48 ± 16, P = 0.04) and remained lower irrespective of STE magnitude. MVO was lower in the U-DR arm among patients with the highest STE (Figure). [Formula presented] Conclusion: A per-protocol analysis of the STEMI-DTU Pilot trial identified reduced infarct size with unloading and delayed reperfusion. These findings are under investigation in the STEMI-DTU Pivotal trial. Categories: CORONARY: Acute Myocardial Infarction

Cardiology/Cardiovascular Research
Karacsonyi J, Kostantinis S, Simsek B, **Alaswad K**, Karmpaliotis D, Kirtane A, McEntegart M, Jaffer F, Choi J, Poommipanit P, Koutouzis M, Tsiafoutis I, Khatri J, Kandzari D, Chandwaney R, Elbarouni B, Gorgulu S, ElGuindy A, Abi-Rafeh N, Goktekin O, Ungi I, Rangan B, Mastrodemos O, Sandoval Y, Allana S, Burke MN, and Brilakis E. TCT-109 Use of Subintimal Tracking and Reentry Technique in Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B44-B45. Full Text

Background: There are limited data on the use of the subintimal tracking and reentry (STAR) technique for chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We analyzed 2,353 CTO PCIs performed using antegrade dissection re-entry (ADR) in the PROGRESS-CTO Registry, between 2012 and June 2022 at 41 centers. Results: STAR was used in 450 cases (19.1%), primary STAR in 325 (13.8%) and secondary STAR (STAR after other ADR approaches) in 125 (5.3%). The Stingray system was used in 1,048 (44.5%), limited antegrade subintimal tracking (LAST) in 177 (7.5%), and contrast-guided STAR in 31 (1.3%) of re-entry cases. The mean patient age was 65.3 ± 10 years and 86.0% were men. STAR cases were more complex with higher Japan-CTO (3.05 ± 1.08 vs 2.87 ± 1.14, P = 0.002) and PROGRESS (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) CTO (1.58 ± 1.14 vs 1.20 ± 1.04, P < 0.001) scores compared to non-STAR cases. The cases where STAR was used had lower technical (69.3% vs 79.1%, P < 0.001) and procedural (67.7% vs 76.3%, P < 0.001) success compared with cases where STAR was not used. The incidence of major cardiac adverse events was similar (3.70% vs 3.52%, P = 0.858) between STAR and non-STAR cases. Primary STAR was associated with higher technical and procedural success and similar MACE compared with secondary STAR (Figure). [Formula presented] Conclusion: STAR is used in 19.1% of antegrade re-entry CTO PCI cases and is associated with higher angiographic complexity, lower technical and procedural success rates and similar major complication rates compared to antegrade re-entry cases that did not use STAR. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Karacsonyi J, Simsek B, Kostantinis S, **Alaswad K**, Krestyaninov O, Karmpaliotis D, Kirtane A, McEntegart M, Khatri J, Poommipanit P, Jaffer F, Choi J, Mahmud E, Patel M, Koutouzis M, Tsiafoutis I, Elbarouni B, Jaber W, Rinfret S, Jefferson B, Patel T, Gorgulu S, ElGuindy A, Abi-Rafeh N, Goktekin O, Ungi I, Rangan B, Mastrodemos O, Sandoval Y, Allana S, Burke MN, and Brilakis E. TCT-110 Use of Atherectomy in Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B45. Full Text

Background: There is limited data on the atherectomy use for chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We analyzed 11,118 CTO PCIs performed in the PROGRESS-CTO Registry, between 2012 and June 2022 at 42 centers, comparing the baseline clinical, angiographic characteristics and procedural outcomes with vs without atherectomy. Results: Atherectomy was used in 498 cases (4.5%): rotational atherectomy in 415 cases (3.7%) and orbital atherectomy in 105 cases (0.9%) and both techniques in 22 cases (0.2%). The mean patient age was 65.4 ± 10 years and 81.4% were men. Patients, where atherectomy was used, were older (68.9 ± 10 vs 64.2 ± 10, P < 0.001) and more likely to have diabetes mellitus (53.9% vs 42.5%, P < 0.001) compared with non-atherectomy patients. Atherectomy cases had higher J-CTO (2.74 ± 1.09 vs 2.34 ± 1.27, P < 0.001) scores and higher technical (93.6% vs 86.0%, P < 0.001) and procedural success rates (89.8% vs 84.6%, P = 0.002) compared with cases where atherectomy was not used. The incidence of major adverse cardiac events was also higher in the atherectomy group (4.67% vs 1.91%, P < 0.001), with higher rates of pericardiocentesis (2.43% vs 0.79%, P < 0.001). Atherectomy cases were associated with longer fluoroscopy time (61 [42-91] vs 42 [25-68] minutes, P < 0.001). Temporal trends of atherectomy use are

demonstrated in the Figure. [Formula presented] Conclusion: Atherectomy is used in 4.5% of CTO PCI cases and is associated with higher patient and angiographic complexity, higher technical and procedural success rates but also higher major complication rates compared to non-atherectomy cases. Categories: CORONARY: Coronary Atherectomy, Plaque Modification, Lithotripsy, and Thrombectomy

Cardiology/Cardiovascular Research
Khalil M, Maqsood MH, **Basir M**, Saad M, Yassa G, Hakam L, Hennawy B, El Etriby S, Garcia S, Brilakis E, **Alaswad K**, and Megaly M. Invasive Versus Conservative Strategy in Elderly Patients With Non–ST-Segment Elevation Myocardial Infarction: A Meta-analysis of Randomized Controlled Trials. *J Am Coll Cardiol* 2022; 80(12):B3. Full Text

Background: Management of non–ST-segment elevation myocardial infarction (NSTEMI) has evolved over the years, but most published data are from younger patients. Data on the NSTEMI management in elderly patients remains limited. Methods: We performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the long-term outcomes of invasive vs conservative strategies in elderly patients with NSTEMI. Results: Of 1,550 reports searched, 4 RCTs (1,126 patients) were included in the analysis with a median follow-up of 1.25 years (range: 1 to 2.5 years). The median age of included patients was 83.6 (IQR 2.8 years). The invasive strategy was associated with significantly lower risk of major adverse cardiac and cerebrovascular event (MACCE) [OR 0.60 (95% CI 0.40-0.91); I2 =54%; 3 trials] and unplanned revascularization [OR 0.31 (95% CI 0.15-0.64); I2 = 1.7%; 3 trials] compared with the conservative strategy. There was no difference in all-cause mortality [OR= 0.88 (95% CI 0.65-1.18); I2 = 0%; 4 trials], myocardial infarction (MI) [OR= 0.70 (95% CI 0.42-1.19); I2 = 54.7%; 4 trials], or bleeding [OR= 0.87 (95% C: 0.39-1.93); I2 = 0%; 3 trials] between both strategies. [Formula presented] Conclusion: The use of initial invasive strategy in elderly patients presenting with NSTEMI was associated with a significantly lower risk of MACCE and unplanned revascularization compared with the initial conservative strategy without increased bleeding. Categories: CORONARY: Acute Coronary Syndromes

Cardiology/Cardiovascular Research
Kostantinis S, Simsek B, Karacsonyi J, **Alaswad K**, Jaffer F, Khatri J, Choi J, Jaber W, Rinfret S, Nicholson W, Patel M, Mahmud E, Toma C, Davies R, Kerrigan J, Haddad E, Gorgulu S, ElGuindy A, Goktekin O, Allana S, Burke MN, Mastrodemos O, Rangan B, and Brilakis E. TCT-170 Development and Validation of a Scoring System for Predicting Clinical Coronary Artery Perforation During Percutaneous Coronary Interventions of Chronic Total Occlusions: The PROGRESS-CTO Perforation Score. *J Am Coll Cardiol* 2022; 80(12):B68. Full Text

Background: Coronary artery perforation is a feared complication of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) and often leads to serious adverse clinical events. Methods: We analyzed clinical and angiographic parameters from 9,618 CTO PCIs in the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention). Logistic regression prediction modeling was used to identify independently associated variables, and models were internally validated with bootstrapping. Clinical coronary artery perforation was defined as any perforation requiring treatment. Results: The incidence of clinical coronary perforation was 3.8% (n = 367). Five factors were independently associated with perforation and were included in the score: patient age ≥ 65 years, +1 point (OR: 1.79; 95% CI: 1.37-2.33); moderate or severe calcification, +1 point (OR: 1.85; 95% CI: 1.41-2.42); blunt or no stump, +1 point (OR: 1.45; 95% CI: 1.10-1.92); use of antegrade dissection and re-entry strategy, +1 point (OR: 2.43; 95% CI: 1.61-3.69); and use of the retrograde approach, +2 points (OR: 4.02; 95% CI: 2.95-5.46). The resulting score showed acceptable performance on receiver-operating characteristic curve (area under the curve: 0.741; 95% CI: 0.712-0.773). The Hosmer-Lemeshow test indicated good fitness (P = 0.991), and internal validation with bootstrapping demonstrated a good agreement with the model (observed area under the curve: 0.736; 95% bias-corrected CI: 0.706-0.767). [Formula presented] Conclusions: The PROGRESS-CTO perforation score is a useful tool for prediction of clinical coronary perforation in CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Kostantinis S, Simsek B, Karacsonyi J, **Alaswad K**, Megaly M, Jaffer F, Khatri J, Poommipanit P, Davies R, Rinfret S, Elbarouni B, Ybarra L, Sheikh A, Toma C, Chandwaney R, Goktekin O, ElGuindy A, Mastrodemos O, Rangan B, Burke MN, and Brilakis E. TCT-128 Saphenous Vein Graft Occlusion Following Native Vessel Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B53. Full Text

Background: The practice of occluding patent saphenous vein grafts (SVGs) after successful chronic total occlusion (CTO) percutaneous coronary intervention (PCI) of the native vessel has received limited study. Methods: We analyzed baseline clinical and angiographic characteristics and procedural outcomes of 51 patients who following successful CTO PCI of the native vessel underwent attempted SVG occlusion between 2015 and 2022 at 14 centers. Results: Mean patient age was 71 ± 8 years and 80% were men. The most common CTO target vessel was the right coronary artery (41%), followed by the left circumflex artery (35%). Retrograde crossing was the successful crossing strategy in 78% (n = 40) and the SVG was the collateral used for all the retrograde cases. Recurrent SVG failure (51%) was the most common reason for treating the native vessel instead of the SVG supplying the same vessel. Coils were used in 71% (n = 36) to occlude the SVG with a mean number of 1.9 ± 1.1 coils, and Amplatzer vascular plugs were used in 29% (n = 15) of the cases. All procedures were technically successful and the SVG was occluded completely (TIMI 0 flow) in 75% (n = 38) of the cases. Follow up was available for 38 patients (75%): during a mean follow up of 312 days, the incidence of target lesion failure was 5.4% (n = 2). There were no other associated periprocedural or in-hospital complications. [Formula presented] Conclusion: SVG occlusion after successful native vessel CTO PCI, is associated with favorable periprocedural and mid-term outcomes. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Kostantinis S, Simsek B, Karacsonyi J, **Alaswad K**, Megaly M, Krestyaninov O, Khelimskii D, Jaffer F, Khatri J, Poommipanit P, Patel M, Mahmud E, Koutouzis M, Tsiafoutis I, Gorgulu S, Elbarouni B, Nicholson W, Jaber W, Rinfret S, Goktekin O, ElGuindy A, Sandoval Y, Burke MN, Allana S, Rangan B, and Brilakis E. TCT-117 Impact of Proximal Cap Ambiguity on the Outcomes of Chronic Total Occlusion Intervention: Insights From the PROGRESS-CTO Registry. *J Am Coll Cardiol* 2022; 80(12):B48-B49. Full Text

Background: The impact of proximal cap ambiguity on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. Methods: We examined the clinical and angiographic characteristics and procedural outcomes of 11,169 CTO PCIs performed in 10,932 patients at 42 US and non-US centers between 2012 and 2022. Results: Proximal cap ambiguity was present in 35% of CTO lesions. Patients whose lesions had proximal cap ambiguity were more likely to have had prior PCI (65% vs 59%; P < 0.01) and prior coronary artery bypass graft surgery (37% vs 24%; P < 0.01). Lesions with proximal cap ambiguity were more complex with higher J-CTO score (3.1 ± 1.0 vs 2.0 ± 1.2; P < 0.01) and lower technical (79% vs 90%; P < 0.01) and procedural success (77% vs 89%; P < 0.01) rates compared with non-ambiguous CTO lesions. The incidence of major adverse cardiovascular events (MACE) was higher in cases with proximal cap ambiguity (2.5% vs 1.7%; P < 0.01). The retrograde approach was more commonly used among cases with ambiguous proximal cap (51% vs 21%; P < 0.01) and was more likely to be the final successful crossing strategy (29% vs 13%; P < 0.01). PCIs of CTOs with ambiguous proximal cap required longer procedure time (140 [95-195] vs 105 [70-150] min; P < 0.01) and more contrast volume (225 [160-305] vs 200 [150-280] mL; P < 0.01). [Formula presented] Conclusion: Proximal cap ambiguity in CTO lesions is associated with higher utilization of the retrograde approach, lower technical and procedural success rates, and higher incidence of in-hospital MACE. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Megaly M, Buda K, **Basir M**, Mashayekhi K, Rinfret S, McEntegart M, Azzalini L, **Alaswad K**, and Brilakis E. TCT-121 Extraplaque Versus Intraplaque Tracking in Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2022; 80(12):B50-B51. Full Text

Background: The impact of modern extraplaque (EP) tracking techniques on long-term outcomes remains controversial. Methods: We performed a systematic review and meta-analysis of studies that compared EP vs intraplaque (IP) tracking in CTO PCI. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Der-Simonian and Laird random-effects method. Results: Our meta-analysis included seven observational studies with 2,982 patients. Patients who underwent EP tracking had significantly more complex CTOs with higher J-CTO scores (2.9 ± 1.2 vs 1.6 ± 1.1, P < 0.001), longer lesion length, more severe calcification, and significantly longer stented segments. During a median follow-up of 12 months (range 9-12 months), EP tracking was associated with a higher risk of major adverse cardiovascular events (MACE) (OR 1.50, 95% CI 1.10-2.06, P = 0.01) and target vessel revascularization (TVR) (OR 1.69, 95% CI 1.15-2.48, P = 0.01) compared with IP tracking. There was no difference in the incidence of all-cause death (OR 1.37, 95% CI 0.67-2.78, P = 0.39), myocardial infarction (MI) (OR 1.48, 95% CI 0.82-2.69, P = 0.20), or stent thrombosis (OR 2.09, 95% CI 0.69-6.33, P = 0.19) between EP and IP tracking. [Formula presented] Conclusion: Compared with IP tracking, EP tracking was utilized in more complex and longer CTOs, required more stents, and was associated with a higher risk of MACE at 12 months, driven by a higher risk of TVR, but without an increased risk of death or MI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Megaly M, Buda K, Mashayekhi K, Werner G, Grantham JA, Rinfret S, McEntegart M, Brilakis E, and **Alaswad K**. TCT-118 Comparative Analysis of Patients' Characteristics in Chronic Total Occlusion Revascularization Studies: Trials Versus Real-World Registries. *J Am Coll Cardiol* 2022; 80(12):B49. Full Text

