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HENRY FORD HEALTH

Henry Ford Health Publication List – October 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 199 unique citations listed this month, including 107 articles, 90 conference abstracts, and 2 books or book chapters.

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

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Articles

Conference Abstracts

Books and Book Chapters

Articles

Administration

Budu-Aggrey A, Kilanowski A, Sobczyk MK, Shringarpure SS, Mitchell R, Reis K, Reigo A, Mägi R, Nelis M, Tanaka N, Brumpton BM, Thomas LF, Sole-Navais P, Flatley C, Espuela-Ortiz A, Herrera-Luis E, Lominchar JVT, Bork-Jensen J, Marenholz I, Arnau-Soler A, Jeong A, Fawcett KA, Baurecht H, Rodriguez E, Alves AC, Kumar A, Sleiman PM, Chang X, Medina-Gomez C, Hu C, Xu CJ, Qi C, El-Heis S, Titcombe P, Antoun E, Fadista J, Wang CA, Thiering E, **Wu B**, Kress S, Kothalawala DM, Kadalayil L, Duan J, Zhang H, Hadebe S, Hoffmann T, Jorgenson E, Choquet H, Risch N, Njølstad P, Andreassen OA, Johansson S, Almqvist C, Gong T, Ullemar V, Karlsson R, Magnusson PKE, Szwajda A, Burchard EG, Thyssen JP, Hansen T, Kårhus LL, Dantoft TM, Jeanrenaud A, Ghauri A, Arnold A, Homuth G, Lau S, Nöthen MM, Hübner N, Imboden M, Visconti A, Falchi M, Bataille V, Hysi P, Ballardini N, Boomsma DI, Hottenga JJ, Müller-Nurasyid M, Ahluwalia TS, Stokholm J, Chawes B, Schoos AM, Esplugues A, Bustamante M, Raby B, Arshad S, German C, Esko T, Milani LA, Metspalu A, Terao C, Abuabara K, Løset M, Hveem K, Jacobsson B, Pino-Yanes M, Strachan DP, Grarup N, Linneberg A, Lee YA, Probst-Hensch N, Weidinger S, Jarvelin MR, Melén E, Hakonarson H, Irvine AD, Jarvis D, Nijsten T, Duijts L, Vonk JM, Koppelmann GH, Godfrey KM, Barton SJ, Feenstra B, Pennell CE, Sly PD, Holt PG, **Williams LK**, Bisgaard H, Bønnelykke K, Curtin J, Simpson A, Murray C, Schikowski T, Bunyavanich S, Weiss ST, Holloway JW, Min JL, Brown SJ, Standl M, and Paternoster L. European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation. *Nat Commun* 2023; 14(1):6172. PMID: 37794016. Full Text

Atopic dermatitis (AD) is a common inflammatory skin condition and prior genome-wide association studies (GWAS) have identified 71 associated loci. In the current study we conducted the largest AD GWAS to date (discovery N = 1,086,394, replication N = 3,604,027), combining previously reported cohorts with additional available data. We identified 81 loci (29 novel) in the European-only analysis (which all replicated in a separate European analysis) and 10 additional loci in the multi-ancestry analysis (3 novel). Eight variants from the multi-ancestry analysis replicated in at least one of the populations tested (European, Latino or African), while two may be specific to individuals of Japanese ancestry. AD loci showed enrichment for DNAse I hypersensitivity and eQTL associations in blood. At each locus we prioritised candidate genes by integrating multi-omic data. The implicated genes are predominantly in immune pathways of relevance to atopic inflammation and some offer drug repurposing opportunities.

Administration

Steen K, VanDenBerg KR, Servoss J, Subramanian S, and **Grieb TA**. A Research Operations, Management, and Strategy Fellowship for Life Sciences PhD Graduates. *Acad Med* 2023; Epub ahead of print. PMID: 37920910. Full Text

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PROBLEM: With less than 25% of PhD-trained scientists in the United States securing a tenure-track faculty position following training, nonacademic careers have become common. As the academic research enterprise has increased, business-oriented careers have emerged. The Research Operations, Management, and Strategy (ROMS) Fellowship was developed to increase awareness of and prepare life

sciences PhD graduates for business-focused careers. APPROACH: The ROMS Fellowship was developed from March through December 2018 by the University of Michigan Medical School. Launched in 2019 and based on real-world experiences, the 2-year ROMS Fellowship combines immersion rotations and project work to develop an understanding of foundational infrastructure across the full spectrum of research. OUTCOMES: From 2019 to 2022, there were 4 ROMS Fellowship recruitment cycles, with a mean of 7 applicants per cycle and 2 fellows selected each year. Of the 8 fellows recruited, 5 (62.5%) joined directly from PhD training, whereas 3 (37.5%) had 2 to 6 years of postdoctoral training. Fellows have worked with 26 departments on 44 rotation projects and 30 impact projects and self-reported significant skill development in communicating with diverse stakeholders, strategic thinking, using new tools and resources, developing and scoping a project plan, and managing and leading a project. To date, 4 fellows have completed the program and were hired immediately into full-time positions at the University of Michigan Medical School. NEXT STEPS: Early feedback indicates that the program has been well received and effective. Previously, program refinement was directed by qualitative input from fellows and unit directors. However, for future cohorts, assessment tools will be implemented to capture qualitative and quantitative data to measure acquired skills and how program components contribute to professional development and career placement. A longitudinal follow-up will also be conducted with program alumni to track longer-term outcomes and career pathways.

