

Henry Ford Health Publication List – March 2023

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 187 unique citations listed this month, including 142 articles and 45 conference abstracts.

Articles are listed first, followed by [conference abstracts](#). 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.

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Articles

Administration

Janfear DE, Luzum JA, She R, Li J, Sabbah HN, Zeld N, Liu B, Peterson E, and Keoki Williams L. Validation of a Polygenic Score for Beta-Blocker Survival Benefit in Patients With Heart Failure Using the United Kingdom Biobank. *Circ Genom Precis Med* 2023; e003835. Epub ahead of print. PMID: 36866666.

[Full Text](#)

Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Hospital, Henry Ford Health System, Detroit, MI. (D.E.L., J.A.L., N.Z., L.K.W.).

Heart and Vascular Institute, Henry Ford Health System, Detroit, MI. (D.E.L., H.N.S.).

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Department of Public Health Sciences, Henry Ford Health System, Detroit, MI. (R.S., J.L., B.L., E.P.).

Administration

Shallal AB, Cherabuddi M, Podsiad L, Gortat C, Shanahan C, Holsey T, Samuel L, Alangaden G, and Suleyman G. Role of diagnostic stewardship in reducing healthcare-facility-onset *Clostridioides difficile* infections. *Antimicrob Steward Healthc Epidemiol* 2023; 3(1):e53. PMID: 36970430. [Full Text](#)

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Infection Prevention and Control, Henry Ford Health, Detroit, Michigan.

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We describe the implementation of an electronic medical record "hard stop" to decrease inappropriate *Clostridioides difficile* testing across a 5-hospital health system, effectively reducing the rates of healthcare-facility-onset *C. difficile* infection. This novel approach included expert consultation with medical director of infection prevention and control for test-order override.

Allergy and Immunology

Miller RL, Schuh H, Chandran A, Aris IM, Bendixsen C, Blossom J, Breton C, Camargo CA, Jr., Canino G, Carroll KN, Commodore S, Cordero JF, Dabelea DM, Ferrara A, Fry RC, Ganiban JM, Gern JE, Gilliland FD, Gold DR, Habre R, Hare ME, Harte RN, Hartert T, Hasegawa K, Khurana Hershey GK, Jackson DJ, **Joseph C**, Kerver JM, **Kim H**, Litonjua AA, Marsit CJ, McEvoy C, Mendonça EA, Moore PE, Nkoy FL, O'Connor TG, Oken E, **Ownby D**, Perzanowski M, Rivera-Spoljaric K, Ryan PH, Singh AM, Stanford JB, Wright RJ, Wright RO, Zanobetti A, **Zoratti E**, and **Johnson CC**. Incidence Rates of Childhood Asthma with Recurrent Exacerbations in the U.S. Environmental influences on Child Health Outcomes (ECHO) Program. *J Allergy Clin Immunol* 2023; Epub ahead of print. PMID: 36972767. [Full Text](#)

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BACKGROUND: Descriptive epidemiological data on incidence rates (IRs) of asthma with recurrent exacerbations (ARE) are sparse. **OBJECTIVE:** We hypothesized that IRs for ARE would vary by time, geography, age, race and ethnicity, irrespective of parental asthma history. **METHODS:** We leveraged data from 17246 children born after 1990 enrolled in 59 U.S. and one Puerto Rican cohort in the Environmental Influences on Child Health Outcomes consortium to estimate IRs for AREs. **RESULTS:** The overall crude IR for ARE was 6.07/1000 person-years (95% confidence intervals (CI) 5.63, 6.51) and was highest for children age 2-4 years, for Hispanic and non-Hispanic Black children and for those with a parental history of asthma. ARE IRs were higher for 2-4 year olds in each race and ethnicity category and for both sexes. Multi-variable analysis confirmed higher adjusted ARE IRs (aIRR) for children born 2000-2009 compared to 1990-1999 and 2010-2017, 2-4 versus 10-19 years old (aIRR=15.36; CI 12.09, 2.99), and for males versus females (aIRR=1.34; CI 1.16, 1.55). Black children (non-Hispanic and Hispanic) had higher rates than non-Hispanic White children (aIRR=2.51; CI 2.10, 2.99 and aIRR=2.04; CI 1.22, 3.39, respectively). Children born in the Midwest, Northeast and South had higher rates than the West ($p<0.01$ for each comparison). Children with a parental history of asthma had rates nearly three times higher than those without such history (aIRR=2.90; CI 2.43-3.46). **CONCLUSIONS:** Factors associated with time,

geography, age, race and ethnicity, sex and parental history appear to influence the inception of ARE among children and adolescents.

Anesthesiology

Ramirez MF, Guerra-Londono JJ, Owusu-Agyemang P, Fournier K, and **Guerra-Londono CE**. Temperature management during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Front Oncol* 2023; 12:1062158. PMID: 36741691. [Full Text](#)

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In addition to attaining complete or near complete cytoreduction, the instillation of select heated chemotherapeutic agents into the abdominal cavity has offered a chance for cure or longer survival in patients with peritoneal surface malignancies. While the heating of chemotherapeutic agents enhances cytotoxicity, the resulting systemic hyperthermia has been associated with an increased risk of severe hyperthermia and its associated complications. Factors that have been associated with an increased risk of severe hyperthermia include intraoperative blood transfusions and longer perfusion duration. However, the development of severe hyperthermia still remains largely unpredictable. Thus, at several institutions, cooling protocols are employed during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Cooling protocols for CRS-HIPEC are not standardized and may be associated with episodes of severe hyperthermia or alternatively hypothermia. In theory, excessive cooling could result in a decreased effectiveness of the intraperitoneal chemotherapeutic agents. This presumption has been supported by a recent study of 214 adults undergoing CRS-HIPEC, where failure to attain a temperature of 38° C at the end of chemo-perfusion was associated with worse survival. Although not statistically significant, failure to maintain a temperature of 38° C for at least 30 minutes was associated with worse survival. Although studies are limited in this regard, the importance of maintaining a steady state of temperature during the hyperthermic phase of intraperitoneal chemotherapy administration cannot be disregarded. The following article describes the processes and physiological mechanisms responsible for hyperthermia during CRS-HIPEC. The challenges associated with temperature management during CRS-HIPEC and methods to avoid severe hypothermia and hyperthermia are also described.

Behavioral Health Services/Psychiatry/Neuropsychology

Anvari MS, **Hampton T**, Tong MP, **Kahn G**, Triemstra JD, Magidson JF, and **Felton JW**. Behavioral Activation Disseminated by Non-Mental Health Professionals, Paraprofessionals, and Peers: A Systematic Review. *Behav Ther* 2023. PMID: Not assigned. [Full Text](#)

M.S. Anvari, University of Maryland, College Park, Department of Psychology, 4049 Campus Drive, College Park, MD

There is a striking disparity between the number of individuals with significant mental health concerns and those who are able to access care globally. One promising solution to expanding the mental health workforce is task-sharing, or employing nonspecialists in the delivery of evidence-based interventions. Behavioral activation (BA), a brief intervention that focuses on scheduling rewarding activities into one's daily life, may have promise for delivery using task-sharing approaches due to its straightforward, flexible nature. The aim of this systematic review was to examine the current state of the literature on non-specialist-delivered BA and evaluate the evidence base of this approach. Three databases (Pubmed, PsycInfo, and Cochrane) were searched, and all articles were screened for inclusion criteria by two research assistants, included the review of titles, abstracts, and full-text. The final dataset consisted of 13 research studies, represented through 15 articles. A meta-analysis was conducted to examine the overall pooled effects of peer-delivered BA on depressive symptoms (the most widely examined clinical outcome). Studies reported on effectiveness and implementation outcomes of non-specialist-delivered BA

for depression, substance use, loneliness, trauma survivors, and individuals with comorbid physical health conditions. Results provide initial support for the effectiveness of BA utilizing a task-sharing approach, and highlight the feasibility and acceptability of using nonspecialists to deliver BA in a variety of contexts, including low-resource settings.

Behavioral Health Services/Psychiatry/Neuropsychology

Anvari MS, Kleinman MB, Dean D, Bradley VD, Abidogun TM, Hines AC, Seitz-Brown CJ, **Felton JW**, and Magidson JF. Adapting a Behavioral Activation Intervention for Opioid Use Disorder and Methadone Treatment Retention for Peer Delivery in a Low-Resource Setting: A Case Series. *Cogn Behav Pract* 2023. PMID: Not assigned. [Request Article](#)

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While methadone treatment (MT) is effective in treating opioid use disorder (OUD), retention remains an issue nationwide, especially among low-income, minoritized populations. Peer recovery specialists (PRSs), individuals with lived substance use experience, are particularly well suited to support vulnerable populations, though often are not trained in delivering evidence-based interventions. Thus, our team developed a Type 1 hybrid effectiveness-implementation open-label pilot trial to evaluate the effectiveness of PRS-delivered BA (Peer Activate) in improving MT retention and establish feasibility, acceptability and PRS fidelity of the intervention. In this case series, we provide a more in-depth depiction of the adaptation of Peer Activate and present three cases to illustrate how Peer Activate can be implemented among patients in routine MT care and adapted to meet the needs of varying clinical presentations. We include descriptive data on participant substance use and MT outcomes to supplement the narrative discussion. While varying participant presentations and needs presented challenges to the PRS interventionist, the PRS utilized his shared, lived substance use and recovery experiences and met participants where they were at, as well as successfully used BA techniques, ultimately leading to intervention success.

Behavioral Health Services/Psychiatry/Neuropsychology

Zhao H, Ma Q, Xie M, Huang Y, Liu Y, Song H, **Gui H**, Li M, and Wang Q. Self-rated health as a predictor of hospitalizations in patients with bipolar disorder or major depressive disorder: A prospective cohort study of the UK Biobank. *J Affect Disord* 2023; 331:200-206. PMID: 36907458. [Full Text](#)

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BACKGROUND: To determine the association between self-rated health (SRH) and subsequent all-cause hospitalizations in patients with bipolar disorder (BD) or major depression (MDD). **METHODS:** We conducted a prospective cohort study on people with BD or MDD in the UK from 2006 to 2010 using UK Biobank touchscreen questionnaire data and linked administrative health databases. The association between SRH and 2-year all-cause hospitalizations was assessed using proportional hazard regression after adjustment for sociodemographics, lifestyle behaviors, previous hospitalization use, the Elixhauser comorbidity index, and environmental factors. **RESULTS:** A total of 29,966 participants were identified, experiencing 10,279 hospitalization events. Among the cohort, the average age was 55.88 (SD 8.01) years, 64.02 % were female, and 3029 (10.11 %), 15,972 (53.30 %), 8313 (27.74 %), and 2652 (8.85 %) reported excellent, good, fair, and poor SRH, respectively. Among patients reporting poor SRH, 54.19 % had a hospitalization event within 2 years compared with 22.65 % for those having excellent SRH. In the adjusted analysis, patients with good, fair, and poor SRH had 1.31 (95 % CI 1.21-1.42), 1.82 (95 % CI 1.68-1.98), and 2.45 (95 % CI 2.22, 2.70) higher hazards of hospitalization, respectively, than those with

excellent SRH. LIMITATIONS: Selection bias can exist as our cohort cannot fully represent all the BD and MDD cases in the UK. Moreover, the causality is questionable. CONCLUSION: SRH was independently associated with subsequent all-cause hospitalizations in patients with BD or MDD. This large study underscores the need for proactive SRH screening in this population, which might inform resource allocation in clinical care and enhance high-risk population detection.

Cardiology/Cardiovascular Research

Ahmad Y, Madhavan MV, Baron SJ, Forrest JK, Borger MA, Leipsic JA, Cavalcante JL, **Wang DD**, McCarthy P, Szerlip M, Kapadia S, Makkar R, Mack MJ, Leon MB, and Cohen DJ. Clinical Research on Transcatheter Aortic Valve Replacement for Bicuspid Aortic Valve Disease: Principles, Challenges, and an Agenda for the Future. *Struct Heart* 2023; 7(1). PMID: Not assigned. [Full Text](#)

D.J. Cohen, The Cardiovascular Research Foundation, New York, NY and Department of Cardiology, St. Francis Hospital, Roslyn, NY

Bicuspid aortic valve disease (BAVD) is present in up to half of all patients referred for surgical aortic valve replacement (SAVR) yet was an exclusion criterion for all randomized controlled trials (RCTs) comparing transcatheter aortic valve replacement (TAVR) to SAVR. Nonetheless, approximately 10% of patients currently treated with TAVR have BAVD and available observational data for performing TAVR in these patients are limited by selection bias. Many in the cardiovascular community have advocated for RCTs in this population, but none have been performed. The Heart Valve Collaboratory (HVC) is a multidisciplinary community of stakeholders with the aim of creating significant advances in valvular heart disease by stimulating clinical research, engaging in educational activities, and advancing regulatory science. In December 2020, the HVC hosted a Global Multidisciplinary workshop involving over 100 international experts in the field. Following this 2-day symposium, working groups with varied expertise were convened to discuss BAVD, including the need for and design of RCTs. This review, conducted under the auspices of the HVC, summarizes available data and knowledge gaps regarding procedural therapy for BAVD, outlining specific challenges for trials in this population. We also propose several potential studies that could be performed and discuss respective strengths and weaknesses of each approach. Finally, we present a roadmap for future directions in clinical research in TAVR for BAVD with an emphasis both on RCTs and also prospective registries focused on disease phenotyping to develop parameters and risk scores that could ultimately be applied to patients to inform clinical decision-making.

Cardiology/Cardiovascular Research

Ashburn NP, Snavely AC, O'Neill JC, Allen BR, Christenson RH, Madsen T, Massoomi MR, **McCord JK**, Mumma BE, **Nowak R**, Stopyra JP, In't Veld MH, Wilkerson RG, and Mahler SA. Performance of the European Society of Cardiology 0/1-Hour Algorithm With High-Sensitivity Cardiac Troponin T Among Patients With Known Coronary Artery Disease. *JAMA Cardiol* 2023; Epub ahead of print. PMID: 36857071. [Request Article](#)

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IMPORTANCE: The European Society of Cardiology (ESC) 0/1-hour algorithm is a validated high-sensitivity cardiac troponin (hs-cTn) protocol for emergency department patients with possible acute coronary syndrome. However, limited data exist regarding its performance in patients with known coronary artery disease (CAD; prior myocardial infarction [MI], coronary revascularization, or $\geq 70\%$ coronary stenosis). **OBJECTIVE:** To evaluate and compare the diagnostic performance of the ESC 0/1-hour algorithm for 30-day cardiac death or MI among patients with and without known CAD and determine if the algorithm could achieve the negative predictive value rule-out threshold of 99% or higher. **DESIGN, SETTING, AND PARTICIPANTS:** This was a preplanned subgroup analysis of the STOP-CP prospective multisite cohort study, which was conducted from January 25, 2017, through September 6, 2018, at 8 emergency departments in the US. Patients 21 years or older with symptoms suggestive of acute coronary syndrome without ST-segment elevation on initial electrocardiogram were included. Analysis took place between February and December 2022. **INTERVENTIONS/EXPOSURES:** Participants with 0- and 1-hour high-sensitivity cardiac troponin T (hs-cTnT) measures were stratified into rule-out, observation, and rule-in zones using the ESC 0/1-hour hs-cTnT algorithm. **MAIN OUTCOMES AND MEASURES:** Cardiac death or MI at 30 days determined by expert adjudicators. **RESULTS:** During the study period, 1430 patients were accrued. In the cohort, 775 individuals (54.2%) were male, 826 (57.8%) were White, and the mean (SD) age was 57.6 (12.8) years. At 30 days, cardiac death or MI occurred in 183 participants (12.8%). Known CAD was present in 449 (31.4%). Among patients with known CAD, the ESC 0/1-hour algorithm classified 178 of 449 (39.6%) into the rule-out zone compared with 648 of 981 (66.1%) without CAD ($P < .001$). Among rule-out zone patients, 30-day cardiac death or MI occurred in 6 of 178 patients (3.4%) with known CAD and 7 of 648 (1.1%) without CAD ($P < .001$). The negative predictive value for 30-day cardiac death or MI was 96.6% (95% CI, 92.8-98.8) among patients with known CAD and 98.9% (95% CI, 97.8-99.6) in patients without known CAD ($P = .04$). **CONCLUSIONS AND RELEVANCE:** Among patients with known CAD, the ESC 0/1-hour hs-cTnT algorithm was unable to safely exclude 30-day cardiac death or MI. This suggests that clinicians should be cautious if using the algorithm in patients with known CAD. The negative predictive value was significantly higher in patients without a history of CAD but remained less than 99%.

Cardiology/Cardiovascular Research

Bhogal S, Garcia-Garcia HM, Klein A, Benzuly K, Mangalmurti S, Moses J, **Alaswad K**, Jaffer F, Yong C, Nanjundappa A, Ben-Dor I, Mintz GS, Hashim H, and Waksman R. Intravascular lithotripsy for the treatment of severely calcified coronary artery disease: A DISRUPT CAD III intravascular ultrasound substudy. *Cardiovasc Revasc Med* 2023; Epub ahead of print. PMID: 36934007. [Full Text](#)

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BACKGROUND: Coronary intravascular lithotripsy (IVL) has emerged as a novel technique for the treatment of severely calcified coronary lesions. We evaluated the mechanism and efficacy of IVL in facilitating optimal stent implantation in heavily calcified coronary lesions using intravascular ultrasound (IVUS). **METHODS:** Forty-six patients were initially enrolled as a part of the Disrupt CAD III study. Of these, 33 had pre-IVL, 24 had post-IVL, and 44 had post-stent IVUS evaluation. The final analysis was performed on 18 patients who had IVUS images interpretable at all three intervals. The primary endpoint was increase in minimum lumen area (MLA) from pre-IVL to post-IVL treatment to post-stenting.

RESULTS: Pre-IVL, MLA was 2.75 ± 0.84 mm(2), percent area stenosis was $67.22 \% \pm 20.95 \%$ with maximum calcium angle of $266.90^\circ \pm 78.30^\circ$, confirming severely calcified lesions. After IVL, MLA increased to 4.06 ± 1.41 mm(2) ($p = 0.0003$), percent area stenosis decreased to $54.80 \% \pm 25.71 \%$ ($p = 0.0009$), and maximum calcium angle decreased to $239.40^\circ \pm 76.73^\circ$ ($p = 0.003$). There was a further increase in MLA to 6.84 ± 2.18 mm(2) ($p < 0.0001$) and decrease in percent area stenosis to $30.33 \% \pm 35.08 \%$ ($p < 0.0001$) post-stenting with minimum stent area of 6.99 ± 2.14 mm(2). The success rate of stent delivery, implantation, and post-stent dilation was 100 % post-IVL. CONCLUSION: In this first study evaluating the mechanism of IVL using IVUS, the primary endpoint of increase in MLA from pre-IVL to post-IVL treatment to post-stenting was successfully achieved. Our study showed that the use of IVL-assisted percutaneous coronary intervention is associated with improved vessel compliance, facilitating optimal stent implantation in de novo severely calcified lesions.

Cardiology/Cardiovascular Research

Devgun J, and Ananthasubramaniam K. Is seeing really believing? The role of the 12 lead electrocardiogram in cardiac amyloidosis. *Trends Cardiovasc Med* 2023; Epub ahead of print. PMID: 36918135. [Full Text](#)

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Cardiology/Cardiovascular Research

DeVon HA, Tintle N, Bronas UG, Mirzaei S, Rivera E, Gutierrez-Kapheim M, Alonso WW, **Keteyian SJ**, Goodyke M, and Dunn SL. Comorbidities are associated with state hopelessness in adults with ischemic heart disease. *Heart Lung* 2023; 60:28-34. PMID: 36878104. [Full Text](#)

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BACKGROUND: In adults with ischemic heart disease (IHD), comorbidities and hopelessness are independently associated with increased risk of mortality. OBJECTIVES: To determine if comorbidities were associated with state and trait hopelessness and explore the influence of specific conditions and hopelessness in individuals hospitalized for IHD. METHODS: Participants completed the State-Trait Hopelessness Scale. Charlson Comorbidity Index (CCI) scores were generated from the medical record. A chi-squared test was used to examine differences in 14 diagnoses included in the CCI by CCI severity. Unadjusted and adjusted linear models were used to explore the relationship between hopelessness levels and the CCI. RESULTS: Participants ($n=132$) were predominantly male (68.9%), with a mean age of 62.6 years, and majority white (97%). The mean CCI was 3.5 (range 0-14), with 36.4% having a score of 1-2 (mild), 41.2% with a score of 3-4 (moderate) and 22.7% with a score of ≥ 5 (severe). The CCI was positively associated with both state ($\beta=0.03$; 95% CI 0.01, 0.05; $p=0.002$) and trait ($\beta=0.04$; 95% CI 0.01, 0.06; $p=0.007$) hopelessness in unadjusted models. The relationship for state hopelessness remained significant after adjusting for multiple demographic characteristics ($\beta=0.03$; 95% CI 0.01, 0.05; $p=0.02$), while trait hopelessness did not. Interaction terms were evaluated, and findings did not differ by age, sex, education level, or diagnosis/type of intervention. CONCLUSION: Hospitalized individuals with IHD with a higher number of comorbidities may benefit from targeted assessment and brief cognitive intervention to identify and ameliorate state hopelessness which has been associated with worse long-term outcomes.

Cardiology/Cardiovascular Research

Drake DH, Zhang P, **Zimmerman KG**, Morrow CD, and Sidebotham DA. Anatomic, stage-based repair of secondary mitral valve disease. *J Thorac Cardiovasc Surg* 2023; Epub ahead of print. PMID: 36775783.

[Full Text](#)

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OBJECTIVE: Intervention for repair of secondary mitral valve disease is frequently associated with recurrent regurgitation. We sought to determine if there was sufficient evidence to support inclusion of anatomic indices of leaflet dysfunction in the management of secondary mitral valve disease. **METHODS:** We performed a systematic review and meta-analysis of published reports comparing anatomic indices of leaflet dysfunction with the complexity of valve repair and the outcome from intervention. Patients were stratified by the severity of leaflet dysfunction. A secondary analysis was performed comparing outcomes when procedural complexity was optimally matched to severity of leaflet dysfunction and when intervention was not matched to dysfunction. **RESULTS:** We identified 6864 publications, of which 65 met inclusion criteria. An association between the severity of leaflet dysfunction and the procedural complexity was highly predictive of satisfactory freedom from recurrent regurgitation. Patients were categorized into 4 groups based on stratification of leaflet dysfunction. Satisfactory results were achieved in 93.7% of patients in whom repair complexity was appropriately matched to severity of leaflet dysfunction and in 68.8% in whom repair was not matched to dysfunction (odds ratio, 0.148; 95% confidence interval, 0.119-0.184; $P < .0001$). **CONCLUSIONS:** For patients with secondary mitral valve disease, satisfactory outcome from valve repair improves when procedural complexity is matched to anatomic indices of leaflet dysfunction. Anatomic indices of leaflet dysfunction should be considered when planning interventions for secondary mitral regurgitation. Routine inclusion of anatomic indices in trial design and reporting should facilitate comparison of results and strengthen guidelines. There are sufficient data to support anatomic staging of secondary mitral valve disease.

Cardiology/Cardiovascular Research

Karacsonyi J, Kostantinis S, Simsek B, Rempakos A, Allana SS, **Alaswad K**, Krestyaninov O, Khatri J, Poommipanit P, Jaffer FA, Choi J, Patel M, Gorgulu S, Koutouzis M, Tsiafoutis I, Sheikh AM, ElGuindy A, Elbarouni B, Patel T, Jefferson B, Wollmuth JR, Yeh R, Karpaliotis D, Kirtane AJ, McEntegart MB, Masoumi A, Davies R, Rangan BV, Mastrodemos OC, Doshi D, Sandoval Y, **Basir MB**, **Megaly MS**, Ungi I, Abi Rafeh N, Goktekin O, and Brilakis ES. Angiographic Features and Clinical Outcomes of Balloon Uncrossable Lesions during Chronic Total Occlusion Percutaneous Coronary Intervention. *J Pers Med* 2023; 13(3). PMID: 36983697. [Full Text](#)

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Background: Balloon uncrossable lesions are defined as lesions that cannot be crossed with a balloon after successful guidewire crossing. **Methods:** We analyzed the association between balloon uncrossable lesions and procedural outcomes of 8671 chronic total occlusions (CTOs) percutaneous coronary interventions (PCIs) performed between 2012 and 2022 at 41 centers. **Results:** The prevalence of balloon uncrossable lesions was 9.2%. The mean patient age was 64.2 ± 10 years and 80% were men. Patients with balloon uncrossable lesions were older (67.3 ± 9 vs. 63.9 ± 10 , $p < 0.001$) and more likely to have prior coronary artery bypass graft surgery (40% vs. 25%, $p < 0.001$) and diabetes mellitus (50% vs. 42%, $p < 0.001$) compared with patients who had balloon crossable lesions. In-stent restenosis (23% vs. 16%, $p < 0.001$), moderate/severe calcification (68% vs. 40%, $p < 0.001$), and moderate/severe proximal vessel tortuosity (36% vs. 25%, $p < 0.001$) were more common in balloon uncrossable lesions. Procedure time (132 (90, 197) vs. 109 (71, 160) min, $p < 0.001$) was longer and the air kerma radiation dose (2.55 (1.41, 4.23) vs. 1.97 (1.10, 3.40) min, $p < 0.001$) was higher in balloon uncrossable lesions, while these lesions displayed lower technical (91% vs. 99%, $p < 0.001$) and procedural (88% vs. 96%, $p < 0.001$) success rates and higher major adverse cardiac event (MACE) rates (3.14% vs. 1.49%, $p < 0.001$). Several techniques were required for balloon uncrossable lesions. **Conclusion:** In a contemporary, multicenter registry, 9.2% of the successfully crossed CTOs were initially balloon uncrossable. Balloon uncrossable lesions exhibited lower technical and procedural success rates and a higher risk of complications compared with balloon crossable lesions.

Cardiology/Cardiovascular Research

Kuchtaruk AA, Sparrow RT, Azzalini L, García S, **Villablanca PA**, Jneid H, Elgendy IY, Alraies MC, Sanjoy SS, Mamas MA, and Bagur R. Unplanned readmissions after Impella mechanical circulatory support. *Int J Cardiol* 2023; Epub ahead of print. PMID: 36893855. [Full Text](#)

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BACKGROUND: Early readmissions significantly impact on patient-wellbeing, burden the health-care system, and are important quality metrics. Data on 30-day readmission following Impella mechanical circulatory support (MCS) are unknown. We aimed to assess the rates, causes and clinical outcomes associated with 30-day unplanned readmissions after Impella mechanical circulatory support (MCS). **METHODS:** Discharged patients who underwent Impella MCS between 2016 and 2019 in the U.S. Nationwide Readmission Database were analyzed. Incidence, causes, and outcomes associated with 30-day unplanned readmissions were assessed. **RESULTS:** Of 22,055 patients who received Impella MCS, 2685 (12.2%) experienced 30-day readmissions. Cardiac readmissions accounted for 51.7% compared to 48.3% of non-cardiac readmissions, and most (70%) patients were readmitted back to the index hospital. Heart failure was the leading cause of cardiac readmissions accounting for 25% of them, whereas infections were the most common cause among non-cardiac readmissions. Patients who were readmitted were significantly older (median age 71 versus 68 years), more likely to be female (31% versus 26%) and had a shorter length-of-stay (index hospitalization, median 8 versus 9 days) compared to those who were not readmitted. Factors independently associated with 30-day readmissions were chronic renal (aOR: 1.46, 95% CI: 1.35-1.57), pulmonary (aOR: 1.23, 95% CI: 1.15-1.33), and liver disease (aOR: 1.38, 95% CI: 1.17-1.63), anemia (aOR: 1.35, 95% CI: 1.26-1.46), female sex (aOR: 1.21, 95% CI: 1.12-1.30), index admission on weekends (aOR: 1.23, 95% CI: 1.13-1.34), STEMI diagnosis (aOR: 1.16, 95% CI: 1.02-1.31), major adverse event during index hospitalization (aOR: 1.11, 95% CI: 1.00-1.24), prolonged length-of-stay (median 9 vs. 8 days, $P < 0.001$), and discharge against medical advice (aOR: 2.06, 95% CI: 1.37-3.09). Significantly higher mortality rates were observed during readmissions to a hospital different than the MCS implanting hospital (12% versus 5.9%, $P < 0.001$). **CONCLUSION:** Thirty-day readmissions after Impella MCS are relatively common and relate to sex, baseline comorbidities, presentation, expected primary payer, discharge destination and initial length of hospital stay. Heart failure was the leading cause of cardiac readmissions, whereas infections were the most common cause among non-cardiac readmissions. Most patients were readmitted to the same hospital as their index admission for MCS. Higher mortality rates were observed when patients were readmitted to a different hospital.

Cardiology/Cardiovascular Research

Lanfeare DE, Luzum JA, She R, Li J, Sabbah HN, Zeld N, Liu B, Peterson E, and Keoki Williams L. Validation of a Polygenic Score for Beta-Blocker Survival Benefit in Patients With Heart Failure Using the United Kingdom Biobank. *Circ Genom Precis Med* 2023; e003835. Epub ahead of print. PMID: 36866666. [Full Text](#)

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Cardiology/Cardiovascular Research

Lanfeare DE, Njoroge JN, Adams KF, Anand I, Fang JC, Ramires F, Sliwa-Hahnle K, Badat A, Burgess L, Gorodeski EZ, Williams C, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon S, Miao ZM, Claggett BL, Heitner SB, Kupfer S, Malik FI, and Teerlink JR. Omecamtiv Mecarbil in Black Patients With Heart Failure and Reduced Ejection Fraction: Insights From GALACTIC-HF. *JACC Heart Fail* 2023; Epub ahead of print. PMID: 36881396. [Full Text](#)

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BACKGROUND: Omecamtiv mecarbil improves cardiovascular outcomes in patients with heart failure (HF) with reduced ejection fraction (EF). Consistency of drug benefit across race is a key public health topic. **OBJECTIVES:** The purpose of this study was to evaluate the effect of omecamtiv mecarbil among self-identified Black patients. **METHODS:** In GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) patients with symptomatic HF, elevated natriuretic peptides, and left ventricular ejection fraction (LVEF) $\leq 35\%$ were randomized to omecamtiv mecarbil or placebo. The primary outcome was a composite of time to first event of HF or cardiovascular death. The authors analyzed treatment effects in Black vs White patients in countries contributing at least 10 Black participants. **RESULTS:** Black patients accounted for 6.8% (n = 562) of overall enrollment and 29% of U.S. enrollment. Most Black patients enrolled in the United States, South Africa, and Brazil (n = 535, 95%). Compared with White patients enrolled from these countries (n = 1,129), Black patients differed in demographics, comorbid conditions, received higher rates of medical therapy and lower rates of device therapies, and experienced higher overall event rates. The effect of omecamtiv mecarbil was consistent in Black vs White patients, with no difference in the primary endpoint (HR = 0.83 vs 0.88, P-interaction = 0.66), similar improvements in heart rate and N-terminal pro-B-type natriuretic peptide, and no significant safety signals. Among endpoints, the only nominally significant treatment-by-race interaction was the placebo-corrected change in blood pressure from baseline in Black vs White patients (+3.4 vs -0.7 mm Hg, P-interaction = 0.02). **CONCLUSIONS:** GALACTIC-HF enrolled more Black patients than other recent HF trials. Black patients treated with omecamtiv mecarbil had similar benefit and safety compared with White counterparts.

Cardiology/Cardiovascular Research

Maskoun W, Alqam B, Habash F, Gheith Z, Sawada SG, and Vallurupalli S. Sex Differences in Stress-Induced (Takotsubo) Cardiomyopathy. *CJC Open* 2023; 5(2):120-127. PMID: 36880077. [Full Text](#)

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BACKGROUND: Takotsubo cardiomyopathy (TC) affects predominantly women. Prior studies have suggested that men might have worse short-term outcomes, but limited data are available regarding long-term outcomes. We hypothesized that men, compared to women, with TC have worse short- and long-term outcomes. **METHODS:** A retrospective study of patients diagnosed with TC between 2005 and 2018 in the Veteran Affairs system was performed. Primary outcomes were in-hospital death, 30-day risk of stroke, death, and long-term mortality. **RESULTS:** A total of 641 patients were included (444 men [69%]; 197 women [31%]). Men had a higher median age (65 vs 60 years; $P < 0.001$), and women were more

likely to present with chest pain (68.7% vs 44.1%; $P < 0.001$). Physical triggers were more common in men (68.7% vs 44.1%, $P < 0.001$). Men had a higher in-hospital mortality rate (8.1% vs 1%; $P < 0.001$). On multivariable regression analysis, female sex was an independent predictor for improved in-hospital mortality, compared to men (odds ratio 0.25, 95% confidence interval 0.06-1.10; $P = 0.04$). On 30-day follow-up, no difference occurred in a combined outcome of stroke and death (3.9% vs 1.5%; $P = 0.12$). On long-term follow-up (3.7 ± 3.1 years), female sex was identified as an independent predictor of lower mortality (hazard ratio 0.71, 95% CI 0.51-0.97; $P = 0.032$). Women were more likely to have TC recurrence (3.6% vs 1.1%; $P = 0.04$). **CONCLUSIONS:** In our study with a predominantly male population, men had less-favourable short- and long-term outcomes after TC, compared to those of women.

Cardiology/Cardiovascular Research

Megaly M, Zakhour S, Karacsonyi J, **Basir MB**, Kunkel K, Gupta A, Neupane S, **Alqarqaz M**, Brilakis ES, and **Alaswad K**. Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention of the Left Anterior Descending Artery. *Am J Cardiol* 2023; 193:75-82. PMID: 36878056. [Full Text](#)

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The left anterior descending artery (LAD) subtends a large myocardial territory. The outcomes of LAD chronic total occlusion (CTO) percutaneous coronary intervention (PCI) have received limited study. We performed a retrospective analysis of all patients who underwent LAD CTO PCI at a high-volume single center. Outcomes included in-hospital and long-term major adverse cardiovascular events (MACEs) and changes in left ventricular ejection fraction (LVEF). We performed a subgroup analysis of patients with ischemic cardiomyopathy, defined as an LVEF of 40% or less. From December 2014 to February 2021, 237 patients underwent LAD CTO PCI. The technical success rate was 97.4%, and the in-hospital MACE rate was 5.4%. A landmark analysis after hospital discharge showed an overall survival of 92% and 85% MACE-free survival at 2 years. There was no difference in overall survival or MACE-free survival between those who had ischemic cardiomyopathy versus those who did not. In patients with ischemic cardiomyopathy, LAD CTO PCI was associated with significant improvement in LVEF (10.9% at 9 months), which was further pronounced when these patients had a proximal LAD CTO and were on optimal medical therapy (14% at 6 months). In a single high-volume center, LAD CTO PCI was associated with 92% overall survival at 2 years, with no difference in survival between patients with or without ischemic cardiomyopathy. LAD CTO PCI was associated with an absolute 10% increase in LVEF at 9 months in patients with ischemic cardiomyopathy.

Cardiology/Cardiovascular Research

Rempakos A, Kostantinis S, Simsek B, Karacsonyi J, Choi JW, Poommipanit P, Khatri JJ, Jaber W, Rinfret S, Nicholson W, Gorgulu S, Jaffer FA, Chandwaney R, Ybarra LF, Bagur R, **Alaswad K**, Krestyaninov O, Khelinskii D, Karmpalotis D, Uretsky BF, Soylyu K, Yildirim U, Potluri S, Rangan BV, Mastrodemos OC, Allana S, Sandoval Y, Burke NM, and Brilakis ES. Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention After a Previous Failed Attempt. *Am J Cardiol* 2023; 193:61-69. PMID: 36871531. [Full Text](#)

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The impact of a previous failure on procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. We examined the clinical and angiographic characteristics and procedural outcomes of 9,393 patients who underwent 9,560 CTO PCIs at 42 United States and non-United States centers between 2012 and 2022. A total of 1,904 CTO lesions (20%) had a previous failed PCI attempt. Patients who underwent reattempt CTO PCI were more likely to have a family history of coronary artery disease (37% vs 31%, $p < 0.001$) and dyslipidemia (87.9% vs 84.3%, $p < 0.001$) but were less likely to have heart failure (25.1% vs 29.5%; $p < 0.001$) and cerebrovascular disease (8.7% vs 10.4%, $p = 0.04$). Patients with previous failure had a higher Japanese CTO (3.33 ± 1.16 vs 2.12 ± 1.19 , $p < 0.001$) score and required longer procedure (120 vs 111 minutes, $p < 0.001$) and fluoroscopy (46.9 vs 40.4 minutes, $p < 0.001$) times and higher air kerma radiation dose (2.3 vs 2.1 gray, $p = 0.013$). Technical success rates (84.3% vs 86.5%, $p = 0.011$) were lower in patients with a previous failure compared with patients who underwent first-attempt CTO PCI with no significant difference in in-hospital major adverse cardiac events. After adjusting for potential confounders, a previous failure was not associated with technical failure. Operators performing >30 CTO PCIs annually were more likely to achieve technical success in patients with previous failure. In conclusion, a previous failed CTO PCI attempt was associated with higher lesion complexity, longer procedure time, and lower technical success; however, the association with lower technical success did not remain significant in multivariable analysis.

Cardiology/Cardiovascular Research

Saw J, Holmes DR, Cavalcante JL, Freeman JV, Goldsweig AM, Kavinsky CJ, Moussa ID, Munger TM, Price MJ, Reisman M, Sherwood MW, Turi ZG, **Wang DD**, and Whisenant BK. SCAI/HRS Expert Consensus Statement on Transcatheter Left Atrial Appendage Closure. *JACC Cardiovasc Interv* 2023; Epub ahead of print. PMID: 36990858. [Full Text](#)

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Exclusion of the left atrial appendage to reduce thromboembolic risk related to atrial fibrillation was first performed surgically in 1949. Over the past 2 decades, the field of transcatheter endovascular left atrial appendage closure (LAAC) has rapidly expanded, with a myriad of devices approved or in clinical development. The number of LAAC procedures performed in the United States and worldwide has increased exponentially since the Food and Drug Administration approval of the WATCHMAN (Boston Scientific) device in 2015. The Society for Cardiovascular Angiography & Interventions (SCAI) has previously published statements in 2015 and 2016 providing societal overview of the technology and institutional and operator requirements for LAAC. Since then, results from several important clinical trials and registries have been published, technical expertise and clinical practice have matured over time, and the device and imaging technologies have evolved. Therefore, SCAI prioritized the development of an updated consensus statement to provide recommendations on contemporary, evidence-based best practices for transcatheter LAAC focusing on endovascular devices.

Cardiology/Cardiovascular Research

Simsek B, Khatri J, Young L, Kostantinis S, Karacsonyi J, Rempakos A, **Alaswad K**, Jaffer FA, Doshi D, Gorgulu S, Goktekin O, Kerrigan J, Haddad EV, Rinfret S, Jaber WA, Nicholson W, Krestyaninov O, Khelimski D, Choi JW, Patel TN, Jefferson BK, Bradley SM, Rao SV, Rangan BV, Allana SS, Sandoval Y, Burke MN, Brilakis ES, and Poommipanit PB. Same day discharge versus overnight observation following chronic total occlusion percutaneous coronary intervention: Insights from the PROGRESS-CTO registry. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 36960766. [Full Text](#)

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BACKGROUND: Same day discharge (SDD) following chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. **METHODS:** We evaluated the clinical, angiographic, and procedural characteristics of patients discharged the same day versus those kept for overnight observation in the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS-CTO, NCT02061436). **RESULTS:** Of the 7181 patients who underwent CTO PCI, 943 (13%) had SDD. The SDD rate increased from 3% in 2015 to 21% in 2022. Patients with SDD were less likely to have a history of heart failure (21% vs. 26%, $p = 0.005$), chronic lung disease (10% vs. 15%, $p = 0.001$), or anemia (12% vs. 19%, $p < 0.001$). Technical success (87% vs. 88%, $p = 0.289$) was similar, but in-hospital major adverse cardiovascular events (0.0% vs. 0.4%, $p = 0.041$) were lower in SDD. In multivariable logistic regression analysis, prior myocardial infarction odds ratio (OR): 0.71 (95% confidence interval [CI]: 0.59-0.87, $p = 0.001$), chronic lung disease OR: 0.64 (95% CI: 0.47-0.88, $p = 0.006$), and increasing procedure time OR: 0.93 (95% CI: 0.91-0.95, $p < 0.001$, per 10-min increase) were associated with overnight observation, while radial-only access OR: 2.45 (95% CI: 2.03-2.96, $p < 0.001$) had the strongest association with SDD. In the SDD, 2 (0.4%) of 514 patients were readmitted, due to retroperitoneal bleeding ($n = 1$) and ischemic stroke ($n = 1$). **CONCLUSION:** The overall frequency of SDD after CTO PCI was 13% and has been increasing over time. SDD is feasible in select patients following CTO PCI, and radial-only access had the strongest association with SDD.

Cardiology/Cardiovascular Research

Singh HP, Maraj D, Hawes E, and Memon M. New-Onset Heart Failure and Ischemic Stroke in Non-compaction Cardiomyopathy: A Case Report. *Cureus* 2023; 15(2):e35371. PMID: 36994256. [Full Text](#)

Internal Medicine, Henry Ford Health System, Jackson, USA.

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Cardiology, Henry Ford Health System, Jackson, USA.

Left ventricular non-compaction (LVNC) cardiomyopathy is an embryological disorder of endocardial trabeculation and can cause heart failure, arrhythmias, and thromboembolism. Lifelong anticoagulation is indicated in patients with reduced ejection fraction due to high risks of thromboembolism. Reduced ejection fraction can develop in these patients as a consequence of this cardiomyopathy, thereby increasing the risk of intracardiac thrombus formation. This new-onset reduced ejection fraction may develop rapidly, which may not be amenable to detection by routine screening. We present a case of non-compaction cardiomyopathy (NCC) with a previously normal ejection fraction who had an ischemic stroke and was found to have new-onset reduced ejection fraction.

Cardiology/Cardiovascular Research

Suhail H, Peng H, Xu J, Sabbah HN, Matrougui K, Liao TD, Ortiz PA, Bernstein KE, and Rhaleb NE. Knockout of ACE-N facilitates improved cardiac function after myocardial infarction. *J Mol Cell Cardiol Plus* 2023; 3. PMID: 36778784. [Full Text](#)

Department of Internal Medicine, Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, MI 48202, USA.

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Angiotensin-converting enzyme (ACE) hydrolyzes N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) into inactive fragments through its N-terminal site (ACE-N). We previously showed that Ac-SDKP mediates ACE inhibitors' cardiac effects. Whether increased bioavailability of endogenous Ac-SDKP caused by knocking out ACE-N also improves cardiac function in myocardial infarction (MI)-induced heart failure (HF) is unknown. Wild-type (WT) and ACE-N knockout (ACE-NKO) mice were subjected to MI by ligating the left anterior descending artery and treated with vehicle or Ac-SDKP (1.6 mg/kg/day, s.c.) for 5 weeks, after which echocardiography was performed and left ventricles (LV) were harvested for histology and molecular biology studies. ACE-NKO mice showed increased plasma Ac-SDKP concentrations in both sham and MI group compared to WT. Exogenous Ac-SDKP further increased its circulating concentrations in WT and ACE-NKO. Shortening (SF) and ejection (EF) fractions were significantly decreased in both WT and ACE-NKO mice post-MI, but ACE-NKO mice exhibited significantly lesser decrease. Exogenous Ac-SDKP ameliorated cardiac function post-MI only in WT but failed to show any additive improvement in ACE-NKO mice. Sarcoendoplasmic reticulum calcium transport ATPase (SERCA2), a marker of cardiac function and calcium homeostasis, was significantly decreased in WT post-MI but rescued with Ac-SDKP, whereas ACE-NKO mice displayed less loss of SERCA2 expression. Our study demonstrates that gene deletion of ACE-N resulted in improved LV cardiac function in mice post-MI, which is likely mediated by increased circulating Ac-SDKP and minimally reduced expression of SERCA2. Thus, future development of specific and selective inhibitors for ACE-N could represent a novel approach to increase endogenous Ac-SDKP toward protecting the heart from post-MI remodeling.

Center for Health Policy and Health Services Research

Anvari MS, **Hampton T**, Tong MP, **Kahn G**, Triemstra JD, Magidson JF, and **Felton JW**. Behavioral Activation Disseminated by Non-Mental Health Professionals, Paraprofessionals, and Peers: A Systematic Review. *Behav Ther* 2023. PMID: Not assigned. [Full Text](#)

M.S. Anvari, University of Maryland, College Park, Department of Psychology, 4049 Campus Drive, College Park, MD

There is a striking disparity between the number of individuals with significant mental health concerns and those who are able to access care globally. One promising solution to expanding the mental health taskforce is task-sharing, or employing nonspecialists in the delivery of evidence-based interventions. Behavioral activation (BA), a brief intervention that focuses on scheduling rewarding activities into one's daily life, may have promise for delivery using task-sharing approaches due to its straightforward, flexible nature. The aim of this systematic review was to examine the current state of the literature on non-specialist-delivered BA and evaluate the evidence base of this approach. Three databases (Pubmed, PsycInfo, and Cochrane) were searched, and all articles were screened for inclusion criteria by two research assistants, included the review of titles, abstracts, and full-text. The final dataset consisted of 13 research studies, represented through 15 articles. A meta-analysis was conducted to examine the overall pooled effects of peer-delivered BA on depressive symptoms (the most widely examined clinical outcome). Studies reported on effectiveness and implementation outcomes of non-specialist-delivered BA for depression, substance use, loneliness, trauma survivors, and individuals with comorbid physical health conditions. Results provide initial support for the effectiveness of BA utilizing a task-sharing approach, and highlight the feasibility and acceptability of using nonspecialists to deliver BA in a variety of contexts, including low-resource settings.

Center for Health Policy and Health Services Research

Anvari MS, Kleinman MB, Dean D, Bradley VD, Abidogun TM, Hines AC, Seitz-Brown CJ, **Felton JW**, and Magidson JF. Adapting a Behavioral Activation Intervention for Opioid Use Disorder and Methadone Treatment Retention for Peer Delivery in a Low-Resource Setting: A Case Series. *Cogn Behav Pract* 2023. PMID: Not assigned. [Request Article](#)

M.S. Anvari, Department of Psychology, 4049 Campus Drive, College Park, MD, United States

While methadone treatment (MT) is effective in treating opioid use disorder (OUD), retention remains an issue nationwide, especially among low-income, minoritized populations. Peer recovery specialists (PRSs), individuals with lived substance use experience, are particularly well suited to support vulnerable populations, though often are not trained in delivering evidence-based interventions. Thus, our team developed a Type 1 hybrid effectiveness-implementation open-label pilot trial to evaluate the effectiveness of PRS-delivered BA (Peer Activate) in improving MT retention and establish feasibility, acceptability and PRS fidelity of the intervention. In this case series, we provide a more in-depth depiction of the adaption of Peer Activate and present three cases to illustrate how Peer Activate can be implemented among patients in routine MT care and adapted to meet the needs of varying clinical presentations. We include descriptive data on participant substance use and MT outcomes to supplement the narrative discussion. While varying participant presentations and needs presented challenges to the PRS interventionist, the PRS utilized his shared, lived substance use and recovery experiences and met participants where they were at, as well as successfully used BA techniques, ultimately leading to intervention success.

Center for Health Policy and Health Services Research

Anvari MS, Kleinman MB, Dean D, Rose AL, Bradley VD, Hines AC, Abidogun TM, **Felton JW**, and Magidson JF. A Pilot Study of Training Peer Recovery Specialists in Behavioral Activation in the United States: Preliminary Outcomes and Predictors of Competence. *Int J Environ Res Public Health* 2023; 20(5). PMID: 36900912. [Full Text](#)

Department of Psychology, University of Maryland, College Park, College Park, MD 20742, USA.
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BACKGROUND: The peer recovery specialist (PRS) workforce has rapidly expanded to increase access to substance-use disorder services for underserved communities. PRSs are not typically trained in evidence-based interventions (EBIs) outside of motivational interviewing, although evidence demonstrates the feasibility of PRS delivery of certain EBIs, such as a brief behavioral intervention,

behavioral activation. However, characteristics that predict PRS competency in delivering EBIs such as behavioral activation remain unknown, and are critical for PRS selection, training, and supervision if the PRS role is expanded. This study aimed to explore the outcomes of a brief PRS training period in behavioral activation and identify predictors of competence. **METHOD:** Twenty PRSs in the United States completed a two-hour training on PRS-delivered behavioral activation. Participants completed baseline and post-training assessments, including roleplay and assessments of PRS characteristics, attitudes towards EBIs, and theoretically relevant personality constructs. Roleplays were coded for competence (behavioral activation specific and PRS skills more broadly, i.e., PRS competence) and changes were assessed from baseline to post-training. Linear regression models tested factors predicting post-training competence, controlling for baseline competence. **RESULTS:** There was a significant pre-post increase in behavioral activation competence ($t = -7.02, p < 0.001$). Years working as a PRS significantly predicted post-training behavioral activation skills ($B = 0.16, p = 0.005$). No variables predicted post-training PRS competence. **CONCLUSIONS:** This study provides preliminary evidence that behavioral activation may be appropriate for dissemination to PRSs through brief trainings, particularly for PRSs with more work experience. However, additional research is needed to examine predictors of competence among PRSs.