Background: The few randomized controlled trials (RCTs) on chronic total occlusion (CTO) percutaneous coronary interventions (PCI) are subject to selection bias. Methods: We performed a meta-analysis of national and dedicated CTO PCI registries and compared patient characteristics and outcomes with those of RCTs that randomized patients to CTO PCI vs medical therapy. Given the large sample size differences between RCTs and registries, we focused on the absolute numbers and their clinical significance. We considered a 5% relative difference between groups to be potentially clinically relevant. Results: From 2012 to 2022, 6 RCTs compared CTO PCI vs medical therapy (n = 1,047) and were compared with 15 registries (5 national and 10 dedicated CTO PCI registries). Compared with registry patients, RCT patients had fewer comorbidities, including diabetes, hypertension, previous myocardial infarction, and prior coronary artery bypass graft surgery. RCT patients had shorter CTO length (29.6 ± 19.7 vs 32.6 ± 23.0 mm, a relative difference of 9.2%) and lower J-CTO scores (2.0 ± 1.1 vs 2.3 ± 1.2, a relative difference of 13%) compared with those enrolled in dedicated CTO registries. Procedural success was similar between RCTs (84.5%) and dedicated CTO registries (81.4%) but was lower in national registries (63.9%). [Formula presented] Conclusion: There is a paucity of randomized data on CTO PCI outcomes (6 RCTs, 1,047 patients). These patients have lower-risk profiles and less complex CTOs than those in real-world registries. Current evidence from RCTs may not be representative of real-world patients and should be interpreted within its limitation. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Megaly M, **Zakhour S**, Karacsonyi J, **Basir M**, Kunkel K, Simsek B, Kostantinis S, Mashayekhi K, Kandzari D, Brilakis E, and **Alaswad K**. TCT-126 Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention of the Left Anterior Descending Artery. *J Am Coll Cardiol* 2022; 80(12):B52. Full Text

Background: Improvement of left ventricular ejection fraction (LVEF) after chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has been modest in prior studies. Methods: Our cohort included patients who underwent LAD CTO PCI at a single center (Henry Ford Hospital) from 2014 to 2021. We evaluate the change in LVEF after LAD CTO PCI using the paired t test in all patients, those with ischemic cardiomyopathy (CM), and those who underwent a viability test. Results: From December 2014 to February 2022, a total of 237 LAD CTO PCI procedures were performed at Henry Ford Hospital (proximal LAD: 56.6%). In-hospital MACE occurred in 13 patients (5.5%; death: 1.3%). Landmark analysis

after discharge showed an overall survival of the cohort was 92.7% and MACE-free survival of 85.0% over a median follow-up of 2 years. The median baseline EF was 50% (IQR 35%-55%). Only 51 patients had reduced baseline LVEF (40% or less). After a median follow-up of 9.2 months (IQR 3-28.6 months), there was a significant improvement in LVEF after LAD CTO PCI (mean 10.9%, 95% CI 7.1%-14.8%, P < 0.001). When limiting the analysis to patients who had ischemic cardiomyopathy, proximal LAD CTO PCI, and were on optimal medical therapy (n = 29), LVEF was significantly improved (mean increase of 14%, 95% CI 9.5-18.5%, P < 0.001) after a median follow-up period of 6.2 months (3-29.5 months). Conclusion: LAD CTO PCI was associated with a significant 10% improvement in LVEF in ICM patients and was more pronounced (14% improvement) in those who had proximal LAD treated and were on optimal medical therapy. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Simsek B, Kostantinis S, Karacsonyi J, **Alaswad K**, Karmpaliotis D, Jaffer F, Khatri J, Poommipanit P, Gorgulu S, Goktekin O, Krestyaninov O, Davies R, ElGuindy A, Haddad E, Kerrigan J, Patel M, Chandwaney R, Mastrodemos O, Allana S, Rangan B, and Brilakis E. TCT-123 Predictors of Success in Primary Retrograde Strategy in Chronic Total Occlusion Percutaneous Coronary Intervention: Insights From the PROGRESS-CTO Registry. *J Am Coll Cardiol* 2022; 80(12):B51-B52. Full Text

Background: An upfront (primary) retrograde strategy is often used in chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We examined the clinical, angiographic characteristics, and procedural outcomes of CTO PCIs that were approached with a primary retrograde strategy in the Prospective Global Registry for the Study of CTO Intervention (PROGRESS-CTO; NCT02061436). Interventional collaterals were defined as collaterals that appeared suitable for retrograde CTO PCI. Results: Of 10,286 CTO PCIs, a primary retrograde strategy was used in 1,329 (13%) with an initial technical success of 66% and a final success of 83% with subsequent strategies. Successful vs unsuccessful primary retrograde cases had similar baseline characteristics with high prior coronary artery bypass graft surgery (52% vs 53%, P = 0.682), respectively. The PROGRESS-CTO score (1.3 ± 0.9 vs 1.6 ± 0.9, P < 0.001), air kerma radiation (3.9 ± 2.8 vs 3.4 ± 2.6 Gray, P = 0.013), and contrast (294 ± 148 mL vs 248 ± 128 mL, P < 0.001) were higher in the unsuccessful group, whereas the presence of interventional collaterals (95% vs 72%, P < 0.001) and Werner collateral connection grade 2 (43% vs 31%, P < 0.001) were higher in the successful group. On multivariable logistic regression analysis, the only variable associated with a successful primary retrograde strategy was the presence of interventional collaterals: odds ratio 6.52, 95% confidence interval 3.5-12.1, P < 0.001 (Figure). [Formula presented] Conclusion: Presence of interventional collaterals is independently associated with higher success rates with a primary retrograde strategy in CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Simsek B, Kostantinis S, Karacsonyi J, **Alaswad K**, Krestyaninov O, Khelimskii D, Davies R, Rier J, Goktekin O, Gorgulu S, ElGuindy A, Chandwaney R, Patel M, Karmpaliotis D, Khatri J, Jaffer F, Poommipanit P, Rangan B, Sandoval Y, Elbarouni B, Nicholson W, Rinfret S, Koutouzis M, Tsiafoutis I, Yeh R, Burke MN, Allana S, and Brilakis E. TCT-113 Predicting the Risk of In-Hospital Major Adverse Cardiovascular Events in Chronic Total Occlusion Percutaneous Coronary Intervention: The PROGRESS-CTO MACE Score. *J Am Coll Cardiol* 2022; 80(12):B47. Full Text

Background: Estimating the risk of complications in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) facilitates risk-benefit assessment and procedural planning. Methods: We analyzed the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS-CTO; NCT02061436) and created a risk score for in-hospital major adverse cardiovascular events (MACE). Logistic regression prediction modeling was used to identify independently associated variables and the model was internally validated with bootstrapping. Results: Of the 10,480 CTO PCI cases performed between 2012-2022 at 40 US and non-US centers, in-hospital MACE occurred in 215 (2.05%). The final prediction model identified 5 independent predictors of MACE: age ≥65 years, odds ratio (OR) 1.57, 95% confidence interval (CI) 1.10-2.26, 1 point; female sex, OR 2.46, 95% CI 1.72-3.53, 2 points; moderate to severe calcification, OR 1.71, 95% CI 1.20-2.44, 1 point; Blunt stump, OR 1.63, 95% CI 1.14-2.33, 1 point; and Antegrade dissection re-entry, OR 2.21, 95% CI 1.32-3.72, 1 point; and retrograde strategy,

OR 2.86, 95% CI 1.94-4.22, 2 points; with a bootstrap corrected c-statistic of 0.72, 95% CI 0.68-0.76. The calculated risk percentages for MACE based on the PROGRESS-CTO MACE score ranged from 0.4% to 9.4% for MACE; 42% of patients had PROGRESS-CTO MACE score of 2-3, corresponding to a MACE risk of 1.1%-2.0% (Figure). [Formula presented] Conclusion: The PROGRESS-CTO in-hospital MACE risk score can facilitate risk-benefit assessment and procedural planning in patients undergoing CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Simsek B, Kostantinis S, Karacsonyi J, **Alaswad K**, Krestyaninov O, Khelimskii D, Davies R, Rier J, Goktekin O, Gorgulu S, ElGuindy A, Chandwaney R, Patel M, Karmpaliotis D, Khatri J, Jaffer F, Poommipanit P, Rangan B, Sandoval Y, Elbarouni B, Nicholson W, Rinfret S, Koutouzis M, Tsiafoutis I, Yeh R, Burke MN, Allana S, Mastrodemos O, and Brilakis E. TCT-171 Predicting the Risk of Perforation Requiring Pericardiocentesis in Chronic Total Occlusion Percutaneous Coronary Intervention: The PROGRESS-CTO Pericardiocentesis Score. *J Am Coll Cardiol* 2022; 80(12):B69. Full Text

Background: Estimating the risk for complications facilitates risk-benefit assessment and procedural planning in chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We analyzed the PROGRESS-CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention; NCT02061436) and created a risk score for pericardiocentesis. Patients with histories of coronary artery bypass graft surgery were excluded. Logistic regression prediction modeling was used to identify independently associated variables, and the model was internally validated with bootstrapping. Results: Of the 7,672 CTO PCI cases performed between 2012 and 2022 at 40 centers, 83 (1.1%) required pericardiocentesis. The final prediction model identified predictors of pericardiocentesis: age ≥ 65 years (OR: 2.10; 95% CI: 1.27-3.46), 1 point; female sex (OR: 2.25; 95% CI: 1.39-3.63), 1 point; moderate to severe calcification (OR: 3.28; 95% CI: 1.96-5.49), 1 point; antegrade dissection re-entry (OR: 2.83, 95% CI: 1.45-5.51), 1 point; and retrograde strategy (OR: 3.50; 95% CI: 2.08-5.87), 2 points; with a bootstrap corrected C statistic of 0.78 (95% CI: 0.72-0.83). The calculated risk percentages for pericardiocentesis on the basis of the PROGRESS-CTO mortality score ranged from 0.18% to 8.74% for pericardiocentesis, and 55% of patients had PROGRESS-CTO pericardiocentesis scores of 1 or 2, corresponding to a pericardiocentesis risk of 0.4% to 1.6% (Figure 1). [Formula presented] Conclusions: The PROGRESS-CTO pericardiocentesis risk score can facilitate risk-benefit assessment and procedural planning in patients undergoing CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Dermatology

Bibeau K, Harris JE, **Hamzavi IH**, Lindley A, LaFiura C, and Ezzedine K. 34631 Do patients with vitiligo and health care professionals treating them recognize the burden in living with the disease in the United States? Findings from the VALIANT study. *J Am Acad Dermatol* 2022; 87(3):AB159. Full Text

Vitiligo is a chronic autoimmune disease characterized by the destruction of melanocytes, resulting in pale or white patches of skin. The population-based Vitiligo and Life Impact Among International Communities (VALIANT) study sought to understand the impact and burden of vitiligo on quality of life (QoL) from the patient and physician perspective from around the world. The VALIANT study recruited adult participants (aged ≥18 years who self-reported a vitiligo diagnosis) via an online panel. Participants were asked questions regarding their mental health, psychosocial burden, and behavior in professional and social situations. Separately, health care professionals (HCPs; physicians, nurse practitioners, or physician assistants) who treat patients with vitiligo completed an online-based questionnaire. In the United States, 608 patients and 250 HCPs (166 dermatologists and 84 primary care providers) participated in the survey. Confidence in the ability to improve QoL and long-term psychological outcomes of their patients with vitiligo was noted in 67% and 58% of HCPs, respectively. HCPs and patients were asked the same questions regarding avoidance/impact behaviors; concordance was achieved on items such as wearing certain clothing to cover vitiligo lesions and avoiding going to beach/pool/social events. However, HCPs often underestimated the impact of vitiligo compared with the patient's perspective in other areas, such as making career choices (33% vs 51%), managing other medical diseases (25% vs 49%), and obtaining other preventive care (20% vs 49%). In summary, increased understanding between

HCPs and patients with vitiligo regarding a holistic understanding of the psychological burden and mental health of patients is needed.

Dermatology
Boothby-Shoemaker W, **Jones B**, **Guan L**, and **Friedman B**. Clinical Outcomes Associated With Melanocytic Lesions Assessed Via Ancillary Gene Expression Profiling (GEP). *Am J Dermatopathol* 2022; 44:S6. Full Text

W. Boothby-Shoemaker, Henry Ford Hospital, United States

Aims/Objectives: Compare GEP assay prediction of 434 melanocytic lesions with dermatopathologist interpretation. Methods: Sensitivity and specificity of assay were calculated based on disagreement of assay prediction with dermatopathologist interpretation. Histologic features were recorded in disagreeing cases. Results: Eighty-five percent of lesions (369/434) had sufficient RNA for scoring. 74.2% 274/369 lesions were classified as “benign”, 11.9% (44/369) “indeterminate”, and 13.8% (51/369) “malignant”. 38/51 of lesions rendered “malignant” by dermatopathologists were classified “malignant” by assay (sensitivity = 74.5%). Lesions rendered by assay as “benign” but “malignant” by dermatopathologists were more likely to have rarer cytologic features. (13/51) lesions rendered “malignant” by dermatopathologists were classified by assay as “benign,” (4/13) or “indeterminate” (9/13). 270/318 lesions rendered “benign” by dermatopathologists were “benign” by assay (specificity = 84.9%). Of 44/369 “indeterminate” lesions, dermatopathologists rendered 9/44.

Dermatology
Buechler CR, **Sagher E**, and **Tisack A**. 32388 Demographic and socioeconomic factors drive disparate outcomes in mycosis fungoides. *J Am Acad Dermatol* 2022; 87(3):AB38. Full Text

Background: Mycosis fungoides (MF) occurs more frequently in young Black patients, though debate persists as to whether this group is at uniformly increased risk of poorer outcomes. Recent studies have postulated that outcomes among Black patients are heterogeneous, though previous literature suggests that demographics may play a role in MF. Methods: Clinicopathologic, sociodemographic, and follow-up data were analyzed for patients with MF at Henry Ford Health Systems in Detroit, MI, over 19 years. Data were analyzed for factors predicting progression-free survival (PFS) via multivariable stepwise Cox proportional hazards regression models and Kaplan-Meier analysis of intersectional demographic groups based on age at diagnosis (<40 or ≥40), race, and sex. Results: Of the 440 patients, a majority (52.7%) were male, and the most common race/ethnicity was White/Caucasian (50.2%), followed by Black/African American (40%). Medicaid insurance was an independent predictor of shortened PFS (HR 3.13, 95% CI 1.46-6.69) regardless of race, and young Black patients had the shortest PFS, with young Black female patients experiencing shorter PFS than their older Black female (P =.027) and younger Black male (P =.014) counterparts. Conclusions: This study provides the strongest evidence to date that demographic and socioeconomic factors should be a part of the prognostic picture in MF. Their predictive value is likely based on societal and additional health-related variables, such as access to care/medication, health literacy, and bias in a provider or health system. It is our hope that this analysis will spur continued discussion as to the cause and effect of such differences in MF outcomes.