Anesthesiology

Munroe ES, Heath ME, **Eteer M**, Gershengorn HB, Horowitz JK, Jones J, **Kaatz S**, Tamae Kakazu M, McLaughlin E, Flanders SA, and Prescott HC. Use and outcomes of peripheral vasopressors in early sepsis-induced hypotension across Michigan hospitals: a retrospective cohort study. *Chest* 2023; Epub ahead of print. PMID: 37898185. Full Text

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BACKGROUND: Vasopressors are traditionally administered via central access, but newer data suggest peripheral administration may be safe and avoid delays and complications associated with central line placement. RESEARCH QUESTION: How commonly are vasopressors initiated through peripheral IVs in routine practice? Is vasopressor initiation route associated with in-hospital mortality? STUDY DESIGN AND METHODS: This retrospective cohort study included adults hospitalized with sepsis (11/2020-9/2022) at 29 hospitals in the Michigan Hospital Medicine Safety Consortium, a Collaborative Quality Initiative sponsored by Blue Cross Blue Shield of Michigan. We assessed route of early vasopressor initiation, factors and outcomes associated with peripheral initiation, and timing of central line placement. RESULTS: 594 patients received vasopressors within 6 hours of hospital arrival and were included in this study. Peripheral vasopressor initiation was common (400/594, 67.3%). Patients with peripheral vs central initiation were similar; body mass index was the only patient factor independently associated with initiation route (aOR of peripheral initiation [per 1 kg/m(2) increase]: 0.98, 95%CI: 0.97-1.00, p=0.015). Hospital had a large impact on initiation route (median OR: 2.19, 95%CI: 1.31-3.07). Compared to central, peripheral initiation was faster (median 2.5 vs 2.7 hours from hospital arrival, p=0.002) but associated with less initial norepinephrine use (84.3% vs 96.8%, p=0.001). We found no independent association between initiation route and in-hospital mortality (32.3% vs 42.2%, aOR 0.66, 95%CI: 0.39-1.12). There was no documented tissue injury from peripheral vasopressors. Of patients with peripheral initiation,

135/400 (33.8%) never had a central line placed. INTERPRETATION: Peripheral vasopressor initiation was common across Michigan hospitals and had practical benefits, including expedited vasopressor administration and avoidance of central line placement in one-third of patients. However, there was wide practice variation not explained by patient case-mix and lower use of first-line norepinephrine with peripheral administration, suggesting additional standardization may be needed.

Anesthesiology
Woodworth GE, Goldstein ZT, Ambardekar AP, Arthur ME, Bailey CF, Booth GJ, Carney PA, Chen F, Duncan MJ, Fromer IR, Hallman MR, Hoang T, Isaak R, Klesius LL, Ladlie BL, Mitchell SA, Miller Juve AK, **Mitchell JD**, McGrath BJ, Shepler JA, Sims CR, 3rd, Spofford CM, Tanaka PP, and Maniker RB. Development and Pilot Testing of a Programmatic System for Competency Assessment in US Anesthesiology Residency Training. *Anesth Analg* 2023; Epub ahead of print. PMID: 37801598. Full Text

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BACKGROUND: In 2018, a set of entrustable professional activities (EPAs) and procedural skills assessments were developed for anesthesiology training, but they did not assess all the Accreditation Council for Graduate Medical Education (ACGME) milestones. The aims of this study were to (1) remap the 2018 EPA and procedural skills assessments to the revised ACGME Anesthesiology Milestones 2.0, (2) develop new assessments that combined with the original assessments to create a system of assessment that addresses all level 1 to 4 milestones, and (3) provide evidence for the validity of the assessments. METHODS: Using a modified Delphi process, a panel of anesthesiology education experts remapped the original assessments developed in 2018 to the Anesthesiology Milestones 2.0 and developed new assessments to create a system that assessed all level 1 through 4 milestones. Following a 24-month pilot at 7 institutions, the number of EPA and procedural skill assessments and mean scores were computed at the end of the academic year. Milestone achievement and subcompetency data for assessments from a single institution were compared to scores assigned by the institution's clinical competency committee (CCC). RESULTS: New assessment development, 2 months of testing and

feedback, and revisions resulted in 5 new EPAs, 11 nontechnical skills assessments (NTSAs), and 6 objective structured clinical examinations (OSCEs). Combined with the original 20 EPAs and procedural skills assessments, the new system of assessment addresses 99% of level 1 to 4 Anesthesiology Milestones 2.0. During the 24-month pilot, aggregate mean EPA and procedural skill scores significantly increased with year in training. System subcompetency scores correlated significantly with 15 of 23 (65.2%) corresponding CCC scores at a single institution, but 8 correlations (36.4%) were <30.0, illustrating poor correlation. CONCLUSIONS: A panel of experts developed a set of EPAs, procedural skill assessment, NTSAs, and OSCEs to form a programmatic system of assessment for anesthesiology residency training in the United States. The method used to develop and pilot test the assessments, the progression of assessment scores with time in training, and the correlation of assessment scores with CCC scoring of milestone achievement provide evidence for the validity of the assessments.

Behavioral Health Services/Psychiatry/Neuropsychology
Aderemi JO, and **Akinyemi E**. According to Which Criteria Should Telemental Health Be Deemed Elder Inclusive? *AMA J Ethics* 2023; 25(10):E740-744. PMID: 37801057. Request Article

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Telepsychiatry offers opportunities to provide better access to and higher quality of psychiatric care for some patients. This commentary on a case considers an analysis of clinical and ethical barriers to equitable telehealth for elders with mental health needs.

Behavioral Health Services/Psychiatry/Neuropsychology
Ahmedani BK, **Yeh HH**, Penfold RB, Simon GE, **Miller-Matero LR**, **Akinyemi E**, **Fallone M**, **Patel S**, **Beebani G**, Hooker SA, Owen-Smith A, Knowlton G, **Levin A**, Eke-Usim A, and Rossom RC. Psychotherapy Disruption Before and After the Transition to Virtual Mental Health Care Induced by the COVID-19 Pandemic. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 37817579. Full Text

Center for Health Policy and Health Services Research (Ahmedani, Yeh, Miller-Matero), Behavioral Health Services (Ahmedani, Miller-Matero, Akinyemi, Fallone, Patel, Beebani), and Public Health Sciences (Levin), Henry Ford Health, Detroit; Kaiser Permanente Washington Health Research Institute, Seattle (Penfold, Simon); HealthPartners Institute, Minneapolis (Hooker, Knowlton, Rossom); Center for Research and Evaluation, Kaiser Permanente Georgia, and Department of Health Policy and Behavioral Sciences, Georgia State University, Atlanta (Owen-Smith); Authority Health, Detroit (Eke-Usim).