Center for Health Policy and Health Services Research

Kleinman MB, Anvari MS, Bradley VD, **Felton JW**, Belcher AM, Seitz-Brown CJ, Greenblatt AD, Dean D, Bennett M, and Magidson JF. "Sometimes you have to take the person and show them how": adapting behavioral activation for peer recovery specialist-delivery to improve methadone treatment retention. *Subst Abuse Treat Prev Policy* 2023; 18(1):15. PMID: 36879304. [Full Text](#)

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BACKGROUND: Despite efficacy of medication for opioid use disorder, low-income, ethno-racial minoritized populations often experience poor opioid use disorder treatment outcomes. Peer recovery specialists, individuals with lived experience of substance use and recovery, are well-positioned to engage hard-to-reach patients in treatment for opioid use disorder. Traditionally, peer recovery specialists have focused on bridging to care rather than delivering interventions. This study builds on research in other low-resource contexts that has explored peer delivery of evidence-based interventions, such as behavioral activation, to expand access to care. **METHODS:** We sought feedback on the feasibility and acceptability of a peer recovery specialist-delivered behavioral activation intervention supporting retention in methadone treatment by increasing positive reinforcement. We recruited patients and staff at a community-based methadone treatment center and peer recovery specialist working across Baltimore City, Maryland, USA. Semi-structured interviews and focus groups inquired about the feasibility and acceptability of behavioral activation, recommendations for adaptation, and acceptability of working with a peer alongside methadone treatment. **RESULTS:** Participants ($N = 32$) shared that peer recovery specialist-delivered behavioral activation could be feasible and acceptable with adaptations. They described common challenges associated with unstructured time, for which behavioral activation could be particularly relevant. Participants provided examples of how a peer-delivered intervention could fit well in the context of methadone treatment, emphasizing the importance of flexibility and specific peer qualities. **CONCLUSIONS:** Improving medication for opioid use disorder outcomes is a national priority that must be met with cost-effective, sustainable strategies to support individuals in treatment. Findings will guide adaptation of a peer recovery specialist-delivered behavioral activation intervention to improve methadone treatment retention for underserved, ethno-racial minoritized individuals living with opioid use disorder.

Center for Health Policy and Health Services Research

Lanfear DE, Luzum JA, She R, Li J, Sabbah HN, Zeld N, Liu B, Peterson E, and Keoki Williams L. Validation of a Polygenic Score for Beta-Blocker Survival Benefit in Patients With Heart Failure Using the United Kingdom Biobank. *Circ Genom Precis Med* 2023; e003835. Epub ahead of print. PMID: 36866666. [Full Text](#)

Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Hospital, Henry Ford Health System, Detroit, MI. (D.E.L., J.A.L., N.Z., L.K.W.).
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Center for Health Policy and Health Services Research

Pampati S, Dana Flanders W, Zhang Q, **Ahmedani BK**, Bhasin S, Getahun D, Lash TL, McCracken C, Sandberg DE, Silverberg MJ, Tangpricha V, Vupputuri S, and Goodman M. Prevalence of Self-Inflicted Injuries Among Transgender and Gender Diverse Adolescents and Young Adults Compared to Their Peers: An Examination of Interaction with Mental Health Morbidity. *Ann Epidemiol* 2023; Epub ahead of print. PMID: 36907519. [Full Text](#)

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Division of Endocrinology, Metabolism and Lipids, Department of Medicine, Emory University, School of Medicine, Atlanta, GA; The Atlanta VA Medical Center, Atlanta GA.

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PURPOSE: Compare occurrence of self-inflicted injuries among transgender and gender diverse (TGD) youth to that of their cisgender peers while accounting for mental health diagnoses. **METHODS:** Review of electronic health records from three integrated health care systems identified 1087 transfeminine and 1431 transmasculine adolescents and young adults. Poisson regression was used to calculate prevalence ratios comparing the proportion of TGD participants with at least one self-inflicted injury (a surrogate for suicide attempt) before index date (first evidence of TGD status) to the corresponding proportions in presumed cisgender male and female referents matched on age, race/ethnicity and health plan. Interactions between gender identities and mental health diagnoses were assessed on multiplicative and additive scales. **RESULTS:** In cisgender persons, self-inflicted injuries were concentrated among those with multiple mental health diagnoses. In contrast, the prevalence of self-inflicted injuries among TGD adolescents and young adults was high even in the absence of mental health diagnoses. Results were consistent with positive additive interaction and negative multiplicative interaction. **CONCLUSIONS:** Universal suicide prevention efforts for all youth, including those with no mental health diagnoses, and more intensive suicide prevention efforts for TGD adolescents and young adults and those with at least one mental health diagnosis are warranted.

Center for Health Policy and Health Services Research

Selim R, Gordon SC, Zhou Y, Zhang T, Lu M, Daida YG, Boscarino JA, Schmidt MA, **Trudeau S, Rupp LB**, and **Gonzalez HC**. Impact of hepatitis C treatment status on risk of Parkinson's disease and secondary parkinsonism in the era of direct-acting antivirals. *J Viral Hepat* 2023; Epub ahead of print. PMID: 36872452. [Full Text](#)

Department of Gastroenterology and Hepatology, Henry Ford Health, Detroit, Michigan, United States.
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Research suggests a possible link between chronic infection with hepatitis C virus (HCV) and the development of Parkinson's Disease (PD) and secondary Parkinsonism (PKM). We investigated the impact of antiviral treatment status (untreated, interferon [IFN] treated, direct-acting antiviral [DAA] treated) and outcome (treatment failure [TF] or sustained virological response [SVR]) on risk of PD/PKM among patients with HCV. Using data from the Chronic Hepatitis Cohort Study (CHeCS), we applied a discrete time-to-event approach with PD/PKM as the outcome. We performed univariate followed by a multivariable modelling that used time-varying covariates, propensity scores to adjust for potential treatment selection bias and death as a competing risk. Among 17,199 confirmed HCV patients, we observed 54 incident cases of PD/PKM during a mean follow-up period of 17 years; 3753 patients died during follow-up. There was no significant association between treatment status/outcome and risk of PD/PKM. Type 2 diabetes tripled risk (hazard ratio [HR] 3.05; 95% CI 1.75-5.32; $p < .0001$) and presence of cirrhosis doubled risk of PD/PKM (HR 2.13, 95% CI 1.31-3.47). BMI >30 was associated with roughly 50% lower risk of PD/PKM than BMI <25 (HR 0.43; 0.22-0.84; $p = .0138$). After adjustment for treatment selection bias, we did not observe a significant association between HCV patients' antiviral treatment status/outcome on risk of PD/PKM. Several clinical risk factors-diabetes, cirrhosis and BMI-were associated with PD/PKM.

Center for Health Policy and Health Services Research

Shortreed SM, Walker RL, Johnson E, Wellman R, Cruz M, Ziebell R, Coley RY, Yaseen ZS, Dharmarajan S, Penfold RB, **Ahmedani BK**, Rossom RC, Beck A, Boggs JM, and Simon GE. Complex modeling with detailed temporal predictors does not improve health records-based suicide risk prediction. *NPJ Digit Med* 2023; 6(1):47. PMID: 36959268. [Full Text](#)

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Suicide risk prediction models can identify individuals for targeted intervention. Discussions of transparency, explainability, and transportability in machine learning presume complex prediction models with many variables outperform simpler models. We compared random forest, artificial neural network, and ensemble models with 1500 temporally defined predictors to logistic regression models. Data from 25,800,888 mental health visits made by 3,081,420 individuals in 7 health systems were used to train and evaluate suicidal behavior prediction models. Model performance was compared across several measures. All models performed well (area under the receiver operating curve [AUC]: 0.794-0.858). Ensemble models performed best, but improvements over a regression model with 100 predictors were minimal (AUC improvements: 0.006-0.020). Results are consistent across performance metrics and subgroups defined by race, ethnicity, and sex. Our results suggest simpler parametric models, which are easier to implement as part of routine clinical practice, perform comparably to more complex machine learning methods.

Center for Individualized and Genomic Medicine Research

Lanfear DE, Luzum JA, She R, Li J, Sabbah HN, Zeld N, Liu B, Peterson E, and Keoki Williams L. Validation of a Polygenic Score for Beta-Blocker Survival Benefit in Patients With Heart Failure Using the United Kingdom Biobank. *Circ Genom Precis Med* 2023; e003835. Epub ahead of print. PMID: 36866666. [Full Text](#)

Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Hospital, Henry Ford Health System, Detroit, MI. (D.E.L., J.A.L., N.Z., L.K.W.).
Heart and Vascular Institute, Henry Ford Health System, Detroit, MI. (D.E.L., H.N.S.).
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Department of Public Health Sciences, Henry Ford Health System, Detroit, MI. (R.S., J.L., B.L., E.P.).

Dermatology

Ceresnie MS, Owji S, Seale L, Friedman BJ, and Veenstra J. A bilateral periocular acneiform eruption. *Clin Exp Dermatol* 2023; Epub ahead of print. PMID: 36994905. [Full Text](#)

Department of Dermatology, Henry Ford Health, Detroit, Michigan, USA.
The University of Texas Medical Branch, Galveston, Texas, USA.

Chloracne is an extremely rare acneiform eruption triggered by exposure to chemicals containing halogenated aromatic hydrocarbons. Unlike acne, which tends to affect areas with a high concentration of sebaceous glands, the most common areas affected by chloracne are the periocular, periauricular, genital, and axillary regions. Histopathology showing characteristic loss of sebaceous glands is supportive of the diagnosis. Numerous open comedones varying in size from small to large and yellow-white inflammatory papules may be appreciated on dermoscopy. Clinicopathologic correlation is essential for clinching the diagnosis. It is important to identify the likely trigger, as avoidance of the substance is the mainstay of treatment. Therapies such as oral steroids and topical and oral retinoids have not demonstrated efficacy in the treatment of chloracne. We present a case of localized chloracne in a Black patient and describe the clinical, dermoscopic, and histopathologic findings to increase awareness of its manifestations in patients with skin of color.

Dermatology

Draelos ZD, Adam DN, Hong CH, Lebwohl MG, Lynde CW, Nahm WK, Papp KA, Pariser DM, Stein Gold L, Stewart D, Higham RC, Berk DR, Krupa D, and Burnett P. Efficacy and safety of roflumilast cream for chronic plaque psoriasis with facial/neck and intertriginous area involvement: a post hoc analysis from a randomized controlled trial. *Br J Dermatol* 2023; Epub ahead of print. PMID: 36890712. [Full Text](#)

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Probity Medical Research and K Papp Clinical Research, Waterloo, ON, Canada.
Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA, USA.
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Michigan Center for Skin Care Research, Clinton Township, MI, USA.
Arcutis, Inc., Westlake Village, CA, USA.

Dermatology

Eichenfield LF, **Stein Gold L**, Kircik LH, Werschler WP, Beer K, Draelos ZD, Tanghetti EA, Papp KA, Baldwin H, Lain E, Sadick N, Gooderham MJ, and Konda A. Triple-combination clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% gel for moderate-to-severe acne in children and adolescents: Randomized phase 2 study. *Pediatr Dermatol* 2023; Epub ahead of print. PMID: 36949579.

[Full Text](#)

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Department of Dermatology, Queens University, Peterborough, Ontario, Canada.

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Ortho Dermatologics (Ortho Dermatologics is a Division of Bausch Health US, LLC), Bridgewater, New Jersey, USA.

BACKGROUND/OBJECTIVES: Topical clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% gel (IDP-126) is the first fixed-dose triple-combination formulation in development for acne. This post hoc analysis investigated efficacy and safety of IDP-126 in children and adolescents with moderate-to-severe acne. **METHODS:** In a randomized, double-blind phase 2 study (NCT03170388), participants ≥ 9 years of age with moderate-to-severe acne were eligible for randomization (1:1:1:1) to once-daily IDP-126, one of three dyad combination gels, or vehicle gel for 12 weeks. This post hoc analysis of pediatric participants ($n = 394$) included children and adolescents up to 17 years of age. Assessments included treatment success, inflammatory/noninflammatory lesion counts, Acne-Specific Quality of Life (Acne-QoL) questionnaire, treatment-emergent adverse events (TEAEs), and cutaneous safety/tolerability. **RESULTS:** At Week 12, treatment success rates were significantly greater with IDP-126 (55.8%) than with vehicle (5.7%; $p < .001$) or any of the dyad combinations (range: 30.8%-33.9%; $p < .01$, all). Lesion reductions with IDP-126 were also significantly greater than with vehicle (inflammatory: 78.3% vs. 45.1%; noninflammatory: 70.0% vs. 37.6%; $p < .001$, both) and 9.2%-16.6% greater than with any of the dyad combinations. Increases (improvements) from baseline in Acne-QoL domain scores were generally greater with IDP-126 than in any other treatment group. The most common treatment-related TEAEs across treatment groups were application site pain and dryness. Most treatment-related TEAEs were of mild-to-moderate severity. **CONCLUSION:** IDP-126 gel-a novel fixed-dose, triple-combination topical formulation for acne-demonstrated superior efficacy to vehicle and three dyad component gels and was well tolerated in children and adolescents with moderate-to-severe acne.

Dermatology

Ezekwe N, Neelam R, **Jones B**, **Ozog D**, and **Hamzavi I**. Retrospective Examination of Keloid Formation after CO(2) Excision Therapy for Hidradenitis Suppurativa. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 36905960. [Full Text](#)

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Dermatology

Filligim SE, **Artz C**, and **Rambhatla P**. Granulomatosis With Polyangiitis Presenting With Strawberry Gums. *JAMA Dermatol* 2023; Epub ahead of print. PMID: 36884226. [Full Text](#)

University of South Alabama College of Medicine, Mobile.
Department of Dermatology, Henry Ford Health System, Detroit, Michigan.

This case report describes an ulcerated violaceous nodule on the right nasal ala as well as 3 small ulcers on the neck, back, and buttocks.

Dermatology

Garg A, Rawal S, Akilov O, Alavi A, Ardon C, Bechara FG, Cohen AD, Cohen SR, Daveluy S, Del Marmol V, Delage M, Esmann S, Fisher S, Giamarellos-Bourboulis EJ, Glowaczewska A, Goldfarb N, Gonzalez Brant E, Grimstad Ø, Guilbault S, **Hamzavi I**, Hughes R, Ingram JR, Jemec GBE, Ju Q, Kappe N, Kirby B, Kirby JS, Lowes MA, Matusiak L, Micha S, Micheletti RG, Miller AP, Moseng D, Naik HB, Nassif A, Nikolakis G, Paek SY, Pascual JC, Prens E, Resnik B, Riad H, Sayed C, Smith SD, Soliman Y, Szepietowski JC, Tan J, Thorlacius L, Tzellos T, van der Zee HH, Villumsen B, Wang L, Zouboulis CC, and Strunk A. Factors associated with disease-specific life impact in patients with hidradenitis suppurativa: results from the Global VOICE project. *Br J Dermatol* 2023; Epub ahead of print. PMID: 36891871. [Full Text](#)

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Dermatology

Granger C, Passeron T, Trullas C, Hosenally M, Sokeechand BN, Krutmann J, and **Lim HW**. Outdoor clinical testing with reference sunscreens to determine differences in skin response between populations of different ethnicity: A combined data analysis from 128 subjects. *Photodermatol Photoimmunol Photomed* 2023; Epub ahead of print. PMID: 36867064. [Full Text](#)

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BACKGROUND: Two previously published clinical studies by our group assessed erythema and pigmentation responses in outdoor conditions with three reference sunscreens, comparing their effectiveness under the full spectrum of natural sunlight. These studies followed an almost identical protocol but were conducted in two different locations and in two ethnic groups: broadly, Chinese (Singapore) and White European (Mauritius). We analysed the data from these two study populations to compare differences in skin response according to ethnicity. **METHODS:** The analysis included 128 subjects (53 were Chinese from Singapore and 75 were White European from Mauritius and Singapore). Products used were the reference sunscreens P3 (sun protection factor [SPF] 15), P5 (SPF 30) and P8 (SPF 50+) from ISO norm 24444:2019. Participants were exposed to outdoor sunlight for 2-3 h, depending on baseline ITA. Endpoints were erythema at 24 h: clinical score and colorimetry (Δa^*) and pigmentation at 1 week based on colorimetry (ΔL^* and ΔITA). **RESULTS:** Among those with baseline ITA > 41, there were differences in erythematous response between the Chinese and White European groups, the White European group being more erythematous and also having a higher rate of photoprotection failure particularly at SPF 15 and 30. **CONCLUSION:** Differences in skin response to sun influenced by ethnicity should be taken into account when making recommendations on sun safety.

Dermatology

Jacob JB, Wei KC, Bepler G, Reyes JD, Cani A, Polin L, White K, Kim S, Viola N, McGrath J, Guastella A, **Yin C, Mi QS**, Kidder BL, Wagner KU, Ratner S, Phillips V, Xiu J, Parajuli P, and Wei WZ.

Identification of actionable targets for breast cancer intervention using a diversity outbred mouse model. *iScience* 2023; 26(4):106320. PMID: 36968078. [Full Text](#)

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HER2-targeted therapy has improved breast cancer survival, but treatment resistance and disease prevention remain major challenges. Genes that enable HER2/Neu oncogenesis are the next intervention targets. A bioinformatics discovery platform of HER2/Neu-expressing Diversity Outbred (DO) F1 Mice was established to identify cancer-enabling genes. Quantitative Trait Loci (QTL) associated with onset ages and growth rates of spontaneous mammary tumors were sought. Twenty-six genes in 3 QTL contain sequence variations unique to the genetic backgrounds that are linked to aggressive tumors and 21 genes are associated with human breast cancer survival. Concurrent identification of TSC22D3, a transcription factor, and its target gene LILRB4, a myeloid cell checkpoint receptor, suggests an immune axis for regulation, or intervention, of disease. We also investigated TIEG1 gene that impedes tumor immunity but suppresses tumor growth. Although not an actionable target, TIEG1 study revealed genetic regulation of tumor progression, forming the basis of the genetics-based discovery platform.

Dermatology

Krevh R, Wang J, Zuniga B, Toor J, Subedi K, Zhou L, and Mi QS. TAK1 is essential for MAIT cell development and the differentiation of MAIT1 and MAIT17. *Cell Mol Immunol* 2023; Epub ahead of print.

PMID: 36973488. [Request Article](#)

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Dermatology

Lim HW. Steps Leaders Can Take to Increase Diversity, Enhance Inclusion, and Achieve Equity.

Dermatol Clin 2023; 41(2):371-375. PMID: 36933927. [Full Text](#)

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The importance of skin of color and diversity, equity, and inclusion (DEI) started to be recognized in the late 1990s. Since then, because of the advocacy and effort of several highly visible leaders in

dermatology, noticeable progress has been achieved. Leadership lessons learned for successful implementation of DEI include the following: (1) commitment by and continued engagement of highly visible leaders; (2) engagement of other societies in dermatology; (3) engagement of dermatology department leaders and educators; (4) education of the next generation of dermatologists; (5) inclusivity in DEI to include gender and sexual orientation; and (6) cultivation of allies and allyship.

Dermatology

Post NF, Rodrigues MA, Liong AJC, Lommerts A, Abdallah M, Bae JM, Bekkenk MW, Silva de Castro CC, Eleftheriadou V, Esmat S, Ezzedine K, van Geel N, **Hamzavi I**, Leone G, Pandya AG, Passeron T, Raboobee N, Seneschal J, Th'ng S, and Wolkerstorfer A. Consensus on the safety and risks of laser and intense pulse light (IPL) treatments in vitiligo patients, an e-Delphi study. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 36967022. [Full Text](#)

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Dermatology

Post NF, Van Broekhoven NX, Lommerts A, Bae JM, Bekkenk MW, de Castro CCS, Eleftheriadou V, Esmat S, Ezzedine K, van Geel N, **Hamzavi I**, Leone G, Pandya AG, Passeron T, Rodrigues MA, Seneschal J, Th'ng S, and Wolkerstorfer A. Expert opinion about laser and intense pulsed light (IPL)-induced leukoderma or vitiligo: a cross-sectional survey study. *Arch Dermatol Res* 2023; Epub ahead of print. PMID: 36964767. [Full Text](#)

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Vitiligo patients may desire laser hair removal, skin rejuvenation, vascular treatments, and other laser or intense pulsed light (IPL) assisted treatments. However, there is a risk of inducing new depigmented patches (Koebner phenomenon). In absence of guidelines on the safe use of laser or IPL in vitiligo patients, dermatologists tend to be reluctant to administer these treatments. The aim of this survey study was to provide an estimation of the occurrence and related risk factors of laser/IPL-induced leukoderma or vitiligo. A cross-sectional survey study was performed among 15 vitiligo experts from 11 countries, with 14 questions about affected patients, involved laser/IPL treatments and the physicians' approach. In a total of 11,300 vitiligo patients, laser/IPL-induced leukoderma or vitiligo was reported in 30 patients (0.27%). Of these, 12 (40%) patients had a medical history of vitiligo and seven (58%) of these patients had stable (> 12 months) vitiligo before the treatment. Most frequently reported were hair removal procedures and localization of the face and legs. Side effects like blistering, crusting, and erosions occurred in 56.7% of the cases. These vitiligo experts based their advice on the risk of the laser treatment on stability of the vitiligo (43%) and activity signs (50%), and 50% discuss the risks before starting a laser treatment. Relevant activity signs are the Koebner phenomenon (57.1%), confetti-like lesions (57.1%) and hypochromic borders (50%). Laser-induced leukoderma or vitiligo is an uncommon phenomenon. Remarkably, a minority had a medical history of vitiligo of which 58% were stable. Consequently, most cases could not have been prevented by not treating vitiligo patients. However, a majority had laser/IPL-induced skin damage. Therefore, caution is advised with aggressive settings and test-spots prior to the treatment are recommended. This study showed significant variation in the current recommendations and approach of vitiligo experts regarding laser/IPL-induced leukoderma or vitiligo.

Dermatology

Ramachandran V, Loya A, **Ozog DM**, and **Lim HW**. Second primary malignancies in patients with Merkel cell carcinoma: a national database study. *Int J Dermatol* 2023; Epub ahead of print. PMID: 36880530.

[Full Text](#)

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Dermatology

Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, **Stein Gold L**, Blauvelt A, Simpson EL, Chu CY, Liu Z, Gontijo Lima R, Pillai SG, and Seneschal J. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. *N Engl J Med* 2023; 388(12):1080-1091. PMID: 36920778. [Full Text](#)

From the Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC (J.I.S.); the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York (E.G.-Y.); the Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany (D.T.); the Department of Clinical Medicine, Trinity College Dublin, Dublin (A.D.I.); Dermatology Clinical Research, Henry Ford Health System, Detroit (L.S.G.); Oregon Medical Research Center (A.B.), and the Department of Dermatology, Oregon Health and Science University (E.L.S.) - both in Portland; the Department of Dermatology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei (C.-Y.C.); Eli Lilly, Indianapolis (Z.L., R.G.L., S.G.P.); and the Department of Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin Disorders, Hospital Saint-André, Bordeaux University, Centre National de la Recherche Scientifique, ImmunoConcept, Unité Mixte de Recherche 5164, Bordeaux, France (J.S.).

BACKGROUND: Lebrikizumab, a high-affinity IgG4 monoclonal antibody targeting interleukin-13, prevents the formation of the interleukin-4R α -interleukin-13R α 1 heterodimer receptor signaling complex. **METHODS:** We conducted two identically designed, 52-week, randomized, double-blind, placebo-controlled, phase 3 trials; both trials included a 16-week induction period and a 36-week maintenance period. Eligible patients with moderate-to-severe atopic dermatitis (adults \geq 18 years of age] and adolescents [12 to <18 years of age, weighing \geq 40 kg]) were randomly assigned in a 2:1 ratio to receive either lebrikizumab at a dose of 250 mg (loading dose of 500 mg at baseline and week 2) or placebo, administered subcutaneously every 2 weeks. Outcomes for the induction period were assessed up to 16

weeks and are included in this report. The primary outcome was an Investigator's Global Assessment (IGA) score of 0 or 1 (indicating clear or almost clear skin; range, 0 to 4 [severe disease]) with a reduction (indicating improvement) of at least 2 points from baseline at week 16. Secondary outcomes included a 75% improvement in the Eczema Area and Severity Index score (EASI-75 response) and assessments of itch and of itch interference with sleep. Safety was also assessed. RESULTS: In trial 1, the primary outcome was met in 43.1% of 283 patients in the lebrikizumab group and in 12.7% of 141 patients in the placebo group (P<0.001); an EASI-75 response occurred in 58.8% and 16.2%, respectively (P<0.001). In trial 2, the primary outcome was met in 33.2% of 281 patients in the lebrikizumab group and in 10.8% of 146 patients in the placebo group (P<0.001); an EASI-75 response occurred in 52.1% and 18.1%, respectively (P<0.001). Measures of itch and itch interference with sleep indicated improvement with lebrikizumab therapy. The incidence of conjunctivitis was higher among patients who received lebrikizumab than among those who received placebo. Most adverse events during the induction period were mild or moderate in severity and did not lead to trial discontinuation. CONCLUSIONS: In the induction period of two phase 3 trials, 16 weeks of treatment with lebrikizumab was effective in adolescents and adults with moderate-to-severe atopic dermatitis. (Funded by Dermira; ADvocate1 and ADvocate2 ClinicalTrials.gov numbers, NCT04146363 and NCT04178967, respectively.).

Dermatology

Taylor S, Elbuluk N, Grimes P, Chien A, **Hamzavi I**, Alexis A, Gonzalez N, Weiss J, Kang S, and Desai SR. TREATMENT RECOMMENDATIONS FOR ACNE-ASSOCIATED HYPERPIGMENTATION: RESULTS OF A DELPHI CONSENSUS PROCESS AND LITERATURE REVIEW. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 36924935. [Full Text](#)

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Acne vulgaris can be associated with hyperpigmentation, particularly in individuals with skin of color. This acne-induced macular hyperpigmentation (AMH), also called post-inflammatory hyperpigmentation or PIH, is often long-lasting and negatively impacts quality of life. Large-scale randomized controlled clinical trials regarding treatment of acne and AMH are lacking. For this reason, evidence-based treatment recommendations cannot be made. Yet AMH is a common condition, and it is important for clinicians to have guidance on management strategies. The authors, a group of 10 board-certified dermatologists, conducted a modified Delphi consensus process to reach consensus on first-line therapy for AMH and whether therapeutic choices may change in different patient sub-groups. We reached consensus that most patients with acne and AMH should receive early and efficacious acne treatment with a topical retinoid and benzoyl peroxide. Therapies aimed at addressing AMH - including hydroquinone, azelaic acid, chemical peel, or antioxidants - may also be considered to enhance the effect of the treatment regimen on acne and pigmentation. Chemical peels may be used as adjunctive or second-line therapy. This publication details the results of the Delphi process, reviews relevant literature in providing recommendations for AMH and discusses appropriate treatment options.

Dermatology

Wuennenberg J, Guan L, Boothby-Shoemaker W, and Ozog DM. Recurrent Dermatofibrosarcoma Protuberans Infiltrating the Skull. *Dermatol Surg* 2023; Epub ahead of print. PMID: 36946701. [Full Text](#)

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Dermatology

Yi Q, Wang J, Liu T, Yao Y, Loveless I, Subedi K, Toor J, Adrianto I, Xiao H, Chen B, Crawford H, Fang D, Zhou L, and Mi QS. scRNA-Seq and imaging mass cytometry analyses unveil iNKT cell-mediated anti-tumor immunity in pancreatic cancer liver metastasis. *Cancer Lett* 2023; 216149. Epub ahead of print. PMID: 36990268. [Full Text](#)

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Invariant natural killer T (iNKT) cells are innate-like T cells that are abundant in liver sinusoids and play a critical role in tumor immunity. However, the role of iNKT cells in pancreatic cancer liver metastasis (PCLM) has not been fully explored. In this study, we employed a hemi-spleen pancreatic tumor cell injection mouse model of PCLM, a model that closely mimics clinical conditions in humans, to explore the role of iNKT cells in PCLM. Activation of iNKT cells with α -galactosylceramide (α GC) markedly increased immune cell infiltration and suppressed PCLM progression. Via single cell RNA sequencing (scRNA-seq) we profiled over 30,000 immune cells from normal liver and PCLM with or without α GC treatment and were able to characterize the global changes of the immune cells in the tumor microenvironment upon α GC treatment, identifying a total of 12 subpopulations. Upon treatment with α GC, scRNA-Seq and flow cytometry analyses revealed increased cytotoxic activity of iNKT/NK cells and skewing CD4 T cells towards a cytotoxic Th1 profile and CD8 T cells towards a cytotoxic profile, characterized by higher proliferation and reduced exhaustion marker PD1 expression. Moreover, α GC treatment excluded tumor associated macrophages. Lastly, imaging mass cytometry analysis uncovered the reduced epithelial to mesenchymal transition related markers and increased active CD4 and CD8 T cells in PCLM with α GC treatment. Overall, our findings uncover the protective function of activated iNKT cells in pancreatic cancer liver metastasis through increased NK and T cell immunity and decreased tumor associated macrophages.

Diagnostic Radiology

Arribas EM, Kelil T, Santiago L, **Ali A**, Chadalavada SC, Chepelev L, Ghodadra A, Ionita CN, Lee J, Ravi P, Ryan JR, Sheikh AM, Rybicki FJ, and Ballard DH. Radiological Society of North America (RSNA) 3D Printing Special Interest Group (SIG) clinical situations for which 3D printing is considered an appropriate representation or extension of data contained in a medical imaging examination: breast conditions. *3D Print Med* 2023; 9(1):8. PMID: 36952139. [Full Text](#)

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The use of medical 3D printing has expanded dramatically for breast diseases. A writing group composed of the Radiological Society of North America (RSNA) Special Interest Group on 3D Printing (SIG) provides updated appropriateness criteria for breast 3D printing in various clinical scenarios. Evidence-based appropriateness criteria are provided for the following clinical scenarios: benign breast lesions and high-risk breast lesions, breast cancer, breast reconstruction, and breast radiation (treatment planning and radiation delivery).

Diagnostic Radiology

Li Y, Tie X, Li K, Zhang R, **Qi Z**, Budde A, Grist TM, and Chen GH. A quality-checked and physics-constrained deep learning method to estimate material basis images from single-kV contrast-enhanced chest CT scans. *Med Phys* 2023; Epub ahead of print. PMID: 36908250. [Full Text](#)

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BACKGROUND: Single-kV CT imaging is one of the primary imaging methods in radiology practices. However, it does not provide material basis images for some subtle lesion characterization tasks in clinical diagnosis. **PURPOSE:** To develop a quality-checked and physics-constrained deep learning (DL) method to estimate material basis images from single-kV CT data without resorting to dual-energy CT acquisition schemes. **METHODS:** Single-kV CT images are decomposed into two material basis images using a deep neural network. The role of this network is to generate a feature space with 64 template features with the same matrix dimensions of the input single-kV CT image. These 64 template image features are then combined to generate the desired material basis images with different sets of combination coefficients, one for each material basis image. Dual-energy CT image acquisitions with two separate kVs were curated to generate paired training data between a single-kV CT image and the

corresponding two material basis images. To ensure the obtained two material basis images are consistent with the encoded spectral information in the actual projection data, two physics constraints, that is, (1) effective energy of each measured projection datum that characterizes the beam hardening in data acquisitions and (2) physical factors of scanners such as detector and tube characteristics, are incorporated into the end-to-end training. The entire architecture is referred to as Deep-En-Chroma in this paper. In the application stage, the generated material basis images are sent to a deep quality check (Deep-QC) network to assess the quality of estimated images and to report the pixel-wise estimation errors for users. The models were developed using 5592 training and validation pairs generated from 48 clinical cases. Additional 1526 CT images from another 13 patients were used to evaluate the quantitative accuracy of water and iodine basis images estimated by Deep-En-Chroma. RESULTS: For the iodine basis images estimated by Deep-En-Chroma, the mean difference with respect to dual-energy CT is -0.25 mg/mL, and the agreement limits are [-0.75 mg/mL, +0.24 mg/mL]. For the water basis images estimated by Deep-En-Chroma, the mean difference with respect to dual-energy CT is 0.0 g/mL, and the agreement limits are [-0.01 g/mL, 0.01 g/mL]. Across the test cohort, the median [25th, 75th percentiles] root mean square errors between the Deep-En-Chroma and dual-energy material images are 14 [12, 16] mg/mL for the water images and 0.73 [0.64, 0.80] mg/mL for the iodine images. When significant errors are present in the estimated material basis images, Deep-QC can capture these errors and provide pixel-wise error maps to inform users whether the DL results are trustworthy. CONCLUSIONS: The Deep-En-Chroma network provides a new pathway to estimating the clinically relevant material basis images from single-kV CT data and the Deep-QC module to inform end-users of the accuracy of the DL material basis images in practice.

Emergency Medicine

Ashburn NP, Snavely AC, O'Neill JC, Allen BR, Christenson RH, Madsen T, Massoomi MR, **McCord JK**, Mumma BE, **Nowak R**, Stopyra JP, In't Veld MH, Wilkerson RG, and Mahler SA. Performance of the European Society of Cardiology 0/1-Hour Algorithm With High-Sensitivity Cardiac Troponin T Among Patients With Known Coronary Artery Disease. *JAMA Cardiol* 2023; Epub ahead of print. PMID: 36857071. [Request Article](#)

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IMPORTANCE: The European Society of Cardiology (ESC) 0/1-hour algorithm is a validated high-sensitivity cardiac troponin (hs-cTn) protocol for emergency department patients with possible acute coronary syndrome. However, limited data exist regarding its performance in patients with known coronary artery disease (CAD; prior myocardial infarction [MI], coronary revascularization, or $\geq 70\%$ coronary stenosis). OBJECTIVE: To evaluate and compare the diagnostic performance of the ESC 0/1-hour algorithm for 30-day cardiac death or MI among patients with and without known CAD and determine if the algorithm could achieve the negative predictive value rule-out threshold of 99% or higher. DESIGN, SETTING, AND PARTICIPANTS: This was a preplanned subgroup analysis of the STOP-CP prospective multisite cohort study, which was conducted from January 25, 2017, through September 6,

2018, at 8 emergency departments in the US. Patients 21 years or older with symptoms suggestive of acute coronary syndrome without ST-segment elevation on initial electrocardiogram were included. Analysis took place between February and December 2022. INTERVENTIONS/EXPOSURES: Participants with 0- and 1-hour high-sensitivity cardiac troponin T (hs-cTnT) measures were stratified into rule-out, observation, and rule-in zones using the ESC 0/1-hour hs-cTnT algorithm. MAIN OUTCOMES AND MEASURES: Cardiac death or MI at 30 days determined by expert adjudicators. RESULTS: During the study period, 1430 patients were accrued. In the cohort, 775 individuals (54.2%) were male, 826 (57.8%) were White, and the mean (SD) age was 57.6 (12.8) years. At 30 days, cardiac death or MI occurred in 183 participants (12.8%). Known CAD was present in 449 (31.4%). Among patients with known CAD, the ESC 0/1-hour algorithm classified 178 of 449 (39.6%) into the rule-out zone compared with 648 of 981 (66.1%) without CAD ($P < .001$). Among rule-out zone patients, 30-day cardiac death or MI occurred in 6 of 178 patients (3.4%) with known CAD and 7 of 648 (1.1%) without CAD ($P < .001$). The negative predictive value for 30-day cardiac death or MI was 96.6% (95% CI, 92.8-98.8) among patients with known CAD and 98.9% (95% CI, 97.8-99.6) in patients without known CAD ($P = .04$). CONCLUSIONS AND RELEVANCE: Among patients with known CAD, the ESC 0/1-hour hs-cTnT algorithm was unable to safely exclude 30-day cardiac death or MI. This suggests that clinicians should be cautious if using the algorithm in patients with known CAD. The negative predictive value was significantly higher in patients without a history of CAD but remained less than 99%.

Emergency Medicine

Bunch CM, Chang E, Moore EE, Moore HB, Kwaan HC, **Miller JB**, Al-Fadhli MD, Thomas AV, Zackariya N, **Patel SS**, **Zackariya S**, **Haidar S**, Patel B, McCurdy MT, Thomas SG, Zimmer D, Fulkerson D, Kim PY, Walsh MR, Hake D, Kedar A, Aboukhaled M, and Walsh MM. SHock-INduced Endotheliopathy (SHINE): A mechanistic justification for viscoelastography-guided resuscitation of traumatic and non-traumatic shock. *Front Physiol* 2023; 14:1094845. PMID: 36923287. [Full Text](#)

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Irrespective of the reason for hypoperfusion, hypocoagulable and/or hyperfibrinolytic hemostatic aberrancies afflict up to one-quarter of critically ill patients in shock. Intensivists and traumatologists have embraced the concept of SHock-INduced Endotheliopathy (SHINE) as a foundational derangement in progressive shock wherein sympatho-adrenal activation may cause systemic endothelial injury. The pro-thrombotic endothelium lends to micro-thrombosis, enacting a cycle of worsening perfusion and increasing catecholamines, endothelial injury, de-endothelialization, and multiple organ failure. The hypocoagulable/hyperfibrinolytic hemostatic phenotype is thought to be driven by endothelial release of anti-thrombogenic mediators to the bloodstream and perivascular sympathetic nerve release of tissue plasminogen activator directly into the microvasculature. In the shock state, this hemostatic phenotype may be a counterbalancing, yet maladaptive, attempt to restore blood flow against a systemically pro-

thrombotic endothelium and increased blood viscosity. We therefore review endothelial physiology with emphasis on glycocalyx function, unique biomarkers, and coagulofibrinolytic mediators, setting the stage for understanding the pathophysiology and hemostatic phenotypes of SHINE in various etiologies of shock. We propose that the hyperfibrinolytic phenotype is exemplified in progressive shock whether related to trauma-induced coagulopathy, sepsis-induced coagulopathy, or post-cardiac arrest syndrome-associated coagulopathy. Regardless of the initial insult, SHINE appears to be a catecholamine-driven entity which early in the disease course may manifest as hyper- or hypocoagulopathic and hyper- or hypofibrinolytic hemostatic imbalance. Moreover, these hemostatic derangements may rapidly evolve along the thrombohemorrhagic spectrum depending on the etiology, timing, and methods of resuscitation. Given the intricate hemochemical makeup and changes during these shock states, macroscopic whole blood tests of coagulative kinetics and clot strength serve as clinically useful and simple means for hemostasis phenotyping. We suggest that viscoelastic hemostatic assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are currently the most applicable clinical tools for assaying global hemostatic function-including fibrinolysis-to enable dynamic resuscitation with blood products and hemostatic adjuncts for those patients with thrombotic and/or hemorrhagic complications in shock states.

Emergency Medicine

Geletu A, Gardner-Gray J, Roche M, and Ngassa M. Cardiac Arrest as the First Presentation of Gitelman Syndrome. *Cureus* 2023; 15(1):e33565. PMID: 36779094. [Full Text](#)

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Gitelman syndrome is a salt-wasting tubulopathy characterized by profound hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. Cardiac arrest is a relatively rare manifestation of Gitelman syndrome. Here we present a case of Gitelman syndrome in a patient with recurrent cardiac arrest. A 43-year-old female was admitted for out-of-hospital cardiac arrest secondary to ventricular fibrillation. Initial workup revealed severe hypokalemia, hypomagnesemia, metabolic alkalosis, and prolonged QTc. The workup revealed a picture of salt-wasting tubulopathy with hypokalemia, hypomagnesemia, and hypocalciuria. Potassium was repleted aggressively, and the patient received potassium-sparing agents resulting in the stabilization of potassium levels. Before discharge, an implantable cardioverter defibrillator (ICD) was placed for secondary prevention of cardiac arrest. The patient remained symptom-free, and electrolytes remained stable. This case highlights the diagnostic challenges of Gitelman syndrome and the importance of accurate diagnosis in improving patient outcomes.

Emergency Medicine

Howard M, Pflaum-Carlson J, Hurst G, Gardner-Gray J, Kinni H, Coba V, Rivers E, and Jayaprakash N. A roadmap for developing an emergency department based critical care consultation service: Building the early intervention team (EIT). *Am J Emerg Med* 2023; 66:81-84. PMID: 36736063. [Full Text](#)

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Emergency Department (ED) crowding and boarding impact safe and effective health care delivery. ED clinicians must balance caring for new arrivals who require stabilization and resuscitation as well as those who need longitudinal care and re-evaluation. These challenges are magnified in the setting of critically ill patients boarding for the intensive care unit. Boarding is a complex issue that has multiple solutions

based on resources at individual institutions. Several different models have been described for delivery of critical care in the ED. Here, we describe the development of an ED based critical care consultation service, the early intervention team, at an urban academic ED.

Emergency Medicine

Mercer CB, **Ball MT**, Powell JR, Cushing RE, Rossi RM, Black H, Kurth JD, and Panchal AR. Comparison of the Scope of Practice of the Army Combat Medic Specialist and Civilian National EMS Certification Levels. *Prehosp Emerg Care* 2023; 1-8. Epub ahead of print. PMID: 36862061. [Full Text](#)

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INTRODUCTION: The transition of Army Combat Medic Specialists (Military Occupational Specialty Code: 68W) from military to civilian emergency medical services (EMS) is challenging, and the pathway is not clearly defined. Our objective was to evaluate the current military requirements for 68W and how they compare to the 2019 EMS National Scope of Practice Model (SoPM) for the civilian emergency medical technician (EMT) and advanced emergency medical technician (AEMT). **METHODS:** This was a cross-sectional evaluation of the 68W skill floor as defined by the Soldier's Manual and Trainer's Guide Healthcare Specialist and Medical Education and Demonstration of Individual Competence in comparison to the 2019 SoPM, which categorizes EMS tasks into seven skill categories. Military training documents were reviewed and extracted for specific information on military scope of practice and task-specific training requirements. Descriptive statistics were calculated. **RESULTS:** Army 68Ws were noted to perform all (59/59) tasks that coincide with the EMT SoPM. Further, Army 68W practiced above scope in the following skill categories: airway/ventilation (3 tasks); medication administration route (7 tasks); medical director approved medication (6 tasks); intravenous initiation maintenance fluids (4 tasks); and miscellaneous (1 task). Army 68W perform 96% (74/77) of tasks aligned with the AEMT SoPM, excluding tracheobronchial suctioning of an intubated patient, end-tidal CO₂ monitoring or waveform capnography, and inhaled nitrous oxide monitoring. Additionally, the 68W scope included six tasks that were above the SoPM for AEMT; airway/ventilation (2 tasks); medication administration route (2 tasks); and medical director approved medication (2 tasks). **CONCLUSIONS:** The scope of practice of U.S. Army 68W Combat Medics aligns well with the civilian 2019 Scope of Practice Model for EMTs and AEMTs. Based on the comparative scope of practice analysis, transitioning from Army 68W Combat Medic to civilian AEMT would require minimal additional training. This represents a promising potential workforce to assist with EMS workforce challenges. Although aligning the scope of practice is a promising first step, future research is needed to assess the relationship of Army 68Ws training with state licensure and certification equivalency to facilitate this transition.

Emergency Medicine

Valley TS, Schutz A, Miller J, Miles L, Lipman K, Eaton TL, **Kinni H**, Cooke CR, and Iwashyna TJ. Hospital factors that influence ICU admission decision-making: a qualitative study of eight hospitals. *Intensive Care Med* 2023; 1-12. Epub ahead of print. PMID: 36952016. [Full Text](#)

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PURPOSE: Some hospitals in the United States (US) use intensive care 20 times more than others. Since intensive care is lifesaving for some but potentially harmful for others, there is a need to understand factors that influence how intensive care unit (ICU) admission decisions are made. **METHODS:** A qualitative analysis of eight US hospitals was conducted with semi-structured, one-on-one interviews supplemented by site visits and clinical observations. **RESULTS:** A total of 87 participants (24 nurses, 52 physicians, and 11 other staff) were interviewed, and 40 h were spent observing ICU operations across the eight hospitals. Four hospital-level factors were identified that influenced ICU admission decision-making. First, availability of intermediate care led to reallocation of patients who might otherwise be sent to an ICU. Second, participants stressed the importance of ICU nurse availability as a key modifier of ICU capacity. Patients cared for by experienced general care physicians and nurses were less likely to receive ICU care. Third, smaller or rural hospitals opted for longer emergency department patient-stays over ICU admission to expedite interhospital transfer of critically ill patients. Fourth, lack of clarity in ICU admission policies led clinicians to feel pressured to use ICU care for patients who might otherwise not have received it. **CONCLUSION:** Health care systems should evaluate their use of ICU care and establish institutional patterns that ensure ICU admission decisions are patient-centered but also account for resources and constraints particular to each hospital.

Emergency Medicine

Wong SA, Lebois LAM, **Lewandowski C**, et al. Internal capsule microstructure mediates the relationship between childhood maltreatment and PTSD following adulthood trauma exposure. *Mol Psychiatry* 2023; Epub ahead of print. PMID: 36932158. [Full Text](#)

Childhood trauma is a known risk factor for trauma and stress-related disorders in adulthood. However, limited research has investigated the impact of childhood trauma on brain structure linked to later posttraumatic dysfunction. We investigated the effect of childhood trauma on white matter microstructure after recent trauma and its relationship with future posttraumatic dysfunction among trauma-exposed adult participants (n = 202) recruited from emergency departments as part of the AURORA Study. Participants completed self-report scales assessing prior childhood maltreatment within 2-weeks in addition to assessments of PTSD, depression, anxiety, and dissociation symptoms within 6-months of their traumatic event. Fractional anisotropy (FA) obtained from diffusion tensor imaging (DTI) collected at 2-weeks and 6-months was used to index white matter microstructure. Childhood maltreatment load predicted 6-month PTSD symptoms (b = 1.75, SE = 0.78, 95% CI = [0.20, 3.29]) and inversely varied with FA in the bilateral internal capsule (IC) at 2-weeks (p = 0.0294, FDR corrected) and 6-months (p = 0.0238, FDR corrected). We observed a significant indirect effect of childhood maltreatment load on 6-month PTSD symptoms through 2-week IC microstructure (b = 0.37, Boot SE = 0.18, 95% CI = [0.05, 0.76]) that fully mediated the effect of childhood maltreatment load on PCL-5 scores (b = 1.37, SE = 0.79, 95% CI = [-0.18, 2.93]). IC microstructure did not mediate relationships between childhood maltreatment and depressive, anxiety, or dissociative symptomatology. Our findings suggest a unique role for IC microstructure as a stable neural pathway between childhood trauma and future PTSD symptoms following recent trauma. Notably, our work did not support roles of white matter tracts previously found to vary with PTSD symptoms and childhood trauma exposure, including the cingulum bundle, uncinate

fasciculus, and corpus callosum. Given the IC contains sensory fibers linked to perception and motor control, childhood maltreatment might impact the neural circuits that relay and process threat-related inputs and responses to trauma.

Endocrinology and Metabolism

Mukherjee S, Arya AK, Bhadada SK, Pal R, Lohani S, Gupta A, and **Rao SD**. Characterization of primary hyperparathyroidism based on target organ involvement: An analysis from the Indian PHPT registry. *Clin Endocrinol (Oxf)* 2023; Epub ahead of print. PMID: 36998119. [Full Text](#)

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BACKGROUND: It has been a matter of debate for long time about the existence of two distinct phenotypes of primary hyperparathyroidism (PHPT) predisposed to either renal or skeletal manifestation. **OBJECTIVE:** To differentiate characteristics of symptomatic PHPT patients based on the presence of skeletal or renal involvement. **DESIGN:** Retrospective analysis of data from the Indian PHPT registry. **PATIENTS:** PHPT patients were divided into four discrete groups: asymptomatic, presenting with renal manifestations alone, skeletal manifestations alone, and both skeletal and renal manifestations. **MEASUREMENTS:** Clinical, biochemical, and tumor weight and histopathological characteristics of these groups were compared. **RESULTS:** Of the 229 eligible patients, 45 were asymptomatic, 62 had renal manifestations, 55 had skeletal manifestations, and 67 had both skeletal and renal manifestations. Patients with both skeletal and renal manifestations had higher serum calcium levels than those with isolated skeletal involvement [12.5 (11.1 - 13.7) mg/dl, 11.2 (10.6 - 12.3) mg/dl, respectively; $p < 0.05$]. Serum alkaline phosphatase (AP), plasma parathyroid hormone (PTH) levels, and parathyroid tumor weight were significantly higher in patients with isolated skeletal, and both skeletal and renal manifestations, compared to the other two groups. A preoperative PTH and AP level of 300 pg/ml and 152 U/L, predicted the risk of developing skeletal involvement with sensitivity and specificity of 71%, 70%, and 69%, 67%, respectively. **CONCLUSIONS:** We observed distinct skeletal and renal phenotypic subgroups among PHPT patients with characteristic biochemical and hormonal patterns with higher parathyroid disease burden in patients with skeletal complications compared to those with isolated renal manifestation. This article is protected by copyright. All rights reserved.