Dermatology
Ceresnie MS, **Kohli I**, **Friedman BJ**, **Lim HW**, and **Hamzavi IH**. 32329 Assessing the utility of Fontana-Masson and MART-1 stains in evaluating skin pigmentary changes induced by ultraviolet radiation and visible light. *J Am Acad Dermatol* 2022; 87(3):AB142. Full Text

One of the observed effects of ultraviolet radiation (UVR) and visible light (VL) on melanocompetent skin is increased pigmentation, also known as skin darkening or tanning. Many methods are used to measure skin pigment, including the Fontana-Masson stain (FMS) and MART-1 immunostain, which histologically highlight melanin and melanocyte density, respectively. While these approaches may be adequate in assessing baseline skin pigment among individuals of different races and phototypes, detecting the skin darkening induced by UVR and VL within the same individual is a challenge, especially in darker skin phototypes. We conducted a literature search and analyzed 16 articles comparing skin pigmentation

changes induced by VL and UVR to their corresponding FMS and MART-1 results. Notably, significant skin darkening could be detected by diffuse reflectance spectroscopy after irradiation in skin phototypes III-VI, but FMS and MART-1 were unable to significantly differentiate these changes and reliably enumerate them within the same studies. Outcome measurements of FMS and MART-1 may be affected by several factors across studies, such as varying spectrums of radiation, radiation doses, skin phototypes, and subjectivity of the rater. Our results indicate that objective instrumental assessments, such as spectroscopy, are likely superior to FMS and MART-1 for measuring skin pigmentary changes induced by UVR and VL. Further research is recommended to investigate the value in performing FMS and MART-1 stains in future studies evaluating skin tanning from UVR and VL.

Dermatology

Eichenfield LF, **Stein Gold LF**, Chiesa Fuxench ZC, Venturanza ME, Ren H, and Brar KK. 34794 Long-term safety and disease control of ruxolitinib cream among Black or African American patients with atopic dermatitis: Pooled results from 2 phase 3 studies. *J Am Acad Dermatol* 2022; 87(3):AB180. Full Text

Atopic dermatitis (AD) is an inflammatory skin disease with a prevalence in the United States of approximately 20%/5%–10% in Black or African American children/adults. In 2 phase 3 studies (TRuE-AD1/TRuE-AD2), 1249 patients (≥12 years old, Investigator's Global Assessment [IGA] score 2/3, 3%–20% affected body surface area [BSA]) were randomized (2:2:1) to twice-daily 0.75% ruxolitinib (Janus kinase [JAK] 1/JAK2 inhibitor) cream, 1.5% ruxolitinib cream, or vehicle for an 8-week, double-blind vehicle-controlled period, followed by a double-blind long-term safety period (LTS; as-needed treatment; assessments every 4 weeks) up to Week 52. Patients initially randomized to ruxolitinib remained on their regimen during the LTS; patients initially on vehicle were rerandomized to either ruxolitinib strength. During the LTS, patients treated areas with active AD only, stopped treatment 3 days after lesion clearance, and restarted treatment at recurrence. Among self-identifying Black or African American patients in the 0.75%/1.5% ruxolitinib groups for the full study in this pooled analysis (n = 91/n = 97), 53.8%/61.9% achieved clear/almost clear skin (IGA 0/1) at Week 8. From Week 12–52, 55.2%–73.3%/59.3%–78.7% of patients (range) achieved IGA 0/1. Mean affected BSA was 8.6%/8.3% at baseline, 3.8%/3.6% at Week 8, and 1.7%–3.3%/1.3%–2.5% (range of mean values) through Week 52. Over 52 weeks, treatment-emergent adverse events were reported in 59.3%/56.7% of patients; treatment-related adverse events were reported in 4.4%/6.2%. Incidence of application site reactions was low. In summary, the majority of Black or African American patients achieved clear/almost clear skin using ruxolitinib cream monotherapy, which was well tolerated.

Dermatology

Enescu C, **Patel A**, and **Friedman BJ**. 33714 Palisaded neutrophilic and granulomatous dermatitis in the setting of SRSF2-mutated chronic myelomonocytic leukemia: Case report and review of the literature. *J Am Acad Dermatol* 2022; 87(3):AB189. Full Text

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a rare cutaneous histopathologic reaction pattern associated with several underlying disorders. Few cases of PNGD have been associated with hematologic malignancies, in particular with chronic myelomonocytic leukemia (CMML), a malignant hematopoietic disorder with features of myeloproliferative neoplasm and myelodysplastic syndrome. CMML is characterized by peripheral blood monocytosis and bone marrow dysplasia, and can be supported by an acquired clonal cytogenetic abnormality most commonly in TET2, SRSF2, ASXL1, RUNX1, NRAS, and CBL. We present a patient with a papulosquamous rash on the neck, chest, and shoulders with histomorphological features on the spectrum of PNGD. Subsequent lab workup demonstrated a persistent mild monocytosis, raising concern for CMML. The patient was referred to hematology-oncology for a bone marrow biopsy, which ultimately led to her diagnosis. Cytogenic studies of the bone marrow biopsy demonstrated mutations in SRSF2, IDH2, and ASXL1, which were strongly supportive of this diagnosis. After discussion at a multidisciplinary tumor board, treatment directed at the skin eruption alone was recommended. She was started on prednisone taper and demonstrated marked clinical improvement. PNGD in the context of CMML has been scarcely reported, with only 4 prior reports in the literature. Our patient is the fifth reported case, and the fourth case with confirmed underlying SRSF2 mutation. This is likely a novel and reproducible clinical-histopathologic-molecular subtype of reactive granulomatous disease. The findings in this case strengthen the previously made association

between PNGD and SRSF2-mutated CMML, and may help better define a unique recognizable subtype for dermatopathologists.

Dermatology
Gold LS, Alonso-Llamazares J, and Zeichner J. 34039 Maintenance of skin clearance in a long-term open-label study of fixed-combination halobetasol propionate and tazarotene lotion for psoriasis in participants with prior use of topical treatments. *J Am Acad Dermatol* 2022; 87(3):AB79. Full Text

Background: Most patients with psoriasis are dissatisfied with their current treatment, primarily because of limited effectiveness. This post hoc subgroup analysis evaluated long-term efficacy and safety of fixed-combination halobetasol propionate (0.01%) and tazarotene (0.045%) lotion (HP/TAZ) in participants with use of topical corticosteroid (TCS; 137/550 [24.9%]) or other antipsoriatic topical medications (51/550 [9.3%]) before entry in an open-label study of HP/TAZ (NCT02462083). Methods: Participants in the open-label study received HP/TAZ once daily. At week 8, participants who achieved treatment success (investigator's global assessment [IGA] score of 0 or 1) stopped treatment and were reevaluated monthly through 52 weeks; those who did not achieve treatment success continued HP/TAZ. Twenty-four continuous weeks of treatment were allowed if participants achieved ≥1-grade improvement in IGA from baseline at week 12, with monthly reevaluation. If at any point the condition intensified to IGA ≥2, HP/TAZ was resumed, otherwise, HP/TAZ was discontinued. Results: From weeks 8 to 52, similar treatment success rates were achieved by participants with prior use of TCS (range, 20.0%-40.0%) or other topicals (range, 21.1%-53.8%). Mean affected body surface area at baseline was 5.7% and 5.5%, respectively, and decreased to 3.8% and 2.4%, respectively, at week 52. Percentage of participants who maintained disease control for 29 to 85 days after HP/TAZ cessation was comparable. Rates of adverse events were similar between groups. Conclusions: Regardless of the type of previous topical therapy, participants with prior use of topical medications maintained skin clearance with HP/TAZ over 52 weeks.

Dermatology
Gold LS, Bagel J, Del Rosso J, Green LJ, Lebwohl M, Kircik LH, Feng A, Snyder S, Higham RC, Burnett P, and Berk DR. 33463 Pooled efficacy and safety results from the DERMIS-1 and DERMIS-2 phase 3 trials of once-daily roflumilast cream 0.3% by baseline body surface area. *J Am Acad Dermatol* 2022; 87(3):AB192. Full Text

Roflumilast cream 0.3% is a selective and potent phosphodiesterase-4 inhibitor under investigation as a once-daily treatment for psoriasis. Here we describe pooled efficacy and safety results from 2 identical phase 3 randomized controlled trials of roflumilast cream (DERMIS-1: NCT04211363 and DERMIS-2: NCT04211389) analyzed by baseline body surface area (BSA) affected (10%). Patients (≥2 years) with psoriasis involving 2-20% BSA were randomized to roflumilast (n = 576) or vehicle (n = 305) for 8 weeks. Overall, significantly more roflumilast- vs. vehicle-treated patients achieved the primary efficacy endpoint of Investigator Global Assessment (IGA) Success (Clear or Almost Clear IGA status plus ≥2-grade improvement from baseline) at Week 8 (39.9% vs. 6.5%; P <.0001). More roflumilast-treated patients achieved IGA Success at Week 8 with generally consistent rates (36.5%-46.7% with roflumilast vs. 1.8%-8.5% with vehicle) across all BSA categories (P <.0001 for all). Differences favoring roflumilast were also observed for percentages achieving 75% reduction in Psoriasis Area Severity Index (38.1%-47.8% with roflumilast vs. 1.8%-9.4% with vehicle) across all BSA categories. Percentages with baseline Worst Itch-Numeric Rating Scale ≥4 achieving a 4-point reduction favored roflumilast (P ≤.0001 for all BSA subgroups). Overall incidence of treatment-emergent adverse events (TEAE), serious adverse events, and TEAEs leading to discontinuation were low with similar rates between roflumilast and vehicle. Local tolerability was highly favorable on patient and investigator assessments. Once-daily roflumilast cream 0.3% provided superior improvement across multiple efficacy endpoints and favorable safety and tolerability in patients with psoriasis in 2 phase 3 trials regardless of BSA affected.

Dermatology
Gold LS, Ehst B, Ferris LK, Brown PM, Rubenstein DS, Tallman AM, and Bagel J. 34613 Tapinarof cream 1% once daily (QD) for plaque psoriasis: Secondary efficacy outcomes from a long-term extension (LTE) trial. *J Am Acad Dermatol* 2022; 87(3):AB208. Full Text

Background: Tapinarof cream 1% QD was efficacious and well tolerated versus vehicle in adults with mild-to-severe plaque psoriasis in 2 double-blind 12-week Phase 3 trials (PSOARING 1&2). We report secondary efficacy from PSOARING 3, the LTE trial assessing tapinarof during intermittent treatment based on Physician Global Assessment (PGA) score. Methods: Eligible PSOARING 1&2 completers could enroll for 40-weeks' open-label tapinarof 1% QD and 4-weeks' follow-up in PSOARING 3. Patients entering with PGA ≥1 were treated until PGA = 0. Patients entering with/achieving PGA = 0 discontinued tapinarof until PGA ≥2, then retreated until PGA = 0. Results: 91.6% (n = 763) eligible patients enrolled in PSOARING 3. Efficacy improved beyond 12-week pivotal trials and was maintained over time. In PSOARING 1&2, overall mean baseline body surface area (BSA) affected was 7.6–7.9% and Psoriasis Area Severity Index (PASI) was 8.87–9.12. PSOARING 3 baseline mean BSA affected was 4.7% (3.3% and 7.3% previously treated with tapinarof and vehicle, respectively) and mean PASI was 4.76 (3.28 and 7.69 tapinarof and vehicle, respectively). At week 40, significant improvements beyond pivotal trials were observed: overall mean improvement from baseline in BSA affected was –2.0%; PASI75 and PASI90 responses were 29.4% and 17.5%, respectively (beyond the PASI75 of 36.1% and 47.6%; PASI90 of 18.8% and 20.9% in PSOARING 1&2, respectively). No new safety signals were observed. Conclusion: Continued improvements beyond 12 weeks and durable responses/no tachyphylaxis were observed across secondary efficacy outcomes which, together with previously reported high rates of complete disease clearance (PGA = 0) and ~4-month remittive effect off-therapy, differentiate tapinarof from other topical therapies.

Dermatology

Gold LS, Friedman AJ, and Brar K. 33731 Use of digital resource centers for atopic dermatitis patients, caregivers, and health care professionals to improve shared decision-making and proactive management. *J Am Acad Dermatol* 2022; 87(3):AB126. Full Text

Overview: To close gaps in atopic dermatitis (AD) care, we developed and analyzed aligned resource centers for patients/caregivers and health care professionals (HCPs). Methods: The patient resource center was designed to support patients/caregivers in being more proactive in their AD care. The HCP-targeted resource center aimed to increase their awareness of AD patient perspectives and improve communication. Surveys were completed by users of both resource centers. Results: Of the 1014 HCPs, 22% were physicians (30% specialists), 19% were nurse practitioners/physician assistants, 47% were nurses, and 12% were pharmacists. Approximately one-half of 801 patients (98% adults) reported that they only treat their AD when experiencing a flare, and only 30% were very satisfied with their care. Only 56% indicated that they make all decisions with their HCP, and only 22% of HCPs reported that they always involve their AD patients/caregivers in shared decision-making. Only 21% of patients always share preferences, goals, or concerns about AD with their HCP, and only 6% of HCPs rated their ability to ask about and understand the impact of AD on patients' quality of life as "very good." Actions that patients planned to take included proactive skin care, asking their HCP about additional treatment options, and telling their HCP about the impact of AD on their quality of life. Nearly 60% of 764 HCPs planned to educate AD patients/caregivers about treatment options and expectations. Conclusions: These results highlight communication gaps between AD patients/caregivers and HCPs. Insights from these data can be used to improve shared decision-making.