OBJECTIVE: This study aimed to examine population-level disruption in psychotherapy before and after the rapid shift to virtual mental health care induced by the onset of the COVID-19 pandemic in the United States. METHODS: This retrospective study used electronic health record and insurance claims data from three U.S. health systems. The sample included 110,089 patients with mental health conditions who were members of the health systems' affiliated health plans and attended at least two psychotherapy visits from June 14, 2019, through December 15, 2020. Data were subdivided into two 9-month periods (before vs. after COVID-19 onset, defined in this study as March 14, 2020). Psychotherapy visits were measured via health records and categorized as in person or virtual. Disruption was defined as a gap of >45 days between visits. RESULTS: Visits in the preonset period were almost exclusively in person (97%), whereas over half of visits in the postonset period were virtual (52%). Approximately 35% of psychotherapy visits were followed by a disruption in the preonset period, compared with 18% in the postonset period. Disruption continued to be less common (adjusted OR=0.45) during the postonset period after adjustment for visit, mental health, and sociodemographic factors. The magnitude of the difference in disruption between periods was homogeneous across sociodemographic characteristics but heterogeneous across psychiatric diagnoses. CONCLUSIONS: This study found fewer population-level disruptions in psychotherapy receipt after rapid transition to virtual mental health care following COVID-19 onset. These data support the continued availability of virtual psychotherapy.

Behavioral Health Services/Psychiatry/Neuropsychology

Haley EN, **Loree AM**, **Maye M**, Coleman KJ, **Braciszewski JM**, **Snodgrass M**, Harry ML, **Carlin AM**, and **Miller-Matero LR**. Racial Differences in Psychiatric Symptoms, Maladaptive Eating, and Lifestyle Behaviors After Bariatric Surgery. *J Racial Ethn Health Disparities* 2023; Epub ahead of print. PMID: 37874488. Full Text

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There are several psychological and behavioral factors associated with poorer outcomes following bariatric surgery, yet it is unknown whether and how these factors may differ by race. In this cross-sectional study, individuals who underwent bariatric surgery from 2018 to 2021 and up to 4 years post-surgery were invited to complete an online survey. Psychiatric symptoms, maladaptive eating patterns, self-monitoring behaviors, and exercise frequency were examined. Participants (N = 733) were 87% women, 63% White, with a mean age of 44 years. Analyses of covariance demonstrated that White individuals endorsed greater anxiety symptoms (p =.01) and emotional eating due to depression (p = .01), whereas Black individuals endorsed greater depression severity (p = .02). Logistic regression analyses demonstrated that White individuals were more likely to experience loss of control eating (OR= 1.7, p = .002), grazing (OR= 2.53, p <.001), and regular self-weighing (OR= 1.41, p <.001) than Black individuals, and were less likely to skip meals (OR= .61, p = .04), or partake in nighttime eating (OR= .40, p <.001). There were no racial differences in binge eating, emotional eating due to anxiety or frustration, use of a food diary, or exercise. Thus, depressive symptoms, skipping meals, and nighttime eating may be important, modifiable intervention targets to optimize the benefits of bariatric surgery and promote equitable outcomes.

Behavioral Health Services/Psychiatry/Neuropsychology

Miller-Matero LR, **Haley EN**, **Loree AM**, **Braciszewski JM**, **Maye M**, **Sehgal M**, and **Carlin AM**. Post-surgical psychiatric symptoms, maladaptive eating patterns, and lifestyle behaviors associated with weight recurrence after bariatric surgery. *Surg Obes Relat Dis* 2023; Epub ahead of print. PMID: 37923621. Full Text

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BACKGROUND: A significant proportion of patients who undergo bariatric surgery experience weight recurrence; however, the most important areas to target to prevent weight recurrence remain unknown. OBJECTIVES: The purpose was to examine whether psychiatric symptoms, maladaptive eating behaviors, and lifestyle factors were associated with weight recurrence. SETTING: Single healthcare system. METHODS: Individuals who underwent bariatric surgery were invited to complete a web-based survey in which they reported their current weight and completed measures of psychiatric symptoms, maladaptive eating behaviors, and lifestyle behaviors. Participants were included if they were at least 2 years postsurgery. Weight recurrence was measured from the 1-year follow-up to the survey date. RESULTS: Participants (n = 169) were predominantly female and White or Black, with a mean age of 45 years. The rate of significant weight recurrence was 23.1%. Those who underwent sleeve gastrectomy

were more likely to experience weight recurrence (odds ratio [OR] = 12.99; P = .01). In bivariate analyses, anxiety and depressive symptoms, emotional eating, loss of control eating, binge eating, and night eating were associated with weight recurrence (P < .05). Those who did not eat mindfully, take 20 minutes to eat, or get adequate sleep were also more likely to have weight recurrence (P < .05). In a multivariate model, only a lack of mindful eating (OR = 4.84; P = .03) and inadequate sleep (OR = 7.30; P = .02) remained statistically significant predictors. CONCLUSION: Engaging in mindful eating and obtaining adequate sleep may protect against weight recurrence following bariatric surgery. Clinicians may want to screen and monitor these behaviors.

Behavioral Health Services/Psychiatry/Neuropsychology
Miller-Matero LR, **Ross K**, **Arellano C**, **Zelenak L**, **DePascale E**, **Gavrilova L**, **Braciszewski JM**, **Hecht LM**, **Haley EN**, **Brescacin C**, and **Carlin AM**. Cannabis use following bariatric surgery is associated with anxiety and maladaptive eating. *Surg Obes Relat Dis* 2023; Epub ahead of print. PMID: 37863791. Full Text