Family Medicine

Reid J, **Tumbarella E**, and Farah-Brunner L. Not All Infant Inspiratory Stridor Is Laryngomalacia. *Clin Pediatr (Phila)* 2023; 99228231159160. Epub ahead of print. PMID: 36908112. [Full Text](#)

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Gastroenterology

Ahmed A, Musa A, Lohman S, Hsieh JC, **Harris K, Faisal S**, Ghanimeh M, **Alsheik E**, and **Zuchelli T**. Attitudes of Gastroenterologists Regarding Delivery of Cancer Diagnoses: a Cross-Sectional Study. *J Gastrointest Cancer* 2023; Epub ahead of print. PMID: 36914843. [Full Text](#)

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GOALS: To determine the attitudes and practices of gastroenterologists regarding the delivery of cancer diagnoses. **BACKGROUND:** Gastroenterologists frequently diagnose colorectal cancer. Receiving the

news of a cancer diagnosis is difficult, and the delivery of the diagnosis can influence a patient's understanding of their disease. No study to date has reported how gastroenterologists deliver cancer diagnoses to their patients. **STUDY:** An anonymous questionnaire was sent online to gastroenterologists of the American College of Gastroenterology to assess views regarding the delivery of cancer diagnoses. **RESULTS:** Of the 280 complete responses (response rate = 1.64%), most respondents were male (n = 205, 73.21%), in practice between 0 and 9 years (n = 133, 47.50%), and at the attending/faculty level (n = 69.53%, 194). Most responded that they would disclose a cancer diagnosis to the patient themselves if they had made the discovery on endoscopy/colonoscopy (n = 255, 94.80%), with the preferred methods being an in person discussion (n = 187, 71.65%). Most respondents were not familiar with any guidelines for delivering cancer diagnoses (n = 202, 75.94%) and would be open to receiving training on cancer diagnosis delivery (n = 207, 78.11%). **CONCLUSIONS:** Most gastroenterologists take personal responsibility in the delivery of cancer diagnoses. Many gastroenterologists receive no specific training on how to deliver this news and are unaware of any guidelines to follow that may be helpful in their practice. However, most displayed a willingness to learn these guidelines through some form of formal education. Future directions should consider the incorporation of education in cancer diagnosis delivery for gastroenterologists and gastroenterology fellows.

Gastroenterology

Kugelmas M, Nouredin M, Gunn N, **Brown K**, Younossi Z, Abdelmalek M, and Alkhouri N. The use of current knowledge and non-invasive testing modalities for predicting at-risk non-alcoholic steatohepatitis and assessing fibrosis. *Liver Int* 2023; Epub ahead of print. PMID: 36864668. [Full Text](#)

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There is ongoing recognition of the burden of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), with fibrosis being the most important histological feature that is associated with progression to cirrhosis and the occurrence of major adverse liver outcomes. Liver biopsy is the gold standard applied to detect NASH and determine the stage of fibrosis, but its use is limited. There is a need for non-invasive testing (NIT) techniques to identify patients considered at-risk NASH (NASH with NAFLD activity score > 4 and ≥ F2 fibrosis). For NAFLD-associated fibrosis, several wet (serological) and dry (imaging) NITs are available and demonstrate a high negative predictive value (NPV) for excluding those with advanced hepatic fibrosis. However, identifying at-risk NASH is more challenging; there is little guidance on how to use available NITs for these purposes, and these NITs are not specifically designed to identify at-risk NASH patients. This review discusses the need for NITs in NAFLD and NASH and provides data to support the use of NITs, focusing on newer methods to non-invasively identify at-risk NASH patients. This review concludes with an algorithm that serves as an example of how NITs can be integrated into care pathways of patients with suspected NAFLD and potential NASH. This algorithm can be used for staging, risk stratification and the effective transition of patients who may benefit from specialty care.

Gastroenterology

Sawinski D, Lai JC, Pinney S, Gray AL, Jackson AM, Stewart D, Levine DJ, Locke JE, Pomposelli JJ, Hartwig MG, Hall SA, Dadhania DM, Cogswell R, Perez RV, Schold JD, Turgeon NA, Kobashigawa J, Kukreja J, Magee JC, Friedewald J, Gill JS, Loor G, Heimbach JK, Verna EC, Walsh MN, Terrault N, Testa G, Diamond JM, Reese PP, **Brown K**, Orloff S, Farr MA, Olthoff KM, Siegler M, Ascher N, Feng S, Kaplan B, and Pomfret E. Addressing sex-based disparities in solid organ transplantation in the United States - a conference report. *Am J Transplant* 2023; 23(3):316-325. PMID: 36906294. [Full Text](#)

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Solid organ transplantation provides the best treatment for end-stage organ failure, but significant sex-based disparities in transplant access exist. On June 25, 2021, a virtual multidisciplinary conference was convened to address sex-based disparities in transplantation. Common themes contributing to sex-based disparities were noted across kidney, liver, heart, and lung transplantation, specifically the existence of barriers to referral and wait listing for women, the pitfalls of using serum creatinine, the issue of donor/recipient size mismatch, approaches to frailty and a higher prevalence of allosensitization among women. In addition, actionable solutions to improve access to transplantation were identified, including alterations to the current allocation system, surgical interventions on donor organs, and the incorporation of objective frailty metrics into the evaluation process. Key knowledge gaps and high-priority areas for future investigation were also discussed.

Gastroenterology

Selim R, Gordon SC, Zhou Y, Zhang T, Lu M, Daida YG, Boscarino JA, Schmidt MA, Trudeau S, Rupp LB, and Gonzalez HC. Impact of hepatitis C treatment status on risk of Parkinson's disease and secondary parkinsonism in the era of direct-acting antivirals. *J Viral Hepat* 2023; Epub ahead of print. PMID: 36872452. [Full Text](#)

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Research suggests a possible link between chronic infection with hepatitis C virus (HCV) and the development of Parkinson's Disease (PD) and secondary Parkinsonism (PKM). We investigated the impact of antiviral treatment status (untreated, interferon [IFN] treated, direct-acting antiviral [DAA] treated) and outcome (treatment failure [TF] or sustained virological response [SVR]) on risk of PD/PKM among patients with HCV. Using data from the Chronic Hepatitis Cohort Study (CHeCS), we applied a discrete time-to-event approach with PD/PKM as the outcome. We performed univariate followed by a multivariable modelling that used time-varying covariates, propensity scores to adjust for potential treatment selection bias and death as a competing risk. Among 17,199 confirmed HCV patients, we observed 54 incident cases of PD/PKM during a mean follow-up period of 17 years; 3753 patients died during follow-up. There was no significant association between treatment status/outcome and risk of PD/PKM. Type 2 diabetes tripled risk (hazard ratio [HR] 3.05; 95% CI 1.75-5.32; $p < .0001$) and presence of cirrhosis doubled risk of PD/PKM (HR 2.13, 95% CI 1.31-3.47). BMI >30 was associated with roughly 50% lower risk of PD/PKM than BMI <25 (HR 0.43; 0.22-0.84; $p = .0138$). After adjustment for treatment selection bias, we did not observe a significant association between HCV patients' antiviral treatment status/outcome on risk of PD/PKM. Several clinical risk factors-diabetes, cirrhosis and BMI-were associated with PD/PKM.

Gastroenterology

Shimada S, Shamaa T, Ivanics T, Miyake K, Kitajima T, Rizzari M, Yoshida A, Abouljoud M, Moonka D, and Nagai S. Effects of the implementation of acuity circle policy on waitlist and post-transplant outcomes of liver re-transplantation. *Clin Transplant* 2023; e14977. Epub ahead of print. PMID: 36951511. [Full Text](#)

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BACKGROUND: Acuity circle (AC) policy implementation improved the waitlist outcomes for certain liver transplant (LT)-candidates. The impact of the policy implementation for liver retransplant (reLT) candidates is unknown. **METHODS:** Using Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data from January, 2018 to September, 2021, we investigated the effect of the AC policy on waitlist and post-LT outcomes among patients who had previously received a LT. Patients were categorized by relisting date: Pre-AC (Era 1: January 1, 2018-February 3, 2020; $n = 750$); and Post-AC (Era 2: February 4, 2020-June 30, 2021; $n = 556$). Patient and donor characteristics, as well as on-waitlist and post-reLT outcomes were compared across eras. **RESULTS:** In Era 2, the probability of transplant within 90 days overall and among patients relisted > 14 days from initial transplant (late relisting) were significantly higher compared to Era 1 (subdistribution hazard ratio [sHR] 1.40, 95% CI 1.18-1.64, $p < .001$; sHR 1.52, 95% CI 1.23-1.88, $p = .001$, respectively). However, there was no difference by era among patients relisted ≤ 14 days from initial transplant (early relisting; sHR 1.21, 95% CI .93-1.57, $p = .15$). Likewise, among early relisting patients, risks for 180-day graft loss and mortality were significantly higher in Era 2 versus Era 1 (adjusted hazard ratio [aHR] 5.77, 95% CI

1.71-19.51, $p = .004$; and aHR 8.22, 95% CI 1.85-36.59, $p = .005$, respectively); for late relisting patients, risks for these outcomes were similar across eras. **CONCLUSION:** Our results show that the implementation of AC policy has improved transplant rates and reduced waiting time for reLT candidates listed > 14 days from initial transplant. However, the impact upon early relisting patients may be mixed.

Gastroenterology

Singal AG, Ghaziani TT, Mehta N, Zhou K, Grinspan LT, Benhammou JN, Moon AM, Yang JD, **Salgia R**, Pillai A, Zheng E, Rich NE, Gopal P, Jalal P, Verna E, Yekkaluri S, Phen S, Melendez-Torres J, Alshuwaykh O, Choi H, Junus K, Grady J, Song M, Leven EA, Yum J, Gowda V, Alsudaney M, Hernandez P, Desai N, and Parikh ND. Recall patterns and risk of primary liver cancer for subcentimeter ultrasound liver observations: a multicenter study. *Hepatol Commun* 2023; 7(3). PMID: 36881615. [Full Text](#)

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BACKGROUND: Patients with cirrhosis and subcentimeter lesions on liver ultrasound are recommended to undergo short-interval follow-up ultrasound because of the presumed low risk of primary liver cancer (PLC). **AIMS:** The aim of this study is to characterize recall patterns and risk of PLC in patients with subcentimeter liver lesions on ultrasound. **METHODS:** We conducted a multicenter retrospective cohort study among patients with cirrhosis or chronic hepatitis B infection who had subcentimeter ultrasound lesions between January 2017 and December 2019. We excluded patients with a history of PLC or concomitant lesions ≥ 1 cm in diameter. We used Kaplan Meier and multivariable Cox regression analyses to characterize time-to-PLC and factors associated with PLC, respectively. **RESULTS:** Of 746 eligible patients, most (66.0%) had a single observation, and the median diameter was 0.7 cm (interquartile range: 0.5-0.8 cm). Recall strategies varied, with only 27.8% of patients undergoing guideline-concordant ultrasound within 3-6 months. Over a median follow-up of 26 months, 42 patients developed PLC (39 HCC and 3 cholangiocarcinoma), yielding an incidence of 25.7 cases (95% CI, 6.2-47.0) per 1000 person-years, with 3.9% and 6.7% developing PLC at 2 and 3 years, respectively. Factors associated with time-to-PLC were baseline alpha-fetoprotein >10 ng/mL (HR: 4.01, 95% CI, 1.85-8.71), platelet count ≤ 150 (HR: 4.90, 95% CI, 1.95-12.28), and Child-Pugh B cirrhosis (vs. Child-Pugh A: HR: 2.54, 95% CI, 1.27-5.08). **CONCLUSIONS:** Recall patterns for patients with subcentimeter liver lesions on ultrasound varied widely. The low risk of PLC in these patients supports short-interval ultrasound in 3-6 months, although diagnostic CT/MRI may be warranted for high-risk subgroups such as those with elevated alpha-fetoprotein levels.

Graduate Medical Education

Frinak S, Kennedy J, **Zasuwa G**, **Passalacqua KD**, and **Yee J**. Detection of Hemodialysis Venous Needle Dislodgment Using Venous Access Pressure Measurements: A Simulation Study. *Kidney360* 2023; Epub ahead of print. PMID: 36960959. [Full Text](#)

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BACKGROUND: In rare instances, hemodialysis venous needles may become dislodged, and when left undetected can lead to severe injury or death. Although dialysis machines have alarms to detect venous needle dislodgment, their range of detection is limited. An understanding of the clinical conditions that may lead to missed needle dislodgments is needed for development of more robust detection systems. **METHODS:** We created a sham dialysis circuit with a Fresenius 2008 K dialysis machine for in vitro simulation testing of machine alarm behavior under variable conditions. The circuit used a blood substitute and mimicked a patient's venous access site. We varied blood flow rate, venous pressure, and upward drift in venous pressure and analyzed the time to alarm for the machine and an improved alarm algorithm. We also performed a cross-sectional retrospective study to identify the clinical occurrence of venous pressure upward drift between September 1, 2016, and November 1, 2016 in patients on hemodialysis with an arteriovenous fistula. **RESULTS:** Of 43,390 venous pressure readings for 147 patients on hemodialysis, 16,594 (38%) showed an upward drift in venous pressure (range 20-79 mmHg), with a mean \pm SD increase of 11 ± 18 mmHg within 20 ± 14 minutes. A total of 19 venous needle dislodgment simulations under different venous pressure and blood flow parameters resulted in 19 (100%) algorithm alarm activations. Only 8 simulations (42%) activated a machine alarm, and machine alarm activation time was longer than the algorithm activation time for all 8 machine alarms (range 1-13 seconds). **CONCLUSIONS:** Patients can experience changes in venous pressure during hemodialysis which may not trigger a machine alarm in the case of a venous needle dislodgment. Our simulations showed that current dialysis machine alarm systems may not compensate for upward drift in venous pressure, and improved algorithms for detecting needle dislodgment during hemodialysis are needed.

Hematology-Oncology

Alkhatib L, Velez Diaz LA, Varma S, Chowdhary A, Bapat P, Pan H, **Kukreja G**, Palabindela P, Selvam SA, and Kalra K. Lifestyle Modifications and Nutritional and Therapeutic Interventions in Delaying the Progression of Chronic Kidney Disease: A Review. *Cureus* 2023; 15(2):e34572. PMID: 36874334. [Full Text](#)

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Chronic kidney disease (CKD) is a debilitating progressive illness that affects more than 10% of the world's population. In this literature review, we discussed the roles of nutritional interventions, lifestyle modifications, hypertension (HTN) and diabetes mellitus (DM) control, and medications in delaying the progression of CKD. Walking, weight loss, low-protein diet (LPD), adherence to the alternate Mediterranean (aMed) diet, and Alternative Healthy Eating Index (AHEI)-2010 slow the progression of CKD. However, smoking and binge alcohol drinking increase the risk of CKD progression. In addition, hyperglycemia, altered lipid metabolism, low-grade inflammation, over-activation of the renin-angiotensin-aldosterone system (RAAS), and overhydration (OH) increase diabetic CKD progression. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend blood pressure (BP) control of $<140/90$ mmHg in patients without albuminuria and $<130/80$ mmHg in patients with albuminuria to prevent CKD progression. Medical therapies aim to target epigenetic alterations, fibrosis, and inflammation. Currently, RAAS blockade, sodium-glucose cotransporter-2 (SGLT2) inhibitors, pentoxifylline, and finerenone are approved for managing CKD. In addition, according to the completed Study of Diabetic Nephropathy with Atrasentan (SONAR), atrasentan, an endothelin receptor antagonist (ERA), decreased the risk of renal events in diabetic CKD patients. However, ongoing trials are studying the role of other agents in slowing the progression of CKD.

Hematology-Oncology

Emole J, Lawal O, Lupak O, Rangarajan H, and Udo I. Neuropsychiatric disorders in adults undergoing chimeric antigen receptor T cells therapy for aggressive lymphomas and acute lymphoblastic leukemia. *Leuk Res Rep* 2023; 19:100364. PMID: 36873581. [Full Text](#)

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OBJECTIVE: To evaluate risk factors for neuropsychiatric disorders (NPD) in recipients of CART therapy. **METHODS:** Patients ≥ 18 years with acute lymphoblastic leukemia (ALL), and aggressive B-cell lymphomas who received CART in 2018 were evaluated. Patients with and without NPD were compared. **RESULTS:** NPD was diagnosed in 31.2% of patients. Compared to patients without NPD, patients with NPD were likely to be females ($P = 0.035$) and have ALL ($P = 0.039$). NPD was significantly associated with female gender (OR = 2.03) and diagnosis of ALL (OR = 2.76). No association between NPD and outcomes. **CONCLUSIONS:** Female gender and ALL were risk factors for NPD.

Hematology-Oncology

Garassino MC, **Gadgeel S**, Novello S, Halmos B, Felip E, Speranza G, Hui R, Garon EB, Horinouchi H, Sugawara S, Rodriguez-Abreu D, Reck M, Cristescu R, Aurora-Garg D, Loboda A, Lunceford J, Kobie J, Ayers M, Piperdi B, Pietanza MC, and Paz-Ares L. Associations of Tissue Tumor Mutational Burden and Mutational Status With Clinical Outcomes With Pembrolizumab Plus Chemotherapy Versus Chemotherapy For Metastatic NSCLC. *JTO Clin Res Rep* 2023; 4(1):100431. PMID: 36793385. [Full Text](#)

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INTRODUCTION: We evaluated tissue tumor mutational burden (tTMB) and mutations in STK11, KEAP1, and KRAS as biomarkers for outcomes with pembrolizumab plus platinum-based chemotherapy (pembrolizumab-combination) for NSCLC among patients in the phase 3 KEYNOTE-189 (ClinicalTrials.gov, NCT02578680; nonsquamous) and KEYNOTE-407 (ClinicalTrials.gov, NCT02775435; squamous) trials. **METHODS:** This retrospective exploratory analysis evaluated prevalence of high tTMB and STK11, KEAP1, and KRAS mutations in patients enrolled in KEYNOTE-189 and KEYNOTE-407 and the relationship between these potential biomarkers and clinical outcomes. tTMB and STK11, KEAP1, and KRAS mutation status was assessed using whole-exome sequencing in patients with available tumor

and matched normal DNA. The clinical utility of tTMB was assessed using a prespecified cutpoint of 175 mutations/exome. RESULTS: Among patients with evaluable data from whole-exome sequencing for evaluation of tTMB (KEYNOTE-189, n = 293; KEYNOTE-407, n = 312) and matched normal DNA, no association was found between continuous tTMB score and overall survival (OS) or progression-free survival for pembrolizumab-combination (Wald test, one-sided p > 0.05) or placebo-combination (Wald test, two-sided p > 0.05) in patients with squamous or nonsquamous histology. Pembrolizumab-combination improved outcomes for patients with tTMB greater than or equal to 175 compared with tTMB less than 175 mutations/exome in KEYNOTE-189 (OS, hazard ratio = 0.64 [95% confidence interval (CI): 0.38–1.07] and 0.64 [95% CI: 0.42–0.97], respectively) and KEYNOTE-407 (OS, hazard ratio = 0.74 [95% CI: 0.50–1.08 and 0.86 [95% CI: 0.57–1.28], respectively) versus placebo-combination. Treatment outcomes were similar regardless of KEAP1, STK11, or KRAS mutation status. CONCLUSIONS: These findings support pembrolizumab-combination as first-line treatment in patients with metastatic NSCLC and do not suggest the utility of tTMB, STK11, KEAP1, or KRAS mutation status as a biomarker for this regimen.

Hematology-Oncology

Gonzalez-Mosquera LF, Moscoso B, Tobar P, Cardenas-Maldonado D, Podrumar AI, Mesa R, and Cuenca JA. Sepsis-Related Outcomes of Patients with Philadelphia-Negative Myeloproliferative Neoplasms. *Cancer Invest* 2023; 1-9. Epub ahead of print. PMID: 36883674. [Request Article](#)

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We analyzed the National Inpatient Sample (NIS) database to study the sepsis-related outcomes in patients with Philadelphia negative myeloproliferative neoplasms (MPN). A total of 82,087 patients were included, most had essential thrombocytosis (83.7%), followed by polycythemia vera (13.7%), and primary myelofibrosis (2.6%). Sepsis was diagnosed in 15,789 (19.2%) patients and their mortality rate was higher than nonseptic patients (7.5% vs 1.8%; p < .001). Sepsis was the most significant risk factor of mortality (aOR, 3.84; 95% CI, 3.51-4.21), others included liver disease (aOR, 2.42; 95% CI, 2.11-2.78), pulmonary embolism (aOR, 2.26; 95% CI, 1.83-2.80), cerebrovascular disease (aOR, 2.05; 95% CI, 1.81-2.33), and myocardial infarction (aOR, 1.73; 95% CI, 1.52-1.96).

Hematology-Oncology

Hung J, Perez SM, Dasa SSK, Hall SP, Heckert DB, Murphy BP, **Crawford HC**, Kelly KA, and Brinton LT. A Bitter Taste Receptor as a Novel Molecular Target on Cancer-Associated Fibroblasts in Pancreatic Ductal Adenocarcinoma. *Pharmaceuticals (Basel)* 2023; 16(3). PMID: 36986488. [Full Text](#)

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Cancer-associated fibroblasts (CAFs) execute diverse and complex functions in cancer progression. While reprogramming the crosstalk between CAFs and cancer epithelial cells is a promising avenue to evade the adverse effects of stromal depletion, drugs are limited by their suboptimal pharmacokinetics and off-target effects. Thus, there is a need to elucidate CAF-selective cell surface markers that can improve drug delivery and efficacy. Here, functional proteomic pulldown with mass spectrometry was used to identify taste receptor type 2 member 9 (TAS2R9) as a CAF target. TAS2R9 target

characterization included binding assays, immunofluorescence, flow cytometry, and database mining. Liposomes conjugated to a TAS2R9-specific peptide were generated, characterized, and compared to naked liposomes in a murine pancreatic xenograft model. Proof-of-concept drug delivery experiments demonstrate that TAS2R9-targeted liposomes bind with high specificity to TAS2R9 recombinant protein and exhibit stromal colocalization in a pancreatic cancer xenograft model. Furthermore, the delivery of a CXCR2 inhibitor by TAS2R9-targeted liposomes significantly reduced cancer cell proliferation and constrained tumor growth through the inhibition of the CXCL-CXCR2 axis. Taken together, TAS2R9 is a novel cell-surface CAF-selective target that can be leveraged to facilitate small-molecule drug delivery to CAFs, paving the way for new stromal therapies.

Hematology-Oncology

Izano MA, Sweetnam C, Zhang C, Weese JL, Reding D, Treisman J, Patel A, **Potugari B**, Stafford A, Wolf FM, Tran M, Brown TD, and **Gadgeel SM**. Brief Report on Use of Pembrolizumab With or Without Chemotherapy for Advanced Lung Cancer: A Real-World Analysis. *Clin Lung Cancer* 2023; Epub ahead of print. PMID: 36863970. [Full Text](#)

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Hematology-Oncology

Johnson DB, Atkins MB, Hennessy C, Wise-Draper T, Heilman H, Awosika J, Bakouny Z, Labaki C, Saliby RM, **Hwang C**, **Singh SRK**, **Balanchivadze N**, Friese CR, Fecher LA, Yoon JJ, Hayes-Lattin B, Bilen MA, Castellano CA, Lyman GH, Tachiki L, Shah SA, Glover MJ, Flora DB, Wulff-Burchfield E, Kasi A, Abbasi SH, Farmakiotis D, Viera K, Klein EJ, Weissman LB, Jani C, Puc M, Fahey CC, Reuben DY, Mishra S, Beeghly-Fadiel A, French B, and Warner JL. Impact of COVID-19 in patients on active melanoma therapy and with history of melanoma. *BMC Cancer* 2023; 23(1):265. PMID: 36949413. [Full Text](#)

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INTRODUCTION: COVID-19 particularly impacted patients with co-morbid conditions, including cancer. Patients with melanoma have not been specifically studied in large numbers. Here, we sought to identify factors that associated with COVID-19 severity among patients with melanoma, particularly assessing outcomes of patients on active targeted or immune therapy. METHODS: Using the COVID-19 and Cancer Consortium (CCC19) registry, we identified 307 patients with melanoma diagnosed with COVID-19. We used multivariable models to assess demographic, cancer-related, and treatment-related factors associated with COVID-19 severity on a 6-level ordinal severity scale. We assessed whether treatment

was associated with increased cardiac or pulmonary dysfunction among hospitalized patients and assessed mortality among patients with a history of melanoma compared with other cancer survivors. RESULTS: Of 307 patients, 52 received immunotherapy (17%), and 32 targeted therapy (10%) in the previous 3 months. Using multivariable analyses, these treatments were not associated with COVID-19 severity (immunotherapy OR 0.51, 95% CI 0.19 - 1.39; targeted therapy OR 1.89, 95% CI 0.64 - 5.55). Among hospitalized patients, no signals of increased cardiac or pulmonary organ dysfunction, as measured by troponin, brain natriuretic peptide, and oxygenation were noted. Patients with a history of melanoma had similar 90-day mortality compared with other cancer survivors (OR 1.21, 95% CI 0.62 - 2.35). CONCLUSIONS: Melanoma therapies did not appear to be associated with increased severity of COVID-19 or worsening organ dysfunction. Patients with history of melanoma had similar 90-day survival following COVID-19 compared with other cancer survivors.

Hematology-Oncology

Monga J, Valeriote F, Hwang C, Gadgeel S, and Ghosh J. Daclatasvir, an Antiviral Drug, Downregulates Tribbles 2 Pseudokinase and Resensitizes Enzalutamide-Resistant Prostate Cancer Cells. *Mol Cancer Ther* 2023; 22(3):381-392. PMID: 36805730. [Request Article](#)

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FDA-approved enzalutamide is commonly prescribed to reduce the growth of advanced prostate cancer by blocking androgen receptor function. However, enzalutamide-resistant prostate cancer (ERPC) invariably develops and progresses to metastatic, lethal disease. Management of ERPC poses a special problem not only because available therapeutic regimens cannot effectively kill ERPC cells but also due to their propensity to invade large bones. Moreover, molecular mechanism(s) behind enzalutamide resistance is not properly understood, which is delaying development of newer agents. We found that the pseudokinase, Tribbles 2 (TRIB2), is overexpressed in ERPC cells and plays a critical role in their survival. Forced overexpression of TRIB2 enhances prostate cancer cell growth and confers resistance to physiologic doses of enzalutamide, suggesting that TRIB2 plays an important role in the development and progression of ERPC. Though TRIB2 has emerged as an excellent molecular target for ERPC, suitable inhibitors are not commercially available for effective targeting. By designing a luciferase-tagged TRIB2 fusion protein-based assay system, we screened a library of about 1,600 compounds and found that daclatasvir (DCV), an antiviral drug, effectively inhibits TRIB2-luciferase. We also found that DCV degrades TRIB2 proteins by direct binding and resensitizes ERPC cells to enzalutamide treatment. Moreover, DCV at lower, sublethal doses synergizes with enzalutamide to decrease the viability and induce apoptosis in prostate cancer cells. Because DCV is already approved by the FDA and well tolerated in humans, based on our findings, it appears that DCV is a promising new agent for development of an effective therapy for advanced, enzalutamide-resistant, lethal prostate cancer.

Hematology-Oncology

Ramin C, Pfeiffer RM, Fan S, Mullooly M, Falk RT, Jones K, Caporaso NE, Bey-Knight L, Sak MA, Simon MS, Gorski DH, **Ali H**, Littrup P, Duric N, Sherman ME, and Gierach GL. Short-term changes in ultrasound tomography measures of breast density and treatment-associated endocrine symptoms after tamoxifen therapy. *NPJ Breast Cancer* 2023; 9(1):12. PMID: 36922547. [Full Text](#)

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Although breast density decline with tamoxifen therapy is associated with greater therapeutic benefit, limited data suggest that endocrine symptoms may also be associated with improved breast cancer outcomes. However, it is unknown whether endocrine symptoms are associated with reductions in breast density after tamoxifen initiation. We evaluated treatment-associated endocrine symptoms and breast density change among 74 women prescribed tamoxifen in a 12-month longitudinal study. Treatment-associated endocrine symptoms and sound speed measures of breast density, assessed via novel whole breast ultrasound tomography (m/s), were ascertained before tamoxifen (T0) and at 1-3 (T1), 4-6 (T2), and 12 months (T3) after initiation. CYP2D6 status was genotyped, and tamoxifen metabolites were measured at T3. Using multivariable linear regression, we estimated mean change in breast density by treatment-associated endocrine symptoms adjusting for age, race, menopausal status, body mass index, and baseline density. Significant breast density declines were observed in women with treatment-associated endocrine symptoms (mean change (95% confidence interval) at T1:-0.26 m/s (-2.17,1.65); T2:-2.12 m/s (-4.02,-0.22); T3:-3.73 m/s (-5.82,-1.63); p-trend = 0.004), but not among women without symptoms (p-trend = 0.18) (p-interaction = 0.02). Similar declines were observed with increasing symptom frequency (p-trends for no symptoms = 0.91; low/moderate symptoms = 0.03; high symptoms = 0.004). Density declines remained among women with detectable tamoxifen metabolites or intermediate/efficient CYP2D6 metabolizer status. Emergent/worsening endocrine symptoms are associated with significant, early declines in breast density after tamoxifen initiation. Further studies are needed to assess whether these observations predict clinical outcomes. If confirmed, endocrine symptoms may be a proxy for tamoxifen response and useful for patients and providers to encourage adherence.

Hematology-Oncology

Sangam S, Sun X, Schwantes-An TH, Yegambaram M, Lu Q, Shi Y, Cook T, Fisher A, Frump AL, Coleman A, Sun Y, Liang S, **Crawford H**, Lutz KA, Maun AD, Pauciulo MW, Karnes JH, Chaudhary KR, Stewart DJ, Langlais PR, Jain M, Alotaibi M, Lahm T, Jin Y, Gu H, Tang H, Nichols WC, Black SM, and Desai AA. SOX17 Deficiency Mediates Pulmonary Hypertension: At the Crossroads of Sex, Metabolism, and Genetics. *Am J Respir Crit Care Med* 2023; Epub ahead of print. PMID: 36913491. [Full Text](#)

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RATIONALE/OBJECTIVES: Genetic studies suggest SOX17 deficiency increases pulmonary arterial hypertension (PAH) risk. Based on pathological roles of estrogen and hypoxia inducible factor 2 α (HIF-2 α) signaling in PA endothelial cells (PAECs), we hypothesized that SOX17 is a target of estrogen signaling that promotes mitochondrial function and attenuates PAH development via HIF-2 α inhibition. **METHODS:** We used metabolic (seahorse) and promoter lucifer assays in PAECs along with the chronic hypoxia murine model to test the hypothesis. **MEASUREMENTS AND MAIN RESULTS:** Sox17 expression was reduced in PAH tissues (rodent models and from patients). Chronic hypoxic PH was exacerbated by mice with conditional Tie2-Sox17 (Sox17EC $^{-/-}$) deletion and attenuated by transgenic Tie2-Sox17 overexpression (Sox17Tg). Based on untargeted proteomics, metabolism was the top pathway altered by SOX17 deficiency in PAECs. Mechanistically, we found HIF-2 α levels were increased in the lungs of Sox17EC $^{-/-}$ and reduced in those from Sox17Tg mice. Increased SOX17 promoted oxidative phosphorylation and mitochondrial function in PAECs, which were partly attenuated by HIF-2 α overexpression. Rat lungs in males displayed higher Sox17 expression versus females, suggesting repression by estrogen signaling. Supporting 16 α -hydroxyestrone (16 α OHE, a pathologic estrogen metabolite)-mediated repression of SOX17 promoter activity, Sox17Tg mice attenuated 16 α OHE-mediated exacerbations of chronic hypoxic PH. Finally, in adjusted analyses in patients with PAH, we report novel associations between a SOX17 risk variant, rs10103692, with reduced plasma citrate levels (n=1326). **CONCLUSIONS:** Cumulatively, SOX17 promotes mitochondrial bioenergetics and attenuates PAH, in part, via inhibition of HIF-2 α . 16 α OHE mediates PAH development via downregulation of SOX17, linking sexual dimorphism and SOX17 genetics in PAH. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Hematology-Oncology

Springfield C, Ferrone CR, Katz MHG, **Philip PA**, Hong TS, Hackert T, Büchler MW, and Neoptolemos J. Neoadjuvant therapy for pancreatic cancer. *Nat Rev Clin Oncol* 2023; Epub ahead of print. PMID: 36932224. [Request Article](#)

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Patients with localized pancreatic ductal adenocarcinoma (PDAC) are best treated with surgical resection of the primary tumour and systemic chemotherapy, which provides considerably longer overall survival (OS) durations than either modality alone. Regardless, most patients will have disease relapse owing to micrometastatic disease. Although currently a matter of some debate, considerable research interest has been focused on the role of neoadjuvant therapy for all forms of resectable PDAC. Whilst adjuvant combination chemotherapy remains the standard of care for patients with resectable PDAC, neoadjuvant chemotherapy seems to improve OS without necessarily increasing the resection rate in those with borderline-resectable disease. Furthermore, around 20% of patients with unresectable non-metastatic PDAC might undergo resection following 4-6 months of induction combination chemotherapy with or without radiotherapy, even in the absence of a clear radiological response, leading to improved OS outcomes in this group. Distinct molecular and biological responses to different types of therapies need to be better understood in order to enable the optimal sequencing of specific treatment modalities to further improve OS. In this Review, we describe current treatment strategies for the various clinical stages of PDAC and discuss developments that are likely to determine the optimal sequence of multimodality therapies by integrating the fundamental clinical and molecular features of the cancer.

Hematology-Oncology

Yi Q, Wang J, Liu T, Yao Y, Loveless I, Subedi K, Toor J, Adrianto I, Xiao H, Chen B, Crawford H, Fang D, Zhou L, and Mi QS. scRNA-Seq and imaging mass cytometry analyses unveil iNKT cell-mediated anti-tumor immunity in pancreatic cancer liver metastasis. *Cancer Lett* 2023; 216149. Epub ahead of print. PMID: 36990268. [Full Text](#)

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Invariant natural killer T (iNKT) cells are innate-like T cells that are abundant in liver sinusoids and play a critical role in tumor immunity. However, the role of iNKT cells in pancreatic cancer liver metastasis (PCLM) has not been fully explored. In this study, we employed a hemi-spleen pancreatic tumor cell injection mouse model of PCLM, a model that closely mimics clinical conditions in humans, to explore the role of iNKT cells in PCLM. Activation of iNKT cells with α -galactosylceramide (α GC) markedly increased immune cell infiltration and suppressed PCLM progression. Via single cell RNA sequencing (scRNA-seq) we profiled over 30,000 immune cells from normal liver and PCLM with or without α GC treatment and were able to characterize the global changes of the immune cells in the tumor microenvironment upon α GC treatment, identifying a total of 12 subpopulations. Upon treatment with α GC, scRNA-Seq and flow cytometry analyses revealed increased cytotoxic activity of iNKT/NK cells and skewing CD4 T cells towards a cytotoxic Th1 profile and CD8 T cells towards a cytotoxic profile, characterized by higher proliferation and reduced exhaustion marker PD1 expression. Moreover, α GC treatment excluded tumor associated macrophages. Lastly, imaging mass cytometry analysis uncovered the reduced epithelial to mesenchymal transition related markers and increased active CD4 and CD8 T cells in PCLM with α GC treatment. Overall, our findings uncover the protective function of activated iNKT cells in pancreatic cancer liver metastasis through increased NK and T cell immunity and decreased tumor associated macrophages.

Hematology-Oncology

Zhang J, Johnson M, Barve M, Bazhenova L, **McCarthy M**, Schwartz R, Horvath-Walsh E, Velastegui K, Qian C, and Spira A. Practical Guidance for the Management of Adverse Events in Patients with KRASG12C-Mutated Non-Small Cell Lung Cancer Receiving Adagrasib. *Oncologist* 2023; Epub ahead of print. PMID: 36892150. [Full Text](#)

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Adagrasib (MRTX849) is a KRASG12C inhibitor with favorable properties, including long half-life (23 h), dose-dependent pharmacokinetics, and central nervous system (CNS) penetration. As of September 1, 2022, a total of 853 patients with KRASG12C-mutated solid tumors, including patients with CNS metastases, had received adagrasib (monotherapy or in combination). Adagrasib-related treatment-related adverse events (TRAEs) are generally mild to moderate in severity, start early in treatment, resolve quickly with appropriate intervention, and result in a low rate of treatment discontinuation. Common TRAEs seen in clinical trials included gastrointestinal-related toxicities (diarrhea, nausea, and vomiting); hepatic toxicities (increased alanine aminotransferase/aspartate aminotransferase) and fatigue, which can be managed through dose modifications, dietary modifications, concomitant medications (such as anti-diarrheals and anti-emetics/anti-nauseants) and the monitoring of liver enzymes and electrolytes. To manage common TRAEs effectively, it is imperative that clinicians are informed, and patients are fully counseled on management recommendations at treatment initiation. In this review, we provide practical guidance on the management of adagrasib TRAEs and discuss some best practices for patient and caregiver counseling to facilitate optimal outcomes for patients. Safety and tolerability data from the phase II cohort of the KRYSTAL-1 study will be reviewed and presented with practical management recommendations based on our experience as clinical investigators.

Hospital Medicine

Caiano L, Kovacs MJ, Lazo-Langner A, Anderson DR, Kahn SR, **Shah V, Kaatz S**, Zide RS, Schulman S, Chagnon I, Mallick R, Rodger MA, and Wells PS. The risk of major bleeding in patients with factor V Leiden or prothrombin G20210A gene mutation while on extended anticoagulant treatment for venous thromboembolism. *J Thromb Haemost* 2023; 21(3):553-558. PMID: 36710196. [Full Text](#)

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BACKGROUND: Thrombophilia predisposes to venous thromboembolism (VTE) because of acquired or hereditary factors. Among them, it has been suggested that gene mutations of the factor V Leiden (FVL) or prothrombin G20210A mutation (PGM) might reduce the risk of bleeding, but little data exist for patients treated using anticoagulants. **OBJECTIVES:** To assess whether thrombophilia is protective against bleeding. **METHODS:** This multicentre, multinational, prospective cohort study evaluated adults receiving long-term anticoagulants after a VTE event. We analyzed the incidence of major bleeding as the primary outcome, according to the genotype for FVL and PGM (wild-type and heterozygous/homozygous carriers). **RESULTS:** Of 2260 patients with genotype testing, during a median follow-up of 3 years, 106 patients experienced a major bleeding event (17 intracranial and 7 fatal). Among 439 carriers of FVL, 19 experienced major bleeding and there were no differences between any mutation vs wild-type (hazard ratio [HR], 0.89 [0.53-1.49]; $p = .66$). The comparison of major bleeding events between the 158 patients with any-PGM mutation (heterozygous or homozygous) vs wild-type also showed a nonstatistically significant difference with HR of 0.53 (0.19-1.43), $p = .21$. However, multivariate analysis demonstrated that major bleeds or clinically relevant nonmajor bleeding were statistically less likely for patients with either FVL and/or PGM compared with patients with both wild-type factor V and prothrombin genes (HR, 0.73; 95% CI = 0.55-0.97; $p = .03$). **CONCLUSION:** This study demonstrates that thrombophilia, defined as the presence of either FVL or the prothrombin G20210A mutation, is related with a lower rate of major/clinically relevant nonmajor bleeding while on anticoagulants in the extended treatment for VTE.

Hospital Medicine

Zuckerman SL, Berven S, Streiff MB, Kerolus M, Buchanan IA, Ha A, Bonfield CM, Buchholz AL, Buchowski JM, Burch S, Devin CJ, Dimar JR, Gum JL, Good C, Kim HJ, Kim JS, Lombardi JM, Mandigo CE, Bydon M, Oppenlander ME, Polly DW, Jr., Poulter G, Shah SA, Singh K, Than KD, Spyropoulos AC, **Kaatz S**, Jain A, Schutzer RW, Wang TZ, Mazique DC, Lenke LG, and Lehman RA. Management of Anticoagulation/Antiplatelet Medication and Venous Thromboembolism Prophylaxis in Elective Spine Surgery: Concise Clinical Recommendations Based on a Modified Delphi Process. *Spine (Phila Pa 1976)* 2023; 48(5):301-309. PMID: 36730667. [Full Text](#)

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STUDY DESIGN: Delphi method. **OBJECTIVE:** To gain consensus on the following questions: (1) When should anticoagulation/antiplatelet (AC/AP) medication be stopped before elective spine surgery?; (2) When should AC/AP medication be restarted after elective spine surgery?; (3) When, how, and in whom should venous thromboembolism (VTE) chemoprophylaxis be started after elective spinal surgery?

SUMMARY OF BACKGROUND DATA: VTE can lead to significant morbidity after adult spine surgery, yet postoperative VTE prophylaxis practices vary considerably. The management of preoperative AC/AP medication is similarly heterogeneous. **MATERIALS AND METHODS:** Delphi method of consensus development consisting of three rounds (January 26, 2021, to June 21, 2021). **RESULTS:** Twenty-one spine surgeons were invited, and 20 surgeons completed all rounds of questioning. Consensus (>70% agreement) was achieved in 26/27 items. Group consensus stated that preoperative Direct Oral Anticoagulants should be stopped two days before surgery, warfarin stopped five days before surgery, and all remaining AC/AP medication and aspirin should be stopped seven days before surgery. For restarting AC/AP medication postoperatively, consensus was achieved for low-risk/medium-risk/high-risk patients in 5/5 risk factors (VTE history/cardiac/ambulation status/anterior approach/operation). The low/medium/high thresholds were POD7/POD5/POD2, respectively. For VTE chemoprophylaxis, consensus was achieved for low-risk/medium-risk/high-risk patients in 12/13 risk factors (age/BMI/VTE history/cardiac/cancer/hormone therapy/operation/anterior approach/staged separate days/staged same days/operative time/transfusion). The one area that did not gain consensus was same-day staged surgery. The low-threshold/medium-threshold/high-threshold ranges were postoperative day 5 (POD5) or none/POD3-4/POD1-2, respectively. Additional VTE chemoprophylaxis considerations that gained consensus were POD1 defined as the morning after surgery regardless of operating finishing time, enoxaparin as the medication of choice, and standardized, rather than weight-based, dose given once per day. **CONCLUSIONS:** In the first known Delphi study to address anticoagulation/antiplatelet recommendations for elective spine surgery (preoperatively and postoperatively); our Delphi consensus recommendations from 20 spine surgeons achieved consensus on 26/27 items. These results will potentially help standardize the management of preoperative AC/AP medication and VTE chemoprophylaxis after adult elective spine surgery.

Hypertension and Vascular Research

Motillo EP, Mladenovic-Lucas L, Zhang H, Zhou L, Kelly CV, **Ortiz PA**, and Granneman JG. A FRET sensor for the real-time detection of long chain acyl-CoAs and synthetic ABHD5 ligands. *Cell Rep Methods* 2023; 3(2):100394. PMID: 36936069. [Full Text](#)

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Intracellular long-chain acyl-coenzyme As (LC-acyl-CoAs) are thought to be under tight spatial and temporal controls, yet the ability to image LC-acyl-CoAs in live cells is lacking. Here, we developed a fluorescence resonance energy transfer (FRET) sensor for LC-acyl-CoAs based on the allosterically regulated interaction between α/β hydrolase domain-containing 5 (ABHD5) and Perilipin 5. The genetically encoded sensor rapidly detects intracellular LC-acyl-CoAs generated from exogenous and endogenous fatty acids (FAs), as well as synthetic ABHD5 ligands. Stimulation of lipolysis in brown adipocytes elevated intracellular LC-acyl-CoAs in a cyclic fashion, which was eliminated by inhibiting PNPLA2 (ATGL), the major triglyceride lipase. Interestingly, inhibition of LC-acyl-CoA transport into mitochondria elevated intracellular LC-acyl-CoAs and dampened their cycling. Together, these observations reveal an intimate feedback control between LC-acyl-CoA generation from lipolysis and utilization in mitochondria. We anticipate that this sensor will be an important tool to dissect intracellular LC-acyl-CoA dynamics as well to discover novel synthetic ABHD5 ligands.

Hypertension and Vascular Research

Suhail H, **Peng H**, **Xu J**, **Sabbah HN**, Matrougui K, **Liao TD**, **Ortiz PA**, Bernstein KE, and **Rhaleb NE**. Knockout of ACE-N facilitates improved cardiac function after myocardial infarction. *J Mol Cell Cardiol Plus* 2023; 3. PMID: 36778784. [Full Text](#)

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Angiotensin-converting enzyme (ACE) hydrolyzes N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) into inactive fragments through its N-terminal site (ACE-N). We previously showed that Ac-SDKP mediates ACE inhibitors' cardiac effects. Whether increased bioavailability of endogenous Ac-SDKP caused by knocking out ACE-N also improves cardiac function in myocardial infarction (MI)-induced heart failure (HF) is unknown. Wild-type (WT) and ACE-N knockout (ACE-NKO) mice were subjected to MI by ligating the left anterior descending artery and treated with vehicle or Ac-SDKP (1.6 mg/kg/day, s.c.) for 5 weeks, after which echocardiography was performed and left ventricles (LV) were harvested for histology and molecular biology studies. ACE-NKO mice showed increased plasma Ac-SDKP concentrations in both sham and MI group compared to WT. Exogenous Ac-SDKP further increased its circulating concentrations in WT and ACE-NKO. Shortening (SF) and ejection (EF) fractions were significantly decreased in both WT and ACE-NKO mice post-MI, but ACE-NKO mice exhibited significantly lesser decrease. Exogenous Ac-SDKP ameliorated cardiac function post-MI only in WT but failed to show any additive improvement in ACE-NKO mice. Sarcoendoplasmic reticulum calcium transport ATPase (SERCA2), a marker of cardiac function and calcium homeostasis, was significantly decreased in WT post-MI but rescued with Ac-SDKP, whereas ACE-NKO mice displayed less loss of SERCA2 expression. Our study demonstrates that gene deletion of ACE-N resulted in improved LV cardiac function in mice post-MI, which is likely mediated by increased circulating Ac-SDKP and minimally reduced expression of

SERCA2. Thus, future development of specific and selective inhibitors for ACE-N could represent a novel approach to increase endogenous Ac-SDKP toward protecting the heart from post-MI remodeling.

Hypertension and Vascular Research

Umanath K, She R, Hassett C, Adrianto I, Levin AM, Savickas G, Yee J, and Ortiz P. Urine Cell Transcriptomes Implicate Specific Renal Inflammatory Pathways Associated With Difficult-to-Control Hypertension. *J Am Heart Assoc* 2023; 12(6):e026242. PMID: 36892045. [Full Text](#)

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Background The renal mechanisms involved in the maintenance of human hypertension and resistance to treatment are not well understood. Animal studies suggest that chronic renal inflammation contributes to hypertension. We studied cells shed in first-morning urine samples from individuals who were hypertensive who exhibited difficult-to-control blood pressure (BP). We performed bulk RNA sequencing of these shed cells to develop transcriptome-wide associations with BP. We also analyzed nephron-specific genes and used an unbiased bioinformatic approach to find signaling pathways activated in difficult-to-control hypertension. **Methods and Results** Participants who completed the SPRINT (Systolic Blood Pressure Intervention Trial) at a single trial site were recruited, and cells shed in first-morning urine samples collected. A total of 47 participants were divided into 2 groups based on hypertension control. The BP-difficult group (n=29) had systolic BP>140 mm Hg, >120 mm Hg after intensive treatment for hypertension, or required more than the median number of antihypertensive drugs used in SPRINT. The easy-to-control BP group (n=18) comprised the remainder of the participants. A total of 60 differentially expressed genes were identified with a >2-fold change in the BP-difficult group. In BP-difficult participants, 2 of the most upregulated genes were associated with inflammation: Tumor Necrosis Factor Alpha Induced Protein 6 (fold change, 7.76; P=0.006) and Serpin Family B Member 9 (fold change, 5.10; P=0.007). Biological pathway analysis revealed an overrepresentation of inflammatory networks, including interferon signaling, granulocyte adhesion and diapedesis, and Janus Kinase family kinases in the BP-difficult group (P<0.001). **Conclusions** We conclude that transcriptomes from cells shed in first-morning urine identify a gene expression profile in difficult-to-control hypertension that associates with renal inflammation.

Infectious Diseases

Jovanović M, Velebit B, Tošić T, **Maki G**, Pavić S, Jovanović S, Stošović R, and **Zervos MJ.** Comparative study of virulence factor genes, β -hemolysis and biofilm production in invasive and colonizing enterococci. *Eur J Inflam* 2023; 21. PMID: Not assigned. [Full Text](#)

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Objectives: In humans, enterococci are among the most important opportunistic pathogens. This study aims to compare invasive isolates obtained from blood cultures of patients with sepsis and endocarditis with colonizing isolates obtained from healthy donors' stool samples. **Methods:** A case-by-case assessment was conducted on invasive infection cases to determine whether enterococci were involved in their pathogenesis. They were tested for the presence of virulence factor genes, β -hemolysis on agars supplemented with human and sheep blood, and biofilm forming capacity. **Results:** Three species of enterococci were identified among invasive isolates: *Enterococcus faecalis*, *Enterococcus faecium*, and *Enterococcus durans*. All endocarditis isolates were biofilm producers. Genes *esp*, *gelE*, *asa1*, *ace*, *hyl*, *cylB*, and *cylA* were present in 7 (41.2%), 11 (64.7%), 11 (64.7%), 13 (76.5%), 0, 3 (17.6%), and 1 (5.9%) invasive isolate, but none of them could be linked to a particular infection (sepsis or endocarditis). Colonizing isolates proved to have had more virulence factor genes, but the differences were not statistically significant. Members of that group produced a greater amount of biofilm when the *ace* gene

was absent ($p = 0.047$). The production of β -hemolysis by noninvasive strains was detected more frequently when agar was supplemented with human blood ($p = 0.021$). In general, the presence of either *cyl* gene on that specific agar was in direct connection with the production of β -hemolysis: *cylA* ($p = 0.047$) or *cylB* ($p = 0.020$). Conclusion: We have been unable to establish any correlation between invasive isolates and any virulence gene carriage and biofilm formation. β -hemolysis was produced significantly more often by colonizing strains when agar had been supplemented with human blood.