Dermatology

Gold LS, Kircik LH, Care PPS, and Tanghetti EA. 32970 Efficacy and safety of a fixed-dose clindamycin 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% gel for moderate-to-severe acne: Randomized phase 2 and phase 3 studies of the first triple-combination drug. *J Am Acad Dermatol* 2022; 87(3):AB50. Full Text

A 3-pronged approach to acne treatment—combining an antibiotic, antibacterial, and retinoid—may provide greater efficacy and tolerability than single/double treatments while potentially reducing antibiotic resistance and increasing patient compliance. Clindamycin 1.2%/BPO 3.1%/adapalene 0.15% (IDP-126) gel is the first triple-combination, fixed-dose topical acne product in development that addresses the major pathophysiological abnormalities in acne patients. A phase 2 (N = 741) and two phase 3 (N = 183; N = 180), double-blind, randomized, 12-week studies enrolled participants aged ≥9 years with moderate-to-severe acne. Participants were randomized to receive once-daily IDP-126 or vehicle; the phase 2 study

included 3 additional randomization arms containing dyad gels: BPO/adapalene; clindamycin phosphate/BPO; and clindamycin phosphate/adapalene (data not shown). Endpoints included participants achieving ≥2-grade reduction from baseline in Evaluator's Global Severity Score and clear/almost clear skin (treatment success) and least-squares mean percent change from baseline in inflammatory and noninflammatory lesion counts. Treatment-emergent adverse events (TEAEs) were also assessed. In all 3 studies at week 12, half of participants achieved treatment success with IDP-126 (phase 2: 52.5%; phase 3: 49.6%, 50.5%) versus less than one-fourth with vehicle (8.1%; 24.9%, 20.5%; P <.01, all). IDP-126 resulted in >70% reductions in inflammatory and noninflammatory lesions at week 12, significantly greater than vehicle (range: inflammatory, 75.7%-80.1% vs 50.4%-59.6%; noninflammatory, 71.0%-73.3% vs 45.8%-49.0%; P <.001, all). Most TEAEs were of mild-moderate severity, and <4% of IDP-126-treated participants discontinued study/treatment due to AEs. The innovative fixed-dose, triple-combination IDP-126 gel was efficacious and well tolerated in three clinical studies of children, adolescents, and adults with moderate-to-severe acne.

Dermatology
Gold LS, Papp K, Pariser D, Sofen H, Chen M, Cheng S, Picard H, Klyachkin Y, and Green L. 33354 Efficacy of apremilast in patients with mild to moderate psoriasis assessed by the physician global assessment and body surface area composite tool: Post hoc analysis from ADVANCE. *J Am Acad Dermatol* 2022; 87(3):AB162. Full Text

Background: In ADVANCE (NCT03721172), apremilast 30 mg BID (APR) demonstrated significantly greater sPGA response vs. PBO at Week 16 (22% vs. 4%; P <.0001) in patients with mild-to-moderate psoriasis. The Physician Global Assessment and Body Surface Area Composite Tool (PGA × BSA) is a simple, sensitive measure of psoriasis severity for patients with BSA<10%. We performed a post hoc analysis of the efficacy results from ADVANCE using the PGA×BSA. Methods: This current post hoc analysis included all randomized patients. Missing data were imputed by multiple imputation. PGAxBSA-50/75/90 was 50%, 75% and 90% improvement in PGAxBSA from baseline. Results: Of 595 randomized patients (APR: 297; PBO: 298), baseline characteristics were similar for mean BSA (APR: 6.4; PBO: 6.3), sPGA score 2 (APR 31%; PBO: 31%), sPGA score 3 (APR: 69%; PBO: 70%), and mean PGA×BSA (APR: 17.6; PBO: 17.5). At Week 16, significantly more patients achieved PGAxBSA-50/75/90 response with APR vs. PBO: PGA×BSA-50, 67% vs. 26% (P <.0001), difference 41%, 95%CI (32.7,48.5) PGA×BSA-75, 46% vs. 13% (P <.0001), difference 33%, 95%CI (25.8,40.2) PGA×BSA-90, 27% vs. 3% (P <.0001), difference 24%, 95%CI (18.3,29.6) A significant improvement from baseline at Week 16 in PGA×BSA was observed with APR vs PBO: Mean % change (SE) in PGA×BSA, -51.8 (4.2) vs. 1.97 (4.3); difference (95%CI): -53.8 (-65.4, -42.2), P <.0001. Conclusions: The PGA×BSA Composite Tool appeared to be a sensitive and a relevant measure for mild-to-moderate psoriasis that showed significantly greater treatment differences at 50%, 75%, and 90% response thresholds at Week 16 with APR compared with PBO in ADVANCE.

Dermatology
Gold LS, Shi V, Vlahos B, Sanders P, Zang CB, and Cha A. Impact of crisaborole in patients with mild-to-moderate atopic dermatitis who received prior treatment. *Br J Dermatol* 2022; 187(3):E118-E119. Full Text

Dermatology
Gold LS, Tuttle E, Cheng WY, Chang R, Nguyen C, Yu LH, Bouloc A, Klyachkin Y, Nazareth T, and Jullien D. 33356 A multinational chart review to examine gastrointestinal symptoms and their management in patients treated with apremilast for plaque psoriasis. *J Am Acad Dermatol* 2022; 87(3):AB131. Full Text

Background: Diarrhea and nausea are the most common adverse events observed in phase 3 clinical trials and real-world studies of apremilast, an oral phosphodiesterase-4 inhibitor indicated for moderate-to-severe plaque psoriasis. Methods: A retrospective chart review was conducted between June and November 2020 in the United States (US) and France among patients with moderate psoriasis experiencing gastrointestinal (GI) symptoms within 3 months of initiating apremilast. Results: Dermatologists in US (200) and in France (52) abstracted patient charts (US: 494, France: 128). The

following GI symptoms were reported: –diarrhea (US: 67% [331/494]; France: 76% [97/128]) with median time from onset to resolution/improvement of 26 days (US) and 21 days (France) –nausea (US: 52% [255/494]; France: 34% [44/128]) with median time from onset to resolution/improvement of 21 days (US) and 24 days (France). Management strategies for diarrhea included pharmacologic (loperamide/bismuth subsalicylate/racecadotril) with or without nonpharmacologic (dietary modifications, taking with food)/fiber (US: 30% [99/331], France: 41% [40/97]) and nonpharmacologic only (US: 32% [105/331], France: 27% [26/97]). Management strategies for nausea included pharmacologic (diphenhydramine/metoclopramide/metopimazine) with or without nonpharmacologic (dietary modifications, taking with food, avoidance of vigorous activity) (US: 5% [14/255], France: 30% [13/44]) and nonpharmacologic only (US: 58% [147/255], France: 36% [16/44]). Resolution/improvement of GI symptoms was observed in patients who used pharmacologic strategies and nonpharmacologic strategies. Conclusions: Recommendations to manage diarrhea and nausea after apremilast initiation with pharmacologic or non-pharmacologic strategies were effective and symptoms usually resolved within 3-4 weeks of onset.

Dermatology
Hamzavi IH. Updates on the hidradenitis suppurativa from the USA. *Exp Dermatol* 2022; 31:58-59. Full Text

Dermatology
Harris JE, Bibeau K, **Hamzavi IH**, Grimes P, Lindley A, LaFiura C, and Ezzedine K. 34612 Exploring the natural history of vitiligo in the United States: Findings from the VALIANT study. *J Am Acad Dermatol* 2022; 87(3):AB167. Full Text

Vitiligo is a chronic autoimmune disease characterized by the destruction of melanocytes, resulting in depigmented skin lesions. Epidemiology studies in vitiligo are often limited to smaller sample sizes and rely on dermatology clinics as the source population. The population-based Vitiligo and Life Impact Among International Communities (VALIANT) study sought to understand the natural history of vitiligo among patients around the world. Here, data from US participants are presented. Participants were recruited via an online panel. Adults (aged ≥18 years) who self-reported a vitiligo diagnosis by a health care professional were eligible to participate. Of 608 US patients, 58% were male; median (range) age at the time of the survey was 36 (18–83) years. Mean disease duration was 11 years, with a mean 1.6 years between first noticing lesions and achieving a formal diagnosis. More than one-third of patients were previously misdiagnosed (37%), with higher rates among patients with darker skin types (67% for Fitzpatrick types IV–VI). Nearly two-thirds (62%) directly sought treatment for vitiligo; vitligo was an incidental finding in the remaining 38%. Nearly two-thirds (64%) were diagnosed by a dermatologist, or a nurse practitioner or physician assistant in a dermatology-focused practice. Most patients (71%) noted a family history of vitiligo (comparable paternal vs maternal). Median body surface area affected by vitiligo was 4.23%, as measured by the self-assessed Vitiligo Extent Scale. In summary, these findings provide a new perspective on the diagnosis journey for patients with vitiligo and highlight the need for accurate, more timely diagnosis.

Dermatology
Jones B, **Veenstra J**, and **Ozog D**. 35224 Identifying a correlation between preceding trauma and development of dermatofibrosarcoma protuberans: A review of the literature. *J Am Acad Dermatol* 2022; 87(3):AB65. Full Text

Background: Dermatofibrosarcoma protuberans (DFSP) is a malignant fibrohistiocytic neoplasm that is slow-growing, has low metastatic potential, and is locally infiltrative with a predisposition for recurrence. The development of DFSP can occur spontaneously, but anecdotal evidence suggests a correlation between preceding injury and tumor onset. Methods: A comprehensive literature search was performed using PubMed, Embase, and web of science for articles with unambiguous reporting of DFSP with a history of physical trauma. Of 139 identified articles, 23 (17%) met criteria and were analyzed. Results: In total, 52 patients were reported as having had some form of physical trauma prior to DFSP development, and of these, sex was reported for half (40% men; 60% women). The mean (standard deviation) age at time of diagnosis was 42 (14) years, and lesions ranged from 1 to 20 cm. Involved locations included the

trunk (62%), lower extremities (19%), upper extremities (12%), and head/neck (8%). The median (range) time between injury and self-reported lesion was 10 (1-19) years, while the median (range) time between injury and DFSP diagnosis was 10 (2-41) years. Types of injuries reported included tattoos (most common), vaccinations/injections, burns, surgeries, radiation, insect bites, and various levels of minor to blunt force. Discussion: A subset of DFSP cases arise in the setting of prior cutaneous trauma, which may play a role in their pathogenesis. Recognition of this possibility is important to avoid misdiagnosis (i.e., hypertrophic scar or keloid) or delay in diagnosis.

Dermatology

Ko D, **Hengy M**, and **McHargue C**. 34441 Keratoderma blenorrhagicum and balanitis circinata: Indicators of reactive arthritis. *J Am Acad Dermatol* 2022; 87(3):AB178. Full Text

A 25-year-old healthy man was admitted with a 3-month history of joint pains in his feet and right knee, leading to difficulty ambulating. The patient had been previously treated without a definitive diagnosis, with NSAIDs and systemic steroids, without improvement. He also endorsed a 3-week history of an extensive, diffuse rash with significant involvement of the palms, soles, and genitals. He denied involvement in the oral mucosa or conjunctiva. Lesions were tender—the plantar lesions contributing significantly to painful ambulation. The physical examination was notable for hyperkeratotic scaly purpuric papules and plaques on the soles and between the toes, hyperkeratotic ostraceous nodules on the arms, knees, trunk, and soles, and erythematous scaly plaque on the groin involving the penis. Right fourth finger PIP with swelling. Oral mucosa and conjunctiva were clear; nails were normal. Labs were notable for leukocytosis and elevated inflammatory markers; the urine was positive for chlamydia trachomatis, negative for gonorrhea and HIV, syphilis, ANA, RF was negative while HLA-B27 positive. The diagnosis of reactive arthritis was made and treatment with indomethacin, doxycycline, and prednisone resulted in mild improvement during his hospitalization. This case represents the classic presentation of reactive arthritis with keratoderma blenorrhagicum and balanitis circinata with chlamydia trachomatis infection. Keratoderma blenorrhagicum is characteristic of reactive arthritis, although occurring in only 10% of patients. In patients with palmoplantar keratoderma or otherwise typically appearing psoriasis and psoriatic arthritis, it is important to consider the diagnosis of reactive arthritis and expand the history and physical to elucidate the diagnosis.

Dermatology

Konda S, **Shetty N**, and **Liu J**. 35360 Recalcitrant pediatric bullous erythema multiforme responsive to oral tofacitinib. *J Am Acad Dermatol* 2022; 87(3):AB102. Full Text

Patient history and physical: A 25-year-old African American female was admitted for painful oral erosions and widespread blistering lesions on the trunk and extremities which had been waxing and waning since age 12 years old. Disease flares requiring hospitalization had been continuing to occur multiple times annually in spite of numerous systemic immunosuppressive agents including chronic corticosteroids (resulting in Cushingoid features and insulin-dependent diabetes) in combination with cyclosporine, dapsone, tacrolimus, anakinra, rituximab, adalimumab, apremilast, mycophenolate mofetil, and intravenous immunoglobulin (IVIG) at various times. Adjunctive therapies including acyclovir and leuprolide had also proven ineffective. Physical examination revealed well-defined, targetoid macules with central vesiculation scattered upon all four extremities. Ill-defined, annular-appearing, hyperpigmented macules were observed on the trunk. Scattered, erythematous erosions were seen on the hard palate and buccal mucosa; in addition, the lips featured hemorrhagic crusts. Biopsies: Punch biopsies of lesions obtained from the left arm revealed a brisk lymphocytic infiltrate at the dermoepidermal junction with necrotic keratinocytes observed at all levels of the epidermis. Laboratory Data: Further work-up revealed negative PCR for EBV & CMV, negative ANA, negative HIV, negative Mycoplasma antibodies, and negative HSV-2 & HSV-2 antibodies. Diagnosis: Bullous erythema multiforme. Clinical Course and Treatment: Patient was transitioned to oral tofacitinib 5 mg twice daily with corresponding complete resolution of active lesions. Disease activity has remained quiescent for over two years, which represents the longest period of time without a disease flare since the patient's initial diagnosis during childhood.

Dermatology

Lyons AB, **Ozog DM**, **Lim HW**, **Viola K**, **Jones LR**, and **Tang A**. 31064 The Detroit Keloid Scale: A validated tool for rating keloids. *J Am Acad Dermatol* 2022; 87(3):AB210. Full Text

Background: No keloid-specific outcome measures exist. Objective: To develop and validate the Detroit Keloid Scale (DKS), a standardized method of keloid assessment to better compare treatments. Methods: Forty-seven physicians were polled to develop the DKS. The scale was validated in 52 patients with keloids against the Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS), and Dermatology Life Quality Index (DLQI) by 3 physicians. Results: The interrater reliability was “substantial” for observer component of the DKS and only “moderate” for the VSS and observer POSAS (ICC were 0.80, 0.60, and 0.47, respectively). Pearson’s correlation indicated a “moderate” association between the observer component of DKS with observer component of POSAS ($\rho = 0.56$, $P < .001$) and a “substantial” relationship between the observer component of DKS and VSS ($\rho = 0.63$, $P < .001$). Pearson’s correlation indicated a “moderate” association between the patient portion of DKS and patient portion of POSAS and the patient portion of the DKS and DLQI (0.61 and 0.60, respectively, $P < .05$). The DKS total score consistently showed “substantial” relationship with POSAS total score ($\rho = 0.65$, $P < .001$). Limitations: Single center study, no intrarater reliability analysis. Conclusions: The substantial interrater reliability of the DKS will allow for improved standardization in future keloid research.