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BACKGROUND: There are limited data regarding the association of cannabis use with outcomes after bariatric surgery. As such, it is challenging to know how to counsel patients using cannabis. OBJECTIVES: The purpose of this study was to examine whether postsurgical cannabis use was associated with psychiatric symptoms and maladaptive eating among individuals up to 4 years after bariatric surgery. SETTING: Single health system. METHODS: All patients who underwent bariatric surgery over a 4-year period were invited to participate. Participants (N = 765) completed questionnaires online regarding postsurgical cannabis use, psychiatric symptoms, and maladaptive eating. RESULTS: Any cannabis use after bariatric surgery was associated with increased likelihood of having elevated symptoms of anxiety (odds ratio [OR] = 1.88, P = .003; 37.8% versus 24.4%), increased likelihood of grazing behaviors (OR = 1.77, P = .01; 71.2% versus 58.2%), and higher scores for eating in response to depression (P = .01; 12.13 versus 10.75). Weekly cannabis use was associated with loss of control eating (OR = 1.81, P = .04; 37.2% versus 24.7%), binge eating (OR = 2.16, P = .03; 20.0% versus 10.4%), and night eating behaviors (OR = 2.11, P = .01; 40.0% versus 24.0%). Cannabis use was not associated with depression (P > .05). CONCLUSIONS: Cannabis use after bariatric surgery was associated with anxiety symptoms and engaging in maladaptive eating behaviors. Frequent cannabis use (i.e., ≥1 per week) was associated with additional types of maladaptive eating. Clinicians involved in presurgical and postsurgical care may want to counsel patients currently using cannabis, especially those who are engaging in frequent use.

Behavioral Health Services/Psychiatry/Neuropsychology
Miller-Matero LR, **Yaldo M**, Chohan S, **Zabel C**, **Patel S**, Chrusciel T, Salas J, Wilson L, Sullivan MD, **Ahmedani BK**, Lustman PJ, and Scherrer JF. Factors Associated with Interest in Engaging in Psychological Interventions for Pain Management. *Clin J Pain* 2023; Epub ahead of print. PMID: 37819213. Full Text

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OBJECTIVE: Engagement in evidence-based psychological interventions for pain management is low. Identifying characteristics associated with interest in interventions can inform approaches to increase uptake and engagement. The purpose of this study was to examine factors associated with interest in psychological interventions among persons with non-cancer pain receiving prescription opioids. METHODSPARTICIPANTS: with non-cancer pain and a new 30-90 day opioid prescription were recruited from two health systems. Participants (N=845) completed measures regarding pain, opioid use, psychiatric symptoms, emotional support, and interest in psychological interventions for pain management. RESULTS: There were 245 (29.0%) participants who reported high interest in psychological interventions for pain management. In bivariate analyses, variables associated with interest included younger age, female gender, greater pain severity, greater pain interference, greater number of pain sites, lower emotional support, depression, anxiety, and post-traumatic stress disorder (P<0.05). In a multivariate model, greater pain severity (OR=1.17; CI: 1.04-1.32), depression (OR=2.10; CI: 1.39-3.16), PTSD (OR=1.85; CI: 1.19-2.95), and lower emotional support (OR=0.69; CI: 0.5-0.97) remained statistically significant. DISCUSSION: The rate of interest in psychological interventions for pain management was low, which may indicate that patients initiating opioid treatment of chronic pain have low interest in psychological interventions. Greater pain severity and psychiatric distress were related to interest, and patients with these characteristics may especially benefit from psychological interventions. Providers may want to refer to psychological interventions prior to or when opioids are initiated. Additional work is needed to determine if this would reduce long-term opioid use.

Behavioral Health Services/Psychiatry/Neuropsychology

Secrest S, **Miller-Matero LR**, Chrusciel T, Salas J, Sullivan MD, **Zabel C**, Lustman P, **Ahmedani B**, Carpenter RW, and Scherrer JF. Baseline Characteristics from a New Longitudinal Cohort of Patients with Non-cancer Pain and Chronic Opioid use in the United States. *J Pain* 2023; Epub ahead of print. PMID: 37907114. Request Article

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Retrospective cohort studies have consistently observed that long-term prescription opioid use is a risk factor for new major depressive episodes. However, prospective studies are needed to confirm these findings and to establish evidence for causation. The Prescription Opioids and Depression Pathways cohort study is designed for this purpose. The present report describes the baseline sample and associations between participant characteristics and odds of daily vs. non-daily opioid use. Second, we report associations between participant characteristics and odds of depression, dysthymia, anhedonia, and vital exhaustion. Patients with non-cancer pain were eligible if they started a new period of prescription opioid use lasting 30 to 90 days. Participants were 54.8 (SD±11.3) years of age, 57.3% female and 73% white race. Less than college education was more common among daily vs. non-daily opioid users (32.4% vs. 27.3%; p=0.0008), as was back pain (64.2% vs. 51.3%; p<0.0001), any non-opioid substance use disorder (12.8% vs. 4.8%; p<0.0001) and current smoking (30.7% vs. 18.4% p<0.0001). High pain interference (50.9% vs. 28.4%; p<0.0001) was significantly associated with depression, as was having more pain sites (6.9±3.6 vs. 5.7±3.6; p<0.0001), and benzodiazepine co-mediation (38.2% vs. 23.4%; p<0.0001). High pain interference was significantly more common among those with anhedonia (46.8% vs. 27.4%; p<0.0001) and more pain sites (7.0±3.7 vs. 5.6±3.6; p<0.0001) were associated with anhedonia. Having more pain sites (7.9±3.6 vs. 5.5±3.50; p<0.0001) was associated with vital exhaustion as was back pain (71.9% vs. 56.8%; p=0.0001) and benzodiazepine co-medication (42.8% vs. 22.8%; p<0.0001). Patients using prescription opioids for non-cancer pain have complex pain, psychiatric, and substance use disorder comorbidities. Longitudinal data will reveal whether long-term opioid therapy leads to depression or other mood disturbances such as anhedonia and vital exhaustion. PERSPECTIVE: This study reports baseline characteristics of a new prospective, non-cancer pain cohort study. Risk factors for adverse opioid outcomes were most common in those with depression and vital exhaustion and less common in dysthymia and anhedonia. Baseline data highlight the complexity of patients receiving long-term opioid therapy for non-cancer pain.