Infectious Diseases

Shallal AB, Cherabuddi M, Podsiad L, Gortat C, Shanahan C, Holsey T, Samuel L, Alangaden G, and Suleyman G. Role of diagnostic stewardship in reducing healthcare-facility-onset *Clostridioides difficile* infections. *Antimicrob Steward Healthc Epidemiol* 2023; 3(1):e53. PMID: 36970430. [Full Text](#)

Division of Infectious Disease, Henry Ford Health, Detroit, Michigan.
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We describe the implementation of an electronic medical record "hard stop" to decrease inappropriate *Clostridioides difficile* testing across a 5-hospital health system, effectively reducing the rates of healthcare-facility-onset *C. difficile* infection. This novel approach included expert consultation with medical director of infection prevention and control for test-order override.

Infectious Diseases

Yared N. The Role of Point-of-Care Testing in Specific Populations. *Clin Lab Med* 2023. PMID: Not assigned. [Full Text](#)

Internal Medicine

Bunch CM, Chang E, Moore EE, Moore HB, Kwaan HC, Miller JB, Al-Fadhli MD, Thomas AV, Zackariya N, Patel SS, Zackariya S, Haidar S, Patel B, McCurdy MT, Thomas SG, Zimmer D, Fulkerson D, Kim PY, Walsh MR, Hake D, Kedar A, Aboukhaled M, and Walsh MM. SHock-INduced Endotheliopathy (SHINE): A mechanistic justification for viscoelastography-guided resuscitation of traumatic and non-traumatic shock. *Front Physiol* 2023; 14:1094845. PMID: 36923287. [Full Text](#)

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, United States.
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Irrespective of the reason for hypoperfusion, hypocoagulable and/or hyperfibrinolytic hemostatic aberrancies afflict up to one-quarter of critically ill patients in shock. Intensivists and traumatologists have embraced the concept of SHock-INduced Endotheliopathy (SHINE) as a foundational derangement in progressive shock wherein sympatho-adrenal activation may cause systemic endothelial injury. The pro-thrombotic endothelium lends to micro-thrombosis, enacting a cycle of worsening perfusion and increasing catecholamines, endothelial injury, de-endothelialization, and multiple organ failure. The hypocoagulable/hyperfibrinolytic hemostatic phenotype is thought to be driven by endothelial release of anti-thrombogenic mediators to the bloodstream and perivascular sympathetic nerve release of tissue plasminogen activator directly into the microvasculature. In the shock state, this hemostatic phenotype may be a counterbalancing, yet maladaptive, attempt to restore blood flow against a systemically pro-thrombotic endothelium and increased blood viscosity. We therefore review endothelial physiology with emphasis on glycocalyx function, unique biomarkers, and coagulofibrinolytic mediators, setting the stage for understanding the pathophysiology and hemostatic phenotypes of SHINE in various etiologies of shock. We propose that the hyperfibrinolytic phenotype is exemplified in progressive shock whether related to trauma-induced coagulopathy, sepsis-induced coagulopathy, or post-cardiac arrest syndrome-associated coagulopathy. Regardless of the initial insult, SHINE appears to be a catecholamine-driven entity which early in the disease course may manifest as hyper- or hypocoagulopathic and hyper- or hypofibrinolytic hemostatic imbalance. Moreover, these hemostatic derangements may rapidly evolve along the thrombohemorrhagic spectrum depending on the etiology, timing, and methods of resuscitation. Given the intricate hemochemical makeup and changes during these shock states, macroscopic whole blood tests of coagulative kinetics and clot strength serve as clinically useful and simple means for hemostasis phenotyping. We suggest that viscoelastic hemostatic assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are currently the most applicable clinical tools for assaying global hemostatic function-including fibrinolysis-to enable dynamic resuscitation with blood products and hemostatic adjuncts for those patients with thrombotic and/or hemorrhagic complications in shock states.

Internal Medicine

Caiano L, Kovacs MJ, Lazo-Langner A, Anderson DR, Kahn SR, **Shah V, Kaatz S**, Zide RS, Schulman S, Chagnon I, Mallick R, Rodger MA, and Wells PS. The risk of major bleeding in patients with factor V Leiden or prothrombin G20210A gene mutation while on extended anticoagulant treatment for venous thromboembolism. *J Thromb Haemost* 2023; 21(3):553-558. PMID: 36710196. [Full Text](#)

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BACKGROUND: Thrombophilia predisposes to venous thromboembolism (VTE) because of acquired or hereditary factors. Among them, it has been suggested that gene mutations of the factor V Leiden (FVL) or prothrombin G20210A mutation (PGM) might reduce the risk of bleeding, but little data exist for patients treated using anticoagulants. **OBJECTIVES:** To assess whether thrombophilia is protective against bleeding. **METHODS:** This multicentre, multinational, prospective cohort study evaluated adults receiving long-term anticoagulants after a VTE event. We analyzed the incidence of major bleeding as the primary outcome, according to the genotype for FVL and PGM (wild-type and heterozygous/homozygous

carriers). RESULTS: Of 2260 patients with genotype testing, during a median follow-up of 3 years, 106 patients experienced a major bleeding event (17 intracranial and 7 fatal). Among 439 carriers of FVL, 19 experienced major bleeding and there were no differences between any mutation vs wild-type (hazard ratio [HR], 0.89 [0.53-1.49]; $p = .66$). The comparison of major bleeding events between the 158 patients with any-PGM mutation (heterozygous or homozygous) vs wild-type also showed a nonstatistically significant difference with HR of 0.53 (0.19-1.43), $p = .21$. However, multivariate analysis demonstrated that major bleeds or clinically relevant nonmajor bleeding were statistically less likely for patients with either FVL and/or PGM compared with patients with both wild-type factor V and prothrombin genes (HR, 0.73; 95% CI = 0.55-0.97; $p = .03$). CONCLUSION: This study demonstrates that thrombophilia, defined as the presence of either FVL or the prothrombin G20210A mutation, is related with a lower rate of major/clinically relevant nonmajor bleeding while on anticoagulants in the extended treatment for VTE.

Internal Medicine

Geletu A, Gardner-Gray J, Roche M, and Ngassa M. Cardiac Arrest as the First Presentation of Gitelman Syndrome. *Cureus* 2023; 15(1):e33565. PMID: 36779094. [Full Text](#)

Internal Medicine, Henry Ford Health System, Detroit, USA.
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Gitelman syndrome is a salt-wasting tubulopathy characterized by profound hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. Cardiac arrest is a relatively rare manifestation of Gitelman syndrome. Here we present a case of Gitelman syndrome in a patient with recurrent cardiac arrest. A 43-year-old female was admitted for out-of-hospital cardiac arrest secondary to ventricular fibrillation. Initial workup revealed severe hypokalemia, hypomagnesemia, metabolic alkalosis, and prolonged QTc. The workup revealed a picture of salt-wasting tubulopathy with hypokalemia, hypomagnesemia, and hypocalciuria. Potassium was repleted aggressively, and the patient received potassium-sparing agents resulting in the stabilization of potassium levels. Before discharge, an implantable cardioverter defibrillator (ICD) was placed for secondary prevention of cardiac arrest. The patient remained symptom-free, and electrolytes remained stable. This case highlights the diagnostic challenges of Gitelman syndrome and the importance of accurate diagnosis in improving patient outcomes.

Internal Medicine

Hinojosa OA, and Ammari O. Herpes Simplex Virus-Associated Aplastic Anemia. *Cureus* 2023; 15(2):e35320. PMID: 36994301. [Full Text](#)

Internal Medicine, Henry Ford Health System, Detroit, USA.

Aplastic anemia is an uncommon condition defined by peripheral pancytopenia in the context of hypocellular bone marrow. In the majority of cases, it is idiopathic in origin. However, exposure to certain drugs and toxins, autoimmune processes, and viral infections have been linked to this entity. This is the case of a 56-year-old female with an acute presentation of fever, odynophagia, and dysphagia. Physical examination revealed multiple hemorrhagic ulcers affecting her oropharyngeal mucosa with regions of necrosis. Mucosal biopsy was compatible with the presence of local necrosis and keratinization. Hematological analysis showed severe peripheral pancytopenia, and the bone marrow biopsy revealed a hypocellular marrow, findings consistent with aplastic anemia. An ample PCR viral panel revealed the presence of herpes simplex virus type 1 (HSV-1). The patient was placed on systemic antiviral therapy, followed by a rapid improvement of the mucositis as well as the peripheral and central pancytopenia. Our case indicated the possible association of HSV-1 infection and the development of aplastic anemia, an important and not yet recognized association considering the rapid improvement of the clinical picture once the underlying etiology was addressed.

Internal Medicine

Mahfooz K, Vasavada AM, Joshi A, Pichuthirumalai S, Andani R, Rajotia A, **Hans A**, Mandalia B, Dayama N, Younas Z, Hafeez N, Bheemisetty N, Patel Y, Tumkur Ranganathan H, and Sodala A. Waterpipe Use and Its Cardiovascular Effects: A Systematic Review and Meta-Analysis of Case-Control, Cross-Sectional, and Non-Randomized Studies. *Cureus* 2023; 15(2):e34802. PMID: 36915837. [Full Text](#)

Internal Medicine, Lincoln Medical Center, New York, USA.

Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA.

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Medicine, B. J. (Byramjee Jeejeebhoy) Medical, Ahmedabad, IND.

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Approximately 100 million people globally smoke cigarettes, making it a significant and quickly spreading global tobacco epidemic. Substance use disorders are frequently evaluated by non-randomized studies. Tobacco use and its impacts on the cardiovascular system were the subjects of a comprehensive search across five electronic databases: Cochrane, MEDLINE, Scopus, Embase, and PubMed. The findings demonstrated that waterpipe smokers in comparison to non-smokers have immediate elevations in heart rate and blood pressure, lower levels of high-density lipoprotein, higher levels of low-density lipoprotein, higher levels of triglycerides, higher levels of fasting blood glucose, and a higher heart rate. Users of waterpipes and cigarettes had similar average heart rates, blood pressure, and lipid levels, with the exception that waterpipe smokers had greater total cholesterol. Smoking a waterpipe has significant negative effects on the cardiovascular system comparable to cigarette smoking, and non-randomized studies proved to yield substantial evidence related to its cardiovascular effects. Such study designs can be used to evaluate substance use and its cardiovascular impact.

Internal Medicine

Panzer AR, **Sitarik AR**, Fadrosch D, **Havstad SL**, **Jones K**, **Davidson B**, **Finazzo S**, **Wegienka GR**, **Woodcroft K**, Lukacs NW, **Levin AM**, **Ownby DR**, **Johnson CC**, **Lynch SV**, and **Zoratti EM**. The impact of prenatal dog keeping on infant gut microbiota development. *Clin Exp Allergy* 2023; Epub ahead of print. PMID: 36916778. [Full Text](#)

Department of Medicine, University of California, San Francisco, California, USA.

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

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Department of Pathology, University of Michigan, Ann Arbor, Michigan, USA.

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INTRODUCTION: Prenatal and early-life dog exposure has been linked to reduced childhood allergy and asthma. A potential mechanism includes altered early immune development in response to changes in the gut microbiome among dog-exposed infants. We thus sought to determine whether infants born into homes with indoor dog(s) exhibit altered gut microbiome development. **METHODS:** Pregnant women living in homes with dogs or in pet-free homes were recruited in southeast Michigan. Infant stool samples were collected at intervals between 1 week and 18 months after birth and microbiome was assessed

using 16S ribosomal sequencing. Perinatal maternal vaginal/rectal swabs and stool samples were sequenced from a limited number of mothers. Mixed effect adjusted models were used to assess stool microbial community trajectories comparing infants from dog-keeping versus pet-free homes with adjustment for relevant covariates. RESULTS: Infant gut microbial composition among vaginally born babies became less similar to the maternal vaginal/rectal microbiota and more similar to the maternal gut microbiota with age-related accumulation of bacterial species with advancing age. Stool samples from dog-exposed infants were microbially more diverse ($p = .041$) through age 18 months with enhanced diversity most apparent between 3 and 6 months of age. Statistically significant effects of dog exposure on β -diversity metrics were restricted to formula-fed children. Across the sample collection period, dog exposure was associated with *Fusobacterium* genera enrichment, as well as enrichment of *Collinsella*, *Ruminococcus*, *Clostridaceae* and *Lachnospiraceae* OTUs. CONCLUSION: Prenatal/early-life dog exposure is associated with an altered gut microbiome during infancy and supports a potential mechanism explaining lessened atopy and asthma risk. Further research directly linking specific dog-attributable changes in the infant gut microbiome to the risk of allergic disorders is needed.

Internal Medicine

Shallal AB, Cherabuddi M, Podsiad L, Gortat C, Shanahan C, Holsey T, Samuel L, Alangaden G, and Suleyman G. Role of diagnostic stewardship in reducing healthcare-facility-onset *Clostridioides difficile* infections. *Antimicrob Steward Healthc Epidemiol* 2023; 3(1):e53. PMID: 36970430. [Full Text](#)

Division of Infectious Disease, Henry Ford Health, Detroit, Michigan.
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Clinical Microbiology, Henry Ford Health, Detroit, Michigan.

We describe the implementation of an electronic medical record "hard stop" to decrease inappropriate *Clostridioides difficile* testing across a 5-hospital health system, effectively reducing the rates of healthcare-facility-onset *C. difficile* infection. This novel approach included expert consultation with medical director of infection prevention and control for test-order override.

Internal Medicine

Singh H, Patel P, Parikh S, Zreik H, Caliman N, and Kak V. Pancreatitis, panniculitis and polyarthralgia syndrome: A rare complication of pancreatic pathology. *Radiol Case Rep* 2023; 18(5):2001-2004. PMID: 37020599. [Full Text](#)

Henry Ford Health, Department of Internal Medicine, Henry Ford Jackson Hospital, 205 N East Ave, Jackson, MI, 49201, USA.
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Pancreatitis, panniculitis, and polyarthralgia (PPP) syndrome is a rare complication of chronic pancreatitis and occurs due to leakage of pancreatic enzymes in the systemic vasculature. This enzyme leakage leads to multiple manifestations such as polyarthralgia, panniculitis, and bone necrosis due to tissue autodigestion. The inciting pancreatic pathology may be masked, and the presentation may be due to one of the systemic consequences of enzyme leakage, which can present as a diagnostic challenge for clinicians. Here we present a patient who presented with nodular lesions and bone necrosis, and was found to have PPP syndrome. Therefore, a proper understanding of pathophysiology and radiology findings can help with prompt diagnosis and early exploration of management options.

Internal Medicine

Singh HP, Maraj D, Hawes E, and Memon M. New-Onset Heart Failure and Ischemic Stroke in Non-compaction Cardiomyopathy: A Case Report. *Cureus* 2023; 15(2):e35371. PMID: 36994256. [Full Text](#)

Internal Medicine, Henry Ford Health System, Jackson, USA.

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Left ventricular non-compaction (LVNC) cardiomyopathy is an embryological disorder of endocardial trabeculation and can cause heart failure, arrhythmias, and thromboembolism. Lifelong anticoagulation is indicated in patients with reduced ejection fraction due to high risks of thromboembolism. Reduced ejection fraction can develop in these patients as a consequence of this cardiomyopathy, thereby increasing the risk of intracardiac thrombus formation. This new-onset reduced ejection fraction may develop rapidly, which may not be amenable to detection by routine screening. We present a case of non-compaction cardiomyopathy (NCC) with a previously normal ejection fraction who had an ischemic stroke and was found to have new-onset reduced ejection fraction.

Internal Medicine

Suhail H, Peng H, Xu J, Sabbah HN, Matrougui K, Liao TD, Ortiz PA, Bernstein KE, and Rhaleb NE. Knockout of ACE-N facilitates improved cardiac function after myocardial infarction. *J Mol Cell Cardiol Plus* 2023; 3. PMID: 36778784. [Full Text](#)

Department of Internal Medicine, Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, MI 48202, USA.

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Angiotensin-converting enzyme (ACE) hydrolyzes N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) into inactive fragments through its N-terminal site (ACE-N). We previously showed that Ac-SDKP mediates ACE inhibitors' cardiac effects. Whether increased bioavailability of endogenous Ac-SDKP caused by knocking out ACE-N also improves cardiac function in myocardial infarction (MI)-induced heart failure (HF) is unknown. Wild-type (WT) and ACE-N knockout (ACE-NKO) mice were subjected to MI by ligating the left anterior descending artery and treated with vehicle or Ac-SDKP (1.6 mg/kg/day, s.c.) for 5 weeks, after which echocardiography was performed and left ventricles (LV) were harvested for histology and molecular biology studies. ACE-NKO mice showed increased plasma Ac-SDKP concentrations in both sham and MI group compared to WT. Exogenous Ac-SDKP further increased its circulating concentrations in WT and ACE-NKO. Shortening (SF) and ejection (EF) fractions were significantly decreased in both WT and ACE-NKO mice post-MI, but ACE-NKO mice exhibited significantly lesser decrease. Exogenous Ac-SDKP ameliorated cardiac function post-MI only in WT but failed to show any additive improvement in ACE-NKO mice. Sarcoendoplasmic reticulum calcium transport ATPase (SERCA2), a marker of cardiac function and calcium homeostasis, was significantly decreased in WT post-MI but rescued with Ac-SDKP, whereas ACE-NKO mice displayed less loss of SERCA2 expression. Our study demonstrates that gene deletion of ACE-N resulted in improved LV cardiac function in mice post-MI, which is likely mediated by increased circulating Ac-SDKP and minimally reduced expression of SERCA2. Thus, future development of specific and selective inhibitors for ACE-N could represent a novel approach to increase endogenous Ac-SDKP toward protecting the heart from post-MI remodeling.

Internal Medicine

Wager SG, Bourdeau NK, and **Collins JD.** Streptococcus constellatus Brain Abscess in a Middle-Aged Man With an Undiagnosed Patent Foramen Ovale. *Cureus* 2023; 15(2):e34626. PMID: 36891022. [Full Text](#)

Internal Medicine, Wayne State University School of Medicine, Detroit, USA.

Internal Medicine, Henry Ford Health System, Detroit, USA.

Brain abscess is a rare diagnosis. Common sources of infection include direct spread from otic sources, sinuses, or oral cavities, and hematogenous spread from distant sources, including the heart and lungs. Brain abscess with cultures growing oral flora species, in rare cases, may develop from bacteria in the

oral cavity entering the bloodstream and then traveling to the brain via a patent foramen ovale. This report highlights a case of brain abscess caused by *Streptococcus constellatus* in a middle-aged man with an undiagnosed patent foramen ovale.

Nephrology

Frinak S, Kennedy J, **Zasuwa G**, **Passalacqua KD**, and **Yee J**. Detection of Hemodialysis Venous Needle Dislodgment Using Venous Access Pressure Measurements: A Simulation Study. *Kidney360* 2023; Epub ahead of print. PMID: 36960959. [Full Text](#)

Nephrology Department of Henry Ford Health, Detroit, MI.
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BACKGROUND: In rare instances, hemodialysis venous needles may become dislodged, and when left undetected can lead to severe injury or death. Although dialysis machines have alarms to detect venous needle dislodgment, their range of detection is limited. An understanding of the clinical conditions that may lead to missed needle dislodgments is needed for development of more robust detection systems. **METHODS:** We created a sham dialysis circuit with a Fresenius 2008 K dialysis machine for in vitro simulation testing of machine alarm behavior under variable conditions. The circuit used a blood substitute and mimicked a patient's venous access site. We varied blood flow rate, venous pressure, and upward drift in venous pressure and analyzed the time to alarm for the machine and an improved alarm algorithm. We also performed a cross-sectional retrospective study to identify the clinical occurrence of venous pressure upward drift between September 1, 2016, and November 1, 2016 in patients on hemodialysis with an arteriovenous fistula. **RESULTS:** Of 43,390 venous pressure readings for 147 patients on hemodialysis, 16,594 (38%) showed an upward drift in venous pressure (range 20-79 mmHg), with a mean \pm SD increase of 11 ± 18 mmHg within 20 ± 14 minutes. A total of 19 venous needle dislodgment simulations under different venous pressure and blood flow parameters resulted in 19 (100%) algorithm alarm activations. Only 8 simulations (42%) activated a machine alarm, and machine alarm activation time was longer than the algorithm activation time for all 8 machine alarms (range 1-13 seconds). **CONCLUSIONS:** Patients can experience changes in venous pressure during hemodialysis which may not trigger a machine alarm in the case of a venous needle dislodgment. Our simulations showed that current dialysis machine alarm systems may not compensate for upward drift in venous pressure, and improved algorithms for detecting needle dislodgment during hemodialysis are needed.

Nephrology

Geletu A, **Gardner-Gray J**, **Roche M**, and **Ngassa M**. Cardiac Arrest as the First Presentation of Gitelman Syndrome. *Cureus* 2023; 15(1):e33565. PMID: 36779094. [Full Text](#)

Internal Medicine, Henry Ford Health System, Detroit, USA.
Critical Care Medicine, Henry Ford Health System, Detroit, USA.
Nephrology, Henry Ford Health System, Detroit, USA.

Gitelman syndrome is a salt-wasting tubulopathy characterized by profound hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. Cardiac arrest is a relatively rare manifestation of Gitelman syndrome. Here we present a case of Gitelman syndrome in a patient with recurrent cardiac arrest. A 43-year-old female was admitted for out-of-hospital cardiac arrest secondary to ventricular fibrillation. Initial workup revealed severe hypokalemia, hypomagnesemia, metabolic alkalosis, and prolonged QTc. The workup revealed a picture of salt-wasting tubulopathy with hypokalemia, hypomagnesemia, and hypocalciuria. Potassium was repleted aggressively, and the patient received potassium-sparing agents resulting in the stabilization of potassium levels. Before discharge, an implantable cardioverter defibrillator (ICD) was placed for secondary prevention of cardiac arrest. The patient remained symptom-free, and electrolytes remained stable. This case highlights the diagnostic challenges of Gitelman syndrome and the importance of accurate diagnosis in improving patient outcomes.

Nephrology

Silberzweig J, Wu S, Sinclair M, Watson T, Welder N, Concepcion D, **Yee J**, Speed F, Cukor D, Schiller B, and Weiner D. Response to COVID-19: The Outpatient Dialysis Setting. *Clin J Am Soc Nephrol* 2023; Epub ahead of print. PMID: 36795086. [Full Text](#)

Division of Nephrology, Weill Medical College of Cornell University, New York, New York.

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Medical Affairs, Satellite Healthcare, San Jose, California.

Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, California.

Division of Nephrology, Tufts Medical Center, Boston, Massachusetts.

Nephrology

Umanath K, She R, Hassett C, Adrianto I, Levin AM, Savickas G, Yee J, and Ortiz P. Urine Cell Transcriptomes Implicate Specific Renal Inflammatory Pathways Associated With Difficult-to-Control Hypertension. *J Am Heart Assoc* 2023; 12(6):e026242. PMID: 36892045. [Full Text](#)

Division of Nephrology and Hypertension Henry Ford Health Detroit MI.

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Department of Public Health Sciences Henry Ford Health Detroit MI.

Center for Bioinformatics Henry Ford Health Detroit MI.

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Background The renal mechanisms involved in the maintenance of human hypertension and resistance to treatment are not well understood. Animal studies suggest that chronic renal inflammation contributes to hypertension. We studied cells shed in first-morning urine samples from individuals who were hypertensive who exhibited difficult-to-control blood pressure (BP). We performed bulk RNA sequencing of these shed cells to develop transcriptome-wide associations with BP. We also analyzed nephron-specific genes and used an unbiased bioinformatic approach to find signaling pathways activated in difficult-to-control hypertension. **Methods and Results** Participants who completed the SPRINT (Systolic Blood Pressure Intervention Trial) at a single trial site were recruited, and cells shed in first-morning urine samples collected. A total of 47 participants were divided into 2 groups based on hypertension control. The BP-difficult group (n=29) had systolic BP>140 mm Hg, >120 mm Hg after intensive treatment for hypertension, or required more than the median number of antihypertensive drugs used in SPRINT. The easy-to-control BP group (n=18) comprised the remainder of the participants. A total of 60 differentially expressed genes were identified with a >2-fold change in the BP-difficult group. In BP-difficult participants, 2 of the most upregulated genes were associated with inflammation: Tumor Necrosis Factor Alpha Induced Protein 6 (fold change, 7.76; P=0.006) and Serpin Family B Member 9 (fold change, 5.10; P=0.007). Biological pathway analysis revealed an overrepresentation of inflammatory networks, including interferon signaling, granulocyte adhesion and diapedesis, and Janus Kinase family kinases in the BP-difficult group (P<0.001). **Conclusions** We conclude that transcriptomes from cells shed in first-morning urine identify a gene expression profile in difficult-to-control hypertension that associates with renal inflammation.

Neurology

Akhter N, and Ahmad S. Molecular Signaling in Stroke. *Int J Mol Sci* 2023; 24(6). PMID: 36983049. [Full Text](#)

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Neurology

Bagić A, **Bowyer S**, Funke M, Mohamed I, Tenney JR, Zhang W, and Zillgitt A. Commentary on "Mapping the Unconscious Brain: Insights From Advanced Neuroimaging". *J Clin Neurophysiol* 2023; 40(3):269. PMID: 36730484. [Full Text](#)

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Neurology

De Georgia M, Bowen T, Duncan KR, and **Chebl AB**. Blood pressure management in ischemic stroke patients undergoing mechanical thrombectomy. *Neurol Res Pract* 2023; 5(1):12. PMID: 36991520. [Full Text](#)

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The relationship between presenting blood pressure in acute ischemic stroke patients and outcome is complex. Several studies have demonstrated a U-shaped curve with worse outcomes when blood pressure is high or low. The American Heart Association/American Stroke Association guidelines recommend values of blood pressure < 185/110 mmHg in patients treated with intravenous t-PA and "permissive hypertension" up to 220/120 mmHg in those not treated with intravenous t-PA. The optimal blood pressure target is less clear in patients undergoing mechanical thrombectomy. Before thrombectomy, the guidelines recommend a blood pressure < 185/110 mmHg though patients with even lower systolic blood pressures may have better outcomes. During and after thrombectomy, the guidelines recommend a blood pressure < 180/105 mmHg. However, several studies have suggested that during thrombectomy the primary goal should be to prevent significant low blood pressure (e.g., target systolic blood pressure > 140 mmHg or MAP > 70 mmHg). After thrombectomy, the primary goal should be to prevent high blood pressure (e.g., target systolic blood pressure < 160 mmHg or MAP < 90 mmHg). To make more specific recommendations, large, randomized-control studies are needed that address factors such as the baseline blood pressure, timing and degree of revascularization, status of collaterals, and estimated risk of reperfusion injury.

Neurology

Hauser RA, **LeWitt PA**, Waters CH, Grosset DG, and Blank B. The Clinical Development of Levodopa Inhalation Powder. *Clin Neuropharmacol* 2023; 46(2):66-78. PMID: 36715241. [Full Text](#)

Parkinson's Disease and Movement Disorders Center, Department of Neurology, University of South Florida, Tampa, FL.
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Oral levodopa is the most effective treatment for Parkinson disease, but OFF periods emerge over time. Gastrointestinal dysfunction and food effects impact levodopa absorption, contributing to unpredictable control of OFF periods. Inhaled levodopa powder (Inbrija) is approved for on-demand treatment of OFF periods in patients receiving oral levodopa-dopa decarboxylase inhibitors. The 84-mg dose is administered via a breath-actuated inhaler. It provides pulmonary delivery of levodopa to the systemic circulation and is taken when a patient has an OFF period in between doses of regular oral levodopa medication. The pivotal SPAN-PD trial in patients experiencing OFF periods on oral dopaminergic therapy showed that levodopa inhalation powder 84 mg produced significant improvement in Unified Parkinson Disease Rating Scale Part III score, as measured 30 minutes postdose at week 12, and improvement was seen as early as 10 minutes. More patients in the levodopa inhalation powder group turned ON within 60 minutes of treatment and remained ON at 60 minutes than in the placebo group. Levodopa inhalation powder can also be used to treat early-morning OFF periods and, when used for up to 12 months, produced no clinically significant differences in pulmonary function compared with an untreated cohort. Levodopa inhalation powder 84 mg increased plasma levodopa concentration rapidly and with less variability than oral levodopa/carbidopa (25/100 mg). Most common adverse event associated with levodopa inhalation powder is cough, found in ~15% of patients in the SPAN-PD trial; otherwise, reported adverse events were consistent with those known to be associated with oral levodopa.

Neurology

Khan MA, Sadaf, Ahmad I, Aloliqi AA, Eisa AA, Najm MZ, Habib M, Mustafa S, Massey S, Malik Z, Sunita K, Pawar JS, Akhter N, **Shukla NK, Deo SVS**, and Husain SA. FOXO3 gene hypermethylation and its marked downregulation in breast cancer cases: A study on female patients. *Front Oncol* 2023; 12:1078051. PMID: 36727057. [Full Text](#)

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BACKGROUND: FOXO3, a member of the FOX transcription factor family, is frequently described as being deregulated in cancer. Additionally, notable role of FOXO3 can be easily recognized in the process of ageing and survival. Even though various studies have been done to acknowledge the tumour-suppressive or oncogenic role of FOXO3 in cancer, still there exist a lack of understanding in terms of cancer prognosis and treatment. Therefore, to provide better insight, our study aims to evaluate the role and function of FOXO3 in breast cancer in Indian female patients. We examined the FOXO3 expression levels in breast cancer samples by analyzing mRNA and protein expression along with its clinicopathological parameters. **RESULTS:** A total of 127 cases of breast cancer with equal normal cases (n=127) were assessed with methylation (MS-PCR), Immunohistochemistry (IHC), mRNA expression using Real-time PCR was analysed and 66.14% cases at mRNA level were found to be downregulated, while 81.10% of cases had little or very little protein expression. Our data state, the promoter hypermethylation of the FOXO3 gene and the downregulated protein expression are significantly correlated (p=0.0004). Additionally, we found a significant correlation between the level of FOXO3 mRNA with ER (p=0.04) and status of lymph node (p=0.01) along with this. **CONCLUSION:** Data suggests the

prognostic significance and the tumour-suppressive role of FOXO3 in breast cancer cases studied in India. However, there is a need for the extended research targeting FOXO3 to measure its clinical potential and develop well-defined therapeutic strategies.

Neurology

Sarigul B, Bell RS, **Mayer S**, et al. Prognostication and Withdrawal of Care Decisions in Severe Traumatic Brain Injury: A Survey of The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) Working Group. *J Neurotrauma* 2023; Epub ahead of print. PMID: 36932737. [Full Text](#)

Best practice guidelines have advanced severe traumatic brain injury (TBI) care, however, little currently informs goals of care decisions and processes despite their importance and frequency. Panelists from the Seattle International severe traumatic Brain Injury Consensus Conference (SIBICC) participated in a survey consisting of 24 questions. Questions queried use of prognostic calculators, variability in and responsibility for goals of care decisions, acceptability of neurological outcomes as well as putative means of improving decisions which may limit care. 97.6% of the 42 SIBICC panelists completed the survey. Responses were highly variable to most questions. Overall panelists reported infrequent use of prognostic calculators and observing variability in patient prognostication and goals of care decisions. They felt that it would be beneficial for physicians to improve consensus on what constitutes an acceptable neurological outcome as well as what chance of achieving that outcome is acceptable. Panelists felt that the public should help to define what constitutes a good outcome and expressed some support for a 'nihilism guard'. Over 50% of panelists felt that if it was certain to be enduring, a vegetative state or lower severe disability would justify a withdrawal of care decision while 15% felt that upper severe disability justified such a decision. Whether conceptualizing an ideal or existing prognostic calculator to predict death or an unacceptable outcome, a 64-69% chance of a poor outcome on average was felt to justify treatment withdrawal. These results demonstrate important variability in goals of care decision making and a desire to reduce this variability. Our panel of recognized TBI experts opined on the neurological outcomes and chances of those outcomes which might prompt consideration of care withdrawal, however imprecision of prognostication and existing prognostication tools is a significant impediment to standardizing the approach to care limiting decisions. Keywords: nihilism, withdrawal of care, survey, SIBICC, brain injury, prognosis.

Neurology

Venkat P, Gao H, Findeis EL, Chen Z, Zacharek A, Landschoot-Ward J, Powell B, Lu M, Liu Z, Zhang Z, and Chopp M. Therapeutic effects of CD133 + Exosomes on liver function after stroke in type 2 diabetic mice. *Front Neurosci* 2023; 17:1061485. PMID: 36968490. [Full Text](#)

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BACKGROUND AND PURPOSE: Non-alcoholic fatty liver disease (NAFLD) is known to adversely affect stroke recovery. However, few studies investigate how stroke elicits liver dysfunction, particularly, how stroke in type 2 diabetes mellitus (T2DM) exacerbates progression of NAFLD. In this study, we test whether exosomes harvested from human umbilical cord blood (HUCBC) derived CD133 + cells (CD133 + Exo) improves neuro-cognitive outcome as well as reduces liver dysfunction in T2DM female mice. **METHODS:** Female, adult non-DM and T2DM mice subjected to stroke presence or absence were considered. T2DM-stroke mice were randomly assigned to receive PBS or Exosome treatment group. CD133 + Exo (20 µg/200 µl PBS, i.v.) was administered once at 3 days after stroke. Evaluation of neurological (mNSS, adhesive removal test) and cognitive function [novel object recognition (NOR) test, odor test] was performed. Mice were sacrificed at 28 days after stroke and brain, liver, and serum were harvested. **RESULTS:** Stroke induces severe and significant short-term and long-term neurological and cognitive deficits which were worse in T2DM mice compared to non-DM mice. CD133 + Exo treatment of T2DM-stroke mice significantly improved neurological function and cognitive outcome indicated by improved discrimination index in the NOR and odor tests compared to control T2DM-stroke mice. CD133 + Exo treatment of T2DM stroke significantly increased vascular and white matter/axon remodeling in the ischemic brain compared to T2DM-stroke mice. However, there were no differences in the lesion volume

between non-DM stroke, T2DM-stroke and CD133 + Exo treated T2DM-stroke mice. In T2DM mice, stroke induced earlier and higher TLR4, NLRP3, and cytokine expression (SAA, IL1 β , IL6, TNF α) in the liver compared to heart and kidney, as measured by Western blot. T2DM-stroke mice exhibited worse NAFLD progression with increased liver steatosis, hepatocellular ballooning, fibrosis, serum ALT activity, and higher NAFLD Activity Score compared to T2DM mice and non-DM-stroke mice, while CD133 + Exo treatment significantly attenuated the progression of NAFLD in T2DM stroke mice. CONCLUSION: Treatment of female T2DM-stroke mice with CD133 + Exo significantly reduces the progression of NAFLD/NASH and improves neurological and cognitive function compared to control T2DM-stroke mice.

Neurosurgery

Allam AK, Viswanathan A, **Schwalb JM**, Patil PG, and Larkin MB. Editorial: Surgical techniques for the management of pain. *Front Pain Res (Lausanne)* 2023; 4:1120174. PMID: 36860332. [Full Text](#)

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Neurosurgery

Koekkoek JAF, van der Meer PB, Pace A, Hertler C, Harrison R, Leeper HE, Forst DA, Jalali R, Oliver K, Philip J, Taphoorn MJB, Dirven L, and **Walbert T**. Corrigendum to: Palliative care and end-of-life care in adults with malignant brain tumors. *Neuro Oncol* 2023; 25(1):212. PMID: 36610983. [Full Text](#)

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Obstetrics, Gynecology and Women's Health Services

Panzer AR, **Sitarik AR**, Fadrosch D, **Havstad SL**, **Jones K**, **Davidson B**, **Finazzo S**, **Wegienka GR**, **Woodcroft K**, Lukacs NW, **Levin AM**, **Ownby DR**, **Johnson CC**, **Lynch SV**, and **Zoratti EM**. The impact of prenatal dog keeping on infant gut microbiota development. *Clin Exp Allergy* 2023; Epub ahead of print. PMID: 36916778. [Full Text](#)

Department of Medicine, University of California, San Francisco, California, USA.

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Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan, USA.

INTRODUCTION: Prenatal and early-life dog exposure has been linked to reduced childhood allergy and asthma. A potential mechanism includes altered early immune development in response to changes in the gut microbiome among dog-exposed infants. We thus sought to determine whether infants born into homes with indoor dog(s) exhibit altered gut microbiome development. **METHODS:** Pregnant women living in homes with dogs or in pet-free homes were recruited in southeast Michigan. Infant stool samples were collected at intervals between 1 week and 18 months after birth and microbiome was assessed using 16S ribosomal sequencing. Perinatal maternal vaginal/rectal swabs and stool samples were sequenced from a limited number of mothers. Mixed effect adjusted models were used to assess stool microbial community trajectories comparing infants from dog-keeping versus pet-free homes with adjustment for relevant covariates. **RESULTS:** Infant gut microbial composition among vaginally born babies became less similar to the maternal vaginal/rectal microbiota and more similar to the maternal gut microbiota with age-related accumulation of bacterial species with advancing age. Stool samples from dog-exposed infants were microbially more diverse ($p = .041$) through age 18 months with enhanced diversity most apparent between 3 and 6 months of age. Statistically significant effects of dog exposure on β -diversity metrics were restricted to formula-fed children. Across the sample collection period, dog exposure was associated with *Fusobacterium* genera enrichment, as well as enrichment of *Collinsella*, *Ruminococcus*, *Clostridaceae* and *Lachnospiraceae* OTUs. **CONCLUSION:** Prenatal/early-life dog exposure is associated with an altered gut microbiome during infancy and supports a potential mechanism explaining lessened atopy and asthma risk. Further research directly linking specific dog-attributable changes in the infant gut microbiome to the risk of allergic disorders is needed.

Ophthalmology and Eye Care Services

Das S, Mehregan C, Richards C, Schneider M, **Le K**, and Lin X. Intraoperative Complication Rates in Cataract Surgery After Resuming Surgery Following the COVID-19 Shutdown. *Clin Ophthalmol* 2023; 17:641-647. PMID: 36861034. [Full Text](#)

Kresge Eye Institute Department of Ophthalmology, Visual and Anatomic Sciences, Wayne State University School of Medicine, Detroit, MI, USA.
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PURPOSE: To evaluate surgeon performance and intraoperative complication rates of cataract surgery after resumption of elective surgeries following the operating room (OR) shutdown from the coronavirus disease 2019 (COVID-19) pandemic. Subjective surgical experience is also evaluated. **METHODS:** This is a retrospective comparative study which analyzes cataract surgeries performed at an inner city, tertiary academic center. Cataract surgeries were categorized into Pre-Shutdown (January 1-March 18, 2020), and Post-Shutdown, for all cases which occurred after surgeries resumed (May 11-July 31, 2020). No cases were performed between March 19 and May 10, 2020. Patients undergoing combined cataract and minimally invasive glaucoma surgery (MIGS) were included, but MIGS complications were not counted as cataract complications. No other combined cataract-other ophthalmic surgeries were included. A survey was used to gather subjective surgeon experience. **RESULTS:** A total of 480 cases (n=306 Pre-Shutdown and n=174 Post-Shutdown) were analyzed. Although there was a higher frequency of complex cataract surgeries performed Post-Shutdown (5.2% vs 21.3%; $p < 0.00001$), complication rates before versus after the shutdown were not statistically significant (9.2% vs 10.3%; $p = 0.75$). Phacoemulsification was the step of cataract surgery in which residents were most concerned about when returning to the OR. **CONCLUSION:** After the surgical hiatus due to COVID-19, significantly more complex cataract surgeries were reported and surgeons reported higher general anxiety level when first returning to the OR. Increased anxiety did not lead to higher surgical complications. This study provides a framework to understand surgical expectations and outcomes for patients whose surgeons faced a prolonged two-month hiatus from cataract surgery.

Ophthalmology and Eye Care Services

Kasetty VM, Starnes DC, Sood N, Qin LG, Moses MM, Frazier HK, Singh H, and Marcus DM. Complications, Compliance, and 3-Year Outcomes After Endolaserless Vitrectomy With Aflibercept Monotherapy for Proliferative Diabetic Retinopathy-Related Vitreous Hemorrhage. *Ophthalmic Surg Lasers Imaging Retina* 2023; 54(2):89-96. PMID: 36780633. [Request Article](#)

BACKGROUND AND OBJECTIVE: To report the 3-year outcomes for endolaserless vitrectomy with intravitreal aflibercept injection (IAI) monotherapy for proliferative diabetic retinopathy (PDR)-related vitreous hemorrhage (VH). **MATERIALS AND METHOD:** Eyes underwent endolaserless vitrectomy and received one preoperative and intraoperative IAI followed by randomization to a q8week or q16week IAI group. Additional IAI was administered as needed. **RESULTS:** 31/40 eyes were randomized (14 q8week eyes, 17 q16week eyes). Through 152 weeks, q8week and q16week eyes received 18.6 and 12.1 IAI, respectively. Q8week eyes observed a 34 letter visual acuity (VA) increase ($P = 0.003$) compared to a 27 letter increase in the q16week group ($P = 0.013$). **CONCLUSIONS:** Endolaserless vitrectomy with aflibercept monotherapy for PDR-related VH provides significant long-term visual gains. Frequent IAI is required for fewer proliferative consequences. [Ophthalmic Surg Lasers Imaging Retina 2023;54:89-96].

Ophthalmology and Eye Care Services

Malach DS, Guest JM, Adam C, **Joffe J, Le K**, Kim C, and **Lin X**. Intraocular Lens Formula Comparison of Flanged Intrasceral Intraocular Lens Fixation with Double Needle Technique. *Clin Ophthalmol* 2023; 17:837-842. PMID: 36960323. [Full Text](#)

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PURPOSE: To analyze visual outcomes and accuracy of intraocular lens (IOL) calculation formulas in predicting postoperative outcomes in patients undergoing flanged intrascleral IOL fixation. **DESIGN:** Case Series. **SUBJECTS:** Twenty-three patients who had undergone secondary IOL placement using flanged intrascleral fixation technique. **METHODS:** Retrospective chart review. **MAIN OUTCOME MEASURES:** Corrected distance visual acuity (CDVA) and postoperative spherical equivalent based on manifest refraction. **RESULTS:** Visual acuity improved from 20/577 to 20/58. Overall, the actual refraction was 0.06 D more myopic than predicted. Holladay 2, Sanders Retzlaff Kraff/Theoretical (SRK/T) and Barrett Universal II resulted in mild myopic surprise (-0.55, -0.18 and -0.20 D). Haigis and Hill-RBF (Radial Basis Function) resulted in mild hyperopic surprise (+0.28 and +0.28 D). Hoffer Q and Holladay 1 were the most accurate (-0.02D and -0.08 D). **CONCLUSION:** Flanged intrascleral IOL fixation improved vision even in patients with other posterior segment pathologies. The effective lens positioning is likely similar to in-the-bag positioning. Hoffer Q and Holladay 1 formulas with in-the-bag calculations were the most accurate.

Ophthalmology and Eye Care Services

Portney DS, Berkowitz ST, Garner DC, **Qalieh A**, Tiwari V, Friedman S, Patel S, Parikh R, and Mian SI. Comparison of Incremental Costs and Medicare Reimbursement for Simple vs Complex Cataract Surgery Using Time-Driven Activity-Based Costing. *JAMA Ophthalmol* 2023; Epub ahead of print. PMID: 36892825. [Full Text](#)

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IMPORTANCE: Cataract surgery is one of the most commonly performed surgeries across medicine and an integral part of ophthalmologic care. Complex cataract surgery requires more time and resources than simple cataract surgery, yet it remains unclear whether the incremental reimbursement for complex cataract surgery, compared with simple cataract surgery, offsets the increased costs. **OBJECTIVE:** To measure the difference in day-of-surgery costs and net earnings between simple and complex cataract surgery. **DESIGN, SETTING, AND PARTICIPANTS:** This study is an economic analysis at a single

academic institution using time-driven activity-based costing methodology to determine the operative-day costs of simple and complex cataract surgery. Process flow mapping was used to define the operative episode limited to the day of surgery. Simple and complex cataract surgery cases (Current Procedural Terminology codes 66984 and 66982, respectively) at the University of Michigan Kellogg Eye Center from 2017 to 2021 were included in the analysis. Time estimates were obtained using an internal anesthesia record system. Financial estimates were obtained using a mix of internal sources and prior literature. Supply costs were obtained from the electronic health record. MAIN OUTCOMES AND MEASURES: Difference in day-of-surgery costs and net earnings. RESULTS: A total of 16 092 cataract surgeries were included, 13 904 simple and 2188 complex. Time-based day-of-surgery costs for simple and complex cataract surgery were \$1486.24 and \$2205.83, respectively, with a mean difference of \$719.59 (95% CI, \$684.09-\$755.09; P < .001). Complex cataract surgery required \$158.26 more for costs of supplies and materials (95% CI, \$117.00-\$199.60; P < .001). The total difference in day-of-surgery costs between complex and simple cataract surgery was \$877.85. Incremental reimbursement for complex cataract surgery was \$231.01; therefore, complex cataract surgery had a negative earnings difference of \$646.84 compared with simple cataract surgery. CONCLUSIONS AND RELEVANCE: This economic analysis suggests that the incremental reimbursement for complex cataract surgery undervalues the resource costs required for the procedure, failing to cover increased costs and accounting for less than 2 minutes of increased operating time. These findings may affect ophthalmologist practice patterns and access to care for certain patients, which may ultimately justify increasing cataract surgery reimbursement.

Ophthalmology and Eye Care Services

Schulte A, **Skarf B**, and **Monsalve P**. Non-arteritic anterior ischemic optic neuropathy secondary to Posner-Schlossman syndrome in a twenty-six-year-old female. *Am J Ophthalmol Case Rep* 2023; 30:101816. PMID: 36865091. [Full Text](#)

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PURPOSE: To describe a case of non-arteritic ischemic optic neuropathy (NAION) secondary to Posner-Schlossman syndrome in a twenty-six-year-old female. OBSERVATIONS: A 26-year-old female presented with painful visual loss of the left eye, elevated intraocular pressure of 38 mmHg, and trace to 1+ anterior chamber cell. Diffuse optic disc edema in the left eye and a small cup-to-disc ratio of the right optic disc were evident. Magnetic resonance imaging was unremarkable. CONCLUSIONS AND IMPORTANCE: The patient was diagnosed with NAION secondary to Posner-Schlossman syndrome, an uncommon ocular entity that can significantly affect vision. Posner-Schlossman syndrome can cause a decrease in ocular perfusion pressure involving the optic nerve and can lead to ischemia, swelling, and infarction. NAION should be considered in the differential diagnosis of young patients with sudden development of optic disc swelling and increased intraocular pressure with normal magnetic resonance imaging findings.

Orthopedics/Bone and Joint Center

Castle JP, Tramer JS, Turner EHG, Cotter D, McGee A, Abbas MJ, Gasparro MA, Lynch TS, and Moutzourous V. Survey of blood flow restriction therapy for rehabilitation in Sports Medicine patients. *J Orthop* 2023; 38:47-52. PMID: 36969302. [Full Text](#)

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BACKGROUND: Blood flow restriction (BFR) therapy has demonstrated benefits across a spectrum of musculoskeletal injuries, including improved strength, endurance, function, and reduction in pain perception. There is, however, no standardized application of BFR therapy among orthopaedic surgeons within the United States (US). HYPOTHESIS: The indication and protocol for BFR therapy vary significantly across providers in the US. METHODS: An online survey of 21 multiple-choice questions was sent to 3,281 surgeons listed on a large orthopaedic registry. A cross-sectional study was performed on all surgeons who successfully completed the questionnaire. Surgeons were queried on current or planned

use of BFR, indications, contraindications, and peri-operative and non-operative management of sports-related injuries. RESULTS: Overall, 250 physicians completed the survey, with 149 (59.8%) reporting current BFR use and 75.2% initiating use in the last 1-5 years. Most protocols (78.8%) utilize the modality 2-3 times per week while 15.9% use it only once weekly. Anterior cruciate ligament reconstruction (ACLR) rehabilitation was the most reported indication for initiating BFR therapy (95.7%) along with medial patellofemoral ligament reconstruction (70.2%), multiligamentous knee reconstruction (68.8%), meniscus repair (62.4%), collateral ligament reconstruction (50.4%), Achilles tendon repairs (30.5%), and meniscectomy (27%). Only 36.5% reported using BFR after upper extremity procedures, such as distal biceps repair (19.7%), ulnar collateral ligament elbow reconstruction (17%), rotator cuff (16.8%), and shoulder labrum repair (15.3%). For non-operative injuries, 65.8% of surgeons utilized BFR. Of those not currently using BFR therapy, 33.3% intended to implement its use in the future. CONCLUSION: BFR therapy has increased in popularity with most physicians implementing its use in the last 5 years. BFR was commonly utilized after ACLR. CLINICAL RELEVANCE: BFR allows light-load resistance to simulate high-intensity resistance training. This study describes US orthopaedic surgeons' common practice patterns and patient populations that utilize BFR therapy.