Dermatology

Maghfour J, and **Olson J**. 35186 Exploring the association between frontal fibrosing alopecia sunscreen and moisturizers. *J Am Acad Dermatol* 2022; 87(3):AB59. Full Text

Frontal fibrosing alopecia (FFA) is an immune-mediated cicatricial alopecia. Skin care products including sunscreen were suggested to influence disease pathogenesis. Given the conflicting data, the aim of this study is to provide a quantitative summary on this topic. A systematic search surveying PubMed database was conducted in August 2021. The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed. The study was prospectively registered in Prospero (ID: 273840). The pooled effect size is presented as odds ratio (OR) with 95% confidence interval (CI). A total of 87 articles were identified; 9 articles were included. Using the Newcastle Ottawa scale (NOS), the quality of studies ranged from 5 to 7, suggestive of moderate quality. 1248 patients in the published literature had FFA (mean age: 58.9, 95.7% female) and were compared with 1459 control subjects (mean age: 56.9, 89.8% female). Six (66.67%) studies assessed the use of sunscreen and moisturizers 5 years before the onset of FFA. Nine studies evaluated the association between sunscreen and FFA (n = 9); the pooled OR was 1.45 95%CI [1.11-1.90], P =.0068. For the 8 studies exploring the relationship between facial moisturizers and FFA, the pooled OR was 1.26 (95% CI 1.10-1.43), P =.006. The results of this study suggest that both sunscreen and moisturizers likely increase the risk of FFA by 45% and 26% respectively. Due to lack of randomized controlled trials and small number of studies, the causality of this association could not be ascertained. As such, high-quality studies are needed.

Dermatology

Messenger N, **Artz CE**, and **Rambhatla PV**. 33396 Nonuremic calciphylaxis precipitated by COVID 19 infection. *J Am Acad Dermatol* 2022; 87(3):AB85. Full Text

A 40-year-old female with a medical history of hypertension, anxiety, and COVID-19 pneumonia in May 2021 that was complicated by cardiac arrest, presented in July 2021 with bilateral lower extremity wounds. Wounds initially were described as ‘sunburns’ that progressed to form multiple large retiform purpura with black necrotic eschars and surrounding induration on bilateral thighs and lower legs. A telescoping punch biopsy was performed showing calciphylaxis with intravascular thrombosis. Labs were significant for a mildly elevated phosphorus, PT/PTT, lupus anticoagulant antibody, and positive ANA. Creatinine, BUN, calcium, PTH, and GFR were within normal limits. Patient had no prior personal or family history of coagulopathies or renal dysfunction. The patient was diagnosed with nonuremic calciphylaxis (NUC) precipitated by a COVID-19 induced coagulopathy. Intravenous sodium thiosulfate and sevelamer was started for treatment. NUC is a rare disease characterized by arterial calcification leading to ischemia and skin necrosis that occurs in the setting of normal renal function. Other conditions associated with NUC include prothrombotic states like Protein C and S deficiency, antithrombin III

deficiency, antiphospholipid antibody, cryofibrogenemia, and malignancy. COVID-19 has been demonstrated to generate a prothrombotic state leading to hypercoagulability. The patient's recent COVID-19 infection and positive lupus anticoagulant antibody together promoted a hypercoagulable state that was the nidus for cutaneous calciphylaxis and making this case of NUC induced by COVID-19 hypercoagulability a novel presentation of an uncommon disease.

Dermatology
Novice T, Novice M, Svigos K, **Powers M**, and Lo Sicco K. 33778 The impact and implications of COVID-19 on using scalp cooling therapy for prevention of chemotherapy-induced alopecia. *J Am Acad Dermatol* 2022; 87(3):AB211. Full Text

Background: Scalp cooling therapy (SCT) is currently the most effective method to reduce chemotherapy-induced alopecia. Manual SCT requires a "capper" to change the caps throughout the infusion day whereas machine SCT only requires a 1-time cap fitting prior to infusion, usually performed by the health care staff. Coronavirus disease 2019 (COVID-19) brought restrictions on permitted infusion center visitors, which we hypothesized would include "cappers," creating an additional barrier to SCT use. Methods: A scripted call was placed during May 2021 by a study author to infusion centers of Commission on Cancer (CoC) accredited hospitals in Michigan, New York City (NYC) and major cities in Texas in order to investigate how COVID-19 impacted SCT at their institution. The University of Michigan's Institutional Review Board (IRB) deemed this study exempt from IRB approval. Results: Forty-one infusion centers were successfully contacted (40/62, 64.5%). Of the 33 that allow SCT, 41% (14) did not allow "cappers" under COVID-19 restrictions. Of the 13 institutions offering machine SCT, 92% (12/13) allowed patients to continue using the machines during the pandemic as it does not require an outside "capper." Conclusion: Our study demonstrates the negative impact of COVID-19 on manual SCT use. As COVID-19 is likely here for the foreseeable future, it is critical to find ways to safely use SCT during these times. Hence, hospital adoption of SCT machines is even more critical given the pandemic, particularly for those of lower socioeconomic status and without strong social support.

Dermatology
Oska S, Kennelly K, and Misra V. 34722 Nail-patella syndrome: An early dermatologic diagnosis. *J Am Acad Dermatol* 2022; 87(3):AB84. Full Text

Presentation: A 3-month-old female presented with congenital onychodystrophy of both upper extremities and unilateral postaxial polydactyly of her left lower extremity. Physical examination was remarkable for dorsal pterygium of both first fingers, triangular lunulae of the 2nd through 5th fingernails, and Type I postaxial polydactyly of 5th digit without evidence of synonychia. Nail-patella syndrome (NPS) was suspected. Course and therapy: At presentation, radiographs did not show evidence of hypoplastic patellae, elbow abnormalities, or iliac horns. Repeat imaging at 7 months of age suggested the presence of bilateral posterior iliac horns. Based on clinical suspicion, molecular genetic testing was sent. A heterozygous pathogenic variant in LMX1B (c.736C>T (p.Arg246*) was found, confirming a diagnosis of NPS. Discussion: NPS is a clinically variable disorder associated with congenital onychodystrophy, skeletal abnormalities including patellar aplasia or hypoplasia, elbow abnormalities, and pathognomonic iliac horns. Early identifications of NPS is important since almost half of affected individuals develop renal abnormalities including proteinuria, hematuria, nephrotic syndrome, that may progress to end-stage renal disease. Patient may also develop primary open-angle glaucoma and ocular hypertension at an early age. The nail changes, including the presence of the triangular lunulae, are among the earliest and most characteristic findings. This case highlights the role of dermatologists in recognizing these early clinical features to facilitate early multidisciplinary care.

Dermatology
Parashar K, **Torres AE**, and **Boothby-Shoemaker WT**. 32622 Imaging technologies for presurgical margin assessment of basal cell carcinoma. *J Am Acad Dermatol* 2022; 87(3):AB66. Full Text

Basal cell carcinoma (BCC) is the most common skin cancer worldwide. Mohs micrographic surgery is a highly used BCC treatment, involving staged resection of the tumor with complete histologic evaluation of the peripheral margins. A reduction in the number of Mohs stages would significantly improve care and

could result in substantial economic benefits, estimated at $36 million USD in savings per annum. Noninvasive imaging modalities can potentially streamline the surgical management of skin cancers by refining presurgical assessments of tumor size. We assessed the current imaging techniques in dermatology and their application for tumor margin assessment of BCCs prior to Mohs micrographic surgery. These include dermoscopy, photodynamic diagnosis (PDD), high-frequency ultrasound (HFUS), optical coherence tomography (OCT), reflectance confocal microscopy (RCM), and optical polarization imaging (OPI). Each technology is limited or strengthened by its resolution, depth, speed of imaging, field of view, maneuverability, and billing. RCM, and a combination of RCM with video mosaicking technique and OCT, appear to be promising imaging techniques in pre-surgical margin assessment because of the superior resolution of RCM and the enhanced depth of imaging of OCT. OPI is also favorable for margin assessment based on its field of view and maneuverability. Further research and efficacy studies are necessary before such techniques can be implemented widely. It is imperative that general dermatologists and Mohs surgeons alike are well informed regarding the existing technologies given the increasing incidence of skin cancer and the associated rising costs.

Dermatology

Ravi M, **Kwa M**, Babu K, and **Lim HW**. 32131 Updating the relative risk of ultraviolet exposure and melanoma in fair skin types: A systematic review. *J Am Acad Dermatol* 2022; 87(3):AB217. Full Text

In 2005, a meta-analysis found that varying types of UV exposure contributed to an increased relative risk of melanoma. Recently, a 2021 review failed to establish a similar link in individuals with skin of color. Within the last 2 decades, no studies have comprehensively reviewed the risk of varying types of UV exposure on melanoma in fair skin. Thus, we performed a systematic review from 2002-2021 analyzing UV exposure and melanoma risk in Fitzpatrick type I-IV individuals. Out of 12,263 studies, 26 met inclusion criteria. A majority showed an association with UV index (6/9), left-sided laterality (1/1), sunburn history (11/13), and outdoor leisure activity (3/3). UV index studies were all ecological and presented primarily positive correlations. For sunburn history, studies encompassed 2309 melanomas, and significant odds ratios (OR) ranged from 1.69 (1.00-2.98) to 8.48 (4.35-16.54) with higher odds ratios for increasing numbers of sunburns. For outdoor leisure correlating with prior definitions of intermittent sun exposure, studies encompassed 514 melanomas, and ORs ranged from 2.70 (1.04-6.80) to 4.18 (1.83-9.93). A positive association was found in 2 (n = 2/6) studies for cumulative or annual sun exposure, 2 (n = 2/5) studies with occupational sun exposure, 2 (n = 2/4) studies with sun vacations, and 0 (n = 0/2) studies with latitude. This study highlights the significant relationships between specific types of UV exposure and melanoma at higher rates than previously summarized due to an emphasis on fair skin types. Critically, there remains high heterogeneity in how UV exposure is captured that may contribute to mixed results.

Dermatology

Shetty N, **Konda S**, and **Veenstra J**. 35180 “Could I be allergic to my new hidradenitis suppurativa Medication?” Characterization of a cutaneous delayed-type drug hypersensitivity reaction to secukinumab. *J Am Acad Dermatol* 2022; 87(3):AB129. Full Text

Patient history and physical: A 32-year-old Asian-American female presented with widespread, pruritic, red papules involving the ears, trunk, and extremities for approximately 6 weeks’ duration. The lesions first developed several days after her second secukinumab injection, which was originally initiated for recalcitrant stage III hidradenitis suppurativa. Physical examination revealed numerous erythematous, scaly papules on the bilateral ears, upper chest, inframammary folds, bilateral upper extremities, and abdomen (including umbilicus). Large, well-demarcated, moist-appearing plaques were observed to involve the bilateral axillary folds symmetrically. Her vital signs were stable, and she denied recent facial swelling or urticaria. Pathology: A punch biopsy obtained from the right flank revealed psoriasiform epidermal hyperplasia with spongiosis, lymphocyte exocytosis, and serous crusting with ample neutrophils in the stratum corneum. A dense superficial perivascular and interstitial infiltrate of lymphocytes with numerous eosinophils was also observed. Periodic acid-Schiff stain was negative for fungal elements. Laboratory data: Bacterial swab revealed mixed skin flora. Diagnosis: A diagnosis of a cutaneous delayed-type drug hypersensitivity reaction to secukinumab was made. SDRIFE was also considered, however, our patient did not exhibit gluteal, perineal, or inguinal involvement. Clinical course

and treatment: Secukinumab was discontinued, and because the mean half-life ranges from 22 to 31 days, an 8-week prednisone taper was initiated with resolution of the rash. Following completion of the original taper, the patient experienced a mild recurrence of the original rash, which fully resolved without recurrence after an additional 4 weeks of prednisone. Ustekinumab was subsequently initiated for control of underlying hidradenitis suppurativa.

Dermatology
Silverberg JI, Thaci D, Seneschal J, **Gold LS**, Blauvelt A, Simpson E, Chu CY, Liu ZQT, Lima RG, Pillai S, and Guttman-Yassky E. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: results from two phase III, randomized, double-blinded, placebo-controlled trials. *Br J Dermatol* 2022; 187(3):E97-E98. Ful Text

Dermatology
Simpson EL, Bissonnette R, and **Stein Gold LF**. 34587 Efficacy of ruxolitinib cream for the treatment of atopic dermatitis by anatomic region: Pooled analysis from two randomized phase 3 studies. *J Am Acad Dermatol* 2022; 87(3):AB53. Full Text

Atopic dermatitis (AD) is a highly pruritic inflammatory skin disease. Two phase 3 studies (TRuE-AD1/TRuE-AD2) enrolled patients aged ≥12 years with AD for ≥2 years, an Investigator's Global Assessment (IGA) score of 2/3, and 3%–20% affected body surface area. Patients (total N = 1249; median age, 32 years) were randomized (2:2:1) to twice-daily 0.75% ruxolitinib (Janus kinase [JAK] 1/JAK2 inhibitor) cream, 1.5% ruxolitinib cream, or vehicle cream for 8 weeks of double-blind treatment, and thereafter continued in a long-term, 44-week period of the studies. In this pooled analysis, mean percentage change from baseline in Eczema Area and Severity Index (EASI) anatomic region subscores is reported up to Week 8 (n = 1208). For the head and neck region, patients applying 0.75%/1.5% ruxolitinib cream (vs vehicle) achieved mean improvements of 59.3%/55.8% (vs 13.4%), 70.4%/71.3% (vs 22.4%), and 70.0%/78.7% (vs 45.0%) at Weeks 2, 4, and 8, respectively (all P <.0001). Results were similar for the upper limbs region (48.5%/54.7% [vs 13.3%], 66.6%/70.3% [vs 25.0%], and 73.5%/74.9% [vs 35.1%] all P <.0001). For the trunk region, patients achieved mean improvements of 49.8%/60.0% (vs 12.1%), 67.3%/73.8% (vs 15.0%), and 72.7%/81.0% (vs 15.6%) at Weeks 2, 4, and 8, respectively (all P <.0001). Similar results were observed for the lower limbs region (46.0%/48.2% [vs 16.3%], 65.9%/66.2% [vs 13.9%], and 76.3%/74.9% [vs 39.8%]; all P <.0001). Ruxolitinib cream was well tolerated, with an adverse event profile similar to vehicle. In summary, ruxolitinib cream demonstrated significant improvements vs vehicle in patients with AD across anatomic regions as early as Week 2.