Cardiology/Cardiovascular Research

Abdelrahim E, Miller J, and **Maskoun W**. Anteroseptal accessory pathways: Killing one bird with two stones. *J Cardiovasc Electrophysiol* 2023; Epub ahead of print. PMID: 37787022. Full Text

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BACKGROUND AND AIMS: Ablation of anteroseptal accessory pathways (AS-AP) is challenging, with lower success and more complications compared to other APs. AS-APs can be successfully ablated from the right atrium (RA) or the aortic valve's noncoronary cusp (NCC). We report two patients who required a hybrid ablation approach to achieve successful abolition of both anterograde and retrograde AS-AP conduction. METHODS AND RESULTS: A 21-year-old female with supraventricular tachycardia (SVT) and pre-excitation on electrocardiogram (ECG) underwent electrophysiology study (EPS) confirming an AS-AP with anterograde and retrograde conduction. Ablation in the NCC achieved immediate and persistent anterograde conduction block. Electrophysiological maneuvers showed persistent retrograde AP conduction and orthodromic reciprocating tachycardia (ORT) remained easily inducible. Additional ablation in the NCC did not eliminate retrograde conduction. Further ablation in the RA opposite the NCC at the site of earliest retrograde atrial activation during ORT restored sinus and eliminated retrograde AP conduction. A 52-year-old male with SVT and ECG with pre-excitation underwent EPS that confirmed an AS-AP with anterograde and retrograde conduction. Ablation was performed in the NCC resulting in immediate elimination of pre-excitation. Retrograde conduction was still present and confirmed by repeating electrophysiological maneuvers. Ablation was performed in the RA opposite the successful ablation site in the NCC, eliminating retrograde AP conduction. CONCLUSION: Two cases of AS-AP with anterograde and retrograde conduction and successful elimination of pathway conduction required a hybrid ablation approach from the NCC and RA. This approach may be helpful in other cases to improve success rates without using excessive ablation near the normal conduction system.

Cardiology/Cardiovascular Research

Allana SS, Rempakos A, Kostantinis S, Alexandrou M, Mutlu D, **Alaswad K**, Azzalini L, Kearney K, Krestyaninov O, Khelimskii D, Gorgulu S, Chandwaney RH, Jaffer FA, Khatri JJ, Davies RE, Benton SM, Jr., Choi JW, Karmpaliotis D, Poommipanit P, Nicholson W, Jaber W, Rinfret S, Frizzel J, Patel T, Jefferson B, Aygul N, Goktekin O, ElGuindy A, Abi-Rafeh N, Rangan BV, Burke MN, Sandoval Y, and Brilakis ES. The tip-in and rendezvous techniques in retrograde chronic total occlusion percutaneous coronary interventions. *EuroIntervention* 2023; Epub ahead of print. PMID: 37823784. Request Article

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Cardiology/Cardiovascular Research

Almajed MR, Almajed A, **Khan N**, **Obri MS**, and **Ananthasubramaniam K**. Systemic right ventricle complications in levo-transposition of the great arteries: A case report and review of literature. *World J Cardiol* 2023; 15(10):542-552. PMID: 37900900. Full Text

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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 in life. sRV dysfunction and remodeling predisposes patients to intracardiac thrombus (ICT) formation. CASE SUMMARY: A 40-year-old male with L-TGA presented with symptoms of acute decompensated heart failure. 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 showed a sRV ejection fraction of 40%, severe sTV regurgitation, and a newly identified sRV ICT. ICT was confirmed by ultrasound-enhancing agents and transesophageal echocardiography. Our patient was optimized with guideline-directed medical therapy and diuresis. Anticoagulation was achieved with a vitamin K antagonist (VKA) and he was later referred for evaluation by advanced heart failure and heart transplant services. CONCLUSION: Anticoagulation with VKA is the mainstay of treatment in the absence of conclusive data supporting direct oral anticoagulant use in ICT in patients

with congenital heart disease. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring with dedicated cardiac imaging to identify complications.

Cardiology/Cardiovascular Research
Aronow HD. Presidential Address: Bigger and better. *Vasc Med* 2023; Epub ahead of print. PMID: 37851795. Full Text

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Cardiology/Cardiovascular Research
Aurora L, and Wanderley MRB. Signaling Pathways in Hypertrophic Cardiomyopathy: Will Proteomic Profiling Guide the Future? *J Card Fail* 2023; Epub ahead of print. PMID: 37890654. Full Text

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Invited Editorial for "Signaling Pathways Associated with Prior Cardiovascular Events in Hypertrophic Cardiomyopathy".

Cardiology/Cardiovascular Research
Cascino TM, Cogswell R, Shah P, **Cowger JA**, Molina EJ, Shah KB, Grinstein J, Wood KL, Gosev I, and Kanwar MK. Equitable Access to Advanced Heart Failure Therapies in the United States - A Call to Action. *J Card Fail* 2023; Epub ahead of print. PMID: 37884168. Full Text

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Cardiology/Cardiovascular Research
Cowger JA, **Basir MB**, Baran DA, Hayward CS, Rangaswami J, Walton A, **Tita C**, Minear S, Hakemi E, Klein L, Cheng R, Wu R, Mohanty BD, Heuring JJ, Neely E, and Shah P. Safety and Performance of the Aortix Device in Acute Decompensated Heart Failure and Cardiorenal Syndrome. *JACC Heart Fail* 2023; Epub ahead of print. PMID: 37804307. Full Text