Orthopedics/Bone and Joint Center

Cross AG, **Khalil LS**, Tomlinson M, **Tramer JS**, **Makhni EC**, and Cox BA. Percutaneous Achilles Tendon Repair Using Ultrasound Guidance: An Intraoperative Ultrasound Technique. *Arthrosc Tech* 2023; 12(2):e173-e180. PMID: 36879876. [Full Text](#)

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Rupture of the Achilles tendon is a common injury seen in patients of varying ages and activity levels. There are many considerations for treatment of these injuries, with both operative and nonoperative management providing satisfactory outcomes in the literature. The decision to proceed with surgical intervention should be individualized for each patient, including the patient's age, future athletic goals, and comorbidities. Recently, a minimally invasive percutaneous approach to repair the Achilles tendon has been proposed as an equivalent alternative to the traditional open repair, while avoiding wound complications associated with larger incisions. However, many surgeons have been hesitant to adopt these approaches due to poor visualization, concern that suture capture in the tendon is not as robust, and the potential for iatrogenic sural nerve injury. The purpose of this Technical Note is to describe a technique using high-resolution ultrasound guidance intraoperatively during minimally invasive repair of the Achilles tendon. This technique minimizes the drawbacks of poor visualization associated with percutaneous repair, while providing the benefit of a minimally invasive approach.

Orthopedics/Bone and Joint Center

Franovic S, **Pietroski AD**, **Druskovich K**, **Page B**, **Burdick GB**, **Fathima B**, **McIntosh MJ**, **King EA**, and **Muh SJ**. A Cost-Effectiveness Analysis of the Various Treatment Options for Distal Radius Fractures. *J Hand Surg Glob Online* 2023; 5(2):169-177. PMID: 36974282. [Full Text](#)

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PURPOSE: To conduct a cost-effectiveness study of nonsurgical and surgical treatment options for distal radius fractures using distinct posttreatment outcome patterns. METHODS: We created a decision tree to model the following treatment modalities for distal radius fractures: nonsurgical management, external fixation, percutaneous pinning, and plate fixation. Each node of the model was associated with specific costs in dollars, a utility adjustment (quality-adjusted life year [QALY]), and a percent likelihood. The nodes of the decision tree included uneventful healing, eventful healing and no further intervention, carpal tunnel syndrome, trigger finger, and tendon rupture as well as associated treatments for each event. The percent probabilities of each transition state, QALY values, and costs of intervention were gleaned from a systematic review. Rollback and incremental cost-effectiveness ratio analyses were conducted to identify optimal treatment strategies. Threshold values of \$50,000/QALY and \$100,000/QALY were used to distinguish the modalities in the incremental cost-effectiveness ratio analysis. RESULTS: Both the rollback analysis and the incremental cost-effectiveness ratio analysis revealed nonsurgical management

as the predominant strategy when compared with the other operative modalities. Nonsurgical management dominated external fixation and plate fixation, although it was comparable with percutaneous fixation, yielding a \$2,242 lesser cost and 0.017 lesser effectiveness. CONCLUSIONS: The cost effectiveness of nonsurgical management is driven by its decreased cost to the health care system. Plate and external fixation have been shown to be both more expensive and less effective than other proposed treatments. Percutaneous pinning has demonstrated more favorable effectiveness in the literature than plate and external fixation and, thus, may be more cost effective in certain circumstances. Future studies may find value in investigating further clinical aspects of distal radius fractures and their association with nonsurgical management versus that with plate fixation. TYPE OF STUDY/LEVEL OF EVIDENCE: Economic/decision analysis II.

Orthopedics/Bone and Joint Center

Gaudiani MA, Samuel LT, Diana JN, DeBattista JL, Coon TM, Moore RE, and Kamath AF. Robotic-arm assisted lateral unicompartmental knee arthroplasty: 5-Year outcomes & survivorship. *J Orthop Surg (Hong Kong)* 2023; 31(1):10225536221138986. PMID: 36775979. [Full Text](#)

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INTRODUCTION: Robotic-arm assisted unicompartmental knee arthroplasty (RA-UKA) has demonstrated accurate component positioning and excellent outcomes for medial components. However, there is a paucity of literature on lateral compartment RA-UKA. The purpose of our study was to assess the midterm clinical outcomes and survivorship of lateral RA-UKA. METHODS: This study was a retrospective review of a single-center prospectively maintained cohort of 33 patients (36 knees) indicated for lateral UKA. Perioperative, and postoperative two- and five-year Knee injury Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Score (WOMAC), and Forgotten Joint Score (FJS) patient reported outcome measures were collected. Five-year follow-up was recorded in 29 patients (32 knees). RESULTS: Mean follow up was 5.1 ± 0.1 years. Mean age and BMI was 70.9 ± 7.2 years and 29.0 ± 4.2 kg/m², respectively. At discharge, mean distance walked was 273.4 ± 70.4 feet, and mean pain score was 2.0 ± 2.5 . At 2-year follow up, mean KOOS, WOMAC, and FJS were 75.1 ± 13.5 , 15.0 ± 7.2 , and 81.0 ± 23.3 , respectively. At 5-year follow up, mean KOOS, WOMAC, and FJS were 75.3 ± 14.6 , 14.9 ± 5.0 , and 75.8 ± 27.4 , respectively. Mean change in KOOS and WOMAC were 35.6 ± 27.1 and 11.7 ± 13.4 ($p < .001$ and $p < .001$). 94% of patients were very satisfied/satisfied, 3% neutral, and 3% dissatisfied. 91% met activity expectations, and 59% were more active than before. Survivorship was 100% at 5 years. DISCUSSION: In this study, lateral RA-UKA demonstrated significantly improved clinical outcomes, high patient satisfaction, met expectations, and excellent functional recovery at midterm follow up. Comparative studies are needed to determine differences between robotic-assisted and conventional lateral UKA, as well as TKA.

Orthopedics/Bone and Joint Center

Hertzberg M, Maier L, Heil H, **Hoegler J, Guthrie T**, and **Hakeos W**. Postoperative Chest X-rays After Open Reduction Internal Fixation of Clavicle Fractures May Not Be Cost-effective or Necessary. *J Orthop Trauma* 2023; Epub ahead of print. PMID: 36862985. [Full Text](#)

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OBJECTIVES: To assess the utility of chest x-rays following open reduction internal fixation of clavicle fractures. Particularly in terms of detection of acute postoperative pneumothorax and cost- effectiveness of obtaining routine chest x-rays post-operatively. DESIGN: A retrospective cohort study. SETTING: Level I trauma centerPatients 236 patients who underwent ORIF from 2013 to 2020 between the ages of 12 and 93. INTERVENTION: Chest x-ray performed post-operatively. MAIN OUTCOME MEASUREMENT: Presence of acute postoperative pneumothorax. RESULTS: Of the 236 patients who underwent surgery 189 (80%) of patients received a CXR post-operatively 7 (3%) of patients experienced respiratory symptoms. All patients who had respiratory symptoms received a post-operative CXR. Those who did not

receive a CXR post-operatively did not experience any respiratory complications. Two patients in the cohort had a postoperative pneumothorax, which were both present pre-operatively and unchanged in size post-operatively. Both of these patients were managed with general anesthesia and endotracheal intubation for surgery. The most common finding on CXR post-operatively was atelectasis. The cost of a portable CXR can be upwards of \$594 when including technology, personnel fees, and radiological interpretation. CONCLUSION: Post-operative chest x-rays after clavicle open reduction and internal fixation did not detect any acute postoperative pneumothorax in asymptomatic patients. It is not cost-effective to routinely get chest x-rays in patients following open reduction internal fixation of clavicle fractures. In our study, of the 189 chest x-rays performed, only seven patients experienced postoperative respiratory symptoms. Our healthcare system as a total could have saved upwards of \$108,108 in total for these patients as they may have been considered non-reimbursable by an insurance provider.

Otolaryngology – Head and Neck Surgery

Salmon MK, Kshirsagar RS, and **Eide JG**. Craniopharyngioma surgery for rhinologists. *Curr Opin Otolaryngol Head Neck Surg* 2023; 31(1):45-52. PMID: 36730658. [Full Text](#)

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PURPOSE OF REVIEW: Craniopharyngiomas are rare tumors that that present with loss of pituitary function in most cases. They present in a bimodal age distribution and the most common treatment paradigms include gross total resection or subtotal resection followed by radiation. Endoscopic transnasal access to intradural tumors has become increasingly common due to improvements in equipment, increased familiarity with the surgical corridor and anatomy, and reconstruction techniques. As such, rhinologists play an increasingly important role in the management of craniopharyngiomas. RECENT FINDINGS: Recent years have highlighted our growing experience with pediatric endonasal skull base surgery. Prior concerns including sphenoid pneumatization, midfacial growth restrictions, and intercarotid space limitations have been studied more extensively. It has been found that there are no increased complications with lack of sphenoid pneumatization, no changes to midfacial growth with endonasal techniques, and the inter-carotid distance is stable after around age 5. Advances in surgical and skull base reconstruction techniques and intraoperative monitoring have reduced the risks of complications from surgery. SUMMARY: Rhinologists play an important role in craniopharyngioma surgery. The approach to and reconstruction after tumor removal are vital portions of the procedure that allow for resection and prevent postsurgical complications.

Otolaryngology – Head and Neck Surgery

Williams AM, Tam SH, and Adjei Boakye E. Firearm Safety for Patients Diagnosed With Cancer-A Role in Suicide Prevention. *JAMA Oncol* 2023; Epub ahead of print. PMID: 36862388. [Request Article](#)

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This Viewpoint discusses firearm safety guidelines among patients diagnosed with cancer and at a higher risk of suicide.

Pathology and Laboratory Medicine

Chen Y, Loveless IM, Nakai T, Newaz R, Abdollah FF, Rogers CG, Hassan O, Chitale D, Arora K, Williamson SR, Gupta NS, Rybicki BA, Sadasivan SM, and Levin AM. Convolutional Neural Network Quantification of Gleason Pattern 4 and Association with Biochemical Recurrence in Intermediate Grade Prostate Tumors. *Mod Pathol* 2023; 100157. Epub ahead of print. PMID: 36925071. [Full Text](#)

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Differential classification of prostate cancer (CaP) grade group (GG) 2 and 3 tumors remains challenging, likely due to the subjective quantification of percentage of Gleason pattern 4 (%GP4). Artificial intelligence assessment of %GP4 may improve its accuracy and reproducibility and provide information for prognosis prediction. To investigate this potential, a convolutional neural network (CNN) model was trained to objectively identify and quantify Gleason pattern (GP) 3 and 4 areas, estimate %GP4, and assess whether CNN-assessed %GP4 is associated with biochemical recurrence (BCR) risk in intermediate risk GG 2 and 3 tumors. The study was conducted in a radical prostatectomy cohort (1999-2012) of African American men from the Henry Ford Health System (Detroit, Michigan). A CNN model that could discriminate four tissue types (stroma, benign glands, GP3 glands, and GP4 glands) was developed using histopathologic images containing GG 1 (n=45) and 4 (n=20) tumor foci. The CNN model was applied to GG 2 (n=153) and 3 (n=62) for %GP4 estimation, and Cox proportional hazard modeling was used to assess the association of %GP4 and BCR, accounting for other clinicopathologic features including GG. The CNN model achieved an overall accuracy of 86% in distinguishing the four tissue types. Further, CNN-assessed %GP4 was significantly higher in GG 3 compared with GG 2 tumors ($p=7.2 \times 10^{-11}$). %GP4 was associated with an increased risk of BCR (adjusted HR=1.09 per 10% increase in %GP4, $p=0.010$) in GG 2 and 3 tumors. Within GG 2 tumors specifically, %GP4 was more strongly associated with BCR (adjusted HR=1.12, $p=0.006$). Our findings demonstrate the feasibility of CNN-assessed %GP4 estimation, which is associated with BCR risk. This objective approach could be added to the standard pathological assessment for patients with GG 2 and 3 tumors and act as a surrogate for specialist genitourinary pathologist evaluation when such consultation is not available.

Pathology and Laboratory Medicine

Gondim DD, **Al-Obaidy KI**, Idrees MT, Eble JN, and Cheng L. Artificial intelligence-based multi-class histopathologic classification of kidney neoplasms. *J Pathol Inform* 2023; 14:100299. PMID: 36915914.

[Full Text](#)

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Artificial intelligence (AI)-based techniques are increasingly being explored as an emerging ancillary technique for improving accuracy and reproducibility of histopathological diagnosis. Renal cell carcinoma (RCC) is a malignancy responsible for 2% of cancer deaths worldwide. Given that RCC is a heterogeneous disease, accurate histopathological classification is essential to separate aggressive subtypes from indolent ones and benign mimickers. There are early promising results using AI for RCC classification to distinguish between 2 and 3 subtypes of RCC. However, it is not clear how an AI-based model designed for multiple subtypes of RCCs, and benign mimickers would perform which is a scenario closer to the real practice of pathology. A computational model was created using 252 whole slide images (WSI) (clear cell RCC: 56, papillary RCC: 81, chromophobe RCC: 51, clear cell papillary RCC: 39, and metanephric adenoma: 6). 298,071 patches were used to develop the AI-based image classifier. 298,071 patches (350 x 350-pixel) were used to develop the AI-based image classifier. The model was applied to a secondary dataset and demonstrated that 47/55 (85%) WSIs were correctly classified. This computational model

showed excellent results except to distinguish clear cell RCC from clear cell papillary RCC. Further validation using multi-institutional large datasets and prospective studies are needed to determine the potential to translation to clinical practice.

Pathology and Laboratory Medicine

Kloberdanz KR, Olenech CM, and Saleh HA. Eccrine Poroma: A Case Report. *J Am Podiatr Med Assoc* 2023; 113(1). PMID: 36905614. [Request Article](#)

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Eccrine poroma is a benign adnexal neoplasm often mistaken for pyogenic granuloma, skin tag, squamous cell carcinoma, and other soft-tissue tumors. We describe a 69-year-old woman with a soft-tissue mass on the lateral aspect of her right hallux that was initially clinically diagnosed as a pyogenic granuloma. Histologic examination proved that this mass was instead an eccrine poroma, the rare benign sweat gland tumor. This case exemplifies the importance of a broad differential diagnosis, especially regarding soft-tissue masses of the lower extremity.

Pathology and Laboratory Medicine

Oyedeji O, Alruwail FI, Hassan O, Gupta N, and Al-Obaidy KI. Chronic Testicular Vasculopathy Presenting as Acute Testicular Torsion and Mimicking Localized Vasculitis. *Int J Surg Pathol* 2023; 10668969231157773. Epub ahead of print. PMID: 36823789. [Full Text](#)

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Pathology and Laboratory Medicine

Rohr JM, **Ginnebaugh K, Tuthill M, Pimentel J,** and Markin R. Real-time Telepathology Is Substantially Equivalent to In-Person Intraoperative Frozen Section Diagnosis. *Arch Pathol Lab Med* 2023; Epub ahead of print. PMID: 36920004. [Full Text](#)

From the Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha (Rohr, Markin).

The Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, Michigan (Ginnebaugh, Tuthill, Pimentel). Rohr is currently located in the Department of Pathology of Brigham and Women's Hospital, Boston, Massachusetts.

CONTEXT.—: Intraoperative diagnosis by frozen section is a mainstay of surgical pathology practice, providing immediate feedback to the surgical team. Despite good accuracy with modern methods, access to intraoperative surgical pathology with an appropriate turnaround time (TAT) has been a limiting factor for small or remote surgical centers, with negative impacts on cost and patient care. Telepathology offers immediate expert anatomic pathology consultation to sites without an in-house or subspecialized pathologist. OBJECTIVE.—: To assess the utility of live telepathology in frozen section practice. DESIGN.—: Frozen section diagnoses by telemicroscopy from 2 tertiary care centers with combined 3 satellite hospitals were queried for anatomic site, TAT per block, pathologist, and concordance with paraffin diagnosis. TAT and concordance were compared to glass diagnoses in the same period. RESULTS.—: For 748 intraoperative diagnoses by telemicroscopy, 694 had TATs with a mean of 18 minutes 56 seconds ± 8 minutes 45 seconds, which was slower than on glass (14 minutes 25 seconds ± 7 minutes 8 seconds, $P < .001$). Twenty-two (2.89% of available) were discordant, which was not significantly different from the on-glass rate ($P = .44$) or categorical distribution ($P = .31$). Two cases (0.27%) had technical failures. CONCLUSIONS.—: Although in-person diagnoses were statistically faster, the great majority of telemicroscopic diagnoses were returned in less than 20 minutes. This remained true through numerous pathologists, pathology assistants and/or technicians, different hospitals, and during a combined 6 years. The concentration of discordant diagnoses among relatively few pathologists suggests individual comfort with telepathology and/or frozen section diagnosis. In rare cases, technologic issues

prevented telemicroscopic diagnosis. Overall, this justifies continued use and expansion of telemicroscopic services in primary intraoperative diagnoses.

Pathology and Laboratory Medicine

Shallal AB, Cherabuddi M, Podsiad L, Gortat C, Shanahan C, Holsey T, Samuel L, Alangaden G, and Suleyman G. Role of diagnostic stewardship in reducing healthcare-facility-onset *Clostridioides difficile* infections. *Antimicrob Steward Healthc Epidemiol* 2023; 3(1):e53. PMID: 36970430.

[Full Text](#)

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We describe the implementation of an electronic medical record "hard stop" to decrease inappropriate *Clostridioides difficile* testing across a 5-hospital health system, effectively reducing the rates of healthcare-facility-onset *C. difficile* infection. This novel approach included expert consultation with medical director of infection prevention and control for test-order override.

Pathology and Laboratory Medicine

Singh H, Patel P, Parikh S, Zreik H, Caliman N, and Kak V. Pancreatitis, panniculitis and polyarthralgia syndrome: A rare complication of pancreatic pathology. *Radiol Case Rep* 2023; 18(5):2001-2004. PMID: 37020599. [Full Text](#)

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Pancreatitis, panniculitis, and polyarthralgia (PPP) syndrome is a rare complication of chronic pancreatitis and occurs due to leakage of pancreatic enzymes in the systemic vasculature. This enzyme leakage leads to multiple manifestations such as polyarthralgia, panniculitis, and bone necrosis due to tissue autodigestion. The inciting pancreatic pathology may be masked, and the presentation may be due to one of the systemic consequences of enzyme leakage, which can present as a diagnostic challenge for clinicians. Here we present a patient who presented with nodular lesions and bone necrosis, and was found to have PPP syndrome. Therefore, a proper understanding of pathophysiology and radiology findings can help with prompt diagnosis and early exploration of management options.

Pathology and Laboratory Medicine

Straughen JK, Sitarik AR, Jones AD, Li J, **Allo G,** Salafia C, **Cassidy-Bushrow AE,** and Paneth N. Comparison of methanol fixation versus cryopreservation of the placenta for metabolomics analysis. *Sci Rep* 2023; 13(1):4063. PMID: 36906704. [Full Text](#)

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Methods for collection of placental tissue at room temperature for metabolic profiling are described. Specimens were excised from the maternal side of the placenta and immediately flash frozen or fixed and stored for 1, 6, 12, 24, or 48 h in 80% methanol. Untargeted metabolic profiling was performed on both the methanol-fixed tissue and the methanol extract. Data were analyzed using Gaussian generalized estimating equations, two sample t-tests with false discovery rate (FDR) corrections, and principal components analysis. Methanol-fixed tissue samples and methanol extracts had a similar number of metabolites ($p = 0.45$, $p = 0.21$ in positive vs. negative ion mode). In positive ion mode, when compared to flash frozen tissue, both the methanol extract and methanol-fixed tissue (6 h) had a higher number of metabolites detected (146 additional metabolites, $p(\text{FDR}) = 0.020$; 149 additional metabolites, $p(\text{FDR}) = 0.017$; respectively), but these associations were not found in negative ion mode (all $p(\text{FDR}) \geq 0.05$). Principle components analysis demonstrated separation of the metabolite features in the methanol extract, but similarity between methanol-fixed tissue and flash frozen tissue. These results show that placental tissue samples collected in 80% methanol at room temperature can yield similar metabolic data to flash frozen specimens.

Pediatrics

Panzer AR, **Sitarik AR**, Fadrosch D, **Havstad SL**, Jones K, Davidson B, **Finazzo S**, **Wegienka GR**, **Woodcroft K**, Lukacs NW, **Levin AM**, **Ownby DR**, **Johnson CC**, **Lynch SV**, and **Zoratti EM**. The impact of prenatal dog keeping on infant gut microbiota development. *Clin Exp Allergy* 2023; Epub ahead of print. PMID: 36916778. [Full Text](#)

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INTRODUCTION: Prenatal and early-life dog exposure has been linked to reduced childhood allergy and asthma. A potential mechanism includes altered early immune development in response to changes in the gut microbiome among dog-exposed infants. We thus sought to determine whether infants born into homes with indoor dog(s) exhibit altered gut microbiome development. **METHODS:** Pregnant women living in homes with dogs or in pet-free homes were recruited in southeast Michigan. Infant stool samples were collected at intervals between 1 week and 18 months after birth and microbiome was assessed using 16S ribosomal sequencing. Perinatal maternal vaginal/rectal swabs and stool samples were sequenced from a limited number of mothers. Mixed effect adjusted models were used to assess stool microbial community trajectories comparing infants from dog-keeping versus pet-free homes with adjustment for relevant covariates. **RESULTS:** Infant gut microbial composition among vaginally born babies became less similar to the maternal vaginal/rectal microbiota and more similar to the maternal gut microbiota with age-related accumulation of bacterial species with advancing age. Stool samples from dog-exposed infants were microbially more diverse ($p = .041$) through age 18 months with enhanced diversity most apparent between 3 and 6 months of age. Statistically significant effects of dog exposure on β -diversity metrics were restricted to formula-fed children. Across the sample collection period, dog exposure was associated with *Fusobacterium* genera enrichment, as well as enrichment of *Collinsella*, *Ruminococcus*, *Clostridaceae* and *Lachnospiraceae* OTUs. **CONCLUSION:** Prenatal/early-life dog exposure is associated with an altered gut microbiome during infancy and supports a potential mechanism explaining lessened atopy and asthma risk. Further research directly linking specific dog-attributable changes in the infant gut microbiome to the risk of allergic disorders is needed.

Pharmacy

Abbas M, **Farhat N**, Hammoud Z, Dickey C, Shuayto A, Chen NW, Hsaiky LM, Sims M, Sengstock D, Schramski J, and Shamon Z. A Propensity-Matched Cohort Assessing Impact of a Neutralizing Monoclonal Antibody in Mild-to-Moderate Coronavirus Disease 2019. *J Intensive Care Med* 2023; 8850666231155822. Epub ahead of print. PMID: 36775970. [Full Text](#)

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic. In randomized clinical trials, patients who were treated with the anti-spike monoclonal antibody bamlanivimab had fewer COVID-19-related hospitalizations or emergency department (ED) visits than the control group. **Methods:** A retrospective cohort was assembled across a multisite healthcare system between November 20, 2020 and March 31, 2021. Ambulatory COVID-19 patients treated with bamlanivimab (n = 209) were propensity score matched without replacement (1:1) to a pool of 1024 eligible control patients who received similar care without bamlanivimab. The primary endpoint was all-cause mortality or admission at 30 days. Secondary endpoints included hospitalization, critical care admission, oxygenation requirements, and infusion-related reactions. Propensity score matching (PSM) analysis was used to assess the effect of bamlanivimab infusion on the composite endpoint and secondary endpoints. **Results:** A total of n = 209 matched patients were included in each arm of the study. The absolute standardized difference (stddiff) was calculated and indicated a balance between the groups. Almost all variables had a stddiff of less than 0.10, except for respiratory rate (RR) (stddiff = -0.11). For the primary composite endpoint of the matched cohort, 10.1% (n = 21) of patients in the intervention group were hospitalized or deceased within 30-day postbamlanivimab infusion versus 27.8% (n = 58) in the control group (adjusted odds ratio [aOR]: 0.29, 95% confidence interval [CI]: 0.17 to 0.51, P < .001). **Conclusion:** Patients with ambulatory COVID-19 who received bamlanivimab in the outpatient setting had a statistically significant reduction on the odds of admission postinfusion. Despite bamlanivimab's lack of efficacy on newer SARS-CoV-2 variants, this study demonstrates that neutralizing monoclonal antibodies can be effective against specific variants. If variant identification becomes a more accessible tool in outpatient centers or EDs, more targeted therapeutic options may be considered.

Pharmacy

Kunz Coyne AJ, El Ghali A, Lucas K, Witucki P, Rebold N, Holger DJ, **Veve MP**, and Rybak MJ. High-dose Cefepime vs Carbapenems for Bacteremia Caused by Enterobacterales With Moderate to High Risk of Clinically Significant AmpC β -lactamase Production. *Open Forum Infect Dis* 2023; 10(3):ofad034. PMID: 36968970. [Full Text](#)

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BACKGROUND: Limited data suggest that serious infections caused by Enterobacterales with a moderate to high risk of clinically significant AmpC production can be successfully treated with cefepime if the cefepime minimum inhibitory concentration (MIC) is ≤ 2 $\mu\text{g/mL}$. However, isolates with a cefepime-susceptible dose-dependent (SDD) MIC of 4-8 $\mu\text{g/mL}$ should receive a carbapenem due to target attainment and extended-spectrum β -lactamase (ESBL) concerns. **METHODS:** This was a retrospective cohort study of hospitalized patients with *E. cloacae*, *K. aerogenes*, or *C. freundii* bacteremia from

January 2015 to March 2022 receiving high-dose cefepime or a carbapenem. Cox regression models were used with incorporation of inverse probability of treatment weighting and time-varying covariates. RESULTS: Of the 315 patients included, 169 received cefepime and 146 received a carbapenem (ertapenem n = 90, meropenem n = 56). Cefepime was not associated with an increased risk of 30-day mortality compared with carbapenem therapy (adjusted hazard ratio [aHR], 1.45; 95% CI, 0.79-2.14), which was consistent for patients with cefepime SDD isolates (aHR, 1.19; 95% CI, 0.52-1.77). Multivariable weighted Cox models identified Pitt bacteremia score >4 (aHR, 1.41; 95% CI, 1.04-1.92), deep infection (aHR, 2.27; 95% CI, 1.21-4.32), and ceftriaxone-resistant AmpC-E (aHR, 1.32; 95% CI, 1.03-1.59) to be independent predictors associated with increased mortality risk, while receipt of prolonged-infusion β -lactam was protective (aHR, 0.67; 95% CI, 0.40-0.89). CONCLUSIONS: Among patients with bacteremia caused by Enterobacterales with moderate to high risk of clinically significant AmpC production, these data demonstrate similar risk of 30-day mortality for high-dose cefepime or a carbapenem as definitive β -lactam therapy.

Podiatry

Kloberdanz KR, Olenech CM, and Saleh HA. Eccrine Poroma: A Case Report. *J Am Podiatr Med Assoc* 2023; 113(1). PMID: 36905614. [Request Article](#)

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Eccrine poroma is a benign adnexal neoplasm often mistaken for pyogenic granuloma, skin tag, squamous cell carcinoma, and other soft-tissue tumors. We describe a 69-year-old woman with a soft-tissue mass on the lateral aspect of her right hallux that was initially clinically diagnosed as a pyogenic granuloma. Histologic examination proved that this mass was instead an eccrine poroma, the rare benign sweat gland tumor. This case exemplifies the importance of a broad differential diagnosis, especially regarding soft-tissue masses of the lower extremity.

Public Health Sciences

Abouelella DK, Watts TL, Rocke DJ, Barnes JM, Osazuwa-Peters N, and **Adjei Boakye E.** Reasons for parental refusal of human papillomavirus vaccine during the COVID-19 pandemic in 2020. *Public Health* 2023; Epub ahead of print. PMID: 36870828. [Full Text](#)

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Public Health Sciences

Chen F, Madduri RK, **Rybicki BA**, et al. Evidence of Novel Susceptibility Variants for Prostate Cancer and a Multiancestry Polygenic Risk Score Associated with Aggressive Disease in Men of African Ancestry. *Eur Urol* 2023; Epub ahead of print. PMID: 36872133. [Full Text](#)

BACKGROUND: Genetic factors play an important role in prostate cancer (PCa) susceptibility.

OBJECTIVE: To discover common genetic variants contributing to the risk of PCa in men of African ancestry. DESIGN, SETTING, AND PARTICIPANTS: We conducted a meta-analysis of ten genome-wide association studies consisting of 19378 cases and 61620 controls of African ancestry. OUTCOME

MEASUREMENTS AND STATISTICAL ANALYSIS: Common genotyped and imputed variants were tested for their association with PCa risk. Novel susceptibility loci were identified and incorporated into a multiancestry polygenic risk score (PRS). The PRS was evaluated for associations with PCa risk and disease aggressiveness. RESULTS AND LIMITATIONS: Nine novel susceptibility loci for PCa were identified, of which seven were only found or substantially more common in men of African ancestry, including an African-specific stop-gain variant in the prostate-specific gene anoctamin 7 (ANO7). A multiancestry PRS of 278 risk variants conferred strong associations with PCa risk in African ancestry studies (odds ratios [ORs] >3 and >5 for men in the top PRS decile and percentile, respectively). More importantly, compared with men in the 40-60% PRS category, men in the top PRS decile had a significantly higher risk of aggressive PCa (OR = 1.23, 95% confidence interval = 1.10-1.38, $p = 4.4 \times 10^{-4}$). CONCLUSIONS: This study demonstrates the importance of large-scale genetic studies in men of African ancestry for a better understanding of PCa susceptibility in this high-risk population and suggests a potential clinical utility of PRS in differentiating between the risks of developing aggressive and nonaggressive disease in men of African ancestry. PATIENT SUMMARY: In this large genetic study in men of African ancestry, we discovered nine novel prostate cancer (PCa) risk variants. We also showed that a multiancestry polygenic risk score was effective in stratifying PCa risk, and was able to differentiate risk of aggressive and nonaggressive disease.

Public Health Sciences

Chen Y, Loveless IM, Nakai T, Newaz R, Abdollah FF, Rogers CG, Hassan O, Chitale D, Arora K, Williamson SR, Gupta NS, Rybicki BA, Sadasivan SM, and Levin AM. Convolutional Neural Network Quantification of Gleason Pattern 4 and Association with Biochemical Recurrence in Intermediate Grade Prostate Tumors. *Mod Pathol* 2023; 100157. Epub ahead of print. PMID: 36925071. [Full Text](#)

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Differential classification of prostate cancer (CaP) grade group (GG) 2 and 3 tumors remains challenging, likely due to the subjective quantification of percentage of Gleason pattern 4 (%GP4). Artificial intelligence assessment of %GP4 may improve its accuracy and reproducibility and provide information for prognosis prediction. To investigate this potential, a convolutional neural network (CNN) model was trained to objectively identify and quantify Gleason pattern (GP) 3 and 4 areas, estimate %GP4, and assess whether CNN-assessed %GP4 is associated with biochemical recurrence (BCR) risk in intermediate risk GG 2 and 3 tumors. The study was conducted in a radical prostatectomy cohort (1999-2012) of African American men from the Henry Ford Health System (Detroit, Michigan). A CNN model that could discriminate four tissue types (stroma, benign glands, GP3 glands, and GP4 glands) was developed using histopathologic images containing GG 1 (n=45) and 4 (n=20) tumor foci. The CNN model was applied to GG 2 (n=153) and 3 (n=62) for %GP4 estimation, and Cox proportional hazard modeling was used to assess the association of %GP4 and BCR, accounting for other clinicopathologic features including GG. The CNN model achieved an overall accuracy of 86% in distinguishing the four tissue types. Further, CNN-assessed %GP4 was significantly higher in GG 3 compared with GG 2 tumors ($p=7.2 \times 10^{-11}$). %GP4 was associated with an increased risk of BCR (adjusted HR=1.09 per 10% increase in %GP4, $p=0.010$) in GG 2 and 3 tumors. Within GG 2 tumors specifically, %GP4 was more strongly associated with BCR (adjusted HR=1.12, $p=0.006$). Our findings demonstrate the feasibility of CNN-assessed %GP4 estimation, which is associated with BCR risk. This objective approach could be added to the standard pathological assessment for patients with GG 2 and 3 tumors and act as a surrogate for specialist genitourinary pathologist evaluation when such consultation is not available.

Public Health Sciences

Hutchings H, Zhang Q, Grady S, Mabe L, and Okereke IC. Gentrification and Air Quality in a Large Urban County in the United States. *Int J Environ Res Public Health* 2023; 20(6). PMID: 36981672. [Full Text](#)

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Introduction: Increases in industrialization and manufacturing have led to worsening pollution in some components of air quality. In addition, gentrification is occurring in large cities throughout the world. As these socioeconomic and demographic changes occur, there have been no studies examining the association of gentrification with air quality. To investigate this association, we studied the trends of gentrification, changes in racial distribution and changes in air quality in each zip code of a large urban county over a 40-year period. **Methods:** We conducted a retrospective longitudinal study over 40 years in Wayne County, Michigan using socioeconomic and demographic data from the National Historical Geographic Information System (NHGIS) and air quality data from the United States Environmental Protection Agency (EPA). To assess gentrification, longitudinal analyses were performed to examine median household income, percentage with a college education, median housing value, median gross rent and employment level. The racial distribution was evaluated in each zip code during the time period. Gentrification was studied in relation to air quality using nonparametric 2-sample Wilcoxon-Mann-Whitney tests and Binomial Generalized Linear Regression models. **Results:** Although air quality improved overall over the 40-year period, there was a lesser rate of improvement in gentrified areas. Furthermore, gentrification was strongly associated with racial distribution. The most substantial gentrification occurred from 2010 to 2020, in which a specific cluster of adjacent zip codes in downtown Detroit experienced intense gentrification and a drop in the percentage of African-American residents. **Conclusions:** Gentrified areas seem to have a less pronounced improvement in air quality over time. This reduction in air quality improvement is likely associated with demolitions and the construction of new buildings, such as sporting arenas and accompanying traffic density. Gentrification is also strongly associated with an increase in non-minority residents in an area. Although previous definitions of gentrification in the literature have not included racial distribution, we suggest that future definitions should include this metric given the strong association. Minority residents who are displaced as a result of gentrification do not experience the improvements in housing quality, accessibility to healthy foods and other associations of gentrification.

Public Health Sciences

Lanfeer DE, Luzum JA, She R, Li J, Sabbah HN, Zeld N, Liu B, Peterson E, and Keoki Williams L. Validation of a Polygenic Score for Beta-Blocker Survival Benefit in Patients With Heart Failure Using the United Kingdom Biobank. *Circ Genom Precis Med* 2023; e003835. Epub ahead of print. PMID: 36866666. [Full Text](#)

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Public Health Sciences

Leis AM, McSpadden E, Segaloff HE, Luring AS, Cheng C, Petrie JG, **Lamerato LE**, Patel M, Flannery B, Ferdinands J, Karvonen-Gutierrez CA, Monto A, and Martin ET. K-medoids clustering of hospital admission characteristics to classify severity of influenza virus infection. *Influenza Other Respir Viruses* 2023; 17(3):e13120. PMID: 36909298. [Full Text](#)

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BACKGROUND: Patients are admitted to the hospital for respiratory illness at different stages of their disease course. It is important to appropriately analyse this heterogeneity in surveillance data to accurately measure disease severity among those hospitalized. The purpose of this study was to determine if unique baseline clusters of influenza patients exist and to examine the association between cluster membership and in-hospital outcomes. **METHODS:** Patients hospitalized with influenza at two hospitals in Southeast Michigan during the 2017/2018 (n = 242) and 2018/2019 (n = 115) influenza seasons were included. Physiologic and laboratory variables were collected for the first 24 h of the hospital stay. K-medoids clustering was used to determine groups of individuals based on these values. Multivariable linear regression or Firth's logistic regression were used to examine the association between cluster membership and clinical outcomes. **RESULTS:** Three clusters were selected for 2017/2018, mainly differentiated by blood glucose level. After adjustment, those in C(17)1 had 5.6 times the odds of mechanical ventilator use than those in C(17)2 (95% CI: 1.49, 21.1) and a significantly longer mean hospital length of stay than those in both C(17)2 (mean 1.5 days longer, 95% CI: 0.2, 2.7) and C(17)3 (mean 1.4 days longer, 95% CI: 0.3, 2.5). Similar results were seen between the two clusters selected for 2018/2019. **CONCLUSION:** In this study of hospitalized influenza patients, we show that distinct clusters with higher disease acuity can be identified and could be targeted for evaluations of vaccine and influenza antiviral effectiveness against disease attenuation. The association of higher disease acuity with glucose level merits evaluation.

Public Health Sciences

Miller RL, Schuh H, Chandran A, Aris IM, Bendixsen C, Blossom J, Breton C, Camargo CA, Jr., Canino G, Carroll KN, Commodore S, Cordero JF, Dabelea DM, Ferrara A, Fry RC, Ganiban JM, Gern JE, Gilliland FD, Gold DR, Habre R, Hare ME, Harte RN, Hartert T, Hasegawa K, Khurana Hershey GK, Jackson DJ, **Joseph C**, Kerver JM, **Kim H**, Litonjua AA, Marsit CJ, McEvoy C, Mendonça EA, Moore PE, Nkoy FL, O'Connor TG, Oken E, **Ownby D**, Perzanowski M, Rivera-Spoljaric K, Ryan PH, Singh AM, Stanford JB, Wright RJ, Wright RO, Zanobetti A, **Zoratti E**, and **Johnson CC**. Incidence Rates of Childhood Asthma with Recurrent Exacerbations in the U.S. Environmental influences on Child Health Outcomes (ECHO) Program. *J Allergy Clin Immunol* 2023; Epub ahead of print. PMID: 36972767. [Full Text](#)

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BACKGROUND: Descriptive epidemiological data on incidence rates (IRs) of asthma with recurrent exacerbations (ARE) are sparse. **OBJECTIVE:** We hypothesized that IRs for ARE would vary by time, geography, age, race and ethnicity, irrespective of parental asthma history. **METHODS:** We leveraged data from 17246 children born after 1990 enrolled in 59 U.S. and one Puerto Rican cohort in the Environmental Influences on Child Health Outcomes consortium to estimate IRs for AREs. **RESULTS:** The overall crude IR for ARE was 6.07/1000 person-years (95% confidence intervals (CI) 5.63, 6.51) and was highest for children age 2-4 years, for Hispanic and non-Hispanic Black children and for those with a parental history of asthma. ARE IRs were higher for 2-4 year olds in each race and ethnicity category and for both sexes. Multi-variable analysis confirmed higher adjusted ARE IRs (aIRR) for children born 2000-2009 compared to 1990-1999 and 2010-2017, 2-4 versus 10-19 years old (aIRR=15.36; CI 12.09, 2.99), and for males versus females (aIRR=1.34; CI 1.16, 1.55). Black children (non-Hispanic and Hispanic) had higher rates than non-Hispanic White children (aIRR=2.51; CI 2.10, 2.99 and aIRR=2.04; CI 1.22, 3.39, respectively). Children born in the Midwest, Northeast and South had higher rates than the West ($p<0.01$ for each comparison). Children with a parental history of asthma had rates nearly three times higher than those without such history (aIRR=2.90; CI 2.43-3.46). **CONCLUSIONS:** Factors associated with time, geography, age, race and ethnicity, sex and parental history appear to influence the inception of ARE among children and adolescents.

Public Health Sciences

Panzer AR, **Sitarik AR**, Fadrosch D, **Havstad SL**, **Jones K**, **Davidson B**, **Finazzo S**, **Wegienka GR**, **Woodcroft K**, Lukacs NW, **Levin AM**, **Ownby DR**, **Johnson CC**, **Lynch SV**, and **Zoratti EM**. The impact of prenatal dog keeping on infant gut microbiota development. *Clin Exp Allergy* 2023; Epub ahead of print. PMID: 36916778. [Full Text](#)

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INTRODUCTION: Prenatal and early-life dog exposure has been linked to reduced childhood allergy and asthma. A potential mechanism includes altered early immune development in response to changes in the gut microbiome among dog-exposed infants. We thus sought to determine whether infants born into homes with indoor dog(s) exhibit altered gut microbiome development. **METHODS:** Pregnant women living in homes with dogs or in pet-free homes were recruited in southeast Michigan. Infant stool samples were collected at intervals between 1 week and 18 months after birth and microbiome was assessed using 16S ribosomal sequencing. Perinatal maternal vaginal/rectal swabs and stool samples were sequenced from a limited number of mothers. Mixed effect adjusted models were used to assess stool microbial community trajectories comparing infants from dog-keeping versus pet-free homes with adjustment for relevant covariates. **RESULTS:** Infant gut microbial composition among vaginally born babies became less similar to the maternal vaginal/rectal microbiota and more similar to the maternal gut microbiota with age-related accumulation of bacterial species with advancing age. Stool samples from dog-exposed infants were microbially more diverse ($p = .041$) through age 18 months with enhanced diversity most apparent between 3 and 6 months of age. Statistically significant effects of dog exposure on β -diversity metrics were restricted to formula-fed children. Across the sample collection period, dog exposure was associated with *Fusobacterium* genera enrichment, as well as enrichment of *Collinsella*, *Ruminococcus*, *Clostridaceae* and *Lachnospiraceae* OTUs. **CONCLUSION:** Prenatal/early-life dog exposure is associated with an altered gut microbiome during infancy and supports a potential mechanism explaining lessened atopy and asthma risk. Further research directly linking specific dog-attributable changes in the infant gut microbiome to the risk of allergic disorders is needed.

Public Health Sciences

Selim R, **Gordon SC**, **Zhou Y**, **Zhang T**, **Lu M**, Daida YG, Boscarino JA, Schmidt MA, **Trudeau S**, **Rupp LB**, and **Gonzalez HC**. Impact of hepatitis C treatment status on risk of Parkinson's disease and secondary parkinsonism in the era of direct-acting antivirals. *J Viral Hepat* 2023; Epub ahead of print. PMID: 36872452. [Full Text](#)

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Research suggests a possible link between chronic infection with hepatitis C virus (HCV) and the development of Parkinson's Disease (PD) and secondary Parkinsonism (PKM). We investigated the impact of antiviral treatment status (untreated, interferon [IFN] treated, direct-acting antiviral [DAA] treated) and outcome (treatment failure [TF] or sustained virological response [SVR]) on risk of PD/PKM

among patients with HCV. Using data from the Chronic Hepatitis Cohort Study (CHeCS), we applied a discrete time-to-event approach with PD/PKM as the outcome. We performed univariate followed by a multivariable modelling that used time-varying covariates, propensity scores to adjust for potential treatment selection bias and death as a competing risk. Among 17,199 confirmed HCV patients, we observed 54 incident cases of PD/PKM during a mean follow-up period of 17 years; 3753 patients died during follow-up. There was no significant association between treatment status/outcome and risk of PD/PKM. Type 2 diabetes tripled risk (hazard ratio [HR] 3.05; 95% CI 1.75-5.32; $p < .0001$) and presence of cirrhosis doubled risk of PD/PKM (HR 2.13, 95% CI 1.31-3.47). BMI >30 was associated with roughly 50% lower risk of PD/PKM than BMI <25 (HR 0.43; 0.22-0.84; $p = .0138$). After adjustment for treatment selection bias, we did not observe a significant association between HCV patients' antiviral treatment status/outcome on risk of PD/PKM. Several clinical risk factors—diabetes, cirrhosis and BMI—were associated with PD/PKM.

Public Health Sciences

Straughen JK, Sitarik AR, Jones AD, Li J, Allo G, Salafia C, Cassidy-Bushrow AE, and Paneth N. Comparison of methanol fixation versus cryopreservation of the placenta for metabolomics analysis. *Sci Rep* 2023; 13(1):4063. PMID: 36906704. [Full Text](#)

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Methods for collection of placental tissue at room temperature for metabolic profiling are described. Specimens were excised from the maternal side of the placenta and immediately flash frozen or fixed and stored for 1, 6, 12, 24, or 48 h in 80% methanol. Untargeted metabolic profiling was performed on both the methanol-fixed tissue and the methanol extract. Data were analyzed using Gaussian generalized estimating equations, two sample t-tests with false discovery rate (FDR) corrections, and principal components analysis. Methanol-fixed tissue samples and methanol extracts had a similar number of metabolites ($p = 0.45$, $p = 0.21$ in positive vs. negative ion mode). In positive ion mode, when compared to flash frozen tissue, both the methanol extract and methanol-fixed tissue (6 h) had a higher number of metabolites detected (146 additional metabolites, $p(\text{FDR}) = 0.020$; 149 additional metabolites, $p(\text{FDR}) = 0.017$; respectively), but these associations were not found in negative ion mode (all $p(\text{FDR}) \geq 0.05$). Principle components analysis demonstrated separation of the metabolite features in the methanol extract, but similarity between methanol-fixed tissue and flash frozen tissue. These results show that placental tissue samples collected in 80% methanol at room temperature can yield similar metabolic data to flash frozen specimens.

Public Health Sciences

Umanath K, She R, Hassett C, Adrianto I, Levin AM, Savickas G, Yee J, and Ortiz P. Urine Cell Transcriptomes Implicate Specific Renal Inflammatory Pathways Associated With Difficult-to-Control Hypertension. *J Am Heart Assoc* 2023; 12(6):e026242. PMID: 36892045. [Full Text](#)

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Background The renal mechanisms involved in the maintenance of human hypertension and resistance to treatment are not well understood. Animal studies suggest that chronic renal inflammation contributes to hypertension. We studied cells shed in first-morning urine samples from individuals who were hypertensive who exhibited difficult-to-control blood pressure (BP). We performed bulk RNA sequencing of these shed cells to develop transcriptome-wide associations with BP. We also analyzed nephron-specific genes and used an unbiased bioinformatic approach to find signaling pathways activated in difficult-to-control hypertension. **Methods and Results** Participants who completed the SPRINT (Systolic Blood Pressure Intervention Trial) at a single trial site were recruited, and cells shed in first-morning urine samples collected. A total of 47 participants were divided into 2 groups based on hypertension control. The BP-difficult group (n=29) had systolic BP>140 mm Hg, >120 mm Hg after intensive treatment for hypertension, or required more than the median number of antihypertensive drugs used in SPRINT. The easy-to-control BP group (n=18) comprised the remainder of the participants. A total of 60 differentially expressed genes were identified with a >2-fold change in the BP-difficult group. In BP-difficult participants, 2 of the most upregulated genes were associated with inflammation: Tumor Necrosis Factor Alpha Induced Protein 6 (fold change, 7.76; P=0.006) and Serpin Family B Member 9 (fold change, 5.10; P=0.007). Biological pathway analysis revealed an overrepresentation of inflammatory networks, including interferon signaling, granulocyte adhesion and diapedesis, and Janus Kinase family kinases in the BP-difficult group (P<0.001). **Conclusions** We conclude that transcriptomes from cells shed in first-morning urine identify a gene expression profile in difficult-to-control hypertension that associates with renal inflammation.

Public Health Sciences

Venkat P, Gao H, Findeis EL, Chen Z, Zacharek A, Landschoot-Ward J, Powell B, Lu M, Liu Z, Zhang Z, and Chopp M. Therapeutic effects of CD133 + Exosomes on liver function after stroke in type 2 diabetic mice. *Front Neurosci* 2023; 17:1061485. PMID: 36968490. [Full Text](#)

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BACKGROUND AND PURPOSE: Non-alcoholic fatty liver disease (NAFLD) is known to adversely affect stroke recovery. However, few studies investigate how stroke elicits liver dysfunction, particularly, how stroke in type 2 diabetes mellitus (T2DM) exacerbates progression of NAFLD. In this study, we test whether exosomes harvested from human umbilical cord blood (HUCBC) derived CD133 + cells (CD133 + Exo) improves neuro-cognitive outcome as well as reduces liver dysfunction in T2DM female mice. **METHODS:** Female, adult non-DM and T2DM mice subjected to stroke presence or absence were considered. T2DM-stroke mice were randomly assigned to receive PBS or Exosome treatment group. CD133 + Exo (20 µg/200 µl PBS, i.v.) was administered once at 3 days after stroke. Evaluation of neurological (mNSS, adhesive removal test) and cognitive function [novel object recognition (NOR) test, odor test] was performed. Mice were sacrificed at 28 days after stroke and brain, liver, and serum were harvested. **RESULTS:** Stroke induces severe and significant short-term and long-term neurological and cognitive deficits which were worse in T2DM mice compared to non-DM mice. CD133 + Exo treatment of T2DM-stroke mice significantly improved neurological function and cognitive outcome indicated by improved discrimination index in the NOR and odor tests compared to control T2DM-stroke mice. CD133 + Exo treatment of T2DM stroke significantly increased vascular and white matter/axon remodeling in the ischemic brain compared to T2DM-stroke mice. However, there were no differences in the lesion volume between non-DM stroke, T2DM-stroke and CD133 + Exo treated T2DM-stroke mice. In T2DM mice, stroke induced earlier and higher TLR4, NLRP3, and cytokine expression (SAA, IL1β, IL6, TNFα) in the liver compared to heart and kidney, as measured by Western blot. T2DM-stroke mice exhibited worse NAFLD progression with increased liver steatosis, hepatocellular ballooning, fibrosis, serum ALT activity, and higher NAFLD Activity Score compared to T2DM mice and non-DM-stroke mice, while CD133 + Exo treatment significantly attenuated the progression of NAFLD in T2DM stroke mice. **CONCLUSION:** Treatment of female T2DM-stroke mice with CD133 + Exo significantly reduces the progression of NAFLD/NASH and improves neurological and cognitive function compared to control T2DM-stroke mice.