Dermatology
Wang R, and **Friedman BJ**. 33111 New onset scrotal lesions in a patient with herpes simplex virus treated with foscarnet. *J Am Acad Dermatol* 2022; 87(3):AB84. Full Text

Introduction: Intravenous (IV) foscarnet is used for the treatment of acyclovir-resistant herpes simplex virus (HSV). Foscarnet-induced penile ulcerations, thought to be due to an irritant contact dermatitis, can occur where urine contacts the skin, such as the glans penis adjacent to the urethral meatus. We present a gentleman who developed serpiginous papules on the scrotum from foscarnet therapy. Case Presentation: A 53-year-old African-American male with a history of HIV was admitted to the hospital for IV foscarnet treatment of HSV of the penile shaft recalcitrant to oral valacyclovir. Nine days after admission, the patient developed new onset burning and painful lesions on the scrotum. On physical examination, grouped serpiginous pink papules coalescing into a plaque on the left scrotum were noted. HSV PCR was negative. Skin biopsy demonstrated an erosive dermatitis with epidermal necrosis, supportive of an irritant contact dermatitis secondary to foscarnet. Subsequently, the patient did endorse urine coming into contact with his scrotum during urination. One week after stopping foscarnet, the scrotal lesions subsided without further treatment. Discussion: Penile ulcerations are a known but uncommonly encountered side effect of foscarnet therapy. Nearly 90% of a foscarnet dose is excreted in the urine, and it is thought that these ulcerations are due to an irritant contact dermatitis from urine. Scrotal lesions presenting as serpiginous papules have less commonly been reported. Foscarnet-induced irritant contact dermatitis should be considered in any patient on foscarnet presenting with new onset lesions in the groin.

Dermatology

Wong N, **Pantelic MN**, and **Kwa M**. 34745 US and EU sunscreens: A review of ultraviolet (UV) filters and safety data. *J Am Acad Dermatol* 2022; 87(3):AB6. Full Text

A broad range of UV filters are available for use in sunscreen products. Knowledge of UV filters available both domestically and abroad remains important, since these products can be found in the online marketplace and may be included in future FDA monographs as a shift is made to an administrative order process. We reviewed the mechanism and safety data of all US and EU approved UV filters. Currently, there are 17 US FDA approved UV filters while the EU possesses an additional 16 UV filters. Of the US filters, 88.2% (15/17) are organic and 11.8% (2/17) are inorganic filters, with 35.3% (6/17) broad-spectrum, 52.9% (9/17) UVB only, and 11.8% (2/17) UVA only. Notably, 94.1% (16/17) have available human data. Of the EU exclusive filters, all (100%, 16/16) are organic filters. 50% (8/16) have human data while the remaining 50% (8/16) have data primarily related to physiochemical or toxicology profiles. Of these EU exclusive UV filters, 43.75% (7/16) are broad-spectrum, 50% (8/16) cover UVB only, and 6.25% (1/16) cover UVA only. Our review demonstrates that the EU possesses an exciting pool of novel UV filters with expanded options for coverage of all forms of UV radiation. Critically, the majority of sunscreens, both in the US and EU, have limited human data available due to prior limited requirements for such information. This information is likely forthcoming in the US as the FDA updates data requirement guidelines for sunscreens to be generally recognized as safe and effective.

Diagnostic Radiology

Wong N, **Pantelic MN**, and **Kwa M**. 34745 US and EU sunscreens: A review of ultraviolet (UV) filters and safety data. *J Am Acad Dermatol* 2022; 87(3):AB6. Full Text

A broad range of UV filters are available for use in sunscreen products. Knowledge of UV filters available both domestically and abroad remains important, since these products can be found in the online marketplace and may be included in future FDA monographs as a shift is made to an administrative order process. We reviewed the mechanism and safety data of all US and EU approved UV filters. Currently, there are 17 US FDA approved UV filters while the EU possesses an additional 16 UV filters. Of the US filters, 88.2% (15/17) are organic and 11.8% (2/17) are inorganic filters, with 35.3% (6/17) broad-spectrum, 52.9% (9/17) UVB only, and 11.8% (2/17) UVA only. Notably, 94.1% (16/17) have available human data. Of the EU exclusive filters, all (100%, 16/16) are organic filters. 50% (8/16) have human data while the remaining 50% (8/16) have data primarily related to physiochemical or toxicology profiles. Of these EU exclusive UV filters, 43.75% (7/16) are broad-spectrum, 50% (8/16) cover UVB only, and 6.25% (1/16) cover UVA only. Our review demonstrates that the EU possesses an exciting pool of novel UV filters with expanded options for coverage of all forms of UV radiation. Critically, the majority of sunscreens, both in the US and EU, have limited human data available due to prior limited requirements for such information. This information is likely forthcoming in the US as the FDA updates data requirement guidelines for sunscreens to be generally recognized as safe and effective.

Hematology-Oncology

Alkhatib S, **Feldman A**, **Gadgeel S**, **Andrew P**, **Ajlouni M**, **Simoff M**, and **Movsas B**. Is Prophylactic Cranial Irradiation Necessary in Stage I-IIA Small Cell Lung Cancer Patients? A Single Institution Experience. *Cancer Clin Trials* 2022; 45(9):S44-S45. Full Text

Hematology-Oncology

Bae J, Prasanna P, and **Gadgeel SM**. 1544P Pre-treatment CT radiomics predicts survival in chemo-immunotherapy-treated small cell lung cancer. *Ann Oncol* 2022; 33:S1253. Full Text

Background: The addition of checkpoint inhibitors to chemotherapy in SCLC patients provides modest benefit, with a median survival of 12 months. Development of non-invasive imaging predictors to identify patients most likely to benefit from chemo-immunotherapy would enable personalized management of SCLC. Methods: A cohort of 31 extensive-stage SCLC patients treated with atezolizumab, carboplatin, and etoposide from June 2020 to May 2021 were identified and pre-treatment CT scans were curated. The axial slice at the level of the carina (S1) was identified and center-cropped. 304 3D radiomic features

from 5 slices surrounding S1 were extracted for analysis. After feature selection, the most discriminative radiomic feature was used to train and evaluate a random forest machine classifier for mortality prediction using leave-one-out cross-validation (LOOCV). A baseline classifier was trained using clinical variables. LOOCV mortality probabilities were recorded for each patient and used to stratify patient risk. Overall survival (OS) analysis was performed using Cox modeling. Results: Median follow-up was 343 days. Patient data included median age of 67 (46-85), race (24 white, 7 black), 58% female, and liver metastases at diagnosis in 29%. The Haralick difference variance feature had an AUC of 0.77 (c-index: 0.70) compared to the clinical baseline AUC of 0.56 (c-index: 0.64) for mortality and OS. The radiomic classifier identified low (N=12) and high (N=19) risk cohorts with median OS of 519.5 and 194 days, respectively (p=.01). There was no significant difference in OS for low and high risk cohorts identified by clinical features (p=0.47). [Formula presented] Conclusions: Patient survival following chemo-immunotherapy in SCLC can be predicted using computational analysis of pre-treatment images. Our results encourage study of larger patient cohorts to further understand the relationship between imaging signatures and survival in SCLC, potentially leading to improved personalized disease management. Legal entity responsible for the study: Stony Brook University. Funding: Has not received any funding. Disclosure: P. Prasanna: Financial Interests, Personal, Research Grant: IBM. S.M. Gadgeel: Financial Interests, Personal, Advisory Board: AstraZeneca, Amgen, Genentech/Roche, Bristol Myers Squibb, Pfizer, Novartis, Blueprint, Daiichii; Financial Interests, Personal, Other, Data Safety Monitoring Board: AstraZeneca. All other authors have declared no conflicts of interest.

Hematology-Oncology

Bakouny Z, Grover P, Labaki C, Awosika J, Gulati S, Hsu CY, Bilen MA, Eton O, Fecher L, **Hwang C**, Khan H, McKay RR, Ruiz E, Weissmann L, Thompson MA, Shah D, Warner J, Shyr Y, Choueiri TK, and Wise-Draper T. Association of immunotherapy and immunosuppression with severe COVID-19 disease in patients with cancer. *Ann Oncol* 2022; 33:S772-S773. Full Text

Background: Cytokine storm due to COVID-19 can cause high morbidity and mortality. Patients with cancer treated with immunotherapy (IO) and those with immunosuppression may have higher rates of cytokine storm due to immune dysregulation. We sought to evaluate the association of IO and immunosuppression with COVID-19 outcomes and cytokine storm occurrence among patients with cancer and COVID-19, based on data from the COVID-19 and Cancer Consortium (CCC19). Methods: A registry-based retrospective cohort study was conducted on patients reported to the CCC19 registry from March 2020 to September 2021. The primary outcome was defined as an ordinal scale of COVID-19 severity. The secondary outcome was the occurrence of a cytokine storm using CCC19 variables, defined as biological and clinical evidence of severe inflammation, with end-organ dysfunction (Fajgenbaum D.C. et al., N Engl J Med., 2020). The association of IO or immunosuppression with the outcomes of interest were evaluated using a multivariable logistic regression balanced for covariate distributions through inverse probability of treatment weighting (IPTW). Results: A total of 10,214 patients were included, among which 482 (4.7%) received IO, 3,715 (36.4%) received non-IO systemic therapies, and 6,017 (58.9%) were untreated in the 3 months prior to COVID-19 diagnosis. No difference in COVID-19 severity or the development of a cytokine storm was found in the IO group compared to the untreated group (aOR: 0.77; 95%CI:0.45-1.32, and aOR: 1.06; 95%CI:0.42-2.67, respectively). On multivariable analysis, baseline immunosuppression was associated with worse outcomes both in relation to COVID-19 severity (aOR: 1.89; 95%CI:1.51-2.35) and the presence of a cytokine storm (aOR: 1.75; 95%CI:1.30-2.35). Conclusions: Administration of IO was not associated with severe outcomes in patients with cancer and COVID-19, whereas pre-existing baseline immunosuppression appears to be independently associated with worse clinical outcomes including cytokine storm.

Hematology-Oncology

Drilon A, Ou SHI, **Gadgeel S**, Johnson M, Spira A, Lopes G, Besse B, Felip E, van der Wekken AJ, Calles A, de Miguel MJ, Camidge DR, Elamin Y, Liu S, Bauman J, Haggstrom D, Riley G, Pelish HE, Zhu VW, and Lin JJ. EP08.02-041 NVL-520, a Highly Selective ROS1 Inhibitor, in Patients with Advanced ROS1-Positive Solid Tumors: The Phase 1/2 ARROS-1 Study. *J Thorac Oncol* 2022; 17(9):S416. Full Text

Introduction: Oncogenic ROS1 gene fusions are implicated in the pathogenesis of various adult and pediatric cancers, including up to 3% of non-small cell lung cancers (NSCLC), where up to 40% of patients present with central nervous system (CNS) metastases. Tyrosine kinase inhibitors (TKIs) approved by the FDA and EMA for ROS1-positive NSCLC (crizotinib and entrectinib) are limited by acquired resistance, frequently mediated by secondary ROS1 kinase domain mutations. In addition, dual TRK/ROS1 kinase inhibitors such as entrectinib are associated with neurologic adverse events. NVL-520 is a novel, brain-penetrant ROS1-selective kinase inhibitor that exhibits preclinical activity against a diverse array of ROS1 fusions and ROS1 mutations including G2032R, while sparing inhibition of TRK. The ARROS-1 study evaluates the safety and activity of NVL-520 in patients with solid tumors harboring ROS1 fusions, including those with ROS1 resistance mutations and CNS metastases. Methods: ARROS-1 (NCT05118789) consists of a phase 1 dose escalation, followed by phase 2 expansion in cohorts defined by tumor type and prior therapies that are designed to support potential registration. Phase 1 includes adult patients with any solid tumor type harboring a ROS1 gene fusion (by local testing), with evaluable disease, who have received ≥ 1 prior ROS1 TKI. Prior platinum-based chemotherapies and/or immunotherapies, as well as stable CNS disease, are allowed. Patients will receive NVL-520 by daily oral administration. Primary phase 1 objectives are to determine the NVL-520 recommended phase 2 dose, and, if applicable, maximum tolerated dose. Additional objectives include evaluation of safety/tolerability, preliminary activity, and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-520. Longitudinal analysis of circulating tumor DNA will be performed, including ROS1 mutation profiling and other relevant biomarkers. The phase 1 portion of the study is ongoing. Keywords: NVL-520, ROS1, NSCLC

Hematology-Oncology

Gadgeel SM, Al-Mondhiry J, Ahn MJ, Kim SW, Paz-Ares L, Prenen H, Boyer M, Bustamante Alvarez JG, Solomon B, Huang S, Minocha M, Kistler M, and Hashemi Sadraei N. 1549TiP DeLLphi-303: Phase Ib first-line combination study of tarlatamab, a DLL3-targeting half-life extended bispecific T-cell engager (HLE BiTE®), with carboplatin, etoposide, and PD-L1 inhibition in extensive stage small cell lung cancer (ES-SCLC). *Ann Oncol* 2022; 33:S1255. Full Text

Background: The inhibitory Notch ligand, delta-like ligand 3 (DLL3), is a compelling therapeutic target due to its aberrant expression on the cell surface in most small cell lung cancer (SCLC). Tarlatamab (AMG 757) is a half-life extended bispecific T-cell engager (HLE BiTE®) molecule designed to specifically bind DLL3 on target cancer cells and CD3 on T cells, resulting in T cell-dependent killing of tumor cells. Data from an ongoing first-in-human monotherapy study show acceptable safety with evidence of tarlatamab efficacy in patients with relapsed/refractory SCLC (NCT03319940). Adding programmed death ligand 1 (PD-L1) inhibitors to first-line platinum chemotherapy is the emerging standard-of-care (SOC) in ES-SCLC and preclinical data suggests increased antitumor activity of BiTE molecules when combined with PD-1/PD-L1 inhibition or chemotherapy.1 These data support a clinical trial of tarlatamab combined with frontline carboplatin, etoposide, and PD-L1 inhibition in ES-SCLC. Trial design: This is a phase 1b, multicenter, open-label study evaluating tarlatamab in combination with first-line SOC chemo-immunotherapy in subjects with ES-SCLC. Tarlatamab will be evaluated in two separate settings: A) In combination with carboplatin, etoposide, and a PD-L1 inhibitor followed by maintenance cycles of tarlatamab plus PD-L1 inhibitor, and B) In combination with PD-L1 inhibitor following SOC chemo-immunotherapy as a maintenance only approach. Key eligibility criteria include patients with histologically or cytologically confirmed ES-SCLC with no prior systemic treatment (except as specified in protocol) and ECOG performance status ≤1. The primary objective is to evaluate the safety, tolerability, and determine the recommended phase 2 dose and/or maximum tolerated dose of tarlatamab in combination with PD-L1 inhibition with or without chemotherapy. Secondary endpoints are objective response rate, duration of response, disease control, progression-free survival, overall survival, and pharmacokinetics.