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BACKGROUND: Cardiorenal syndrome (CRS) complicates 33% of acute decompensated heart failure (ADHF) admissions, and patients with persistent congestion at discharge have high 30-day event rates. OBJECTIVES: The purpose of this study was to evaluate a novel catheter-deployed intra-aortic entrainment pump (IAEP) in patients with ADHF with CRS and persistent congestion. METHODS: A multicenter (n = 14), nonrandomized, single-arm, safety and feasibility study of IAEP therapy was conducted. Within patient changes (post-pre IAEP therapy) in fluid loss, hemodynamics, patient-reported dyspnea, and serum biomarkers were assessed using Wilcoxon signed-rank testing. RESULTS: Of 21 enrolled patients, 18 received Aortix therapy. Mean ± SD patient age was 60.3 ± 7.9 years. The median left ventricular ejection fraction was 22.5% (25th-75th percentile: 10.0%-53.5%); 27.8% had a left ventricular ejection fraction ≥50%. Pre-therapy, patients received 8.7 ± 4.1 days of loop diuretic agents and 44% were on inotropes. Pump therapy averaged 4.6 ± 1.6 days, yielding net fluid losses of 10.7 ± 6.5 L ($P < 0.001$) and significant ($P < 0.01$) reductions in central venous pressure (change from baseline: -8.5 mm Hg [25th-75th percentile: -3.5 to -10.0 mm Hg]), pulmonary capillary wedge pressure (-11.0 mm Hg [25th-75th percentile: -5.0 to -14.0 mm Hg]), and serum creatinine (-0.2 mg/dL [25th-75th percentile: -0.1 to -0.5 mg/dL]) with improved estimated glomerular filtration rate (+5.0 mL/min/1.73 m(2) [25th-75th percentile: 2.0-9.0 mL/min/1.73 m(2)]) and patient-reported dyspnea score (+16 [25th-75th percentile: 3-37]). Dyspnea scores, natriuretic peptides, and renal function improvements persisted through 30 days. CONCLUSIONS: This pilot study of patients with ADHF, persistent congestion, and worsening renal function due to CRS supports the potential for safely achieving decongestion using IAEP therapy. These initial promising results provide the basis for future randomized clinical trials of this novel pump. (An Evaluation of the Safety and Performance of the Aortix System for Intra-Aortic Mechanical Circulatory Support in Patients with Cardiorenal Syndrome [The Aortix CRS Pilot Study]; NCT04145635).

Cardiology/Cardiovascular Research

Gupta K, **Zahedi S**, **Kakar TS**, Khuttan A, Kalra R, and **Zweig BM**. Independent prognostic value of high-risk ventricular premature complexes during exercise or recovery in asymptomatic patients: A meta-analysis of observational studies. *Indian Heart J* 2023; Epub ahead of print. PMID: 37858721. Full Text

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INTRODUCTION: Ventricular premature contractions (VPCs) are a common finding during cardiac stress tests. The independent prognostic value of these findings in patients in asymptomatic patients is unclear. METHODS: We conducted a systematic review and meta-analysis of observational studies exploring the independent prognostic value of VPCs to predict all-cause mortality. The secondary outcome was cardiovascular (CV) mortality. We excluded studies that did not report outcomes after adjusting for ≥1 confounder. Random effect meta-analyses were used to predict cumulative hazard ratios. We stratified results based on VPC during exercise or recovery. RESULTS: We found 7 studies with 24,518 patients that met our inclusion criteria. Two studies reported all-cause mortality only, 1 study reported CV mortality only, rest 4 reported both. There was significant heterogeneity in the baseline population, definition of high-risk VPCs, and variables used in adjusted models. Using multivariable summary estimates from individual studies, only VPCs during exercise were associated with a higher risk of all-cause mortality (HR 1.27, 95 % CI 1.07, 1.48). Both VPCs during exercise and recovery were associated with a higher risk CV

mortality (HR 1.69, 95 % CI 1.19, 2.20, I(2) = 17.6 % and 1.62, 95 % CI 1.25, 2.00, p < 0.001 for both). CONCLUSION: High-risk VPCs during exercise is associated with increased risk of all-cause and CV mortality, while those during recovery are associated with an increased risk of CV mortality only.

Cardiology/Cardiovascular Research
Kapur NK, Pahuja M, Kochar A, Karas RH, Udelson JE, Moses JW, Stone GW, Aghili N, Faraz H, and **O'Neill WW**. Delaying reperfusion plus left ventricular unloading reduces infarct size: Sub-analysis of DTU-STEMI pilot study. *Cardiovasc Revasc Med* 2023; Epub ahead of print. PMID: 37891053. Full Text

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INTRODUCTION: The STEMI-DTU pilot study tested the early safety and practical feasibility of left ventricular (LV) unloading with a trans-valvular pump before reperfusion. In the intent-to-treat cohort, no difference was observed for microvascular obstruction (MVO) or infarct size (IS) normalized to either the area at risk (AAR) at 3-5 days or total LV mass (TLVM) at 3-5 days We now report a per protocol analysis of the STEMI-DTU pilot study. METHODS: In STEMI-DTU STUDY 50 adult patients (25 in each arm) with anterior STEMI [sum of precordial ST-segment elevation (ΣSTE) ≥4 mm] requiring primary percutaneous coronary intervention (PCI) were enrolled. Only patients who met all inclusion and exclusion criteria were included in this analysis. Cardiac magnetic resonance (CMR) imaging 3-5 days after PCI quantified IS/AAR and IS/TLVM and MVO. Group differences were assessed using Student's t-tests and linear regression (SAS Version-9.4). RESULTS: Of the 50 patients enrolled, 2 died before CMR imaging. Of the remaining 48 patients those without CMR at 3-5 days (n = 8), without PCI of a culprit left anterior descending artery lesion (n = 2), with OHCA (n = 1) and with ΣSTE < 4 mm (n = 5) were removed from this analysis leaving 32/50 (64 %) patients meeting all inclusion and exclusion criteria (U-IR, n = 15; U-DR, n = 17) as per protocol. Despite longer symptom-to-balloon times in the U-DR arm (228 ± 80 vs 174 ± 59 min, p < 0.01), IS/AAR was significantly lower with 30 min of delay to reperfusion in the presence of active LV unloading (47 ± 16 % vs 60 ± 15 %, p = 0.02) and remained lower irrespective of the magnitude of precordial ΣSTE. MVO was not significantly different between groups (1.5 ± 2.8 % vs 3.5 ± 4.8 %, p = 0.15). Among patients who received LV unloading within 180 min of symptom onset, IS/AAR was significantly lower in the U-DR group. CONCLUSION: In this per-protocol analysis of the STEMI-DTU pilot study we observed that LV unloading for 30 min before reperfusion significantly reduced IS/AAR compared to LV unloading and immediate reperfusion, whereas in the ITT cohort no difference was observed between groups. This observation supports the design of the STEMI-DTU pivotal trial and suggests that strict adherence to the study protocol can significantly influence the outcome.