Public Health Sciences

Williams AM, Tam SH, and Adjei Boakye E. Firearm Safety for Patients Diagnosed With Cancer-A Role in Suicide Prevention. *JAMA Oncol* 2023; Epub ahead of print. PMID: 36862388. [Request Article](#)

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This Viewpoint discusses firearm safety guidelines among patients diagnosed with cancer and at a higher risk of suicide.

Pulmonary and Critical Care Medicine

Howard M, Pflaum-Carlson J, Hurst G, Gardner-Gray J, Kinni H, Coba V, Rivers E, and Jayaprakash N. A roadmap for developing an emergency department based critical care consultation service: Building the early intervention team (EIT). *Am J Emerg Med* 2023; 66:81-84. PMID: 36736063. [Full Text](#)

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Emergency Department (ED) crowding and boarding impact safe and effective health care delivery. ED clinicians must balance caring for new arrivals who require stabilization and resuscitation as well as those who need longitudinal care and re-evaluation. These challenges are magnified in the setting of critically ill patients boarding for the intensive care unit. Boarding is a complex issue that has multiple solutions based on resources at individual institutions. Several different models have been described for delivery of critical care in the ED. Here, we describe the development of an ED based critical care consultation service, the early intervention team, at an urban academic ED.

Radiation Oncology

Huang Y, Liang E, Schaff EM, Zhao B, Snyder KC, Chetty IJ, Shah MM, and Siddiqui SM. Impact of MRI resolution for Linac-based stereotactic radiosurgery. *Front Oncol* 2023; 13:1090582. PMID: 36761944. [Full Text](#)

Department of Radiation Oncology, Henry Ford Health, Detroit, MI, United States.

OBJECTIVE: Magnetic resonance imaging (MRI) is a standard imaging modality in intracranial stereotactic radiosurgery (SRS) for defining target volumes. However, wide disparities in MRI resolution exist, which could directly impact accuracy of target delineation. Here, sequences with various MRI resolution were acquired on phantoms to evaluate the effect on volume definition and dosimetric consequence for cranial SRS. **MATERIALS/METHODS:** Four T1-weighted MR sequences with increasing 3D resolution were compared, including two Spin Echo (SE) 2D acquisitions with 5mm and 3mm slice thickness (SE5mm, SE3mm) and two gradient echo 3D acquisitions (TFE, BRAVO). The voxel sizes were 0.4x0.4x5.0, 0.5x0.5x3.0, 0.9x0.9x1.25, and 0.4x0.4x0.5 mm(3), respectively. Four phantoms with simulated lesions of different shape and volume (range, 0.53-25.0 cm(3)) were imaged, resulting in 16 total sets of MRIs. Four radiation oncologists provided contours on individual MR image set. All observer contours were compared with ground truth, defined on CT image according to the absolute dimensions of the target structure, using Dice similarity coefficient (DSC), Hausdorff distance (HD), mean distance-to-agreement (MDA), and the ratio between reconstructed and true volume (Ratio(vol)). For dosimetric consequence, SRS plans targeting observer volumes were created. The true Paddick conformity index (C_p/paddick_{true}), calculated with true target volume, was correlated with quality of observer volume. **RESULTS:** All measures of observer contours improved as increasingly higher MRI resolution was

provided from SE5mm to BRAVO. The improvement in DSC, HD and MDA was statistically significant ($p < 0.01$). Dosimetrically, C₁paddicktrue strongly correlated with DSC of the planning observer volume (Pearson's $r = 0.94$, $p < 0.00001$). CONCLUSIONS: Significant improvement in target definition and reduced inter-observer variation was observed as the MRI resolution improved, which also improved the quality of SRS plans. Results imply that high resolution 3D MR sequences should be used to minimize potential errors in target definition, and multi-slice 2D sequences should be avoided.

Radiation Oncology

Snyder KC, Mao WH, Kim JP, Cunningham J, Chetty IJ, Siddiqui SM, Parikh P, and Dolan J.

Commissioning, clinical implementation, and initial experience with a new brain tumor treatment package on a low-field MR-linac. *J Appl Clin Med Phys* 2023. PMID: Not assigned. [Full Text](#)

Sleep Medicine

Greenwald MK, Moses TEH, Lundahl LH, and **Roehrs TA**. Anhedonia modulates benzodiazepine and opioid demand among persons in treatment for opioid use disorder. *Front Psychiatry* 2023; 14:1103739. PMID: 36741122. [Full Text](#)

Substance Abuse Research Division, Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, MI, United States.

Sleep Disorders Center, Henry Ford Health System, Detroit, MI, United States.

BACKGROUND: Benzodiazepine (BZD) misuse is a significant public health problem, particularly in conjunction with opioid use, due to increased risks of overdose and death. One putative mechanism underlying BZD misuse is affective dysregulation, via exaggerated negative affect (e.g., anxiety, depression, stress-reactivity) and/or impaired positive affect (anhedonia). Similar to other misused substances, BZD consumption is sensitive to price and individual differences. Although purchase tasks and demand curve analysis can shed light on determinants of substance use, few studies have examined BZD demand, nor factors related to demand. **METHODS:** This ongoing study is examining simulated economic demand for alprazolam (among BZD lifetime misusers based on self-report and DSM-5 diagnosis; $n = 23$ total; 14 male, 9 female) and each participant's preferred-opioid/route using hypothetical purchase tasks among patients with opioid use disorder ($n = 59$ total; 38 male, 21 female) who are not clinically stable, i.e., defined as being early in treatment or in treatment longer but with recent substance use. Aims are to determine whether: (1) BZD misusers differ from never-misusers on preferred-opioid economic demand, affective dysregulation (using questionnaire and performance measures), insomnia/behavioral alertness, psychiatric diagnoses or medications, or urinalysis results; and (2) alprazolam demand among BZD misusers is related to affective dysregulation or other measures. **RESULTS:** Lifetime BZD misuse is significantly ($p < 0.05$) related to current major depressive disorder diagnosis, opioid-negative and methadone-negative urinalysis, higher trait anxiety, greater self-reported affective dysregulation, and younger age, but not preferred-opioid demand or insomnia/behavioral alertness. Alprazolam and opioid demand are each significantly positively related to higher anhedonia and, to a lesser extent, depression symptoms but no other measures of negative-affective dysregulation, psychiatric conditions or medications (including opioid agonist therapy or inpatient/outpatient treatment modality), or sleep-related problems. **CONCLUSION:** Anhedonia (positive-affective deficit) robustly predicted increased BZD and opioid demand; these factors could modulate treatment response. Routine assessment and effective treatment of anhedonia in populations with concurrent opioid and sedative use disorder may improve treatment outcomes. **CLINICAL TRIAL REGISTRATION:** <https://clinicaltrials.gov/ct2/show/NCT03696017>, identifier NCT03696017.

Sleep Medicine

Ong JC, and **Kalmbach DA**. Mindfulness as an Adjunct or Alternative to CBT-I. *Sleep Med Clin* 2023; 18(1):59-71. PMID: 36764787. [Full Text](#)

Department of Neurology, Center for Circadian and Sleep Medicine, Northwestern University Feinberg School of Medicine, 710 N. Lake Shore Dr, Chicago, IL 60625, USA; Behavioral Sleep Medicine, Nox Health, 5000 Research Court, Suite 500, Suwanee, GA 30024, USA. Electronic address: jong@noxhealth.com.

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Mindfulness-based interventions (MBIs) are programs that teach mindfulness concepts through guided meditation and self-regulation practices. MBIs have been found to improve sleep and reduce cognitive arousal, which are central to the development and perpetuation of insomnia. In this article, we review theoretic frameworks and clinical trial effectiveness data supporting MBIs for insomnia. Based on this review, we provide suggestions for using MBIs as an adjunct or alternative treatment option to CBT-I with regard to how, when, and for whom. We conclude with an agenda for future directions that can clarify the use of mindfulness as a treatment option for insomnia.

Sleep Medicine

Reffi AN, and **Cheng P**. Healthy sleep may bolster resilience to depression and PTSD in new paramedics. *Sleep* 2023; Epub ahead of print. PMID: 36883766. [Full Text](#)

Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, 1 Ford Place, Detroit, MI 48202 USA.

Surgery

Asai M, and **Dobesh KD**. Combined Resection Approaches: Decision Making for Synchronous Resection, Timing of Staged Intervention to Optimize Outcome. *Clin Colon Rectal Surg* 2023. PMID: Not assigned. [Request Article](#)

Surgery

Behinaein P, and **Okereke IC**. Ascending heartbreak hill: the pursuit of cardiothoracic residency through forgotten eyes. *J Thorac Cardiovasc Surg* 2023; Epub ahead of print. PMID: 36997462. [Full Text](#)

School of Medicine, Wayne State University, Detroit, Mich.
Department of Surgery, Henry Ford Health, Detroit, Mich.

Surgery

Chacko P, **Hans SS**, **Nahirniak P**, and **Morton K**. Clinical Patterns, Predictors, and Results of Graft Limb Occlusion Following Endovascular Aneurysm Repair. *Ann Vasc Surg* 2023; Epub ahead of print. PMID: 36918093. [Full Text](#)

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Institution: Henry Ford Health System, Macomb.

OBJECTIVE: To assess the incidence, clinical patterns, and outcomes of graft limb occlusion (GLO) following endovascular aneurysm repair (EVAR). **METHODS:** A retrospective study of patients undergoing EVAR from 2002-2017 at two mid-sized suburban teaching hospitals. The ipsilateral and contralateral aorto-common iliac artery angle (A-CIA) and common iliac-external iliac artery angle (CIA-EIA) was determined. The diameter of the EIA, graft extension to the EIA, and prior CIA stenting was recorded. **RESULTS:** Of the 373 patients who underwent EVAR, 319 were analyzed. 22 patients had 23 limbs with GLO (21 unilateral and one bilateral) with a mean follow up of 9.1 +/- 2.1 years. There were no statistically significant differences in mean age, gender, size of the abdominal aortic aneurysm, and risk factors of hypertension, coronary artery disease, diabetes mellitus, and chronic obstructive pulmonary disease in patients with and without GLO. There was no statistically significant difference in A-CIA and CIA-EIA angles. A smaller diameter EIA (6mm or less), graft extension to EIA, and prior CIA stenting were significant predictors of GLO. Four limbs had GLO within one month of EVAR, only open thrombectomy was performed in 2 limbs, open thrombectomy with simultaneous axillo-femoral graft in one limb, and open thrombectomy with self-expandable stent placement in one limb. 12 limbs had GLO within 1-12 months treated with only open thrombectomy in three limbs, open thrombectomy with fasciotomy in one limb, open thrombectomy with graft extension to EIA in one limb, and crossover femoral-femoral graft performed in three limbs. Seven limbs had GLO within 1-5 years with a crossover femoral-femoral graft

performed in four limbs and open thrombectomy with graft extension to EIA was performed in one limb. Six limbs with GLO following EVAR did not undergo any intervention. One patient had an above the knee amputation 3 years following occlusion of the axillo-femoral graft and one patient returned in 4 years with an increase in size of the excluded aneurysm leading to acute rupture and death. CONCLUSIONS: Graft limb occlusion leads to significant morbidity and mortality following EVAR. Predictors of GLO following EVAR include a small diameter EIA, prior CIA stenting and graft limb extension to the EIA.

Surgery

deLahunta D, and **Nalamati S**. Management of Surgically Accessible Lymph Nodes Beyond Normal Resection Planes. *Clin Colon Rectal Surg* 2023. [Request Article](#)

Surgery

Hutchings H, **Zhang Q**, Grady S, Mabe L, and Okereke IC. Gentrification and Air Quality in a Large Urban County in the United States. *Int J Environ Res Public Health* 2023; 20(6). PMID: 36981672. [Full Text](#)

Department of Surgery, Henry Ford Health System, 2799 W. Grand Blvd, Detroit, MI 48202, USA.

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Introduction: Increases in industrialization and manufacturing have led to worsening pollution in some components of air quality. In addition, gentrification is occurring in large cities throughout the world. As these socioeconomic and demographic changes occur, there have been no studies examining the association of gentrification with air quality. To investigate this association, we studied the trends of gentrification, changes in racial distribution and changes in air quality in each zip code of a large urban county over a 40-year period. **Methods:** We conducted a retrospective longitudinal study over 40 years in Wayne County, Michigan using socioeconomic and demographic data from the National Historical Geographic Information System (NHGIS) and air quality data from the United States Environmental Protection Agency (EPA). To assess gentrification, longitudinal analyses were performed to examine median household income, percentage with a college education, median housing value, median gross rent and employment level. The racial distribution was evaluated in each zip code during the time period. Gentrification was studied in relation to air quality using nonparametric 2-sample Wilcoxon-Mann-Whitney tests and Binomial Generalized Linear Regression models. **Results:** Although air quality improved overall over the 40-year period, there was a lesser rate of improvement in gentrified areas. Furthermore, gentrification was strongly associated with racial distribution. The most substantial gentrification occurred from 2010 to 2020, in which a specific cluster of adjacent zip codes in downtown Detroit experienced intense gentrification and a drop in the percentage of African-American residents. **Conclusions:** Gentrified areas seem to have a less pronounced improvement in air quality over time. This reduction in air quality improvement is likely associated with demolitions and the construction of new buildings, such as sporting arenas and accompanying traffic density. Gentrification is also strongly associated with an increase in non-minority residents in an area. Although previous definitions of gentrification in the literature have not included racial distribution, we suggest that future definitions should include this metric given the strong association. Minority residents who are displaced as a result of gentrification do not experience the improvements in housing quality, accessibility to healthy foods and other associations of gentrification.

Surgery

Jesse MT, Jackson WE, Liapakis A, Ganesh S, Humar A, Goldaracena N, Levitsky J, Mulligan D, Pomfret EA, Ladner DP, Roberts JP, Mavis A, Thiessen C, Trotter J, Winder GS, Griesemer AD, Pillai A, Kumar V, Verna EC, LaPointe Rudow D, and Han HH. Living donor liver transplant candidate and donor selection and engagement: Meeting report from the living donor liver transplant consensus conference. *Clin Transplant* 2023; e14954. Epub ahead of print. PMID: 36892182. [Full Text](#)

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Recanati/Miller Transplantation Institute, Mount Sinai Hospital, New York, New York, USA.
Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.

INTRODUCTION: Living donor liver transplantation (LDLT) is a promising option for mitigating the deceased donor organ shortage and reducing waitlist mortality. Despite excellent outcomes and data supporting expanding candidate indications for LDLT, broader uptake throughout the United States has yet to occur. **METHODS:** In response to this, the American Society of Transplantation hosted a virtual consensus conference (October 18-19, 2021), bringing together relevant experts with the aim of identifying barriers to broader implementation and making recommendations regarding strategies to address these barriers. In this report, we summarize the findings relevant to the selection and engagement of both the LDLT candidate and living donor. Utilizing a modified Delphi approach, barrier and strategy statements were developed, refined, and voted on for overall barrier importance and potential impact and feasibility of the strategy to address said barrier. **RESULTS:** Barriers identified fell into three general categories: 1) awareness, acceptance, and engagement across patients (potential candidates and donors), providers, and institutions, 2) data gaps and lack of standardization in candidate and donor selection, and 3) data gaps regarding post-living liver donation outcomes and resource needs. **CONCLUSIONS:** Strategies to address barriers included efforts toward education and engagement across populations, rigorous and collaborative research, and institutional commitment and resources.

Surgery

Liapakis A, Agbim U, Bittermann T, Dew MA, Deng Y, Gan G, Emre S, Hunt HF, Olthoff KM, Locke JE, **Jesse MT**, Kumar V, Pillai A, Verna E, and Lentine KL. A survey of transplant providers regarding attitudes, barriers, and facilitators to living donor liver transplantation in the United States. *Clin Transplant* 2023; e14967. Epub ahead of print. PMID: 36938716. [Full Text](#)

Department of Medicine, Yale University, New Haven, Connecticut, USA.
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Center for Liver Disease and Transplantation, Columbia University, New York, New York, USA.

INTRODUCTION: A successful living donor liver transplant (LDLT) is the culmination of a multifaceted process coordinated among key stakeholders. **METHODS:** We conducted an electronic survey of US liver transplant (LT) centers (August 26, 2021-October 10, 2021) regarding attitudes, barriers, and facilitators of LDLT to learn how to expand LDLT safely and effectively in preparation for the American Society of Transplantation Living Donor Liver Transplant Consensus Conference. **RESULTS:** Responses were received from staff at 58 programs (40.1% of US LT centers). There is interest in broadening LDLT (100% of LDLT centers, 66.7% of non-LDLT centers) with high level of agreement that LDLT mitigates donor shortage (93.3% of respondents) and that it should be offered to all suitable candidates (87.5% of respondents), though LDLT was less often endorsed as the best first option (29.5% of respondents). Key barriers at non-LDLT centers were institutional factors and surgical expertise, whereas those at LDLT centers focused on waitlist candidate and donor factors. Heterogeneity in candidate selection for LDLT, candidate reluctance to pursue LDLT, high donor exclusion rate, and disparities in access were important barriers. **CONCLUSION:** Findings from this study may help guide current and future expansion of LDLT more efficiently in the US. These efforts require clear and cohesive messaging regarding LDLT benefits, engagement of the public community, and dedicated resources to equitably increase LDLT access.

Surgery

Liapakis A, **Jesse MT**, Pillai A, Bittermann T, Dew MA, Emre S, Hunt H, Kumar V, Locke J, Mohammad S, Olthoff K, Verna EC, and Lentine KL. Living donor liver transplantation: A multi-disciplinary collaboration towards growth, consensus, and a change in culture. *Clin Transplant* 2023; e14953. Epub ahead of print. PMID: 36890717. [Full Text](#)

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Saint Louis University Transplant Center, St. Louis, Missouri, USA.

INTRODUCTION: Living donor liver transplantation (LDLT) reduces liver transplant waitlist mortality and provides excellent long-term outcomes for persons with end stage liver disease. Yet, utilization of LDLT has been limited in the United States (US). **METHODS:** In October 2021, the American Society of Transplantation held a consensus conference to identify important barriers to broader expansion of LDLT in the US, including data gaps, and make recommendations for impactful and feasible mitigation strategies to overcome these barriers. Domains addressed encompassed the entirety of the LDLT process. Representation from international centers and living donor kidney transplantation were included for their perspective/experience in addition to members across disciplines within the US liver transplantation community. A modified Delphi approach was employed as the consensus methodology. **RESULTS:** The predominant theme permeating discussion and polling results centered on culture; the beliefs and behaviors of a group of people perpetuated over time. **CONCLUSIONS:** Creating a culture of support for LDLT in the US is key for expansion and includes engagement and education of stakeholders across the spectrum of the process of LDLT. A shift from awareness of LDLT to acknowledgement of benefit of LDLT is the primary goal. Propagation of the maxim "LDLT is the best option" is pivotal.

Surgery

Lu AK, Baldwin J, and Hans SS. Acute limb ischemia secondary to external iliac and common femoral artery dissection in a body builder. *J Vasc Surg Cases Innov Tech* 2023; 9(1):101099. PMID: 36852317.

[Full Text](#)

General Surgery Residency Program, Henry Ford Macomb Hospital, Clinton Township, MI.
Henry Ford Vascular Surgery, Henry Ford Macomb Hospital, Clinton Township, MI.

Spontaneous external iliac artery dissection in highly trained athletes is becoming more recognized, but the reason as to why they are occurring remains a mystery. We present a patient with acute limb ischemia secondary to arterial dissection after strenuous exercise. Imaging showed complete occlusion of the distal common iliac artery, and the patient underwent successful revascularization of the right lower extremity using a hybrid approach.

Surgery

Pillai A, Verna EC, Parikh ND, Cooper M, Thiessen C, Heimbach J, Gordon EJ, Sapisochin G, Selzner N, Mathur A, Perito ER, **Jesse M**, Liapakis A, and Kumar V. Financial, policy, and ethical barriers to the expansion of living donor liver transplant: Meeting report from a living donor liver transplant consensus conference. *Clin Transplant* 2023; e14955. Epub ahead of print. PMID: 36880375. [Full Text](#)

Department of Medicine, University of Chicago Medicine, Chicago, Illinois, USA.

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Yale Medicine Digestive Diseases, New Haven, Connecticut, USA.

Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.

INTRODUCTION: In October 2021, the American Society of Transplantation (AST) hosted a virtual consensus conference aimed at identifying and addressing barriers to the broader, safe expansion of living donor liver transplantation (LDLT) throughout the United States (US). **METHODS:** A multidisciplinary group of LDLT experts convened to address issues related to financial implications on the donor, transplant center crisis management, regulatory and oversight policies, and ethical considerations by assessing the relative significance of issues in preventing LDLT growth, with proposed strategies to overcome barriers. **RESULTS:** Living liver donors endure multiple obstacles including financial instability, loss of job security, and potential morbidity. These concerns, along with other center, state, and federal specific policies can be perceived as significant barriers to expanding LDLT. Donor safety is of paramount importance to the transplant community; however, regulatory and oversight policies aimed at ensuring donor safety can be viewed as ambiguous and complicated leading to time-consuming evaluations that may deter donor motivation and program expansion. **CONCLUSION:** Transplant programs need to establish appropriate crisis management plans to mitigate potential negative donor outcomes and ensure program viability and stability. Finally, ethical aspects, including informed consent for high-risk recipients and use of non-directed donors, can be perceived as additional barriers to expanding LDLT.

Surgery

Rajendran L, Choi WJ, Muaddi H, **Ivanics T**, Feld JJ, Claasen M, Castelo M, and Sapisochin G. ASO Visual Abstract: The Association of Viral Hepatitis Status and Post-hepatectomy Outcomes in the Era of Direct-Acting Antivirals. *Ann Surg Oncol* 2023; Epub ahead of print. PMID: 36859703. [Full Text](#)

Department of Surgery, Division of General Surgery, University of Toronto, Toronto, Ontario, Canada.
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Surgery

Reickert CA. Management of Stage 4 Colon and Rectal Cancer. *Clin Colon Rectal Surg* 2023. PMID: Not assigned. [Request Article](#)

Surgery

Shah RP, and Gangi A. Role of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in the Management of Colorectal Peritoneal Metastases. *Clin Colon Rectal Surg* 2023. PMID: Not assigned. [Request Article](#)

Surgery

Shimada S, Shamaa T, Ivanics T, Miyake K, Kitajima T, Rizzari M, Yoshida A, Abouljoud M, Moonka D, and Nagai S. Effects of the implementation of acuity circle policy on waitlist and post-transplant outcomes of liver re-transplantation. *Clin Transplant* 2023; e14977. Epub ahead of print. PMID: 36951511. [Full Text](#)

Division of Transplant and Hepatobiliary Surgery, Henry Ford Health System, Detroit, Michigan, USA.

Division of Gastroenterology and Hepatology, Henry Ford Health System, Detroit, Michigan, USA.

BACKGROUND: Acuity circle (AC) policy implementation improved the waitlist outcomes for certain liver transplant (LT)-candidates. The impact of the policy implementation for liver retransplant (reLT) candidates is unknown. **METHODS:** Using Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data from January, 2018 to September, 2021, we investigated the effect of the AC policy on waitlist and post-LT outcomes among patients who had previously received a LT. Patients were categorized by relisting date: Pre-AC (Era 1: January 1, 2018-February 3, 2020; n = 750); and Post-AC (Era 2: February 4, 2020-June 30, 2021; n = 556). Patient and donor characteristics, as well as on-waitlist and post-reLT outcomes were compared across eras. **RESULTS:** In Era 2, the probability of transplant within 90 days overall and among patients relisted > 14 days from initial transplant (late relisting) were significantly higher compared to Era 1 (subdistribution hazard ratio [sHR] 1.40, 95% CI 1.18-1.64, p < .001; sHR 1.52, 95% CI 1.23-1.88, p = .001, respectively). However, there was no difference by era among patients relisted ≤14 days from initial transplant (early relisting; sHR 1.21, 95% CI .93-1.57, p = .15). Likewise, among early relisting patients, risks for 180-day graft loss and mortality were significantly higher in Era 2 versus Era 1 (adjusted hazard ratio [aHR] 5.77, 95% CI 1.71-19.51, p = .004; and aHR 8.22, 95% CI 1.85-36.59, p = .005, respectively); for late relisting patients, risks for these outcomes were similar across eras. **CONCLUSION:** Our results show that the

implementation of AC policy has improved transplant rates and reduced waiting time for reLT candidates listed > 14 days from initial transplant. However, the impact upon early relisting patients may be mixed.

Surgery

Varban OA. Comment on: Black-versus-White racial disparities in 30-day outcomes at MBSAQIP-accredited centers: a needed quality indicator. *Surg Obes Relat Dis* 2023; 19(4):281-282. PMID: 36804997. [Full Text](#)

Department of Surgery, Bariatric Surgery and Weight Management, Henry Ford Hospital, Detroit, Michigan.

Surgery

Varban OA, Hassett KP, Yost M, **Carlin AM,** Ghaferi AA, Finks JF, and Ehlers AP. Financial Impact of Metabolic Surgery on Prescription Diabetes Medications in Michigan. *JAMA Surg* 2023; Epub ahead of print. PMID: 36857073. [Full Text](#)

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This study compares expenditures for diabetes medications before and after metabolic surgery among patients with diabetes in Michigan.

eng Cross Blue Shield of Michigan for leadership and participation in the Michigan Bariatric Surgery Collaborative during the conduct of the study. Dr Carlin reported an honorarium from Blue Cross Blue Shield Blue Care Network of Michigan for a leadership role in the Michigan Bariatric Surgery Collaborative outside the submitted work. Dr Ghaferi reported grants from Blue Cross Blue Shield of Michigan during the conduct of the study. Dr Finks reported salary support from Blue Cross Blue Shield of Michigan Blue Care Network for a leadership role in the Michigan Bariatric Surgery Collaborative outside the submitted work. No other disclosures were reported.

Urology

Blasdel G, Kloer C, Parker A, **Shakir N,** Zhao LC, and Bluebond-Langner R. Genital Hypoplasia before Gender-Affirming Vaginoplasty: Does the Robotic Peritoneal Flap Method Create Equivalent Vaginal Canal Outcomes? *Plast Reconstr Surg* 2023; 151(4):867-874. PMID: 36729740. [Full Text](#)

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BACKGROUND: Insufficient genital tissue has been reported as a barrier to achieving depth in gender-affirming vaginoplasty. The authors sought to characterize vaginal depth and revision outcomes in patients with genital hypoplasia undergoing robotic peritoneal flap vaginoplasty. **METHODS:** Retrospective case-control analysis of patients undergoing robotic peritoneal vaginoplasty between September of 2017 and August of 2020 was used. All 43 patients identified as having genital hypoplasia (genital length <7 cm) were included with 49 random controls from the remaining patients with greater than 7 cm genital length. Baseline clinical characteristics and perioperative variables were recorded to identify potential confounders. Outcomes measured included vaginal size reported at last visit and undergoing revision surgery for depth or for vulvar appearance. **RESULTS:** Patients were well matched other than median body mass index at the time of surgery, which was greater in the hypoplasia cohort by 3.6 kg/m² ($P < 0.0001$). Patients had a median of 1-year of follow-up, with a minimum follow-up of 90 days. No significant differences in outcomes were observed, with a median vaginal depth of 14.5 cm (interquartile range, 13.3 to 14.5 cm), and a median width of dilator used of 3.8 cm (interquartile range, 3.8 to 3.8 cm). No depth revisions were observed, and an 11% ($n = 10$) rate of external revision

occurred. CONCLUSIONS: Patients with genital hypoplasia had equivalent dilation outcomes in a case-control analysis with consistent follow-up past 90 days. The robotic peritoneal flap vaginoplasty technique provides vaginal depth of 14 cm or greater regardless of genital tissue before surgery. Further investigation with patient-reported outcome measures is warranted. CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, II.

Urology

Butaney M, Wilder S, Patel AK, Qi J, Mirza M, Noyes SL, Johnson A, Van Til M, Jafri SM, Ginsburg KB, Rogers CG, and Lane BR. Initial Management of Indeterminate Renal Lesions in a Statewide Collaborative: A MUSIC-KIDNEY Analysis. *J Urol* 2023; Epub ahead of print. PMID: 36947795. [Full Text](#)

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PURPOSE: Renal masses (RM) can be characterized as "indeterminate" due to lack of differentiating imaging characteristics. Optimal management of indeterminate renal lesions (IRLs) remains nebulous and poorly defined. We assess management of IRLs within the MUSIC-KIDNEY collaborative. **MATERIALS AND METHODS:** Each RM is classified as suspicious, benign, or indeterminate based on radiologist and urologist assessment. Objectives were to assess initial management of IRL and the impact of additional imaging and biopsy on characterization prior to treatment. **RESULTS:** Of 2109 patients, 444 (21.1%) had IRL on their initial imaging, which included CT without contrast (36.2%), CT with contrast (54.1%), and MRI (9.7%). Eighty-nine patients (20.0%) underwent additional imaging within 90 days, 8.3% (37/444) underwent renal mass biopsy (RMB), and 3.6% (16/444) had re-imaging and RMB. Additional imaging reclassified 58.1% (61/105) of IRL lesions as suspicious and 21.0% (22/105) as benign, with only 20.9% (22/105) remaining indeterminate. RMB yielded a definitive diagnosis for 87%. Treatment was performed for 149 IRLs (33.6%), including 117 without re-imaging and 123 without RMB. At surgery for IRL, benign pathology was more common in patients who did not have repeat imaging (9.9%) than in those who did (6.7%); for ≤ 4 cm IRL, these rates were 11.8% and 4.3%. **CONCLUSION:** About 33% of patients diagnosed with an IRL underwent immediate treatment without subsequent imaging or RMB, with a 10.1% rate of non-malignant pathology. This highlights a QI opportunity for patients with cT1RM: confirmation that the lesion is suspicious for RCC based on high-quality, multi-phase cross-sectional imaging and/or histopathologic features prior to surgery, even if obtaining subsequent follow-up imaging and/or RMB is necessary. When performed, these steps lead to reclassification in 79% and 87% of IRLs, respectively.

Urology

Chen Y, Loveless IM, Nakai T, Newaz R, Abdollah FF, Rogers CG, Hassan O, Chitale D, Arora K, Williamson SR, Gupta NS, Rybicki BA, Sadasivan SM, and Levin AM. Convolutional Neural Network Quantification of Gleason Pattern 4 and Association with Biochemical Recurrence in Intermediate Grade Prostate Tumors. *Mod Pathol* 2023; 100157. Epub ahead of print. PMID: 36925071. [Full Text](#)

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Differential classification of prostate cancer (CaP) grade group (GG) 2 and 3 tumors remains challenging, likely due to the subjective quantification of percentage of Gleason pattern 4 (%GP4). Artificial intelligence

assessment of %GP4 may improve its accuracy and reproducibility and provide information for prognosis prediction. To investigate this potential, a convolutional neural network (CNN) model was trained to objectively identify and quantify Gleason pattern (GP) 3 and 4 areas, estimate %GP4, and assess whether CNN-assessed %GP4 is associated with biochemical recurrence (BCR) risk in intermediate risk GG 2 and 3 tumors. The study was conducted in a radical prostatectomy cohort (1999-2012) of African American men from the Henry Ford Health System (Detroit, Michigan). A CNN model that could discriminate four tissue types (stroma, benign glands, GP3 glands, and GP4 glands) was developed using histopathologic images containing GG 1 (n=45) and 4 (n=20) tumor foci. The CNN model was applied to GG 2 (n=153) and 3 (n=62) for %GP4 estimation, and Cox proportional hazard modeling was used to assess the association of %GP4 and BCR, accounting for other clinicopathologic features including GG. The CNN model achieved an overall accuracy of 86% in distinguishing the four tissue types. Further, CNN-assessed %GP4 was significantly higher in GG 3 compared with GG 2 tumors ($p=7.2 \times 10^{-11}$). %GP4 was associated with an increased risk of BCR (adjusted HR=1.09 per 10% increase in %GP4, $p=0.010$) in GG 2 and 3 tumors. Within GG 2 tumors specifically, %GP4 was more strongly associated with BCR (adjusted HR=1.12, $p=0.006$). Our findings demonstrate the feasibility of CNN-assessed %GP4 estimation, which is associated with BCR risk. This objective approach could be added to the standard pathological assessment for patients with GG 2 and 3 tumors and act as a surrogate for specialist genitourinary pathologist evaluation when such consultation is not available.

Urology

Grossmann NC, Soria F, Juvet T, Potretzke AM, Djaladat H, Ghoreifi A, Kikuchi E, Mari A, Khene ZE, Fujita K, Raman JD, Breda A, Fontana M, Sfakianos JP, Pfail JL, Laukhtina E, Rajwa P, Pallauf M, Poyet C, Cacciamani GE, van Doeveren T, Boormans JL, Antonelli A, **Jamil M, Abdollah F**, Ploussard G, Heidenreich A, Storz E, Daneshmand S, Boorjian SA, Rouprêt M, Rink M, Shariat SF, and Pradere B. Comparing Oncological and Perioperative Outcomes of Open versus Laparoscopic versus Robotic Radical Nephroureterectomy for the Treatment of Upper Tract Urothelial Carcinoma: A Multicenter, Multinational, Propensity Score-Matched Analysis. *Cancers (Basel)* 2023; 15(5). PMID: 36900201. [Full Text](#)

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OBJECTIVES: To identify correlates of survival and perioperative outcomes of upper tract urothelial carcinoma (UTUC) patients undergoing open (ORNU), laparoscopic (LRNU), and robotic (RRNU) radical nephroureterectomy (RNU). **METHODS:** We conducted a retrospective, multicenter study that included non-metastatic UTUC patients who underwent RNU between 1990-2020. Multiple imputation by chained equations was used to impute missing data. Patients were divided into three groups based on their surgical treatment and were adjusted by 1:1:1 propensity score matching (PSM). Survival outcomes per group were estimated for recurrence-free survival (RFS), bladder recurrence-free survival (BRFS), cancer-specific survival (CSS), and overall survival (OS). Perioperative outcomes: Intraoperative blood loss, hospital length of stay (LOS), and overall (OPC) and major postoperative complications (MPCs; defined as Clavien-Dindo > 3) were assessed between groups. **RESULTS:** Of the 2434 patients included, 756 remained after PSM with 252 in each group. The three groups had similar baseline clinicopathological characteristics. The median follow-up was 32 months. Kaplan-Meier and log-rank tests demonstrated similar RFS, CSS, and OS between groups. BRFS was found to be superior with ORNU. Using multivariable regression analyses, LRNU and RRNU were independently associated with worse BRFS (HR 1.66, 95% CI 1.22-2.28, $p = 0.001$ and HR 1.73, 95%CI 1.22-2.47, $p = 0.002$, respectively). LRNU and RRNU were associated with a significantly shorter LOS (beta -1.1, 95% CI -2.2-0.02, $p = 0.047$ and beta -6.1, 95% CI -7.2-5.0, $p < 0.001$, respectively) and fewer MPCs (OR 0.5, 95% CI 0.31-0.79, $p = 0.003$ and OR 0.27, 95% CI 0.16-0.46, $p < 0.001$, respectively). **CONCLUSIONS:** In this large international cohort, we demonstrated similar RFS, CSS, and OS among ORNU, LRNU, and RRNU. However, LRNU and RRNU were associated with significantly worse BRFS, but a shorter LOS and fewer MPCs.

Urology

Monga J, Valeriote F, Hwang C, Gadgeel S, and Ghosh J. Daclatasvir, an Antiviral Drug, Downregulates Tribbles 2 Pseudokinase and Resensitizes Enzalutamide-Resistant Prostate Cancer Cells. *Mol Cancer Ther* 2023; 22(3):381-392. PMID: 36805730. [Request Article](#)

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FDA-approved enzalutamide is commonly prescribed to reduce the growth of advanced prostate cancer by blocking androgen receptor function. However, enzalutamide-resistant prostate cancer (ERPC) invariably develops and progresses to metastatic, lethal disease. Management of ERPC poses a special problem not only because available therapeutic regimens cannot effectively kill ERPC cells but also due to their propensity to invade large bones. Moreover, molecular mechanism(s) behind enzalutamide resistance is not properly understood, which is delaying development of newer agents. We found that the pseudokinase, Tribbles 2 (TRIB2), is overexpressed in ERPC cells and plays a critical role in their survival. Forced overexpression of TRIB2 enhances prostate cancer cell growth and confers resistance to physiologic doses of enzalutamide, suggesting that TRIB2 plays an important role in the development and progression of ERPC. Though TRIB2 has emerged as an excellent molecular target for ERPC, suitable inhibitors are not commercially available for effective targeting. By designing a luciferase-tagged TRIB2

fusion protein-based assay system, we screened a library of about 1,600 compounds and found that daclatasvir (DCV), an antiviral drug, effectively inhibits TRIB2-luciferase. We also found that DCV degrades TRIB2 proteins by direct binding and resensitizes ERPC cells to enzalutamide treatment. Moreover, DCV at lower, sublethal doses synergizes with enzalutamide to decrease the viability and induce apoptosis in prostate cancer cells. Because DCV is already approved by the FDA and well tolerated in humans, based on our findings, it appears that DCV is a promising new agent for development of an effective therapy for advanced, enzalutamide-resistant, lethal prostate cancer.

Urology

Ray CH, Davaro F, Hamilton ZA, and **Raza J**. Perioperative outcomes of open versus robot-assisted radical cystectomy in octogenarians: a population based analysis. *J Robot Surg* 2023; Epub ahead of print. PMID: 36933124. [Full Text](#)

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Octogenarians undergoing cystectomy experience higher morbidity and mortality compared to younger patients. Though the non-inferiority of robot-assisted radical cystectomy (RARC) compared to open radical cystectomy (ORC) has been established in a generalized population, the benefits of the robotic approach have not been well studied in an aged population. The National Cancer Database (NCDB) was queried for all patients who underwent cystectomy for bladder cancer from 2010 to 2016. Of these, 2527 were performed in patients age 80 or older; 1988 and 539 underwent ORC and RARC, respectively. On Cox regression analysis, RARC was associated with significantly reduced odds for both 30- and 90-day mortality (HR 0.404, $p = 0.004$; HR 0.694, $p = 0.031$, respectively), though the association with overall mortality was not significant (HR 0.877, $p = 0.061$). The robotic group had a significantly shorter length of stay (LOS) compared to open surgery (10.3 days ORC vs. 9.3 days RARC, $p = 0.028$). The proportion of cases performed robotically increased over the study period from 12.2% in 2010 to 28.4% in 2016 ($p = 0.009$, $R(2) = 0.774$). The study is limited by a retrospective design and a selection bias, which was not completely controlled for in the analysis. In conclusion, RARC provides improved perioperative outcomes in aged patients compared to ORC and a trend toward greater utilization of this technique was observed.

Urology

Shahinyan GK, Hu MY, Jiang T, Osadchiy V, Sigalos JT, Mills JN, **Kachroo N**, and Eleswarapu SV. Cannabis and male sexual health: contemporary qualitative review and insight into perspectives of young men on the internet. *Sex Med Rev* 2023; Epub ahead of print. PMID: 36763944. [Full Text](#)

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INTRODUCTION: Cannabis use is increasing across the United States, yet its short- and long-term effects on sexual function remain controversial. Currently, there is a paucity of studies exploring the relationship between cannabis and men's health. **OBJECTIVES:** To summarize the available literature on cannabis and men's health and provide insight into lay perceptions of this topic. **METHODS:** We performed a qualitative PubMed review of the existing literature on cannabis and men's health according to the PRISMA guidelines. Separately, we analyzed relevant themes in online men's health forums. We utilized a Google cloud-based platform (BigQuery) to extract relevant posts from 5 men's health Reddit forums from August 2018 to August 2019. We conducted a qualitative thematic analysis of the posts and quantitatively analyzed them using natural language processing and a meaning extraction method with principal component analysis. **RESULTS:** Our literature review revealed a mix of animal and human studies demonstrating the negative effects of cannabis on semen parameters and varying effects on erectile function and hormone levels. In our analysis of 372 686 Reddit posts, 1190 (0.3%) included relevant discussion on cannabis and men's health. An overall 272 posts were manually analyzed,

showing that online discussions revolve around seeking answers and sharing the effects of cannabis on various aspects of sexual health and quality of life, often with conflicting experiences. Quantitative analysis revealed 1 thematic cluster related to cannabis, insecurity, and mental/physical health.

CONCLUSIONS: There is a limited number of quality human studies investigating the effects of cannabis on men's health. Men online are uncertain about how cannabis affects their sexual health and seek more information. As the prevalence of cannabis use increases, so does the need for research in this area.

Conference Abstracts

Anesthesiology

Ali H, Ahmed M, Sarwar A, **Mitchell J**, Matyal R, Baribeau V, Wong V, Palmer M, MacLellan C, and Weinstein J. Abstract No. 593 Hand Motion Analysis of Different Segments of a Procedure: Is One Segment Enough? *J Vasc Interv Radiol* 2023; 34(3):S170-S171. [Full Text](#)

Purpose: While hand motion analysis can be used to distinguish between experts and novices performing central venous access, it is unknown whether certain portions of a procedure are more critical than others for distinguishing between operators of differing proficiency levels not. Materials and Methods: Trainees (n = 30) and attendings (experts; n = 10) performed ultrasound-guided central venous access on a manikin as their motion was tracked. The setup and steps were standardized across all trials. Metrics including path length, rotational sum, translational movements, rotational movements, and time were calculated for each trial. Path length-time graphs from each trial were used to divide the procedure into three discrete segments. The first segment (access segment) involved visualizing the jugular vein on ultrasound and needle placement; the second segment (wire segment) involved passing a wire through the needle; the third segment (dilation segment) consisted of confirming the intravascular wire position in transverse and longitudinal planes and threading a dilator on the wire. The transition points were selected based on their reliability and correlation with the video. Comparisons between trainees (115 trials) and experts (41 trials) were made for the full trial and each segment using Mann-Whitney U tests and corrected with the Benjamini-Hochberg method. Logistic regression and ROC analysis were performed to compare the performance of each model in differentiating between experts and trainees. Results: Trainees and experts differed significantly for all 5 metrics for the full trial and wire segment (P < 0.001). The access and dilation segments were significantly different for all metrics except path length. Regression models showed the best fit model to be using the access segment (R² = 0.66, AUC = 0.97, P < 0.001), followed by full trial (McFadden R² = 0.54, AUC = 0.95, P < 0.001), wire segment (McFadden R² = 0.30, AUC = 0.88, P < 0.001) and finally dilation segment (McFadden R² = 0.18, AUC = 0.80, P < 0.001). Conclusion: The access segment of simulated central venous access can differentiate between experts and trainees with great accuracy. This segment should be an area of focus when evaluating technical proficiency. [Formula presented]

Behavioral Health Services/Psychiatry/Neuropsychology

Patel S, Yeh HH, Eke-Usim A, **Beebani G, Ahmedani B**, Rossom R, and **Akinyemi E**. IMPACT AND IMPLICATIONS OF RAPID TRANSITION TO VIRTUAL MENTAL HEALTH CARE DURING COVID-19 IN OLDER ADULTS. *Am J Geriatr Psychiatry* 2023; 31(3):S75-S76. [Full Text](#)

Cardiology/Cardiovascular Research

Almajed MR, Stephan J, Khan N, Gregerson S, and **Ananthasubramaniam K**. THE COMPLICATION-RIDDEN DESTINY OF THE SYSTEMIC RIGHT VENTRICLE IN L-TRANSPOSITION OF THE GREAT ARTERIES: MANAGEMENT DILEMMAS. *J Am Coll Cardiol* 2023; 81(8):3056. [Full Text](#)

Background Congenitally corrected levo-transposition of the great arteries (L-TGA) is a congenital heart disease in which the ventricles and great arteries are transposed from their typical anatomy. In L-TGA, the double discordance, atrioventricular and ventriculoarterial, create an acyanotic milieu which allows patients to survive their early decades, however, progressive systemic right ventricle (sRV) dysfunction creates complications later on. Case A 40-year-old male with L-TGA presented with symptoms of acute decompensated heart failure (ADHF). In childhood, he had surgical repair of a ventricular septal defect. In adulthood, he developed sRV dysfunction, systemic tricuspid valve (sTV) regurgitation, and left-bundle branch block for which he underwent cardiac resynchronization therapy. Transthoracic echocardiogram obtained during the admission showed a sRV ejection fraction of 40%, severe sTV regurgitation, and a newly identified sRV apical thrombus; the thrombus was confirmed by ultrasound-enhancing agents and transesophageal echocardiography. Decision-making Our patient was optimized with guideline-directed medical therapy and diuresis. The presence of a sRV thrombus posed a dilemma given the limited literature. Guidelines for intracardiac thrombus in patients with structurally typical hearts recommend anticoagulation with a vitamin K antagonist (VKA) followed by echocardiography to assess for resolution. However, multiple case reports and small-scale studies support the use of direct oral anticoagulants. It is

unknown whether these principles can be extrapolated to patients with congenital heart disease. Review of literature identified no cases of sRV thrombus making this one of the first reports. Our patient was anticoagulated with a VKA and later referred for evaluation by advanced heart failure and heart transplant services. Conclusion We describe one of the first reported cases of sRV thrombus in L-TGA presenting with ADHF. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring in these patients with dedicated cardiac imaging including advanced imaging modalities to identify complications.

Cardiology/Cardiovascular Research

Arno S, Fadel R, Kim HE, and Zaidan M. TYPE A AORTIC DISSECTION PRESENTING AS POSITIONAL CHEST PAIN AND DIFFUSE ST-ELEVATIONS ON ELECTROCARDIOGRAM - A DIAGNOSTIC DILEMMA. *J Am Coll Cardiol* 2023; 81(8):3845. [Full Text](#)

Background Stanford type A aortic dissection (AD) with concomitant diffuse STEMI is rare. Misdiagnosis may lead to a delay in care or inappropriate loading of antiplatelet therapy. Case A 47-year-old male presented to the Emergency Department with 2 days of mid-sternal chest pain. The pain was positional and relieved by sitting up. ECG demonstrated ST-elevation in inferior and anterior leads. The patient was ultimately diagnosed with an acute Type A aortic dissection; but given his chest pain and EKG findings, he was initially loaded with ticagrelor prior to his diagnosis. Decision-making An emergent echocardiogram was obtained to assess for ejection fraction and wall motion abnormalities, which demonstrated a Stanford type A aortic dissection with severe aortic regurgitation (Figure 1 A-D demonstrates the dissection flap with concurrent aortic insufficiency). Despite the insensitivity of transthoracic echo in detecting dissection, our study aborted catheterization of his coronaries, which would have potentially worsened outcomes, and triggered urgent surgical consultation. Scanning the proximal aorta using color Doppler resulted in prompt diagnosis with rapid intervention. Conclusion Point of care ultrasound to assess for dissection should be used routinely in the emergency department prior to loading with antiplatelet agents. [Formula presented]

Cardiology/Cardiovascular Research

Aujla S, and Patel V. WHEN AN INCIDENTAL HEART MURMUR BECOMES ISCHEMIC BOWEL: A CASE OF AORTIC VALVE PAPILLARY FIBROELASTOMA. *J Am Coll Cardiol* 2023; 81(8):3760. [Full Text](#)

Background Papillary fibroelastomas have a prevalence of up to 0.28%. These benign endocardial tumors can result in embolic phenomena, myocardial infarction, and sudden cardiac death. Case A 59 year-old woman with depression, hypertension, and hypothyroidism was found to have an incidental murmur at a routine office visit. TTE revealed a mobile mass on the aortic valve non-coronary cusp. She was scheduled for TEE but presented to the emergency department for abdominal pain. Troponin levels and EKG were normal. TEE showed an aortic valve mass 1 × 1 cm on the ventricular surface of the noncoronary cusp with mild aortic valve insufficiency. The mass was resected and biopsy revealed papillary fibroelastoma. She was found to have ischemic bowel and underwent subtotal colectomy. CT abdomen showed bilateral renal cortical infarcts. She was discharged home on apixaban 5 mg twice daily. Decision-making Our patient developed bowel and renal infarcts, likely embolic phenomena due to the fibroelastoma. There are no evidence-based guidelines regarding anticoagulation choice, duration, or initiation. She was placed on apixaban 5 mg twice daily due to her extensive thrombotic complications. There may be a possible benefit to starting anticoagulation at suspicion of diagnosis. Conclusion This case highlights the importance of prompt diagnosis of papillary fibroelastoma in order to prevent critical complications. We hope that our patient has reduced risk of thromboembolic events compromising quality of life. [Formula presented]

Cardiology/Cardiovascular Research

Chaudry HA, and Maskoun W. PATIENT WITH IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR AND HIGH DEFIBRILLATION THRESHOLDS WITH LIMITED OPTIONS! *J Am Coll Cardiol* 2023; 81(8):3264. [Full Text](#)

Background In patients with implantable cardioverter-defibrillators (ICD) and high defibrillation thresholds (DFT) who fail appropriate shocks, steps should be taken to lower DFT. However, options might be limited. Here, we present a case of a patient whose DFT was lowered using an intuitive method. Case A 64-year-old male with non-ischemic cardiomyopathy status post ICD implant presented to the ER with ICD shocks. Patient had prior history of ventricular tachycardia (VT) that resulted in multiple ICD shocks. He had VT storm on sotalol with acute renal failure. He had a VT ablation but continued to have VT afterwards while on amiodarone and mexiletine. The ICD was initially implanted in 2005 with a Medtronic 6949 Sprint Fidelis DF-1 lead in the right ventricular (RV) high septum. A Medtronic 6996 subcutaneous (SQ) coil was added in 2011 after some failed shocks. In 2013, a new Medtronic 6935 RV Quattro DF-1 ICD lead in the RV apex was added. A device upgrade to a dual chamber biventricular ICD was done due to being pacer-dependent and due to a secondary prevention indication for his ICD. His Fidelis lead was abandoned. In the ER, his device interrogation showed he failed his first shock at the maximum of 35 J. His following shock at the same output succeeded. Decision-making Options in this patient included adding a second coil (azygous or coronary sinus vein) or a second SQ, using a generator with a higher output, and/or reversing polarity. A venogram was done that showed extensive occlusion, likely to the azygous vein origin. A Medtronic Cobalt DTPB2D1 ICD 40 J generator was placed. We decided to use a Medtronic DF-1 6726 y-adapter to combine the RV coils of the Quattro and abandoned Fidelis leads. DFT testing was performed twice successfully at 15 J. Due to low RV impedance (24 Ω), we tested DFT twice more without the SQ coil successfully at 15 J (34 Ω). If that failed, we would have added a second SQ coil and merged it with the previous SQ coil. If that failed, extraction and reimplantation of coil in the coronary sinus vein would have been done. Conclusion Combining 2 RV coils from different locations is an effective way to significantly lower DFT, likely by lowering the shock impedance and increasing the shock tissue surface area.