Hematology-Oncology

Gadgeel SM, Gainor J, Cappuzzo F, Garralda E, Lee DH, Mazieres J, Kim DW, Zhu V, Lopes G, Miller S, Nowicka M, Trinh H, Arndorfer SM, Rahman A, Noe J, Zhang Q, and Subbiah V. Relationship between RET fusion partner and treatment outcomes in patients (pts) with non-small cell lung cancer (NSCLC) from the phase I/II ARROW study and real-world data (RWD). *Ann Oncol* 2022; 33:S1001-S1002. Full Text

Background: The ARROW study is assessing the anti-tumour activity of pralsetinib, a highly-selective RET inhibitor in advanced solid tumours, including RET fusion+ NSCLC. Prolonged overall survival (OS) was reported with RET inhibitor therapy in NSCLC pts with CCDC6 vs KIF5B RET fusions (Tan AC, et al. JTO 2020). We examined the relationship between RET fusion partner and treatment outcomes in pts with RET fusion+ NSCLC from ARROW and RWD. Methods: In phase 2 of ARROW, 233 pts with RET fusion+ NSCLC (KIF5B n=164, CCDC6 n=41, Other n=28) received 400mg/day pralsetinib until progression, intolerance or withdrawal. Primary endpoints: overall response rate (ORR) and safety. In Q4 2021, 67 pts with RET fusion+ NSCLC (KIF5B n=46, CCDC6 n=8, Other n=13) met eligibility criteria from the nationwide (US-based) de-identified Flatiron Health-FMI NSCLC clinico-genomic database. Cox regression analyses are reported. Results: Baseline characteristics by RET fusion partner were balanced across subgroups within ARROW. ORR was similar with KIF5B and CCDC6, but lower with Other RET fusions (Table); the same trend was seen in treatment-naïve and prior treatment subgroups. Disease control rate (DCR) was high in all pts, but lowest in the Other RET fusions subgroup. Median duration of response (DOR) and progression-free survival (PFS) were higher with CCDC6 vs KIF5B RET fusions irrespective of prior treatment. OS data are immature. In the RWD cohort, median OS was numerically longer in CCDC6 and Other RET fusions vs KIF5B RET-driven disease (52.8 and 38.5 vs 19.1 months); when adjusted for covariates including RET inhibitor usage (KIF5B n=12, CCDC6 n=5, Other n=5), OS HRs for CCDC6 and Other RET fusions vs KIF5B were 0.49 (95% CI: 0.08–3.11) and 0.41 (95% CI: 0.13–1.30), respectively. [Formula presented] Conclusions: Pralsetinib is active in RET fusion+ NSCLC, regardless of fusion partner or prior treatment. CCDC6 RET-driven disease may have a better prognosis vs KIF5B. Clinical trial identification: NCT03037385.

Hematology-Oncology

Garassino MC, **Gadgeel SM**, Speranza G, Felip E, Esteban Gonzalez E, Domine Gomez M, Hochmair MJ, Powell SF, Bischoff H, Peled N, Grossi F, Jennens R, Reck M, Hui R, Garon EB, Kurata T, Gray JE, Schwarzenberger PO, Jensen E, and Rodriguez Abreu D. 973MO KEYNOTE-189 5-year update: First-line pembrolizumab (pembro) + pemetrexed (pem) and platinum vs placebo (pbo) + pem and platinum for metastatic nonsquamous NSCLC. *Ann Oncol* 2022; 33:S992-S993. Full Text

Background: Pembro + pem-platinum significantly improved survival vs pbo + pem-platinum in patients (pts) with previously untreated, metastatic nonsquamous NSCLC without sensitizing EGFR/ALK alterations, regardless of PD-L1 TPS, in the phase III KEYNOTE-189 study (NCT02578680). We report updated results with ~5 y of follow-up. Methods: Pts were randomized 2:1 to receive pembro 200 mg or pbo Q3W for up to 35 cycles (2y). All pts also received pem and investigator's choice of carboplatin/cisplatin for 4 cycles, followed by maintenance pem until PD/unacceptable toxicity. Crossover from the pbo + pem-platinum group to pembro monotherapy was permitted after PD. Primary endpoints were OS and PFS. Results: Among 616 pts randomized (pembro + pem-platinum, n = 410; pbo + pem-platinum, n = 206), median time from randomization to data cutoff (Mar 8, 2022) was 64.6 (range, 60.1–72.4) mo. 116/202 (57.4%) treated pts crossed over from pbo + pem-platinum to anti–PD-(L)1 therapy during/outside the study. Median (95% CI) OS was 22.0 (19.5–24.5) mo vs 10.6 (8.7–13.6) mo with pembro + pem-platinum vs pbo + pem-platinum (HR, 0.60; 95% CI, 0.50–0.72) and 5-y OS rates were 19.4% vs 11.3%, respectively. Median (95% CI) PFS was 9.0 (8.1–10.4) mo vs 4.9 (4.7–5.5) mo (HR, 0.50; 95% CI, 0.42–0.60). Additional efficacy results are in the table. Among pts with ≥1 dose of assigned treatment, grade 3–5 AEs occurred in 295/405 (72.8%) vs 136/202 (67.3%) of pts. Among 57 pts who completed 35 cycles of pembro, ORR was 86.0% (CR, n = 8; PR, n = 41); 3-y OS rate after completion of 35 cycles of pembro was 71.9%. Conclusions: First-line pembro + pem-platinum continued to show OS and PFS benefits with manageable toxicity vs pbo + pem-platinum, irrespective of PD-L1 expression. Pts who completed 35 cycles of pembro experienced durable responses. These data further support pembro + pem-platinum as a standard of care for metastatic nonsquamous NSCLC without sensitizing EGFR/ALK alterations.

Hematology-Oncology

Halabi S, Luo B, Dzimitrowicz H, **Hwang C**, Wise-Draper TM, Labaki C, McKay RR, Ruiz E, Rangel-Escareño C, Farmakiotis D, Griffiths EA, Jani CT, Accordino M, Friese C, Wulff-Burchfield E, Puc M, Yu P, Topaloglu U, Mishra S, and Warner J. A prognostic model of all-cause mortality at 30 days in patients with cancer and COVID-19. *Ann Oncol* 2022; 33:S771-S772. Full Text

Background: Patients with cancer are at higher risk of dying of COVID-19. Known risk factors for 30-day all-cause mortality (ACM-30) in patients with cancer are older age, sex, smoking status, performance status, obesity, and co-morbidities. We hypothesized that common clinical and laboratory parameters would be predictive of a higher risk of 30-day ACM, and that a machine learning approach (random forest) could produce high accuracy. Methods: In this multi-institutional COVID-19 and Cancer Consortium (CCC19) registry study, 12,661 patients enrolled between March 17, 2020 and December 31, 2021 were utilized to develop and validate a model of ACM-30. ACM-30 was defined as death from any cause within 30 days of COVID-19 diagnosis. Pre-specified variables were: age, sex, race, smoking status, ECOG performance status (PS), timing of cancer treatment relative to COVID19 diagnosis, severity of COVID19, type of cancer, and other laboratory measurements. Missing variables were imputed using random forest proximity. Random forest was utilized to model ACM-30. The area under the curve (AUC) was computed as a measure of predictive accuracy with out-of-bag prediction. One hundred bootstrapped samples were used to obtain the standard error of the AUC. Results: The median age at COVID-19 diagnosis was 65 years, 53% were female, 18% were Hispanic, and 16.7% were Black. Over half were never smokers and the median body mass index was 28.2. Random forest with under sampling selected 20 factors prognostic of ACM-30. The AUC was 88.9 (95% CI 88.5-89.2). Highly informative parameters included: COVID-19 severity at presentation, cancer status, age, troponin level, ECOG PS and body mass index. Conclusions: This prognostic model based on readily available clinical and laboratory values can be used to estimate individual survival probability within 30-days for COVID-19. In addition, this model can be used to select or classify patients with cancer and COVID-19 into risk groups based on validated cut points, for treatment selection, prophylaxis prioritization, and/or enrollment in clinical trials. Future work includes external validation using other large datasets of patients with COVID-19 and cancer. Clinical trial identification: NCT04354701.

Hematology-Oncology

Hamid O, **Weise A**, Kim TM, McKean MA, Lakhani NJ, Kaczmar J, Papadopoulos KP, Chen S, Mani J, Jankovic V, Kroog G, Sims T, Lowy I, and Gullo G. 790MO Phase I study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma (mel). *Ann Oncol* 2022; 33:S905. Full Text

Background: Concurrent blockade of LAG-3 may enhance efficacy of anti-programmed cell death-1 (PD-1) therapies. We present updated safety and clinical activity data from patients (pts) with advanced mel treated with concurrent anti-LAG-3 (fianlimab) and anti-PD-1 (cemiplimab). Methods: This phase 1 study included pts with unresectable or metastatic mel (excluding uveal mel) who were anti–PD-(L)1 treatment naïve (expansion cohort [EC] 6) or anti–PD-(L) 1 experienced within 3 months of screening (EC7). Pts received fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks for 12 months (optional additional 12 months if clinically indicated). Tumour measurements were performed every 6 weeks for 24 weeks, then every 9 weeks. Results: As of the 9 Feb 2022 data cutoff date, 40 EC6 and 15 EC7 pts were enrolled and treated with fianlimab + cemiplimab. For EC6 and EC7 cohorts respectively, median age was 69.5 and 59.0 years, 62.5% and 46.7% were male, 90.0% and 60.0% were White. Median treatment duration was 37.1 weeks (EC6) and 9.0 weeks (EC7). Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 37.5% (EC6) and 46.7% (EC7) of pts; serious TEAEs occurred in 32.5% (EC6) and 33.3% (EC7) of pts; 17.5% (EC6) and 13.3% (EC7) of pts discontinued treatment due to a TEAE. Rate of adrenal insufficiency (AI) was 12.5% (EC6) and 6.7% (EC7); none led to treatment discontinuation. Investigator-assessed objective response rate was 62.5% (6 complete responses; 19 partial responses [PRs]) in EC6 and 13.3% (2 PRs) in EC7 pts. Kaplan-Meier estimation of median progression-free survival was 14.2 (95% CI: 5.6–not estimated) months in EC6 and 1.4 (95% CI: 1.3–7.7) months in EC7 pts. Median duration of response had not been reached in both cohorts. LAG-3 and PD-L1 correlative biomarkers analysis will be included in the presentation. Conclusions: Fianlimab + cemiplimab in advanced mel pts had a similar safety profile to anti–PD-1 agents; clinical activity in anti-PD-(L)1-naïve

patients appears higher than previously reported for anti-PD-1 monotherapy or anti–LAG-3 + anti–PD-1. A phase 3 trial (NCT05352672) investigating fianlimab + cemiplimab in advanced mel pts is ongoing. Clinical trial identification: NCT03005782.

Hematology-Oncology
Kulkarni A, Hennessy C, Wislon G, Ramesh V, **Hwang C**, Joy A, Bakouny Z, Khan H, Vilar-Compte D, McKay R, Jani C, Riess JW, Puc M, Kasi A, Berg S, Castillo DR, Hayes-Lattin B, Hosmer W, Flora D, Mishra S, French B, Warner J, Lopes G, Peters S, and Duma N. OA06.06 Impact of Systemic Anti-cancer Treatments on Outcomes of COVID-19 in Patients with Thoracic Cancers: CCC19 Registry Analysis. *J Thorac Oncol* 2022; 17(9):S19-S20. Full Text

Introduction: Patients with thoracic cancers (TC) have one of the highest rates of mortality among patients with cancer and COVID-19. Data evaluating the impact of recent anti-cancer therapies on COVID-19 outcomes in patients with TC are confined to small heterogenous retrospective studies, with limited follow-up data. We analyzed data from the COVID-19 and Cancer Consortium (CCC19) (NCT04354701) to examine the impact of recent systemic therapies on the clinical outcomes of COVID-19 in patients with TC. Methods: The CCC19 registry was queried for adult patients with TC and lab-confirmed SARS-CoV-2 infection. Only patients with data quality scores of 0-4 were included in the analysis. The primary outcome was 30-day all-cause mortality. Secondary outcomes were need for oxygen supplementation, hospitalization, ICU admission, and mechanical ventilation. The outcomes were further stratified by demographics, smoking history, ECOG PS (0, 1, >2), cancer status (remission, responding/stable, progressing) and type of systemic treatment <3 months prior to COVID-19 (chemotherapy with or without immunotherapy, chemotherapy plus radiation, immunotherapy alone or targeted therapy). Results: From January 2020 to December 2021, 900 patients with thoracic cancer met the inclusion criteria. The median age was 70 years (IQR 62-77), 53% were female, 79% were former or current tobacco users, 56% of patients had ECOG PS of 0 or 1, and 34% of patients had active but stable or responding cancer. Fifty-three percent (N=477) of patients received at least one anti-cancer systemic therapy <3 months prior to COVID-19 diagnosis. Chemotherapy with or without immunotherapy was the most prevalent treatment exposure (51%; N=242). After a median follow-up of 70 days (IQR 28-180), 30-day all-cause mortality was similar in patients who received any systemic cancer treatment versus no cancer treatment (23% and 22% respectively). Patients treated with immunotherapy and targeted therapy had the lowest mortality (15% and 18% respectively), the majority of whom were treated with palliative intent. Similar trends were also noted with secondary outcomes (Table 1). Conclusions: We report one of the largest studies evaluating the clinical outcomes of COVID-19 in the context of recent systemic anti-cancer treatments for TC. While continued caution is required when utilizing systemic treatments, delays in treatment may not be justified. The study provides reassuring data that patients receiving immunotherapy or targeted therapy even in the context of palliative treatment appear to have a lower risk for all-cause COVID-19 mortality. Further analysis exploring the prognostic factors associated with poor outcomes in patients with chemoradiation is planned. [Formula presented] Keywords: COVID-19, Immunotherpay, Thoracic Cancers

Hematology-Oncology
Spira A, Spigel DR, Camidge R, de Langen AJ, Kim TM, Goto K, Elamin Y, Shum E, Reckamp KL, Rotow J, Goldberg S, **Gadgeel S**, Leal TA, Albayya F, Fitzpatrick S, Louie-Gao M, Parepally J, Zalutskaya A, and Yu H. EP08.02-019 Phase 1/2 Study of BLU-701, a Highly Selective EGFR Inhibitor, in Patients With EGFR-Mutant Non-Small Cell Lung Cancer. *J Thorac Oncol* 2022; 17(9):S406. Full Text