Cardiology/Cardiovascular Research
Ramanan S, **Singh H**, **Ahmed O**, **Zande M**, and **Trimble M**. A Rare Case of Splenic Infarct Secondary to Mobile Cardiac Echodensity. *Cureus* 2023; 15(10):e46434. PMID: 37927647. Full Text

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Lambl's excrescences (LE) are mobile filiform lesions, mostly found on the left-sided heart valves. Histologically, they have a mesenchymal origin with a single endothelial layer. They have the potential to detach, resulting in catastrophic thromboembolic events. Their rarity often leads to them being misdiagnosed as vegetations of endocarditis with patients failing to improve on conventional therapy. A 48-year-old female with a history of hypertension presented to the Emergency Department with a one-

week history of sharp left upper quadrant pain. She was vitally stable; the only lab abnormality was revealed to be a mildly elevated white cell count. CT abdomen revealed a splenic infarct involving 25% of the parenchyma. Patients had no history of abdominal trauma, coagulation disorders, exogenous estrogen use or IV drug abuse. Subsequent investigations failed to reveal any cause of hypercoagulability. An extensive cardiac workup revealed no arrhythmias, but transesophageal echocardiogram showed a mobile echo density on the ventricular side of the aortic valve attached at the coaptation zone, approximately 2.7 cm long and 0.1 cm wide, suggesting a very prominent Lambl's excrescence. In the absence of any other findings, the patient's splenic infarct was determined to be secondary to an embolic event from the aortic valve lesion. Rivaroxaban was initiated and the patient subsequently improved. Existing literature describes most LEs as being asymptomatic and discovered incidentally on echocardiograms. This case illustrates the need to develop a criterion for prompt identification of LEs and differentiating them from the vegetations of endocarditis. It also brings forth the question of prophylactic treatment of these lesions while highlighting the lack of guidelines regarding the management of embolic phenomena secondary to LE.

Cardiology/Cardiovascular Research

Rawlley B, Sanchez AC, **Gupta K**, Ramm M, and Chaudhuri D. ARNI vs ACE inhibitor use in patients with a Left Ventricular Assist Device: A propensity score matched analysis. *Am J Cardiol* 2023; Epub ahead of print. PMID: 37866448. Full Text

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Cardiology/Cardiovascular Research

Rempakos A, Alexandrou M, Simsek B, Kostantinis S, Karacsonyi J, Mutlu D, Ybarra LF, Bagur R, Choi JW, Poommipanit P, Khatri JJ, Davies R, Benton S, Gorgulu S, Jaffer FA, Chandwaney R, Jaber W, Rinfret S, Nicholson W, Azzalini L, Kearney KE, Kerrigan JL, Haddad EV, **Alaswad K**, **Basir MB**, Krestyaninov O, Khelimskii D, Abi-Rafeh N, ElGuindy A, Goktekin O, Rangan BV, Mastrodemos OC, Al-Ogaili A, Allana SS, Sandoval Y, Burke MN, and Brilakis ES. Trends and Outcomes of Antegrade Dissection and Re-Entry in Chronic Total Occlusion Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2023; Epub ahead of print. PMID: 37877912. Full Text

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BACKGROUND: The contemporary frequency and outcomes of antegrade dissection and re-entry (ADR) for chronic total occlusion (CTO) percutaneous coronary intervention (PCI) have received limited study. OBJECTIVES: The aim of this study was to determine the frequency and outcomes of ADR use in a large multicenter CTO PCI registry. METHODS: The characteristics and outcomes of ADR were examined among 12,568 patients who underwent 12,841 CTO PCIs at 46 U.S. and non-U.S. centers between 2012 and 2023. RESULTS: ADR was used in 2,385 of the procedures (18.6%). ADR use declined from 37.9% in 2012 to 14.5% in 2022 ($P < 0.001$). Patients in whom ADR was used had a high prevalence of comorbidities. Compared with cases that did not use ADR, ADR cases had more complex angiographic characteristics, higher mean J-CTO (Multicenter CTO Registry in Japan) score (2.94 ± 1.11 vs 2.23 ± 1.26; $P < 0.001$), lower technical success (77.0% vs 89.3%; $P < 0.001$), and higher in-hospital major adverse cardiac events (3.7% vs 1.6%; $P < 0.001$). The use of the CrossBoss declined from 71% in 2012 to 1.4% in 2022 and was associated with higher technical success (87%) compared with wire-based techniques (73%). The Stingray device displayed higher technical success (86%) compared with subintimal tracking and re-entry (STAR) (74%) and limited antegrade subintimal tracking (78%); however, its use has been decreasing, with STAR becoming the most used re-entry technique in 2022 (44% STAR vs 38% Stingray). CONCLUSIONS: The use of ADR has been decreasing. ADR was used in more complex lesions and was associated with lower technical success and higher major adverse cardiac events compared with non-ADR cases. There has been a decrease in Stingray use and an increase in the use of STAR for re-entry.

Cardiology/Cardiovascular Research

Shpilsky D, **von Buchwald CL**, **Villablanca PA**, **O'Neill BP**, **Engel Gonzalez P**, **Frisoli T**, **Lee J**, **Guruswamy J**, **Yeldo N**, **Reeser N**, **Song T**, **O'Neill WW**, and **Wang DD**. 3D print and multi-modality imaging guided transcatheter closure of multiple left ventricular pseudoaneurysms. *Echocardiography* 2023; Epub ahead of print. PMID: 37842844. Full Text

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Left ventricular pseudoaneurysm (PSA) after surgical aortic valve replacement (AVR) is a known but uncommon complication. It is associated with risks such as thromboembolism and life-threatening rupture. Surgical repair has traditionally been utilized in low-risk patients but transcatheter closure has become a promising therapeutic option. This case report describes the utility of multimodality imaging in pre-, intra-, and post-procedural evaluation of transcatheter PSA closure and is among the first to demonstrate the utility of 3D print model.