Cardiology/Cardiovascular Research

Ellaoui R, Gelovani D, Ellaoui H, and Frisoli TM. UTILIZING TRANSCAVAL LEFT ATRIAL VENOUS ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION AS A BRIDGE TO MITRACLIP IN ACUTE MITRAL REGURGITATION. *J Am Coll Cardiol* 2023; 81(8):3701. [Full Text](#)

Background Transcaval Left-atrial venous arterial ECMO (TC-LAVA-ECMO), mechanical circulatory support (MCS) device, can be utilized as a bridge to provide biventricular cardiac support and improve oxygenation in cardiogenic shock. A single cannula is inserted using the inferior vena cava (IVC) access which necessitates transeptal puncture to decompress the right and left atria. Case 49-year-old renal transplant patient on tacrolimus and prednisone with a history of hypertension, type 2 DM, adrenal insufficiency, and significant recurrent infections presented with cardiogenic shock complicated by sepsis and hypoxic respiratory failure. The patient was admitted to the MICU, intubated, and placed on vasopressors, inotropes, wide-spectrum antibiotics, and antifungals. Radiographic imaging was consistent with edema and multifocal pneumonia. Echocardiography revealed new flail P2 characteristic of chordal apparatus rupture causing acute mitral regurgitation. Infectious endocarditis secondary to methicillin-susceptible staphylococcus epidermidis bacteremia was suspected to cause the chordal apparatus rupture. The patient's hospital course was complicated by renal failure, persistent ventricular tachycardia, escalating vasopressors and inotropes, and worsening hemodynamics. Decision-making The patient was evaluated for surgical mitral valve repair or replacement but deemed high risk for surgical intervention. A decision was made to utilize LAVA-ECMO as a bridge to MitraClip procedure to improve the patient's condition. Conclusion We report the utilization of TC-LAVA-ECMO as a bridge providing biventricular cardiac support and hemodynamic improvement. Unlike veno-arterial-ECMO, which increases the left ventricle (LV) afterload and myocardial oxygen demand without an additional left atrial cannula to unload the LV. TC-LAVA-ECMO eliminates the need for additional MCS devices with single arterial access with a significantly lower risk for bleeding and access site-related ischemia. This approach should be considered for complicated cases in centers with experienced ECMO programs.

Cardiology/Cardiovascular Research

Gregerson S, Rana F, Mahmood S, Almajed MR, Obri M, Stephan J, and Russell C. A CASE OF MARANTIC ENDOCARDITIS OF THE AORTIC VALVE IN A PATIENT WITH METASTATIC COLON CANCER. *J Am Coll Cardiol* 2023; 81(8):2999. [Full Text](#)

Background A 74-year-old male with history of coronary artery disease and complex peripheral arterial disease presented to our emergency department with shortness of breath and melena. Case The patient presented with a two-week history of shortness of breath and melena. Physical exam was significant for a 4/6 systolic ejection murmur at the left sternal border and cold lower extremities with diminished pedal pulses. Laboratory evaluation revealed hemoglobin of 5.8 g/dL and CEA level > 950 ng/mL. CT scan of the abdomen demonstrated findings concerning for metastatic disease to the liver and concern for peritoneal carcinomatosis. Subsequently, colonoscopy demonstrated a large ascending colonic mass with biopsy revealing invasive, poorly-differentiated carcinoma. A transesophageal echocardiogram (TEE) revealed large (1.35 cm x 0.29 cm) highly mobile sub-valvular and valvular-proper aortic vegetations. Serial blood cultures were negative, including HACEK organisms. Patient's course was complicated with development of scattered, punctate erythematous macules of the right foot consistent with emboli. Decision-making Given TEE findings and diagnosis of colonic adenocarcinoma, the initial leading diagnosis was aortic valve endocarditis. After infectious etiologies were excluded, the presumptive diagnosis of marantic endocarditis with thromboemboli was made. Antibiotics were stopped and the patient was started on anticoagulation. Conclusion Marantic endocarditis is a rare, noninfectious endocarditis. It predominantly affects the mitral and aortic valves, with deposition of platelet thrombi. Advanced malignancies of the lung and gastrointestinal tract comprise a majority of cases, yet most cases are diagnosed at autopsy. Antemortem cases most commonly present with thromboembolic phenomena. We describe an antemortem case of aortic valve marantic endocarditis in a patient with advanced colon adenocarcinoma who developed thromboembolic sequela.

Cardiology/Cardiovascular Research

Gregerson S, Zimmerman A, and Ananthasubramaniam K. DIFFERENT FACES OF TAKOTSUBO CARDIOMYOPATHY WITH TRIPLE OCCURRENCE IN A PATIENT. *J Am Coll Cardiol* 2023; 81(8):2649. [Full Text](#)

Background We present a case of triple occurrence of Takotsubo Cardiomyopathy (TCM) to highlight 2 key features: 1. Although uncommon, TCM can be recurrent 2. Multiple variations of TCM can present in the same patient. Case A 64 year old female presented with acute shortness of breath, cough, and orthopnea. Physical examination was notable for coarse crackles throughout both lungs, a holosystolic murmur at the apex, and bilateral lower extremity edema. Labs showed elevated high sensitivity troponin with a peak of 3000 with normal EKG. Transthoracic echocardiogram (TTE) demonstrated an ejection fraction of 51%, new severe mitral regurgitation (MR), hypokinesis of the basal and inferior wall as well as hyperkinesis of the apical wall. Diagnostic catheterization was negative. She was diagnosed with reverse Takotsubo Cardiomyopathy (rTCM) and managed with aggressive diuresis, afterload reduction, and goal directed medical therapy. One week after hospitalization, repeat TTE demonstrated resolution of all wall motion abnormalities, marked improvement of mitral regurgitation and normalization of left ventricle function. She was readmitted 2 months later with acute heart failure and diagnosed with recurrent TCM, her third occurrence of Takotsubo Cardiomyopathy. Decision-making TCM has similar presentation to acute coronary syndrome (ACS) but without angiographic evidence of obstructive coronary disease. As such, an essential feature of TCM or its variants is to first rule out ACS in these patients. Her history of TCM assisted in diagnosis as she carried a risk of recurrent TCM. Severe MR in this case was likely due to involvement of basal LV segments with resolution of MR on follow-up echo and no recurrence of MR with the third episode. Conclusion Recurrent TCM can happen in up to 4% of cases, with 20% being TCM variants. rTCM is an uncommon variant of TCM and presents similarly to acute coronary syndrome. Basal hypokinesis/akinesis with or without apical hyperkinesis will be seen on TTE. Treatment is largely supportive. We describe a dramatic case of triple recurrence of TCM which is extremely rare.

Cardiology/Cardiovascular Research

Ivers T, Albusoul L, and Tita C. ACUTE MYOCARDITIS: SECONDARY TO VIRAL INFECTION OR PHEOCHROMOCYTOMA? *J Am Coll Cardiol* 2023; 81(8):3829. [Full Text](#)

Background In a young healthy patient, acute cardiogenic shock with a dilated, thickened left ventricle is strongly suggestive of acute myocarditis. Case SM is a 33 year-old healthy man who presented with decompensated heart failure with severe hypervolemia. Notably, he was exposed to Hand-Foot-Mouth

disease (HFMD) two weeks prior. B-type natriuretic peptide was elevated at 3,417 pg/mL (normal range < 50 pg/mL), and troponin was elevated. Echocardiogram revealed dilated, severe systolic dysfunction with thickened left ventricular walls. He progressed to cardiogenic shock and multi-organ failure. Right heart catheterization revealed significantly reduced cardiac output and index of 2.36 and 1.2, respectively. His course was complicated by left ventricular thrombus and subacute embolic stroke, acute renal failure and liver failure. He was treated with afterload reduction, inotropes, and diuresis. His shock resolved, and he improved with medical therapy for cardiomyopathy. Decision-making The clinical course is consistent with acute myocarditis leading to cardiogenic shock with multi-organ failure. A broad differential was considered, including viral etiologies, autoimmune diseases, vasculitis, and toxin-mediated myocarditis. Viral labs including COVID-19 and influenza, as well as HIV, and hepatitis B and C viruses were negative. Coxsackie B2 antibody was positive at 1:80, which is consistent with past or current infection. Rheumatology evaluation was unrevealing, and vasculitis was deemed unlikely given normal inflammatory markers. Urine drug screen was unrevealing. However, adrenergic myocarditis remained on the differential given an adrenal nodule noted on imaging. Plasma free metanephrines were significantly elevated, consistent with pheochromocytoma. Conclusion This is a case of acute myocarditis with two likely etiologies. The patient's presentation correlates temporally with exposure to HFMD, suggesting viral myocarditis. However, he had gross hypervolemia and diuresed 50 pounds, which suggests a more indolent course. We propose that he had adrenergic myocarditis and undetected cardiomyopathy which was exacerbated by a second insult, the Coxsackie virus.

Cardiology/Cardiovascular Research

McCord JK, Cook B, Fadel R, Gandolfo C, Parikh S, Klausner H, Abdul-Nour K, Lewandowski A, Hudson MP, Perrotta GS, Zweig B, Gunaga S, Lanfear DE, Gindi R, Levy PD, Mills NL, Mahler SA, Kim HE, Danagoulian S, Nassereddine H, Todter E, Wittenberg S, Xu N, Keerie C, and Miller J. ACCELERATED PROTOCOL FOR MYOCARDIAL INFARCTION (MI) RULE-OUT WITHIN 1-HOUR OF PRESENTATION REDUCES HEALTHCARE RESOURCE UTILIZATION - SECONDARY ANALYSIS OF RACE-IT TRIAL. *J Am Coll Cardiol* 2023; 81(8):1125. [Full Text](#)

Background We compared healthcare resource utilization between a 3-hour standard care protocol for exclusion of myocardial infarction (MI) in the Emergency Department (ED) to a more rapid 0/1-hour high-sensitivity cardiac troponin (hs-cTnI) accelerated protocol. **Methods** This was a secondary analysis of the RACE-IT trial, a stepped-wedge randomized trial performed across 9 EDs in the Henry Ford Health System (Detroit, MI) from 7/2020-3/2021. A hs-cTnI assay was used (Beckman Coulter, 99th percentile 18 ng/L). In the accelerated protocol, MI was excluded if hs-cTnI was < 4 ng/L at presentation, or = 4 ng/L at presentation with a 1-hour value < 8 ng/L. In the standard care protocol, MI was excluded if hs-cTnI values were ≤18 ng/L at 0 and 3 hours. **Outcomes** included ED discharge, cardiac stress testing, cardiology consultation, and cardiac revascularization within 30 days. Generalized linear mixed models were used to compare the two arms. **Results** A total of 23,949 patients were analyzed, including 10,444 in the accelerated protocol and 13,505 in the standard care arm. Patients in the accelerated arm had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation (table). There was no difference in odds of coronary angiograms or revascularization procedures. **Conclusion** Patients that had MI excluded by the 0/1-hour protocol had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation when compared to the standard care 3-hour protocol [Formula presented]

Cardiology/Cardiovascular Research

Ungureanu C, Yamane M, Kayaert P, Knaapen P, Mashayekhi K, **Alaswad K**, Spratt J, Gasparini GL, Dens J, Carlier S, Sgueglia G, and Avran A. The safety and feasibility of live-stream proctoring for CTO procedures. *Acta Cardiol* 2023; 78:21-22. [Request Article](#)

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Background/Introduction: Compared with other percutaneous coronary interventions, chronic total occlusions carries a higher risk of complications, has lower success rates, and higher costs. Multiple types of educational programs have been offered (theoretical courses, live demonstrations) and for the moment on-site direct supervision with proctoring seems to be the most effective method to improve the outcome of CTO PCI procedures. In-person proctoring requires a considerable amount of arrangements

and planning, which limits the number of proctoring sessions, prolong the training period, and makes the training process less efficient. Purpose: To assess a new method of educational training, based on audio-video communication between a physician and all cath lab members with an expert that are in different locations. Methods: The study group consisted of nine patients who underwent PCI CTO using the Virtual Proctoring approach. The strategy of the CTO PCI procedure and all the decisions through the intervention were taken only by the proctor. Results: All the procedural steps were performed by the operator guided by the remote proctor. No single decision was taken by the operator alone as the proctor was able to notice perfectly all the angiographic details and all the other important parameters recorded by the AV system. No major complications occurred during the index hospitalization. Conclusions: A new method of virtual proctoring based on live video-communication is feasible and safe even in the case of highly complex CTO PCI procedures. This modern approach is easy to organize between physicians regardless of their location. It could potentially increase global interaction between colleagues and facilitate sharing of knowledge which are both major key aspects in the development of the CTO PCI field. This trial could serve as a basis for future large studies to fully analyze the potential role and benefits of virtual proctoring for complex CTO PCI procedures.

Center for Health Policy and Health Services Research

Patel S, Yeh HH, Eke-Usim A, Beebani G, Ahmedani B, Rossom R, and Akinyemi E. IMPACT AND IMPLICATIONS OF RAPID TRANSITION TO VIRTUAL MENTAL HEALTH CARE DURING COVID-19 IN OLDER ADULTS. *Am J Geriatr Psychiatry* 2023; 31(3):S75-S76. [Full Text](#)

Center for Health Policy and Health Services Research

Tam SMD, Su WTK, Cannella CE, Tang A, Latack KA, Elssis F, Ali H, Chang SS, Popoff AM, Neslund-Dudas C, Ahmedani B, and Johnson CC. Treatment fragmentation and timely treatment in racially and socioeconomically diverse patients with head and neck cancers. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):49-49. [Request Article](#)

Dermatology

Yamaguchi Y, Peeva E, Shore R, Han G, Cox LA, Banerjee A, Thaci D, **Hamzavi I**, Sloan A, Ganesan AK, and Ezzedine K. Ritlecitinib (PF-06651600), an oral JAK3/TEC inhibitor, stabilizes active lesions and promotes re-pigmentation of stable lesions in patients with active nonsegmental vitiligo: results from a phase 2b, randomized, placebocontrolled, dose-ranging study. *Br J Dermatol* 2023; 188:i1-i2. [Full Text](#)

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Patients with active nonsegmental vitiligo (NSV) may experience active lesions (confetti-like and trichrome lesions) or stable lesions (where lesions may remain unchanged for ~1 year or more). In a phase 2b trial, the oral JAK3/TEC inhibitor ritlecitinib demonstrated a significant improvement in the Facial-Vitiligo Area Scoring Index at Week 24 for patients with active NSV at 50 mg daily with or without a loading dose (100 or 200 mg daily for 4 weeks). To evaluate the efficacy of ritlecitinib on active vs. stable lesions in patients with active NSV who participated in the phase 2b trial (NCT0371529). Patients were randomized to daily ritlecitinib or placebo for 24 weeks, with or without a 4-week loading dose: 200/50, 100/50, 50, 30, 10 mg, or placebo. Mean percent change from baseline (%CFB) in depigmentation extent (100%, 90%, 75%, 50%, 25%, or 10%) within the lesion at baseline and Week 24 was evaluated centrally using photographs obtained from both active (clinical signs including confetti-like and trichrome lesions) and stable target lesions, other than on the face. The analysis included 317 patients who had active and stable lesions simultaneously among 364 treated patients. Within active lesions, ritlecitinib induced a statistically significant reduction in depigmentation extent [%CFB: 200/50 mg, +0.8 (P=0.0388); 100/50 mg, -1.7 (P=0.0035); 30 mg, -1.6 (P=0.0086)] compared with a progressive increase in depigmentation in the placebo group (%CFB: +5.6). No significant reduction was seen with ritlecitinib 50 mg (+28) or 10 mg (+14%). Within stable lesions, ritlecitinib showed a statistically significant reduction in depigmentation extent, reflecting re-pigmentation [%CFB: 200/50 mg, -7.2 (P=0.0045); 100/50 mg, -6.1 (P=0.0082); 50 mg, -5.9 (P=0.0134); 30 mg, -8.0 (P=0.0092)] compared with the placebo group, where %CFB in depigmentation increased (%CFB: +0.5). No significant reduction was seen with ritlecitinib 10 mg (-3.3%). The magnitude of the re-pigmentation was numerically greater in stable

lesions compared with that in active lesions. In patients with active NSV, ritlicitinib treatment for 24 weeks stabilized active lesions and promoted re-pigmentation of stable lesions.

Emergency Medicine

McCord JK, Cook B, Fadel R, Gandolfo C, Parikh S, Klausner H, Abdul-Nour K, Lewandowski A, Hudson MP, Perrotta GS, Zweig B, Gunaga S, Lanfear DE, Gindi R, Levy PD, Mills NL, Mahler SA, Kim HE, Danagoulian S, Nassereddine H, Todter E, Wittenberg S, Xu N, Keerie C, and Miller J. ACCELERATED PROTOCOL FOR MYOCARDIAL INFARCTION (MI) RULE-OUT WITHIN 1-HOUR OF PRESENTATION REDUCES HEALTHCARE RESOURCE UTILIZATION - SECONDARY ANALYSIS OF RACE-IT TRIAL. *J Am Coll Cardiol* 2023; 81(8):1125. [Full Text](#)

Background We compared healthcare resource utilization between a 3-hour standard care protocol for exclusion of myocardial infarction (MI) in the Emergency Department (ED) to a more rapid 0/1-hour high-sensitivity cardiac troponin (hs-cTnI) accelerated protocol. **Methods** This was a secondary analysis of the RACE-IT trial, a stepped-wedge randomized trial performed across 9 EDs in the Henry Ford Health System (Detroit, MI) from 7/2020-3/2021. A hs-cTnI assay was used (Beckman Coulter, 99th percentile 18 ng/L). In the accelerated protocol, MI was excluded if hs-cTnI was < 4 ng/L at presentation, or = 4 ng/L at presentation with a 1-hour value < 8 ng/L. In the standard care protocol, MI was excluded if hs-cTnI values were ≤18 ng/L at 0 and 3 hours. **Outcomes** included ED discharge, cardiac stress testing, cardiology consultation, and cardiac revascularization within 30 days. Generalized linear mixed models were used to compare the two arms. **Results** A total of 23,949 patients were analyzed, including 10,444 in the accelerated protocol and 13,505 in the standard care arm. Patients in the accelerated arm had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation (table). There was no difference in odds of coronary angiograms or revascularization procedures. **Conclusion** Patients that had MI excluded by the 0/1-hour protocol had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation when compared to the standard care 3-hour protocol [Formula presented]

Endocrinology and Metabolism

Aleppo G, Gal R, Raghinaru D, Kruger D, Beck R, Bergenstal R, Cushman T, Hood K, Johnson M, McArthur T, Bradshaw A, Olsen B, Oser S, Oser T, Kollman C, and Weinstock R. VIRTUAL DIABETES SPECIALTY CARE - INDIVIDUALIZED TELEMEDICINE AND TECHNOLOGY SUPPORT. *Diabetes Technol Ther* 2023; 25:A75-A76. [Request Article](#)

G. Aleppo, Northwestern University, Feinberg School of Medicine, Chicago, United States

Background and Aims: The feasibility and efficacy of establishing a comprehensive care virtual diabetes clinic model including initiation and support for continuous glucose monitor (CGM) use was examined. **Methods:** 234 adults ≥18 years old with type 1 diabetes (T1D; N= 160) or type 2 diabetes (T2D, N= 74) using basal-bolus insulin (73 pump, 161 multiple daily insulin injections) were assigned a certified diabetes care and education specialist to provide telehealth support including remote CGM training. Participants not using a Dexcom G6 CGM (N = 187) at enrollment were provided a Dexcom G6; current users (N = 47) continued use. Participants were followed for 6 months to assess CGM use, glycemic and quality of life outcomes. **Results:** Mean HbA1c reduction from baseline to 6 months was 0.6% (P < 0.001)(T1D) and 1.0% (P < 0.001)(T2D). Mean glucose decreased from 183mg/dL to 165mg/dL (T1D) and 199mg/dL to 166mg/dL (T2D). Over 6 months, mean% time in range 70-180 mg/dL increased from 50% at baseline to 61% (T1D) and 48% to 66% (T2D); median use of CGM was 96% (T1D) and 94% (T2D). Glycemic outcomes improvements were observed in both current CGM users and those initiating CGM. Surveys indicated substantial benefit of CGM with reduced diabetes distress, and increased glucose monitoring satisfaction. **Conclusions:** Virtual clinic support was successful in achieving sustained CGM use and improved glycemic and quality of life outcomes. This approach could substantially increase CGM adoption by people with diabetes using insulin and improve outcomes among current CGM users by eliminating barriers such as geography and access to specialty care.

Hematology-Oncology

Broderick A, Li J, Chu A, **Hwang C**, Barata PC, Cackowski FC, Labriola M, Ghose A, Bilen MA, Kilari D, Graham L, Tripathi A, Garje R, Koshkin VS, Pan E, Dorff TB, McKay RR, Schweizer MT, Alva AS, and Armstrong AJ. Clinical implications of Wnt signaling alterations in patients (pts) with advanced prostate cancer (aPC). *J Clin Oncol* 2023; 41(6):229. [Full Text](#)

A. Broderick

Background: Aberrant Wnt signaling has been implicated in prostate cancer tumorigenesis, progression, and metastasis in preclinical models. While studies have identified recurrent molecular alterations in the Wnt signaling components in about 20% of aPC pts, the clinical significance of these alterations has been incompletely characterized. Methods: PROMISE is a multi-institutional, retrospective, clinical-genomic database - inclusive of aPC pts who had tissue and/or blood-based genomic testing by commercially available CLIA-certified platforms. We evaluated outcomes in pts with alterations leading to the activation of the canonical Wnt pathway, specifically activating mutations in CTNNB1 or RSPO2 or inactivating mutations in APC, RNF43, or ZNRF3 (Wnt altered), compared to those lacking such alterations (Wnt wild type). Multiple endpoints were evaluated, including the frequency of metastatic disease to different sites and co-occurring alterations. Results: 1596 pts with aPC were included with a median age of 63 years at diagnosis. Wnt pathway alterations were identified in 12.4% (198/1596). Wnt altered pts had a statistically significant increase in liver and lung metastases compared with Wnt wild type pts at diagnosis (4.5% vs 2.1%, $p=0.0438$; 6.1% vs 2.9%, $p=0.0292$), at first metastatic disease (11.6% vs 5.4%, $p=0.0015$; 14.8% vs 6.6%, $p<0.0001$), and at diagnosis of CRPC (14.2% vs 7.9%, $p=0.01436$; 16.1% vs 6.8%, $p=0.0003$). Fewer Wnt altered pts had bone metastases at CRPC compared with wild type pts (67.7% vs 75.2%, $p=0.04948$) without significant difference of bone metastases at the time of diagnosis or at the time of first metastatic disease. The frequency of metastases to other sites was similar between the cohorts. More Wnt altered pts had ductal features on histology at diagnosis compared with Wnt wild type pts (4.0% vs 1.6%, $p=0.02415$) without difference in PSA, Gleason score, TNM stage, or presence of neuroendocrine or intraductal features. Co-occurring genomic alterations that were more common in Wnt altered pts included PTEN loss/ mutation (25.3% vs 18.3%, $p=0.0270$), RB1 loss/mutation (10.6% vs 5.8%, $p=0.0079$), AR mutations or gain (37.9% vs 24.0%, $p=0.0001$), and SPOP mutations (14.1% vs 3.9%, $p=0.0001$) as compared with Wnt wild type pts. Conclusions: Wnt pathway alterations were associated with ductal histology, an increase in visceral metastases at all time points evaluated, and an increase in co-occurring PTEN, RB1, AR, and SPOP alterations. The clinical heterogeneity of aPC and differences in co-occurring mutations between the cohorts make isolating the effect of alterations in a single pathway challenging. Analysis of overall survival outcomes is currently in process, and future multivariable analysis is planned to adjust for established clinical factors and co-occurring mutations to identify the independent contributions of Wnt alterations to clinical outcomes.

Hematology-Oncology

Riess JW, Johnson ML, **Gadgeel S**, Skoulidis F, Sumrow B, Kuriakose E, Albert K, Kittrell N, Akella L, Fiji G, and Paik P. PP01.10 A Randomized, Open-Label Phase 2 Study of the TORC 1/2 Inhibitor Sapanisertib in Relapsed/Refractory (R/R) NFE2L2 (NRF2)-Mutated and Wild-Type (WT) Squamous Non-Small Cell Lung Cancer (sqNSCLC). *J Thorac Oncol* 2023; 18(3):e14. [Request Article](#)

Background: Activation of the transcription factor NRF2 increases the expression of genes that regulate defense against reactive oxygen species and cellular stress, which is implicated in tumorigenesis of several cancer types. NRF2 activation in tumor cells has also been found to accelerate metabolic inactivation of certain antitumor agents and decrease intracellular drug concentrations, promoting drug resistance and tumor growth. Aberrant activation of NRF2 results from gain-of-function mutations in NFE2L2 (the gene that encodes NRF2) or loss-of-function mutations in KEAP1 (a negative regulator of NRF2) leading to upregulated signaling through the mTOR pathway. This event occurs early in NSCLC tumorigenesis and is associated with poor prognosis in patients with metastatic sqNSCLC. sqNSCLC cell lines harboring NFE2L2 or KEAP1 mutations have demonstrated selective sensitivity to the dual TORC1/2 inhibitor sapanisertib, compared to TORC1-only inhibitors (Paik et al. ASCO 2020). In a phase 2 trial, single agent sapanisertib was well tolerated and led to an overall response rate (ORR) of 25%, disease control rate (DCR) of >90%, and median progression-free survival (PFS) of 8.9 months in 12

patients with NFE2L2-mutated sqNSCLC (Paik et al. ASCO 2020). Preclinical data and encouraging early clinical activity formed the rationale for conducting this phase 2 study to evaluate the efficacy and further refine the dose of sapanisertib monotherapy in patients with R/R NFE2L2-mutant and wild-type (WT) sqNSCLC (NCT05275673). Methods: This multicenter, randomized, open-label study will enroll approximately 50 patients with histologically or cytologically documented stage IV sqNSCLC in 2 arms: NFE2L2-mutant cohort (Group A) or NFE2L2-WT cohort (Group B). Patients must have disease that progressed during or after prior systemic therapy for metastatic disease, including a platinum doublet and immune checkpoint inhibitor. Additional eligibility criteria include measurable disease per RECIST v1.1, and ECOG performance status 0-1. Study-eligible mutation in NFE2L2 or NFE2L2-WT status will be determined via next generation sequencing. Both Group A and Group B patients (NFE2L2-mutated) will be randomized to sapanisertib 3 mg once daily or 2 mg twice daily in 21-day cycles. The primary endpoints are investigator-assessed ORR per RECIST v1.1 and safety. Secondary endpoints are duration of response, PFS, and overall survival. Exploratory endpoints include PK/PD and biomarker analyses. Findings from this study will inform on the optimal dose/schedule and further confirm previously shown efficacy and safety of sapanisertib in patients with metastatic R/R NFE2L2-mutated sqNSCLC and evaluate its activity in NFE2L2-WT sqNSCLC.

Hematology-Oncology

Yap TA, Gainor J, McKean M, Bockorny B, Barve M, Sweis R, Vaishampayan UN, Tarhini A, Kilari D, Chand A, **Abdul-Karim R**, Park D, Babu S, Ju Y, Dewall S, Liu L, Kennedy AM, Marantz J, and Gan L. 10 Safety, pharmacokinetics, efficacy, and biomarker results of SRK-181 (a latent TGF β 1 inhibitor) from a phase I trial (DRAGON trial). *ESMO Open* 2023; 8(1). [Full Text](#)

Background: SRK-181 is an investigational, fully human, IgG4 monoclonal antibody that selectively binds to latent transforming growth factor-beta 1 (TGF β 1). TGF β 1 activation has been associated with primary resistance to PD-1/PD-L1 [PD-(L)1] blockade. Compared to broad TGF β inhibitors, SRK-181 was observed to have an improved safety profile (no cardiotoxicities) in 4-week GLP toxicology studies. Methods: NCT04291079 is a multicenter ongoing phase I study with a 3+3 dose escalation design to evaluate SRK-181 in patients (pts) with advanced solid tumors at 80-3000mg q3w and 2000mg q2w (Part A1), and SRK-181 + anti-PD-(L)1 in pts with no response to prior anti-PD-(L)1 therapy at 240-2400mg q3w (Part A2). In Part B, SRK-181 (1500mg q3w or 1000mg q2w) + anti-PD-(L)1 are expanded in anti-PD-(L)1-resistant pts with non-small cell lung cancer, urothelial carcinoma, melanoma, clear cell renal cell carcinoma (ccRCC), or other advanced solid tumors. Results: As of Dec 2, 2022, the study enrolled 19 pts in Part A1 and 15 in Part A2 with no DLTs observed. The median prior lines of therapies were 4 (range 1-10). In Part A1, the most common treatment-related AEs (TRAEs, >10%) of any grade were fatigue (16%, n=3), decreased appetite and nausea (each 11%, n=2). Best response of stable disease (SD) was observed in 8 pts. All 3 ovarian cancer pts were stable for 25 to 42 weeks. In Part A2, the TRAEs (>10%) of any grade were rash maculo-papular (33%, n=5), pruritus (27%, n=4), rash (20%, n=3), diarrhea and pemphigoid (each 13%, n=2). One confirmed RECIST 1.1 partial response (cPR) was observed at 800mg in a pt with anti-PD-1 resistant ccRCC who stayed on study for 30 weeks. Of 9 pts with best response of SD, 5 were stable >16 weeks. SRK-181 treatment resulted in increased levels of circulatory TGF β 1, indicating target engagement. Part B enrollment is ongoing (N=9 in ccRCC cohort); two cPR were observed in pts with anti-PD-1 resistant ccRCC. Conclusions: SRK-181 has been tolerated as monotherapy and in combination with anti-PD-(L)1. No DLTs were observed up to 3000mg q3w/2000mg q2w as monotherapy and up to 2400mg q3w as combination treatment. Early signs of efficacy were observed with 3 cPR in pts with anti-PD-1 resistant ccRCC. Clinical trial identification: NCT04291079. Legal entity responsible for the study: Scholar Rock, Inc. Funding: Scholar Rock, Inc.

Hospital Medicine

Bui T, Tenenbaum L, Choi A, **Gupta J**, and Prsic E. To Create or Not to Create: How to Establish a System-Wide Proportionate Palliative Sedation Guideline Through Comprehensive Interdisciplinary Collaboration (TH108A). *J Pain Symptom Manage* 2023; 65(3):e251. [Full Text](#)

Outcomes: 1. Assess the need to create a proportionate palliative sedation (PPS) guideline for one's clinical setting 2. Describe one health system's process of designing and establishing a PPS guideline across its multiple institutions Proportionate palliative sedation (PPS) for the terminally ill involves the use

of sedating medications to treat distressing, refractory symptoms as a “last resort” intervention for patients pursuing comfort-focused care. This intervention has moral, ethical, spiritual, regulatory, and operational implications. Studies and several palliative organizations advocate the need for institutional PPS guidelines; however, there is a lack of recommendations on the process for establishing them. We present a clinical case, which served as a catalyst for an interdisciplinary collaboration of designing and establishing a PPS guideline for a healthcare system. A 70-year-old male with metastatic lung cancer was admitted with uncontrolled, cancer-related pain. Palliative care was consulted and his regimen was escalated and optimized, but his pain persisted. He requested to be sedated, even to the point of unconsciousness if necessary, and the family agreed. An interdisciplinary consensus was reached to proceed with PPS while addressing significant distress among providers for various reasons—no institutional guideline, uncertainty of patient’s prognosis, providers’ inexperience, etc. The patient passed comfortably 5 days after initiation of PPS. This case highlighted the need to establish a system-wide guideline that is culturally sensitive, inclusive, and equitable for this vulnerable patient population. Key stakeholders were recruited from palliative care, interventional pain, ethics, psychiatry, pharmacy, nursing, social work, chaplaincy, and regulatory. Sensitive issues such as defining terminal illness, differentiating physical versus existential distress, and addressing different regulations among institutions created challenges. Reflective and active listening skills were utilized to address these concerns. Small workgroups were designated to reconcile multiple perspectives and draft a cohesive guideline. This process aligns with the Responsible, Accountable, Consulted, Informed (RACI) model, an organizational tool widely used in project management. We plan to share additional challenges and lessons learned during the subsequent implementation and re-evaluation phases.

Hypertension and Vascular Research

Romero CA, **Wang H, Ren Y**, and Wall SM. N-METHYL-D-ASPARTATE (NMDA) RECEPTORS INDUCE RENAL VASODILATION AND REGULATES BLOOD PRESSURE. *J Hypertens* 2023; 41:e379. [Full Text](#)

C.A. Romero, Renal Division, Department of Medicine, Emory University, United States

Introduction: N-methyl-D-aspartate receptors (NMDAr) are glutamate/glycine receptors expressed in the kidney. NMDAr induce renal vasodilation through an unknown mechanism. Connecting tubule-glomerular feedback (CNTGF) is a vasodilator feedback mechanism, initiated by ENaC in the connecting tubule producing afferent arteriole (AffA) vasodilatation and promoting sodium excretion. We hypothesized that NMDAr activation stimulate CNTGF and that the inhibition of NMDAr decrease CNTGF vasodilation inducing hypertension. Methods: We explore the presence of NMDAr receptors in mouse by transcriptome analysis of microdissected tubules segments, total kidney western blot and immunofluorescence. We used mpkCCD cells (mouse principal cells) to explore the interaction between NMDAr and ENaC in PC using trasnwell current analysis and split-open tubule using patch clamp method. To determine the effect of NMDAr on CNTGF, we measured CNTGF-mediated AffA dilation in the presence or absence of NMDAr agonists glutamate and glycine with and without NMDAr antagonist (MK801), using a double-microperfusion method in rabbits, and invivo by micropuncture technique in rats. To evaluate the effect of NMDAr on blood pressure (BP), we measure BP in NMDA 2C global knock out mice. BP was measure using tail cuff methods. To confirm the effect of NMDAr on BP we infused subcutaneously NMDAr inhibitor MK801 for 7 days in a gain of function β ENaC mutated allele mice on129/Sv background on normal salt diet. Results: NMDAr was found to be expressed in connecting tubule and co-localized with AQP2 and ENaC. In mpkCCD cells and open split tubules, NMDAr activation increase ENaC activity, while NMDAr inhibition decrease ENaC activity ($p < 00.1$). In-vitro, tubular microperfusion of NMDAr agonist increased AffA dilation ($p < 0.001$). NMDAr agonist-induced dilation was blunted with MK-801 (NMDAr blocker) and totally blocked with benzamil (CNTGF inhibitor). In vivo, NMDAr agonist increase CNTGF mediated vasodilation ($P < 0.01$). NMDAr 2C knock out mice showed high BP in comparison with wildtype (SBP 114.6 ± 7.3 vs 100.4 ± 2.2 mmHg, respectively, $p = 0.01$). In β ENaC mutated mice, the infusion of NMDAr inhibitor (Mk-801) induces hypertension (SBP 146 ± 8 mmHg) while the vehicle infused mice remained normotensives (110.7 ± 7.7 mmHg; $p < 0.01$). Conclusions: NMDAr in the connecting tubule increase renal vasodilation by activating CNTGF. The genetic ablation of NMDAr 2C or the pharmacological inhibition of NMDAr increase blood pressure. Future studies need to confirm the role of NMDAr in the pathogenesis of hypertension.

Internal Medicine

Almajed MR, Stephan J, Khan N, Gregerson S, and Ananthasubramaniam K. THE COMPLICATION-RIDDEN DESTINY OF THE SYSTEMIC RIGHT VENTRICLE IN L-TRANSPOSITION OF THE GREAT ARTERIES: MANAGEMENT DILEMMAS. *J Am Coll Cardiol* 2023; 81(8):3056. [Full Text](#)

Background Congenitally corrected levo-transposition of the great arteries (L-TGA) is a congenital heart disease in which the ventricles and great arteries are transposed from their typical anatomy. In L-TGA, the double discordance, atrioventricular and ventriculoarterial, create an acyanotic milieu which allows patients to survive their early decades, however, progressive systemic right ventricle (sRV) dysfunction creates complications later on. Case A 40-year-old male with L-TGA presented with symptoms of acute decompensated heart failure (ADHF). In childhood, he had surgical repair of a ventricular septal defect. In adulthood, he developed sRV dysfunction, systemic tricuspid valve (sTV) regurgitation, and left-bundle branch block for which he underwent cardiac resynchronization therapy. Transthoracic echocardiogram obtained during the admission showed a sRV ejection fraction of 40%, severe sTV regurgitation, and a newly identified sRV apical thrombus; the thrombus was confirmed by ultrasound-enhancing agents and transesophageal echocardiography. **Decision-making** Our patient was optimized with guideline-directed medical therapy and diuresis. The presence of a sRV thrombus posed a dilemma given the limited literature. Guidelines for intracardiac thrombus in patients with structurally typical hearts recommend anticoagulation with a vitamin K antagonist (VKA) followed by echocardiography to assess for resolution. However, multiple case reports and small-scale studies support the use of direct oral anticoagulants. It is unknown whether these principles can be extrapolated to patients with congenital heart disease. Review of literature identified no cases of sRV thrombus making this one of the first reports. Our patient was anticoagulated with a VKA and later referred for evaluation by advanced heart failure and heart transplant services. **Conclusion** We describe one of the first reported cases of sRV thrombus in L-TGA presenting with ADHF. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring in these patients with dedicated cardiac imaging including advanced imaging modalities to identify complications.

Internal Medicine

Aujla S, and Patel V. WHEN AN INCIDENTAL HEART MURMUR BECOMES ISCHEMIC BOWEL: A CASE OF AORTIC VALVE PAPILLARY FIBROELASTOMA. *J Am Coll Cardiol* 2023; 81(8):3760. [Full Text](#)

Background Papillary fibroelastomas have a prevalence of up to 0.28%. These benign endocardial tumors can result in embolic phenomena, myocardial infarction, and sudden cardiac death. Case A 59 year-old woman with depression, hypertension, and hypothyroidism was found to have an incidental murmur at a routine office visit. TTE revealed a mobile mass on the aortic valve non-coronary cusp. She was scheduled for TEE but presented to the emergency department for abdominal pain. Troponin levels and EKG were normal. TEE showed an aortic valve mass 1 × 1 cm on the ventricular surface of the noncoronary cusp with mild aortic valve insufficiency. The mass was resected and biopsy revealed papillary fibroelastoma. She was found to have ischemic bowel and underwent subtotal colectomy. CT abdomen showed bilateral renal cortical infarcts. She was discharged home on apixaban 5 mg twice daily. **Decision-making** Our patient developed bowel and renal infarcts, likely embolic phenomena due to the fibroelastoma. There are no evidence-based guidelines regarding anticoagulation choice, duration, or initiation. She was placed on apixaban 5 mg twice daily due to her extensive thrombotic complications. There may be a possible benefit to starting anticoagulation at suspicion of diagnosis. **Conclusion** This case highlights the importance of prompt diagnosis of papillary fibroelastoma in order to prevent critical complications. We hope that our patient has reduced risk of thromboembolic events compromising quality of life. [Formula presented]

Internal Medicine

Ellauzi R, Gelovani D, Ellauzi H, and Frisoli TM. UTILIZING TRANSCAVAL LEFT ATRIAL VENOUS ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION AS A BRIDGE TO MITRACLIP IN ACUTE MITRAL REGURGITATION. *J Am Coll Cardiol* 2023; 81(8):3701. [Full Text](#)

Background Transcaval Left-atrial venous arterial ECMO (TC-LAVA-ECMO), mechanical circulatory support (MCS) device, can be utilized as a bridge to provide biventricular cardiac support and improve oxygenation in cardiogenic shock. A single cannula is inserted using the inferior vena cava (IVC) access which necessitates transeptal puncture to decompress the right and left atria. Case 49-year-old renal transplant patient on tacrolimus and prednisone with a history of hypertension, type 2 DM, adrenal insufficiency, and significant recurrent infections presented with cardiogenic shock complicated by sepsis and hypoxic respiratory failure. The patient was admitted to the MICU, intubated, and placed on vasopressors, inotropes, wide-spectrum antibiotics, and antifungals. Radiographic imaging was consistent with edema and multifocal pneumonia. Echocardiography revealed new flail P2 characteristic of chordal apparatus rupture causing acute mitral regurgitation. Infectious endocarditis secondary to methicillin-susceptible staphylococcus epidermidis bacteremia was suspected to cause the chordal apparatus rupture. The patient's hospital course was complicated by renal failure, persistent ventricular tachycardia, escalating vasopressors and inotropes, and worsening hemodynamics. Decision-making The patient was evaluated for surgical mitral valve repair or replacement but deemed high risk for surgical intervention. A decision was made to utilize LAVA-ECMO as a bridge to MitraClip procedure to improve the patient's condition. Conclusion We report the utilization of TC-LAVA-ECMO as a bridge providing biventricular cardiac support and hemodynamic improvement. Unlike veno-arterial-ECMO, which increases the left ventricle (LV) afterload and myocardial oxygen demand without an additional left atrial cannula to unload the LV. TC-LAVA-ECMO eliminates the need for additional MCS devices with single arterial access with a significantly lower risk for bleeding and access site-related ischemia. This approach should be considered for complicated cases in centers with experienced ECMO programs.

Internal Medicine

Gregerson S, Rana F, Mahmood S, Almajed MR, Obri M, Stephan J, and Russell C. A CASE OF MARANTIC ENDOCARDITIS OF THE AORTIC VALVE IN A PATIENT WITH METASTATIC COLON CANCER. *J Am Coll Cardiol* 2023; 81(8):2999. [Full Text](#)

Background A 74-year-old male with history of coronary artery disease and complex peripheral arterial disease presented to our emergency department with shortness of breath and melena. Case The patient presented with a two-week history of shortness of breath and melena. Physical exam was significant for a 4/6 systolic ejection murmur at the left sternal border and cold lower extremities with diminished pedal pulses. Laboratory evaluation revealed hemoglobin of 5.8 g/dL and CEA level > 950 ng/mL. CT scan of the abdomen demonstrated findings concerning for metastatic disease to the liver and concern for peritoneal carcinomatosis. Subsequently, colonoscopy demonstrated a large ascending colonic mass with biopsy revealing invasive, poorly-differentiated carcinoma. A transesophageal echocardiogram (TEE) revealed large (1.35 cm x 0.29 cm) highly mobile sub-valvular and valvular-proper aortic vegetations. Serial blood cultures were negative, including HACEK organisms. Patient's course was complicated with development of scattered, punctate erythematous macules of the right foot consistent with emboli. Decision-making Given TEE findings and diagnosis of colonic adenocarcinoma, the initial leading diagnosis was aortic valve endocarditis. After infectious etiologies were excluded, the presumptive diagnosis of marantic endocarditis with thromboemboli was made. Antibiotics were stopped and the patient was started on anticoagulation. Conclusion Marantic endocarditis is a rare, noninfectious endocarditis. It predominantly affects the mitral and aortic valves, with deposition of platelet thrombi. Advanced malignancies of the lung and gastrointestinal tract comprise a majority of cases, yet most cases are diagnosed at autopsy. Antemortem cases most commonly present with thromboembolic phenomena. We describe an antemortem case of aortic valve marantic endocarditis in a patient with advanced colon adenocarcinoma who developed thromboembolic sequela.

Internal Medicine

Gregerson S, Zimmerman A, and Ananthasubramaniam K. DIFFERENT FACES OF TAKOTSUBO CARDIOMYOPATHY WITH TRIPLE OCCURRENCE IN A PATIENT. *J Am Coll Cardiol* 2023; 81(8):2649. [Full Text](#)

Background We present a case of triple occurrence of Takotsubo Cardiomyopathy (TCM) to highlight 2 key features: 1. Although uncommon, TCM can be recurrent 2. Multiple variations of TCM can present in the same patient. Case A 64 year old female presented with acute shortness of breath, cough, and

orthopnea. Physical examination was notable for coarse crackles throughout both lungs, a holosystolic murmur at the apex, and bilateral lower extremity edema. Labs showed elevated high sensitivity troponin with a peak of 3000 with normal EKG. Transthoracic echocardiogram (TTE) demonstrated an ejection fraction of 51%, new severe mitral regurgitation (MR), hypokinesis of the basal and inferior wall as well as hyperkinesis of the apical wall. Diagnostic catheterization was negative. She was diagnosed with reverse Takotsubo Cardiomyopathy (rTCM) and managed with aggressive diuresis, afterload reduction, and goal directed medical therapy. One week after hospitalization, repeat TTE demonstrated resolution of all wall motion abnormalities, marked improvement of mitral regurgitation and normalization of left ventricle function. She was readmitted 2 months later with acute heart failure and diagnosed with recurrent TCM, her third occurrence of Takotsubo Cardiomyopathy. Decision-making TCM has similar presentation to acute coronary syndrome (ACS) but without angiographic evidence of obstructive coronary disease. As such, an essential feature of TCM or its variants is to first rule out ACS in these patients. Her history of TCM assisted in diagnosis as she carried a risk of recurrent TCM. Severe MR in this case was likely due to involvement of basal LV segments with resolution of MR on follow-up echo and no recurrence of MR with the third episode. Conclusion Recurrent TCM can happen in up to 4% of cases, with 20% being TCM variants. rTCM is an uncommon variant of TCM and presents similarly to acute coronary syndrome. Basal hypokinesis/akinesis with or without apical hyperkinesis will be seen on TTE. Treatment is largely supportive. We describe a dramatic case of triple recurrence of TCM which is extremely rare.

Internal Medicine

Ivers T, Albusoul L, and Tita C. ACUTE MYOCARDITIS: SECONDARY TO VIRAL INFECTION OR PHEOCHROMOCYTOMA? *J Am Coll Cardiol* 2023; 81(8):3829. [Full Text](#)

Background In a young healthy patient, acute cardiogenic shock with a dilated, thickened left ventricle is strongly suggestive of acute myocarditis. Case SM is a 33 year-old healthy man who presented with decompensated heart failure with severe hypervolemia. Notably, he was exposed to Hand-Foot-Mouth disease (HFMD) two weeks prior. B-type natriuretic peptide was elevated at 3,417 pg/mL (normal range < 50 pg/mL), and troponin was elevated. Echocardiogram revealed dilated, severe systolic dysfunction with thickened left ventricular walls. He progressed to cardiogenic shock and multi-organ failure. Right heart catheterization revealed significantly reduced cardiac output and index of 2.36 and 1.2, respectively. His course was complicated by left ventricular thrombus and subacute embolic stroke, acute renal failure and liver failure. He was treated with afterload reduction, inotropes, and diuresis. His shock resolved, and he improved with medical therapy for cardiomyopathy. Decision-making The clinical course is consistent with acute myocarditis leading to cardiogenic shock with multi-organ failure. A broad differential was considered, including viral etiologies, autoimmune diseases, vasculitis, and toxin-mediated myocarditis. Viral labs including COVID-19 and influenza, as well as HIV, and hepatitis B and C viruses were negative. Coxsackie B2 antibody was positive at 1:80, which is consistent with past or current infection. Rheumatology evaluation was unrevealing, and vasculitis was deemed unlikely given normal inflammatory markers. Urine drug screen was unrevealing. However, adrenergic myocarditis remained on the differential given an adrenal nodule noted on imaging. Plasma free metanephrines were significantly elevated, consistent with pheochromocytoma. Conclusion This is a case of acute myocarditis with two likely etiologies. The patient's presentation correlates temporally with exposure to HFMD, suggesting viral myocarditis. However, he had gross hypervolemia and diuresed 50 pounds, which suggests a more indolent course. We propose that he had adrenergic myocarditis and undetected cardiomyopathy which was exacerbated by a second insult, the Coxsackie virus.