Introduction: Third-generation tyrosine kinase inhibitors (TKIs), such as osimertinib, are highly effective in front-line metastatic EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC), but treatment resistance can ultimately occur, including the emergence of the on-target C797X mutation for which there are no approved TKIs. BLU-701 is an investigational, reversible, central nervous system (CNS)-penetrant, wildtype-sparing oral TKI with nanomolar potency on common activating (exon 19 deletion and L858R) and C797X resistance mutations. BLU-701 has shown promising preclinical data, including antitumor CNS activity that may improve patient outcomes. Additionally, combining BLU-701 with standard of care therapies may provide enhanced disease control across multiple lines of treatment, including against heterogenous tumors, in patients with EGFRm NSCLC. An abstract describing this study was previously

submitted to the American Society of Clinical Oncology 2022 Annual Meeting. Methods: HARMONY (NCT05153408) is an ongoing, global phase 1/2, open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of BLU-701 as a monotherapy or in combination with osimertinib or platinum-based chemotherapy in patients with EGFRm NSCLC. Key inclusion criteria include patients ≥18 years of age with metastatic EGFRm NSCLC; Eastern Cooperative Oncology Group performance status 0-1; and previous treatment with ≥1 EGFR-targeted TKI. Patients in the phase 2 monotherapy part must harbor an EGFR C797X resistance mutation (locally assessed). Key exclusion criteria are tumors harboring EGFR T790M mutations, EGFR exon 20 insertions, or other known driver alterations, including KRAS, BRAF V600E, NTRK1/2/3, HER2, ALK, ROS1, MET, or RET. Phase 1 primary endpoints are maximum tolerated dose, recommended phase 2 dose (RP2D), and safety. The phase 2 primary endpoint is overall response rate (ORR) by RECIST v1.1. Secondary endpoints include ORR (phase 1), duration of response, and PK/PD (phase 1 and phase 2); disease control rate, progression-free survival, overall survival, antitumor CNS activity, and safety (phase 2). The phase 1 dose escalation will adopt a Bayesian optimal interval design. Patients will be enrolled into 3 treatment cohorts: part 1A (n≈40-80; BLU-701), part 1B (n≈35; BLU-701 + osimertinib), and part 1C (n≈18; BLU-701 + carboplatin and pemetrexed). Patients in the phase 2 dose expansion (n≈24) will be treated at the RP2D of BLU-701 as monotherapy. Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Enrollment has started, and sites will be open across North America, Europe, and Asia. Keywords: EGFR TKI, EGFR C797S, Clinical trial

Internal Medicine

Ghandour A, **Alsaadi A**, **Ignatius A**, **Martin A**, **Lee J**, **Rabbani B**, **Zweig B**, **Parikh S**, **Villablanca P**, **Wilson C**, **Frisoli T**, **O'Neill B**, **O'Neill W**, and **Wang DD**. TCT-378 Not Every TEE Is a "Standard of Care" TEE. *J Am Coll Cardiol* 2022; 80(12):B152. Full Text

Background: Intraprocedural structural heart imaging is more challenging and has unique differences from standard of care (SOC) imaging. However, the variations in time and complexity of different types of SOC transesophageal echocardiographs (TEEs) versus interventional TEEs is not well studied. In this study, we aim to compare the complexity of SOC nonvalvular indication TEE with SOC valvular TEE studies and interventional TEEs performed in the guidance of transcatheter edge-to-edge repair (TEER) MitraClip (Abbott Vascular) procedures. Methods: A retrospective case-control analysis was performed on 200 patients who underwent TEE in the Henry Ford Health System. One hundred cases of interventional TEE-guided TEER were compared with 73 nonvalvular (endocarditis and stroke evaluation) SOC TEEs and 27 valvular (preprocedural mitral, aortic, and tricuspid valve evaluations) SOC TEEs. Complexity was quantified by the total procedure duration, the total number of images, and the number of 3-dimensional (3D) clips captured. The mean, median, and SD were compared between these groups. The Kruskal-Wallis test was used to evaluate statistical significance. Results: The mean duration of TEE procedures, the number of images, and the number of 3D clips were all significantly higher in the interventional imaging TEER group compared with the noninterventional groups ($P < 0.0001$) (Table 1). The duration and number of images were also significantly higher among valvular compared with nonvalvular SOC TEE groups ($P < 0.0002$) as well as number of 3D clips ($P < 0.0012$). [Formula presented] Conclusion: Interventional TEE was more complicated and time-consuming compared with SOC TEE performed for both nonvalvular and valvular indications. The latter was also more complex than SOC nonvalvular TEE. This is the first study of its kind demonstrating objective differences between interventional and 2 SOC TEE groups. These results emphasize the need of dedicated training for intraprocedural imaging as well as restructuring of reimbursement codes. Categories: STRUCTURAL: Valvular Disease: Mitral

Pathology and Laboratory Medicine

Aryal SC, **Zia S**, **Mehrotra H**, **Oyedeji O**, and **Otrock ZK**. Clinico-Laboratory Profile and Outcome of COVID-19 in Patients with Chronic Immune Thrombocytopenia. *Transfusion* 2022; 62:116A-117A. Full Text

Public Health Sciences

Lyons AB, **Ozog DM**, **Lim HW**, **Viola K**, **Jones LR**, and **Tang A**. 31064 The Detroit Keloid Scale: A validated tool for rating keloids. *J Am Acad Dermatol* 2022; 87(3):AB210. Full Text

Background: No keloid-specific outcome measures exist. Objective: To develop and validate the Detroit Keloid Scale (DKS), a standardized method of keloid assessment to better compare treatments. Methods: Forty-seven physicians were polled to develop the DKS. The scale was validated in 52 patients with keloids against the Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS), and Dermatology Life Quality Index (DLQI) by 3 physicians. Results: The interrater reliability was “substantial” for observer component of the DKS and only “moderate” for the VSS and observer POSAS (ICC were 0.80, 0.60, and 0.47, respectively). Pearson’s correlation indicated a “moderate” association between the observer component of DKS with observer component of POSAS ($\rho = 0.56$, $P < .001$) and a “substantial” relationship between the observer component of DKS and VSS ($\rho = 0.63$, $P < .001$). Pearson’s correlation indicated a “moderate” association between the patient portion of DKS and patient portion of POSAS and the patient portion of the DKS and DLQI (0.61 and 0.60, respectively, $P < .05$). The DKS total score consistently showed “substantial” relationship with POSAS total score ($\rho = 0.65$, $P < .001$). Limitations: Single center study, no intrarater reliability analysis. Conclusions: The substantial interrater reliability of the DKS will allow for improved standardization in future keloid research.

Public Health Sciences

Osazuwa-Peters N, Osazuwa-Peters OL, **Adjei Boakye E**, Abouelella D, Barnes JM, Bates N, and Ramos K. 1428P Suicidal outcomes among cancer survivors: Examining associations with depression and non-medical pain prescriptions. *Ann Oncol* 2022; 33:S1198. Full Text

Background: A cancer diagnosis results in significant distress and adverse psychosocial sequelae, including suicide, the 10th leading cause of death in the United States. Primary risks for death by suicide include depression, and opioid abuse, which are prevalent amongst cancer survivors. Yet, it remains unclear whether they are also associated with other suicidal outcomes, such as ideation, planning, and suicidal attempt. This study examined associations between suicide-related outcomes, depression and non-medical use of pain prescriptions among cancer survivors in the United States. Methods: We used cross-sectional data from the National Survey on Drug Use and Health (NSDUH; 2015-2019), a nationwide study in the United States that provides data on mental health and other health concerns. Outcomes of interest were patient-reported suicidal ideation, suicidal planning, and suicidal attempt. Participants were grouped as: individuals with a history of cancer, individuals without a history of cancer, but with fair/poor health, and individuals without a history of cancer but with excellent/very good/good health. Results: Weighted logistic regression analyses that adjusted for sociodemographics and substance use showed associations between a history of cancer and suicidal ideation (aOR = 1.32, 95% CI 1.10, 1.58). Among individuals with a history of cancer, depression and non-medical use of pain prescriptions were consistently associated with suicidal ideation (aORdepression = 7.37, 95% CI 4.52, 12.03; aORpain prescriptions = 3.36, 95% CI 1.27, 8.91, planning (aORdepression = 10.31, 95% CI 5.79, 18.34; and aORpain prescriptions = 3.77, 95% CI 1.20, 11.85), and attempt (aORdepression = 4.29, 95% CI 1.41, 13.06). Conclusions: Individuals with a history of cancer are at increased odds of adverse suicidal outcomes, driven by depression and non-medical pain prescription. Routinely assessing for depression and non-medical use of pain prescriptions may be a crucial suicide prevention strategy in oncology.

Pulmonary and Critical Care Medicine

Alkhatib S, **Feldman A**, **Gadgeel S**, **Andrew P**, **Ajlouni M**, **Simoff M**, and **Movsas B**. Is Prophylactic Cranial Irradiation Necessary in Stage I-IIA Small Cell Lung Cancer Patients? A Single Institution Experience. *Cancer Clin Trials* 2022; 45(9):S44-S45. Full Text

Radiation Oncology

Alkhatib S, **Feldman A**, **Gadgeel S**, **Andrew P**, **Ajlouni M**, **Simoff M**, and **Movsas B**. Is Prophylactic Cranial Irradiation Necessary in Stage I-IIA Small Cell Lung Cancer Patients? A Single Institution Experience. *Cancer Clin Trials* 2022; 45(9):S44-S45. Full Text

Radiation Oncology

Ringash J, DeMora L, Gillison ML, Adelstein DJ, Harari P, Sturgis EM, Basch EM, Koyfman SA, Krempl GA, Blakaj DM, Bates JE, Galloway T, Jones CU, Beadle BM, Torres-Saavedra P, Le QT, and **Movsas B**. 655MO Quality of life in patients with p16+ oropharyngeal cancer receiving accelerated radiotherapy (RT) with either cisplatin or cetuximab in NRG/RTOG 1016. *Ann Oncol* 2022; 33:S841-S842. Full Text

Background: This phase 3 randomized non-inferiority de-escalation trial compared cetuximab (cetux) vs cisplatin (cis), concurrent with accelerated RT 70 Gy/6 weeks, in p16+ oropharyngeal cancer (OPC). Quality of life (QOL) was an important secondary endpoint. Methods: EORTC QLQ-C30/HN35 was completed at baseline, end of treatment, 3, 6, and 12 months post. The substudy aimed for 400 eligible patients. We report completion rates and compare by arm for change from baseline in each domain (0.05 two-sided alpha and MID of 10 points) using linear mixed models. Results: Consent was 91% (381/419 offered substudy); 6 protocol deviations excluded (n=375). No significant differences in patient/tumor characteristics were found by participation status. Completion rates (%) at the 5 times did not differ by arm (cis/cetux): 92/94, 74/77, 76/81, 76/81, and 73/74. The swallowing domain of HN35 (previously reported) did not differ significantly by arm. No significant difference was seen by arm for the 6-mo change from baseline on any domain. At end of RT (only), dry mouth was significantly worse for RT+cetux. At end of treatment, all domains showed statistically and clinically significant mean worsening across both arms except Emotional Functioning, Dyspnea, Diarrhea, and Teeth. Most domains returned within 10 points of baseline by 6 mo, with the following maintaining significant impairment: Senses (taste/smell), Social Eating, Opening Mouth, Dry Mouth, Sticky Saliva. At 12 mo post-treatment, worsening from baseline persisted for Senses, Dry Mouth, Sticky Saliva, and Weight Gain. Pain Killer use improved significantly from baseline to 3, 6, and 12 mo. Conclusions: Although replacing RT+cis with RT+cetux did not benefit QOL, this study has confirmed the responsiveness of EORTC QLQ-C30/HN35 to the effects of concurrent systemic/RT for OPC. Dry Mouth, Sticky Saliva, and Senses showed large, significant, and persistent impairments, and remain worthwhile targets for future de-escalation efforts. Domains related to eating (Swallowing, Appetite, Nutritional Supplements, Social Eating, Weight Loss) did not show sustained significant impairment on this instrument in this study. Clinical trial identification: NCT01302834.

Surgery

Natour AK, **Rteil A**, **Shepard A**, **Weaver M**, **Nypaver T**, **Nemeh H**, **Tanaka D**, and **Kabbani L**. Outcomes of patients with acute type A aortic dissection and concomitant lower extremity malperfusion. *J Vasc Surg* 2022; 76(3):631-638.e631. Full Text

L. Kabbani, Division of Vascular Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, United States

Objective: The occurrence of acute lower limb ischemia (ALLI) is a serious risk within the context of aortic dissection repair. The aim of the present study was to examine the outcomes of patients with acute type A aortic dissection (ATAD) and concomitant lower extremity malperfusion. Methods: We performed a retrospective medical record review at our tertiary referral center of patients who underwent ATAD repair from January 2002 to June 2018. We used univariate and multivariate analyses to compare the outcomes of patients with and without lower extremity malperfusion. The primary outcomes were 30-day and 1-year mortality. Results: A total of 378 patients underwent ATAD repair during the study period. Their mean age was 57 years, 68% were men, and 51% were White. A total of 62 patients (16%) presented with concomitant ALLI, including 35 (9%) who presented with isolated ALLI and 27 (7%) who presented with ALLI and concomitant malperfusion of at least one other organ. Of the 62 patients with ALLI, 46 underwent only proximal aortic repair. Of the 378 patients, 6 died within the first 24 hours, and their limb perfusion was not assessed. Among the 40 patients who underwent isolated proximal repair and survived >24 hours, 34 (85%) had resolution of their ALLI. Of the 16 patients who underwent concomitant lower extremity peripheral vascular procedures, 10 had bypass procedures and 1 died within 24 hours due to refractory coagulopathy and hypotension. All six patients with adequate follow-up imaging studies had asymptomatic occlusion of the bypass graft with recanalization of the occluded native arteries. Patients who presented with any organ malperfusion had increased 30-day (odds ratio, 1.8; P = .04) and 1-year (odds ratio, 1.8; P = .04) mortality and decreased overall survival (P < .01). For the patients with isolated

ALLI, no significant differences were found in 30-day or 1-year mortality or overall survival (P = .57). Conclusions: Proximal repair of ATAD resolves most cases of associated ALLI, and isolated ALLI does not affect short- or long-term survival. All patients with follow-up in our study who underwent extra-anatomic bypass developed asymptomatic graft occlusion, which could be attributed to competitive flow from the remodeled native arterial system. We believe that rapid and aggressive restoration of flow to the lower extremity is the best method to treat ALLI malperfusion syndrome. Close monitoring for the development of compartment syndrome is recommended.

Books and Book Chapters

Hematology-Oncology
Singh SRK, **Mattour AH**, and Malapati SJ. Leptomeningeal Carcinomatosis. In: Leong SP, Nathanson SD, and Zager JS, eds. *Cancer Metastasis Through the Lymphovascular System*. Springer International Publishing AG; 2022**:** 575-583. Full Text

Neurosurgery
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Neurosurgery
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Neurosurgery
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Surgery
Potti C, **Nasser H**, **Popoff A**, and **Hammoud Z**. Metastatic Disease of the Lung. In: Leong SP, Nathanson SD, and Zager JS, eds. *Cancer Metastasis Through the Lymphovascular System*. Springer International Publishing AG; 2022**:** 447-461. Full Text