Obstetrics, Gynecology and Women's Health Services

Ayyash M, McNitt M, Miller ME, and Swain M. Racial & ethnic disparities in prenatal care & pregnancy outcomes - an ongoing challenge. *Am J Obstet Gynecol* 2023; 228(1):S694-S695. [Full Text](#)

Objective: The aim of this study is to compare adequacy of prenatal care among various races and ethnicities in the state of Michigan and associated pregnancy and birth outcomes. Study Design: A population-based retrospective cohort study was performed using the state of Michigan's birth registry data for the years 2019-2020. Inclusion was made for all women who delivered after 20 weeks of gestation. Pregnancy and birth outcomes were compared by race and ethnicity. Results: A total of 211,801 births took place in Michigan between 2019 and 2020. The cohort included 143,400 (67.7%) who

identified as non-hispanic White, 39,139 (18.5%) who identified as non-hispanic Black, 14,704 (6.9%) who identified as hispanic, and 14,557 (6.9%) who identified as others. Adequate prenatal care received, defined by the Kessner Index, was highest among non-hispanic White women at 71.9% (n=103,127), followed by hispanic women at 61.2% (n=9,006), followed by non-hispanic Black women at 56.1% (n=21,969), $p < 0.0001$. The incidence of preterm birth was highest among non-hispanic Black women at 16.7% (n=6,525), followed by non-hispanic White women and hispanic women at 10.0% (n=14,358) and 10.8% (n=1,582) respectively, $p < 0.0001$. The incidence of preeclampsia was also highest among non-hispanic Black women at 9.1% (n=3,550), followed by hispanic women and non-hispanic White women at 6.4% (n=948) and 1.3% (n=1,858) respectively, $p < 0.0001$. The incidence of maternal ICU admission was 39% higher among non-hispanic Black women compared to non-hispanic White women (0.17% vs 0.12%). The incidence of neonatal ICU admission was 62% higher among non-hispanic Black women compared to non-hispanic White women (11.4% vs 7.0%). Conclusion: Disparities in prenatal care, pregnancy complications, and birth outcomes remain prevalent to our current day where non-hispanic Black women are receiving the least adequate prenatal care and having the most significant adverse pregnancy outcomes. More efforts should focus on access to care for Black women, as a modifiable step towards improving health outcomes for this population.

Obstetrics, Gynecology and Women's Health Services

Cope Z, Warehime J, Feroz R, Francis S, Davis L, Valadon C, Siegel S, and Choi KB. Contemporary management of sacral neuromodulation lead fragments and ghost leads. *Am J Obstet Gynecol* 2023; 228(3):S928-S929. [Full Text](#)

Objective: With the advent of MRI compatible Sacral Neuromodulation (SNM) devices coming to market, previous concerns pertaining to patients with implanted devices having contraindications to that imaging modality are slowly being resolved. There remain however, a significant number of patients who presently have, in part or whole, implanted SNM devices. Currently, there is no standardized method of removing intact or fragmented retained SNM leads or "ghost leads"- a term used to describe retained plastic housing and contacts with all filament remnants removed. This video provides a summary of currently published, proposed methods for the removal of retained leads, fragments, and ghost leads while also discussing the method used at our high-volume institution. Description: A contemporary review of published SNM lead removal methods is demonstrated as well as the method used at our institution. Conclusion: There are very few published articles describing procedures to safely and efficiently remove various types of retained leads. We believe our technique provides certain advantages over the previously published methods. Removal of intact or fragmented leads or ghost leads may be necessary secondary to an encountered adverse event, the uncertainty of future device complications, or conditions that frequently require MRI patient evaluation. Using our technique, we have been able to remove even the most challenging leads and fragments in their entirety without adverse sequelae.

Obstetrics, Gynecology and Women's Health Services

Miller ME, **Bell M**, Holland P, Ibrahim V, **Jacobsen G**, and **Swain M**. The impact of race and glycemic control on triple negative breast cancer in type 2 diabetics. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):56-57. [Request Article](#)

Obstetrics, Gynecology and Women's Health Services

Thorsen M, **McNitt M**, **Miller ME**, and **Swain M**. A cross-sectional survey of prenatal care providers' knowledge, barriers, and confidence in prenatal genetic counseling. *Am J Obstet Gynecol* 2023; 228(1):S694-S694. [Full Text](#)

Otolaryngology – Head and Neck Surgery

Boakye EA, **Nair M**, **Williams A**, **Alleman E**, **Joseph C**, Abouelella D, Babatunde OA, and Osazuwa-Peters N. Disparities in HPV vaccine uptake and provider recommendation by provider facility type. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):105-105. [Request Article](#)

Otolaryngology – Head and Neck Surgery

Tam SMD, Su WTK, Cannella CE, Tang A, Latack KA, Elssis F, Ali H, Chang SS, Popoff AM, Neslund-Dudas C, Ahmedani B, and Johnson CC. Treatment fragmentation and timely treatment in racially and socioeconomically diverse patients with head and neck cancers. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):49-49. [Request Article](#)

Otolaryngology – Head and Neck Surgery

Vidovich A, Williams A, Tam SH, Miller MK, Olex M, Nassar S, Rodriguez A, and Boakye EA. Disparities in health literacy in patients with head and neck cancer: Considerations for understanding. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):269-270. [Request Article](#)

Pathology and Laboratory Medicine

McCord JK, Cook B, Fadel R, Gandolfo C, Parikh S, Klausner H, Abdul-Nour K, Lewandowski A, Hudson MP, Perrotta GS, Zweig B, Gunaga S, Lanfear DE, Gindi R, Levy PD, Mills NL, Mahler SA, Kim HE, Danagoulian S, Nassereddine H, Todter E, Wittenberg S, Xu N, Keerie C, and Miller J. ACCELERATED PROTOCOL FOR MYOCARDIAL INFARCTION (MI) RULE-OUT WITHIN 1-HOUR OF PRESENTATION REDUCES HEALTHCARE RESOURCE UTILIZATION - SECONDARY ANALYSIS OF RACE-IT TRIAL. *J Am Coll Cardiol* 2023; 81(8):1125. [Full Text](#)

Background We compared healthcare resource utilization between a 3-hour standard care protocol for exclusion of myocardial infarction (MI) in the Emergency Department (ED) to a more rapid 0/1-hour high-sensitivity cardiac troponin (hs-cTnI) accelerated protocol. **Methods** This was a secondary analysis of the RACE-IT trial, a stepped-wedge randomized trial performed across 9 EDs in the Henry Ford Health System (Detroit, MI) from 7/2020-3/2021. A hs-cTnI assay was used (Beckman Coulter, 99th percentile 18 ng/L). In the accelerated protocol, MI was excluded if hs-cTnI was < 4 ng/L at presentation, or = 4 ng/L at presentation with a 1-hour value < 8 ng/L. In the standard care protocol, MI was excluded if hs-cTnI values were ≤18 ng/L at 0 and 3 hours. **Outcomes** included ED discharge, cardiac stress testing, cardiology consultation, and cardiac revascularization within 30 days. Generalized linear mixed models were used to compare the two arms. **Results** A total of 23,949 patients were analyzed, including 10,444 in the accelerated protocol and 13,505 in the standard care arm. Patients in the accelerated arm had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation (table). There was no difference in odds of coronary angiograms or revascularization procedures. **Conclusion** Patients that had MI excluded by the 0/1-hour protocol had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation when compared to the standard care 3-hour protocol [Formula presented]

Public Health Sciences

Babatunde OA, Zahnd WE, Boakye EA, Jefferson MS, Osazuwa-Peters N, Halbert CH, and Adams SA. Statewide variability in predictors of survival among geographically and racially diverse breast cancer cohorts. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):274-275. [Request Article](#)

Public Health Sciences

Boakye EA, Nair M, Williams A, Alleman E, Joseph C, Abouelella D, Babatunde OA, and Osazuwa-Peters N. Disparities in HPV vaccine uptake and provider recommendation by provider facility type. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):105-105. [Request Article](#)

Public Health Sciences

McCord JK, Cook B, Fadel R, Gandolfo C, Parikh S, Klausner H, Abdul-Nour K, Lewandowski A, Hudson MP, Perrotta GS, Zweig B, Gunaga S, Lanfear DE, Gindi R, Levy PD, Mills NL, Mahler SA, Kim HE, Danagoulian S, Nassereddine H, Todter E, Wittenberg S, Xu N, Keerie C, and Miller J. ACCELERATED PROTOCOL FOR MYOCARDIAL INFARCTION (MI) RULE-OUT WITHIN 1-HOUR OF PRESENTATION REDUCES HEALTHCARE RESOURCE UTILIZATION - SECONDARY ANALYSIS OF RACE-IT TRIAL. *J Am Coll Cardiol* 2023; 81(8):1125. [Full Text](#)

Background We compared healthcare resource utilization between a 3-hour standard care protocol for exclusion of myocardial infarction (MI) in the Emergency Department (ED) to a more rapid 0/1-hour high-sensitivity cardiac troponin (hs-cTnI) accelerated protocol. **Methods** This was a secondary analysis of the

RACE-IT trial, a stepped-wedge randomized trial performed across 9 EDs in the Henry Ford Health System (Detroit, MI) from 7/2020-3/2021. A hs-cTnI assay was used (Beckman Coulter, 99th percentile 18 ng/L). In the accelerated protocol, MI was excluded if hs-cTnI was < 4 ng/L at presentation, or = 4 ng/L at presentation with a 1-hour value < 8 ng/L. In the standard care protocol, MI was excluded if hs-cTnI values were ≤18 ng/L at 0 and 3 hours. Outcomes included ED discharge, cardiac stress testing, cardiology consultation, and cardiac revascularization within 30 days. Generalized linear mixed models were used to compare the two arms. Results A total of 23,949 patients were analyzed, including 10,444 in the accelerated protocol and 13,505 in the standard care arm. Patients in the accelerated arm had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation (table). There was no difference in odds of coronary angiograms or revascularization procedures. Conclusion Patients that had MI excluded by the 0/1-hour protocol had higher odds of ED discharge, and lower odds of stress testing and cardiology consultation when compared to the standard care 3-hour protocol [Formula presented]

Public Health Sciences

Miller ME, Bell M, Holland P, Ibrahim V, Jacobsen G, and Swain M. The impact of race and glycemic control on triple negative breast cancer in type 2 diabetics. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):56-57. [Request Article](#)

Public Health Sciences

Neslund-Dudas C, Tang A, Zarins K, Alleman E, Holm A, Gupta V, and Simoff M. Smoking cessation and relapse among Black and White patients referred for lung cancer screening. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):92-93. [Request Article](#)

Public Health Sciences

Rakic I, Davis M, Corsi N, Stephens A, Arora S, Rakic N, Morrison C, Malchow T, Affas R, Sood A, Rogers C, and Abdollah F. Evaluating the role of lymphovascular invasion as an indicator for adverse outcomes for patients with upper tract urothelial carcinoma and its histological subtypes. *Eur Urol* 2023; 83:S1313. [Full Text](#)

Introduction & Objectives: Lymphovascular invasion (LVI) is recognized as an adverse prognostic factor in many cancers. However, its utility in upper tract urothelial carcinoma (UTUC) has not been well-defined. Our aim is to assess the prognostic ability of LVI in UTUC urothelial carcinoma (UC) and micropapillary urothelial carcinoma (MPUC) subtypes as a predictor of overall survival (OS) using a large North American cohort. **Materials & Methods:** Our cohort included 9750 cM0 UTUC patients who underwent a radical nephroureterectomy (RNU), between 2004 and 2015, within the National Cancer Database (NCDB). The main variable of interest was LVI status and its interaction with pathological nodal (pN) status. Kaplan-Meier curves were used to estimate the OS. Cox regression analysis tested the impact of LVI status on OS after accounting for covariates: age, sex, race, year of diagnosis, Charlson Comorbidity Index, income, treatment center type, insurance status, pathological tumor, and pN status. **Results:** Mean (SD) age was 70.90 10.9 years. Overall, 14.4% had LVI, and 6.77% had pN+ (pN1-3) disease. The rate of advanced stage (pT3 or higher), and pN+ disease was 78.8% and 18.1% in patients with LVI vs. 34.7% and 3.32% in patients without LVI. The histological subtypes were UC, pure squamous, sacromatoid/spindle cell carcinoma, and MPUC in respectively 49.8%, 0.608%, 0.708%, and 48.9% of patients. The mean (SD) follow-up was 42.9 35.3 months. In patients with UC at 5-years post-RNU, the OS rates were 60.2%, 29.9%, 28.9%, and 20.8% in patient with pN0 without LVI, pN0 with LVI, pN+ without LVI, and pN+ with LVI, respectively (p<0.001). In patients with MPUC at 5-years post-RNU, the OS rates were 65.3%, 40.2%, 54.7%, and 36.5% in patient with pN0 without LVI, pN0 with LVI, pN+ without LVI, and pN+ with LVI, respectively (p<0.001). On multivariable analysis, LVI was an independent predictor of less favorable OS outcomes, as those with LVI had a 1.82-fold higher risk of death (95% CI: 1.21-1.54, p<0.001), when compared to their counterpart without LVI. **Conclusions:** To the best of our knowledge, our report is the first to examine the impact of LVI on OS in a large North American nationwide cohort. Our results indicate that LVI is associated with less favorable survival outcomes in patient with UTUC who are treated surgically, and can be utilized for counseling after RNU and as a risk-stratification tool for future clinical trials.

Public Health Sciences

Shato T, Nwaozuru U, **Boakye EA**, Fu QJ, Iwelunmor J, and Kuhlmann AS. Uptake of cervical cancer screening services in urban Zimbabwe: Healthcare provider perspectives. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):99-100. [Request Article](#)

Public Health Sciences

Tam SMD, Su WTK, Cannella CE, Tang A, Latack KA, Elssis F, Ali H, Chang SS, Popoff AM, Neslund-Dudas C, Ahmedani B, and Johnson CC. Treatment fragmentation and timely treatment in racially and socioeconomically diverse patients with head and neck cancers. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):49-49. [Request Article](#)

Public Health Sciences

Vidovich A, Williams A, Tam SH, Miller MK, Olex M, Nassar S, Rodriguez A, and Boakye EA. Disparities in health literacy in patients with head and neck cancer: Considerations for understanding. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):269-270. [Request Article](#)

Public Health Sciences

White MC, Osazuwa-Peters OL, Abouelella DK, Barnes JM, **Boakye EA**, Cannon TY, Watts TL, and Osazuwa-Peters N. Trends and factors associated with receipt of human papillomavirus (HPV) vaccine in private, public and alternative settings. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):110-111. [Request Article](#)

Pulmonary and Critical Care Medicine

Neslund-Dudas C, Tang A, Zarins K, Alleman E, Holm A, Gupta V, and Simoff M. Smoking cessation and relapse among Black and White patients referred for lung cancer screening. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):92-93. [Request Article](#)

Sleep Medicine

Viola A, Thiesse L, Staner L, Fuchs G, **Roth T**, Schaffhausser JY, Saoud J, and Luthringer R. Variabilité interscoreurs entre 5 centres de sommeil comparé à une analyse cardio-actimétrique. *Medecine du Sommeil* 2023; 20(1):25. [Request Article](#)

A. Viola, PPRS, Colmar, France

Déclaration de liens d'intérêts: Les auteurs déclarent ne pas avoir de liens d'intérêts.

Sleep Medicine

Viola A, Thiesse L, Staner L, Fuchs G, **Roth T**, Schaffhausser JY, Saoud J, and Luthringer R. Effet de la Paroxetine sur le sommeil de patients dépressifs analysé avec Somno-Art et la polysomnographie. *Medecine du Sommeil* 2023; 20(1):47. [Request Article](#)

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Déclaration de liens d'intérêts: Les auteurs déclarent ne pas avoir de liens d'intérêts.

Surgery

Tam SMD, Su WTK, Cannella CE, Tang A, Latack KA, Elssis F, Ali H, Chang SS, Popoff AM, Neslund-Dudas C, Ahmedani B, and Johnson CC. Treatment fragmentation and timely treatment in racially and socioeconomically diverse patients with head and neck cancers. *Cancer Epidemiol Biomarkers Prev* 2023; 32(1):49-49. [Request Article](#).

Urology

Arora S, Wilder S, Davis M, Corsi N, Rakic I, Morrison C, Affas R, Sood A, Autorino R, Rogers C, and Abdollah F. Inpatient outcomes of radical Nephroureterectomy (NU) for Upper Tract Urothelial Cancer (UTUC), with trends in utilization and impact of robotic surgery – National Inpatient Sample (NIS) analysis. *Eur Urol* 2023; 83:S735-S736. [Full Text](#)

Introduction & Objectives: Our primary aim was to evaluate the inpatient morbidity, mortality, and cost of radical NU for UTUC. We also aimed to evaluate the trends in utilization of robotic surgery for this procedure, and to assess the difference in outcomes between robotic NU and open NU in terms of the above outcomes from within the NIS. **Materials & Methods:** We focused on 9581 records of adult patients with nonmetastatic UTUC undergoing radical NU from 2003-14, representing an estimated 47204 NUs performed in the US during this period. Data after 2014 was excluded due to International Classification of Diseases (ICD) coding change in 2015. ICD-9 code for robotics was introduced in 2008, so data before 2008 was not used when comparing surgical approaches. ICD-9 codes were used to define complications. Complex-survey procedures were used to study descriptive characteristics, and outcomes of patients undergoing NU. Cost of admission was inflation-adjusted to 2014 US dollars. **Results:** Overall, the median age of the patients was 72 (IQR 63-79) years. 22974 (49%) patients had a Charlson comorbidity index of 3 or more. 33693 (71%) patients had Medicare/Medicaid insurance. 14692 (31%) patients had complications, with 6814 (14%) having major complications. Significant trend towards utilization of robotic approach was seen during the study period. Overall, 4635 NUs were performed robotically: accounting for 33% of NUs in 2014. Table 1 shows the outcomes after stratification for approach. Robotic surgery was associated with significantly lower rate of any complications 962 (21%) vs 7675 (33%) for open; $p < 0.001$. This was also true for in hospital mortality (0.3% vs 1.2%; $p = 0.02$), and major complications (10% vs 19%; $p < 0.001$). **Conclusions:** Nephroureterectomy is associated with a high inpatient morbidity and mortality. There is increasing utilization of robotic approach in the US. Robotic surgery is associated with lower morbidity and in hospital mortality in these patients. **Table:** Descriptive statistics and outcomes of radical NU for upper tract urothelial carcinoma in 47204 records from the National Inpatient sample from 2008-2014, stratified by surgical approach. IQR: Interquartile range; NU: Nephroureterectomy. *ICD code for robotics was introduced in 2008. Therefore, for comparison between surgical approaches, years before 2008 were excluded. [Table presented]

Urology

Corsi N, Pandolfo S, Eilender BM, Bell SH, Wang L, Tuderti G, Ghoreifi A, Tozzi M, Taylor J, Dhanji S, Yong C, Checcucci E, Derweesh IH, Eun DD, Porpiglia F, Gonzalgo ML, Mehrazin R, Simone G, Ferro M, Margulis V, Sundaram CP, Djaladat H, Wu Z, Autorino R, and **Abdollah F**. Radical therapy for low-risk upper tract urothelial carcinoma (ROBUUST collaborative group). *Eur Urol* 2023; 83:S1324-S1325. [Full Text](#)

Introduction & Objectives: Inaccurate preoperative staging is common in upper tract urothelial carcinoma (UTUC). It is useful to stratify low- and high-risk disease to appropriately select patients more likely to benefit from renal-sparing surgery (RSS) versus radical nephroureterectomy (RNU). We provide an update of contemporary management of low-risk UTUC across high volume centers and hypothesize that many low-risk patients are still frequently treated with RNU. **Materials & Methods:** Patients were abstracted from an international cohort of 13 high-volume centers in the United States, Europe, and Asia (Robotic surgery for Upper Tract Urothelial Cancer Study, ROBUUST 2.0) undergoing treatment for UTUC from 2011-2022. We focused on patients with cN0M0 low-risk disease, as defined by: Unifocal disease, tumor size < 2 cm, negative for high-grade cytology, low-grade on ureteroscopic biopsy, and no invasive aspect on preoperative CT. Clinical, pathologic, and recurrence data was collected. Descriptive statistics and Kaplan-Meier survival curves with log rank testing were performed. A trend analysis was completed to evaluate low-risk treatment modality by year. **Results:** Of the 1596 cases, 148 patients met the criteria of low-risk disease. 90% were treated with RNU. Trend analysis showed a peak utilization of RNU for low-risk disease around years 2016-2018, with a decline in more recent years (Figure 1A). Mean age at surgery was 69.3 (11.9) years, with most patient's males (62%), normal weight (BMI: 24.7 ± 5.3), ECOG of 0 (66%), and no prior history of bladder cancer (91%). Mean follow-up time was 40 months, and 52% of patients were $\leq pT1$ on final pathology. 15.6% (21/134) experienced recurrence following treatment with RNU, with a mean time to recurrence 21.8 (23.2) months. 57% (8/14) experienced recurrence following RSS, with a mean time to recurrence of 14.6 (10.6) months (Figure 1B; log-rank $p = 0.62$). Most recurred within the bladder (90% in RNU, 50% in RSS) with the other recurrences occurring in the ipsilateral/contralateral upper urinary tract. No distant recurrences were recorded in RSS. **Conclusions:** A significant majority of low-risk patients still undergo RNU. While recurrence rate was higher in RSS (albeit non-statistically significant), none of these recurrences represented a distant

metastasis. Our results should be considered within the framework of a retrospective design but provide insight to treatment patterns at high volume centers. [Figure presented]

Urology

Corsi N, Stephens A, Malchow T, Piontkowski AJ, Corsi MP, Davis M, Arora S, Rakic I, Morrison C, Autorino R, Sood A, Rogers CG, and Abdollah F. Testing the external validity of the POUT III trial (adjuvant platinum-based chemotherapy in upper tract urothelial carcinoma) in a North American cohort. *Eur Urol* 2023; 83:S729-S730. [Full Text](#)

Introduction & Objectives: The management of patients with locally advanced upper tract urothelial carcinoma (UTUC) is challenging given the lack of level-one evidence, due to the disease' overall rarity. The European POUT III randomized controlled trial provided convincing evidence that adjuvant platinum based chemotherapy is the new standard of care following nephroureterectomy for locally-invasive or node-positive UTUC. We assessed this European randomized controlled trial's generalizability (external validity) to a North American cohort, using a nationwide database. **Materials & Methods:** To compare the trial patients with those seen in practice, we simulated the trial inclusion criteria using data from the National Cancer Database (NCDB). We identified adult patients with histologically confirmed, transitional cell carcinoma who underwent radical nephroureterectomy and met the trial inclusion criteria. The available demographic characteristics of the NCDB cohort were then compared with the POUT III trial cohort using Chi-squared test. **Results:** The NCDB cohort included 3,380 patients. The NCDB cohort had a significantly higher proportion of older patients (age \geq 80 23.5% vs 5%), and more males (68% vs. 56.2%) than the POUT cohort (Table 1, both $p < 0.001$). Additionally, the rate of advanced nodal disease was higher in the NCDB (N1 9.6%, N2 9.3%) than in the POUT (N1 6%, N2 3%) cohort ($p < 0.001$). Finally, a more extensive lymph node dissection was performed in NCDB vs POUT patients (node \geq 10 10.9% vs 3%, $p < 0.001$). Sensitivity analysis removing all subjects with a Charlson Comorbidity Index > 0 , as a proxy of health fitness, did not change the significance of any results. **Conclusions:** While the primary disease stage was similar between the NCDB and POUT, the rate of advanced disease was higher in NCDB (might be explained partially by the more extensive lymph node dissection performed). Moreover, NCDB patients were older and more frequently male, compared to the European trial patients. With these differences, the applicability of the POUT III findings in North American patients may warrant further investigation. [Table presented]

Urology

Davis M, Aftab O, Rogers A, Cadwell J, Hou L, Sheckley F, Abdollah F, Ahmed M, and Billah MS. Frequentist and Bayesian analysis of potential adverse events of the COVID-19 immunization. *Eur Urol* 2023; 83:S199-S200. [Full Text](#)

Introduction & Objectives: Although there is emerging literature on the urologic side effects of COVID-19, there are few, if any, large volume studies examining the urologic side effects of immunization against COVID-19. We sought to quantify and analyze urologic adverse events and symptoms after COVID-19 immunization. **Materials & Methods:** We queried the FDA Vaccine Adverse Event Reporting System (VAERS) for all reported symptoms following COVID-19 immunization for the period of December, 2020 through April 1st, 2022 as well as for all other immunizations since 1990. We identified the fifty most common adverse urologic events. Using proportional reporting ratio, reporting odds ratio, information component, and empirical Bayes geometric mean, we analyzed the reporting data in the VAERS database. In line with prior methodology, symptoms were then categorized into either haematuria, lower urinary tract symptoms, skin and/or soft tissue, urinary infection, or other. **Results:** A total of 2,629,200 non-COVID immunizations and 3,679,330 COVID-19 immunizations were identified from the queried periods with 770,975 and 865,585 adverse events reported, respectively. No potential adverse event produced a positive signal across all four measures of disproportionality. Out of all adverse events reported following COVID-19 immunization, the most common adverse event was urinary tract infection, which only accounted for 2,313 adverse events. The median age of the patients reporting urologic symptoms was 50 years old (interquartile range, 22 - 64) and 66% of the patients were female. [Figure presented] **Conclusions:** Although there have been anecdotal reports of adverse events associated with the COVID-19 vaccine and urologic symptoms reported after COVID-19 immunization continue to be extremely rare, our review of the VAERS database did not produce positive signals across all four

measures for any potential adverse event. Our findings suggest these adverse events are not related to the COVID-19 immunization but further evaluation and analysis of the COVID-19 immunization is ongoing.

Urology

Davis M, Stephens A, Morrison C, Majdalany S, Affas R, Arora S, Corsi N, Rakic I, Sood A, Rogers C, and Abdollah F. Baseline PSA levels in midlife & future development of lethal prostate cancer: A diverse North American cohort analysis. *Eur Urol* 2023; 83:S367. [Full Text](#)

Introduction & Objectives: The aim of our study was to examine prostate cancer (PCa) mortality based on midlife prostate-specific antigen (PSA) results in a racially diverse North American population. **Materials & Methods:** Our cohort included all men aged 40-59 years, who received their first PSA through our health system between the years 1995 and 2019. Next, patients were divided into 4 categories based on age as follows: 40 to 44, 45 to 49, 50 to 54, and 55 to 59 years. First PSA testing represented the main predictor of interest, and it was categorized based on median and 90th percentile for each age category. Fine-Gray regression was used to examine the impact of the value of PSA at first testing on the risk of developing lethal PCa (i.e. prostate cancer-specific mortality) after accounting for all confounders including race and comorbidity among others. Cancer-specific mortality and overall mortality were obtained by linking our database to the Michigan Vital Records registry. **Results:** A total of 129,067 men met inclusion criteria during the study period, of which 82,084 (64%) were White, 30,883 (24%) were Black, and 16,100 (12%) were other race. Median and 90th percentile PSA were 0.7 and 2.0 ng/ml, respectively. For men aged 40 to 44, 45 to 49, 50 to 54, and 55 to 59 years, median PSA was respectively 0.6, 0.7, 0.7, and 0.9 ng/ml, and the 90th percentile PSA was respectively 1.4, 1.6, 2.1, and 3.0 ng/ml. For the same age categories, the estimated rate (95% CI) of lethal PCa at 20 years was 0.023% (0.003 - 0.130%), 0.14% (0.071 - 0.25%), 0.33% (0.19 - 0.54%), 0.51% (0.34 - 0.75%) in men with PSA < median, and 0.79% (0.22 - 2.2%), 0.16% (1.04 - 2.45%), 2.5% (1.80 - 3.35%), 5.4% (4.28 - 6.76%) in men with PSA ≥90th percentile. Median (IQR) follow-up was 7.8 (3.2 - 15.0) years. On multivariable analysis, men with a PSA ≥90th percentile had a 11.57 HR (95% CI: 8.71 - 15.35) times higher risk of developing lethal PCa, when compared to those with PSA < median at first testing. This HR (95% CI) was 11.03 (2.01 - 60.57), 13.96 (6.93 - 28.13), 13.01 (7.62 - 22.23), and 10.47 (7.09 - 15.47) for men aged 40 to 44, 45 to 49, 50 to 54, and 55 to 59 years, respectively. **Conclusions:** Our findings suggest that midlife first-time PSA is an important predictor of the subsequent risk of developing lethal PCa. This information can be used to develop a PSA screening program, which is tailored to the patient's specific risk. To the best of our knowledge, our report is the first to examine the role of first-time PSA in a diverse North American cohort.

Urology

Fletcher SA, Pallauf M, Watts EK, Lombardo KA, Campbell JA, Mari A, Rouprét M, Boorjian SA, Djaladat H, Kikuchi E, Soria F, Rink M, Raman JD, **Abdollah F**, Ploussard G, Hoffman-Censits JH, McConkey DJ, Shariat SF, Pradere B, and Singla N. Oncologic outcomes in patients with residual invasive upper tract urothelial carcinoma following neoadjuvant chemotherapy. *J Clin Oncol* 2023; 41(6):475. [Full Text](#)

S.A. Fletcher

Background: Emerging evidence supports use of neoadjuvant chemotherapy (NAC) prior to radical nephroureterectomy (RNU) for appropriately selected patients with upper tract urothelial carcinoma (UTUC). However, oncologic outcomes have not been well characterized for patients with residual muscle-invasive disease after NAC. **Methods:** We used a multi-institutional cohort from 24 centers in the U.S., Europe, and Japan to retrospectively identify patients who underwent RNU for UTUC from 1985-2022 and had high-grade muscle-invasive disease. We stratified the cohort based on receipt of NAC (>ypT2 vs. >pT2). Exclusion criteria included receipt of adjuvant chemotherapy, concurrent cystectomy with RNU, and distant metastatic disease. Baseline characteristics were compared between groups. Kaplan-Meier survival analysis with log-rank test was used to compare differences in recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS). Multivariable Cox regression and Fine-Gray competing risk regression were used to determine predictors of these outcomes. **Results:** A total of 1,233 patients were included, 62 of whom received NAC prior to RNU. A platinum-based regimen was used in 90% of NAC recipients, and the median number of cycles administered was 4 (IQR:

3-5). Median follow-up time among all patients was 22 months (IQR: 8-47 mo.). NAC recipients were more likely to have pathologic node positivity (35% vs. 13%) and less likely to have positive tumor margins (8% vs. 28%). On Kaplan-Meier analysis, NAC recipients with residual >ypT2 disease had poorer outcomes than those with >pT2 disease (2-year RFS [NAC vs. no NAC]: 52% vs. 80%, $p<0.001$; 2-year OS: 60% vs. 78%, $p=0.003$; 2-year CSS: 61% vs. 86%, $p<0.001$). Multivariable analyses also showed a statistically significant association between residual muscle-invasive disease after NAC and poorer RFS, OS, and CSS (Table). Conclusions: NAC recipients with >ypT2 disease at RNU after exhibit poorer outcomes than stage-matched chemotherapy naïve counterparts. This may reflect effects of occult micrometastatic disease or chemoresistant primary tumors in non-responders. Our data highlight the need to improve prospective identification of candidates most likely to respond to NAC prior to RNU for UTUC in order to maximize its therapeutic benefit.

Urology

Frego N, Labban M, Stone BV, Koelker M, Beatrice E, Filipas DK, Lughezzani G, Buffi NM, **Abdollah F**, Osman NY, Solomon SR, Lipsitz SR, Kibel AS, Sammon JD, Trinh QD, and Cole AP. Effect of shared decision making on racial and ethnic disparity in prostate cancer screening: Results from a national behavioral survey. *Eur Urol* 2023; 83:S1279-S1280. [Full Text](#)

Introduction & Objectives: The 2018 United States Preventive Services Task Force recommendations endorsed shared decision making (SDM) for men aged 55-69 and encouraged consideration of patient race and ethnicity for prostate specific antigen (PSA) screening. We sought to assess whether SDM modified the effect of race and ethnicity on the likelihood of PSA screening. **Materials & Methods:** A cross-sectional analysis of men aged between 55 and 69 who responded to the PSA screening portions of the 2020 U.S.-based Behavioral Risk Factor Surveillance System (BRFSS) survey was performed. Men without a diagnosis of prostate cancer who self-reported a PSA test in the previous 12 months as part of a routine examination were considered screened. SDM was defined based upon whether the respondents had been informed by a physician about the benefits and harms of PSA screening. The main predictors were patient race and the interaction between race/ethnicity and SDM. Complex weighted sample multivariable logistic regression models were fitted to test the associations. **Results:** Out of a weighted sample of 26.8 million men eligible for PSA screening, 25.7% (6.9 million men) reported PSA screening. In adjusted analysis, SDM was a significant predictor of PSA screening (aOR:2.65, 95%CI:2.36-2.98, $p<0.001$). The interaction between race/ethnicity and SDM on the receipt of PSA screening was significant ($p=0.001$), meaning that the effect of race on the odds of PSA screening varied based on SDM. Among those who did not report SDM, both non-Hispanic Black (OR:0.77, 95%CI: 0.61–0.97, $p=0.026$) and Hispanic (OR:0.51, 95%CI: 0.39–0.68, $p<0.001$) men were significantly less likely to undergo PSA screening than non-Hispanic white men. On the contrary, among respondents who reported SDM, we found no race-based differences in the odds of PSA screening (Figure 1). [Figure presented] **Conclusions:** SDM was a significant predictor of PSA screening use and has a direct impact on reducing disparities in PSA screening among racial and ethnic groups.

Urology

Grossmann NC, Soria F, Juvet T, Potretzka A, Djaladat H, Kikuchi E, Mari A, Khene Z, Fujita K, Raman JD, Breda A, Sfakianos JP, Pfail JL, Laukhtina E, Rajwa P, Pallauf M, Cacciamani GE, Poyet C, Van Doeveren T, Boormans JL, Antonelli A, **Jamil M**, Ploussard G, Shariat SF, and Pradere B. Comparing oncological and perioperative outcomes of open versus laparoscopic versus robotic radical nephroureterectomy for the treatment of upper tract urothelial carcinoma: A multicenter, multinational, propensity score-matched analysis. *Eur Urol* 2023; 83:S737-S738. [Full Text](#)

Introduction & Objectives: The growth of minimally invasive methods for radical nephroureterectomy (RNU) has significantly changed the surgical treatment of upper tract urothelial carcinoma (UTUC). Laparoscopic and robotic RNU (LRNU and RRNU) increased during the last two decades while open RNU (ORNU) decreased. However, the current evidence regarding oncologic and perioperative outcomes between LRNU, RRNU and ORNU is weak. The aim of the study was to compare survival and perioperative outcomes between these approaches using a large, multicenter database. **Materials & Methods:** Multi-institutional, retrospective study including high-risk non-metastatic UTUC patients who underwent RNU between 1990 - 2020. Multiple imputation by chained equations was used to impute

missing data. Patients were divided into 3 groups based on their surgical treatment and were adjusted by 1:1:1 propensity score matching (PSM). The primary objective was to compare survival outcomes between surgical approaches with bladder recurrence-free survival (BRFS), recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) as primary endpoints. The secondary objective was to compare perioperative outcomes with intraoperative blood loss, length of inpatient stay (LOIS), overall and major postoperative complications (MPC) as secondary endpoints. Results: Of the 2434 patients included, 756 remained after PSM with 252 in each group. The three groups had similar clinico-pathological characteristics. The median follow-up was 32 months. Kaplan-Meier and log-rank tests showed similar RFS, CSS, OS between groups, while a better BRFS was found in favor of ORNU. In multivariable regression analyses, LRNU and RRNU were shown to be independent predictors of worse BRFS (HR 1.66, 95% CI 1.22- 2.28; $p = 0.001$ and HR 1.73, 95%CI 1.22- 2.47; $p = 0.002$ respectively). LRNU and RRNU were an independent predictor of shorter LOIS (beta -1.1, 95% CI -2.2- 0.02; $p = 0.047$ and beta -6.1, 95% CI -7.2- 5.0; $p < 0.001$, respectively) and less MPC (OR 0.5, 95% CI 0.31- 0.79; $p = 0.003$ and OR 0.27, 95% CI 0.16- 0.46; $p < 0.001$, respectively). Conclusions: We could confirm previous findings that ORNU, LRNU and RRNU have comparable RFS, CSS and OS. However, LRNU and RRNU were shown to have a significantly worse BRFS, highlighting the need to improve the bladder-cuff technique and the importance of postoperative intravesical chemotherapy. LRNU and RRNU were independent predictors of shorter LOIS and less MPC.

Urology

Majdalany SE, Leavitt D, and Kachroo N. Watt's in a name? - The people that focused laser lithotripsy. *Eur Urol* 2023; 83:S173. [Full Text](#)

Introduction & Objectives: Laser applications have been a significant development in urology, revolutionizing urinary stone disease treatment. We sought to examine the pivotal figures associated with laser lithotripsy and understand their contributions to the evolution of this technology. **Materials & Methods:** A comprehensive literature review was performed using PubMed database, Google Scholar, and texts regarding the discovery, initial trials and advancements in laser lithotripsy. **Results:** In 1957, Gordon Gould debuted an optical device, Light Amplification for the Stimulated Emission of Radiation (LASER). Theodore Maiman laid the cornerstone for laser lithotripsy in 1960, in a pivotal Nature publication utilizing a ruby crystal medium, the foundation for the first in vitro destruction of urinary calculi by William Mulvaney and Carl Beck, using 50-300J of energy. In 1962, FJ McClung and Robert Hellwarth used 'Q-switching' where an attenuator stores energy in a medium until a maximum level was reached. This insight allowed J.E. Geusic in 1964 to develop the first commercially available solid-state laser medium and laser – Neodymium-doped-YAG (Nd:YAG). In 1983, Graham Watson, applied a laser pulse technique demonstrating fragmentation capability of Nd:YAG. Q-switching did not generate adequate energy, so Watson used a flashlamp to pump laser energy in short pulses highlighting calculi fragmentation with minimal energy, whilst using small laser fiber sizes – leading to the creation of the ubiquitous 200 μ m laser fiber. The lack of power from Nd:YAG to fragment all stone types, propagated the development of holmium (Ho:YAG) laser by the Wellman Center for Photo Medicine at Massachusetts General Hospital – providing a range of laser settings for frequency (Hertz), energy (Joule), and ultimately power (Watt). Although not associated with the invention of laser lithotripsy, these eponyms are the fundamental units of laser. James Prescott Joule, an English physicist, determined the first law of thermodynamics; the conservation of energy. In 1852, he collaboratively created the 'Joule-Thompson effect', significantly contributing to the refrigeration industry. Heinrich Hertz, a German physicist, proved the existence of electromagnetic waves. James Watt, a Scottish engineer, invented horsepower in the 18th century and his modification of the steam engine transformed the Industrial revolution. **Conclusions:** Laser lithotripsy is constantly improving our management of urinary calculi, fundamentally built upon decades of innovative and collaborative minds. No matter the 'Watts' in our arsenal, we must remember the 'who' behind them.

Urology

Rakic I, Davis M, Corsi N, Stephens A, Arora S, Rakic N, Morrison C, Malchow T, Affas R, Sood A, Rogers C, and Abdollah F. Evaluating the role of lymphovascular invasion as an indicator for adverse outcomes for patients with upper tract urothelial carcinoma and its histological subtypes. *Eur Urol* 2023; 83:S1313. [Full Text](#)

Introduction & Objectives: Lymphovascular invasion (LVI) is recognized as an adverse prognostic factor in many cancers. However, its utility in upper tract urothelial carcinoma (UTUC) has not been well-defined. Our aim is to assess the prognostic ability of LVI in UTUC urothelial carcinoma (UC) and micropapillary urothelial carcinoma (MPUC) subtypes as a predictor of overall survival (OS) using a large North American cohort. **Materials & Methods:** Our cohort included 9750 cM0 UTUC patients who underwent a radical nephroureterectomy (RNU), between 2004 and 2015, within the National Cancer Database (NCDB). The main variable of interest was LVI status and its interaction with pathological nodal (pN) status. Kaplan-Meier curves were used to estimate the OS. Cox regression analysis tested the impact of LVI status on OS after accounting for covariates: age, sex, race, year of diagnosis, Charlson Comorbidity Index, income, treatment center type, insurance status, pathological tumor, and pN status. **Results:** Mean (SD) age was 70.90 10.9 years. Overall, 14.4% had LVI, and 6.77% had pN+ (pN1-3) disease. The rate of advanced stage (pT3 or higher), and pN+ disease was 78.8%% and 18.1% in patients with LVI vs. 34.7% and 3.32% in patients without LVI. The histological subtypes were UC, pure squamous, sacromatoid/spindle cell carcinoma, and MPUC in respectively 49.8%, 0.608%, 0.708%, and 48.9% of patients. The mean (SD) follow-up was 42.9 35.3 months. In patients with UC at 5-years post-RNU, the OS rates were 60.2%, 29.9%, 28.9%, and 20.8% in patient with pN0 without LVI, pN0 with LVI, pN+ without LVI, and pN+ with LVI, respectively ($p<0.001$). In patients with MPUC at 5-years post-RNU, the OS rates were 65.3%, 40.2%, 54.7%, and 36.5% in patient with pN0 without LVI, pN0 with LVI, pN+ without LVI, and pN+ with LVI, respectively ($p<0.001$). On multivariable analysis, LVI was an independent predictor of less favorable OS outcomes, as those with LVI had a 1.82-fold higher risk of death (95% CI: 1.21-1.54, $p<0.001$), when compared to their counterpart without LVI. **Conclusions:** To the best of our knowledge, our report is the first to examine the impact of LVI on OS in a large North American nationwide cohort. Our results indicate that LVI is associated with less favorable survival outcomes in patient with UTUC who are treated surgically, and can be utilized for counseling after RNU and as a risk-stratification tool for future clinical trials.

Urology

Rakic I, Davis M, Stephens A, Corsi N, Rakic N, Morrison C, Arora S, Sood A, Rogers C, Hassan O, and Abdollah F. The impact of histological subtypes on stage at presentation and overall survival of patients with upper tract urothelial carcinoma: A nationwide cohort analysis. *Eur Urol* 2023; 83:S1312.

[Full Text](#)

Introduction & Objectives: The impact of urinary upper tract cancer histology on patient prognosis and outcomes has been poorly elucidated in literature. This might stem from the rarity of certain histological subtypes. To address this void, we set to examine the impact of cancer histology on stage at presentation and overall survival (OS) of patient with urinary upper tract cancer who were treated surgically within a large North American nationwide cohort. **Materials & Methods:** Our cohort included 9750 cM0 UTUC patients who underwent a radical nephroureterectomy (RNU), between 2004 and 2015, within the National Cancer Database (NCDB). These patients had either pathologically proven urothelial carcinoma (UC)/papillary urothelial carcinoma, or one of the following variant histology: pure squamous, sarcomatoid/spindle cell carcinoma, or micropapillary urothelial carcinoma (MPUC). Kaplan-Meier curves and log-rank test were used to depict and compare survival curves among the different histological subtypes. Cox regression analysis tested the impact of histological subtypes on OS after accounting for: age, sex, race, year of diagnosis Charlson Comorbidity Index, income, treatment center type, insurance status, pathological tumor stage, nodal stage, and pathological LVI status. **Results:** Mean (SD) age was 70.90 10.9 years. The histological subtype was UC, pure squamous, sacromatoid/spindle cell carcinoma, and MPUC in respectively 49.8%, 0.61%, 0.71%, and 48.9% of patients. For these histological subtypes, the rate of pT3/4 disease was respectively 46.5%, 48.6%, 68.2%, and 31.0% ($p<0.001$), and the rate of pN1 or higher disease was 9.47%, 5.45%, 9.375%, and 3.98% ($p<0.001$), respectively. The mean (SD) follow-up was 42.9 35.3 months. The 5-year OS rate for these histological subtypes was respectively 42.5%, 28.1%, 26.7%, and 56.8% ($p<0.001$). On multivariate analysis, patients with pure squamous had a 1.94-fold higher risk of death (95% CI: 1.28-2.82, $p<0.001$), those with sarcomatoid/spindle cell carcinoma had a 1.89-fold higher risk of death (95% CI: 1.41-2.53, $P<0.001$), while those with MPUC were 27% less likely to die (HR 0.73; 95% CI: 0.67-0.79, $p<0.001$) than their counterparts with UC. **Conclusions:** To the best of our knowledge, our report is the first to examine the impact of urinary upper tract cancer

histological subtype on cancer control outcomes in a large North American cohort. Our results indicated that the sarcomatoid/spindle cell carcinoma have a higher tumor and nodal stage at presentations in comparison to the other subtype, and that this subtype along with pure squamous have the least favorable survival outcomes. On the other hand, MPUC seem to have most favorable survival outcomes.

Urology

Sharma G, Shah M, Ahluwalia P, Gautam G, Dasgupta P, Challacombe B, Bhandari M, Ahlawat R, Rawal S, Buffi N, Sivaraman A, Porter J, **Rogers C**, Mottire, Abaza R, Rha KH, Moon D, Yuvaraja TB, Parekh DJ, Capitanio U, Maes KK, Porpiglia F, and Turkeri L. Off-clamp versus on-clamp robot-assisted partial nephrectomy: A propensity-matched analysis. *Eur Urol* 2023; 83:S1470-S1471. [Full Text](#)

Introduction & Objectives: To compare perioperative and functional outcomes following off and on-clamp robot-assisted partial nephrectomy (RAPN). **Materials & Methods:** This study used prospective multinational collaborative Vattikuti Collective Quality Initiative (VCQI) database for RAPN. The primary objective of this study was comparison of perioperative and functional outcomes between patients who underwent off-clamp and on-clamp RAPN. Propensity scores were calculated for age, sex, BMI, renal nephrometry score (RNS) and preoperative estimated glomerular function rate (eGFR). **Results:** Of the 2,114 patients, 210 had undergone off-clamp RAPN and others on-clamp. Two groups were not comparable at baseline with different ages, tumors, and renal nephrometry scores before matching. Propensity matching was possible for 205 patients in a 1:1 ratio. The two groups were comparable for age, sex, BMI, tumor size, multifocality, tumor side, the face of tumor, RNS, polar location of the tumor, surgical access and preoperative hemoglobin, creatinine and eGFR post matching. There was no difference between two groups for intraoperative (4.8% vs. 5.3%, $p=0.823$) and postoperative complications (11.2% vs. 8.3%, $p=0.318$). Need for blood transfusion (2.92% vs. 0, $p=0.030$) and conversion to radical nephrectomy (10.2% vs. 1%, $p<0.0001$) were significantly higher in off-clamp group. At the last follow-up, there was no difference between the two groups for creatinine and eGFR. Mean fall in eGFR at last follow-up compared to baseline was comparable between the two groups (-16.03 ml/min vs. -17.3 ml/min, $p=0.985$). **Conclusions:** Off-clamp RAPN doesn't result in better renal functional preservation, albeit its associated with increased rates of conversion to radical nephrectomy and blood transfusion.

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Tuderti G, Autorino R, Mastroianni R, Misuraca L, Derweesh IH, Sundaram CP, Eun DD, Porpiglia F, Mehrazin R, Tozzi M, Checcucci E, Savio P, Margulis V, Wang L, Gonzalgo ML, Ferro M, **Abdollah F**, Djaladat H, Wu Z, and Simone G. Role of perioperative chemotherapy in upper tract urothelial carcinoma patients undergoing nephroureterectomy: Analysis from the ROBUUST 2.0 Registry. *Eur Urol* 2023; 83:S1326-S1327. [Full Text](#)

Introduction & Objectives: In this study we assessed the role of perioperative chemotherapy (CHT) in a large multicenter cohort of patients with Upper tract Urothelial carcinoma (UTUC) undergoing nephroureterectomy (NUT). **Materials & Methods:** A multicenter retrospective analysis utilizing the ROBUUST (for RObotic surgery for Upper Tract Urothelial Cancer Study) registry was performed. Baseline, preoperative and pathologic variables of three groups of patients receiving surgery only, Nad CHT or Adjuvant (Ad) CHT were compared. Categorical and continuous variables among the three subgroups were compared with Chi square and Kruskal-Wallis tests, respectively. Stage-specific Kaplan-Meier analysis was performed to compare cancer-specific survival (CSS) probabilities between patients treated with direct NUT, NadCHT prior to surgery, NUT followed by Ad-CHT. **Results:** Overall, 669 of them were included in the analysis. NadCHT patients displayed a significantly higher rate of cT stage ≥ 3 ($p<0.001$) and clinically positive nodes ($p=0.001$). AdCHT group showed a higher rate of low grade complications (54.8% AdCHT vs 34.6% NUT vs 16.9% NadCHT, $p<0.001$), while severe complications were comparable between groups (1.7% AdCHT vs 3.1% NUT vs 2.2% NadCHT, $p=0.82$). At Kaplan Meier, focused to cT stage ≥ 3 , patients receiving surgery only vs NadCHT vs AdCHT displayed comparable CSS probabilities (12-mo NUT 91%, Nad-NUT 80.6%, NUT+Ad-CHT 92.3%, $p=0.56$). When restricting survival analysis to clinically positive nodes (cN+) patients, patients who required Ad-CHT after surgery had a significantly lower survival (12-mo: 74.1%, $p=0.04$), while Nad-CHT and direct NUT rates were comparable (12-mo 90.3% and 89.8%, respectively). [Figure presented] **Conclusions:** According to

our retrospective analysis of a large multicenter dataset, Nad-CHT in specific subgroups of high-risk patients (such as locally advanced disease and clinically positive nodes) has negligible impact on incidence of severe perioperative complications; however it does not seem to provide an advantage in terms of CSS. Further data from randomised trials are expected.