Cardiology/Cardiovascular Research

Smith RL, Lim DS, Gillam LD, Zahr F, Chadderdon S, Rassi AN, Makkar R, Goldman S, Rudolph V, Hermiller J, Kipperman RM, Dhoble A, Smalling R, Latib A, Kodali SK, Lazkani M, Choo J, Lurz P, **O'Neill WW**, Laham R, Rodés-Cabau J, Kar S, Schofer N, Whisenant B, Inglessis-Azuaje I, Baldus S, Kapadia S, Szerlip M, Kliger C, Boone R, Webb JG, Williams MR, Stephan von Bardeleben R, Ruf TF, Guerrero M, Eleid M, McCabe JM, Davidson C, Hiesinger W, Kaneko T, Shah PB, Yadav P, Koulogiannis K, Marcoff L, and Hausleiter J. One-year Outcomes of Transcatheter Edge-to-Edge Repair in Anatomically Complex Degenerative Mitral Regurgitation Patients. *JACC Cardiovasc Interv* 2023; Epub ahead of print. PMID: 37905772. Full Text

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BACKGROUND: Favorable six-month outcomes from the CLASP IID Registry demonstrated that mitral valve transcatheter edge-to-edge repair with the PASCAL transcatheter valve repair system is safe and beneficial for treating prohibitive surgical risk degenerative mitral regurgitation (DMR) patients with complex mitral valve anatomy. OBJECTIVES: To assess 1-year safety, echocardiographic and clinical outcomes from the CLASP IID Registry. METHODS: Patients with 3+ or 4+ DMR who were at prohibitive surgical risk, had complex mitral valve anatomy based on the MitraClip Instructions for Use, and deemed suitable for treatment with the PASCAL system were enrolled prospectively. Safety, clinical, echocardiographic, functional, and quality of life outcomes were assessed at one year. Study oversight included a central screening committee, echocardiographic core laboratory and clinical events committee. RESULTS: Ninety-eight patients were enrolled. One-year Kaplan-Meier estimates of freedom from composite major adverse events, all-cause mortality and heart failure hospitalization were 83.5%, 89.3% and 91.5%, respectively. Significant MR reduction was achieved at 1 year ($p<0.001$ vs. baseline) including 93.2% at MR≤2+ and 57.6% at MR≤1+ with improvements in related echocardiographic measures. New York Heart Association functional class and Kansas City Cardiomyopathy Questionnaire score also improved significantly ($p<0.001$ vs. baseline). CONCLUSIONS: At one year, treatment with the PASCAL system demonstrated safety and significant MR reduction, with continued improvement in clinical, echocardiographic, functional, and quality-of-life outcomes, illustrating the value of the PASCAL system in the treatment of prohibitive surgical risk patients with 3+ or 4+ DMR and complex mitral valve anatomy.

Cardiology/Cardiovascular Research

Tedford RJ, Leacche M, Lorts A, Drakos SG, Pagani FD, and **Cowger J**. Durable Mechanical Circulatory Support: JACC Scientific Statement. *J Am Coll Cardiol* 2023; 82(14):1464-1481. PMID: 37758441. Full Text

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Despite advances in medical therapy for patients with stage C heart failure (HF), survival for patients with advanced HF is <20% at 5 years. Durable left ventricular assist device (dLVAD) support is an important treatment option for patients with advanced HF. Innovations in dLVAD technology have reduced the risk of several adverse events, including pump thrombosis, stroke, and bleeding. Average patient survival is now similar to that of heart transplantation at 2 years, with 5-year dLVAD survival now approaching 60%. Unfortunately, greater adoption of dLVAD therapy has not been realized due to delayed referral of patients to advanced HF centers, insufficient clinician knowledge of contemporary dLVAD outcomes (including gains in quality of life), and deprioritization of patients with dLVAD support waiting for heart transplantation. Despite these challenges, novel devices are on the horizon of clinical investigation, offering smaller size, permitting less invasive surgical implantation, and eliminating the percutaneous lead for power supply.

Cardiology/Cardiovascular Research

Thompson MP, Hou H, Stewart JW, 2nd, Pagani FD, Hawkins RB, **Keteyian SJ**, Sukul D, and Likosky DS. Relationship Between Community-Level Distress and Cardiac Rehabilitation Participation, Facility Access, and Clinical Outcomes After Inpatient Coronary Revascularization. *Circ Cardiovasc Qual Outcomes* 2023; Epub ahead of print. PMID: 37855157. Full Text

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BACKGROUND: Although disparities in cardiac rehabilitation (CR) participation are well documented, the role of community-level distress is poorly understood. This study evaluated the relationship between community-level distress and CR participation, access to CR facilities, and clinical outcomes. METHODS: A retrospective cohort study was conducted on a 100% sample of Medicare beneficiaries undergoing inpatient coronary revascularization between July 2016 and December 2018. Community-level distress was defined using the Distressed Community Index quintile at the beneficiary zip code level, with the first and fifth quintiles representing prosperous and distressed communities, respectively. Outpatient claims were used to identify any CR use within 1 year of discharge. Beneficiary and CR facility zip codes were used to describe access to CR facilities. Adjusted logistic regression models evaluated the association between Distressed Community Index quintiles, CR use, and clinical outcomes, including one-year mortality, all-cause hospitalization, and acute myocardial infarction hospitalization. RESULTS: A total of 414 730 beneficiaries were identified, with 96 929 (23.4%) located in the first and 67 900 (16.4%) in the fifth quintiles, respectively. Any CR use was lower for beneficiaries in distressed compared with prosperous communities (26.0% versus 46.1%, P<0.001), which was significant after multivariable adjustment (odds ratio, 0.41 [95% CI, 0.40-0.42]). A total of 98 458 (23.7%) beneficiaries had a CR facility within their zip code, which increased from 16.3% in prosperous communities to 26.6% in distressed communities. Any CR use was associated with absolute reductions in mortality (-6.8% [95% CI, -7.0% to -6.7%]), all-cause hospitalization (-5.9% [95% CI, -6.3% to -5.6%]), and acute myocardial infarction hospitalization (-1.3% [95% CI, -1.5% to -1.1%]), which were similar across each Distressed Community Index quintiles. CONCLUSIONS: Although community-level distress was associated with lower CR participation, the clinical benefits were universally received. Addressing barriers to CR in distressed communities should be considered a significant priority to improve survival after coronary revascularization and reduce disparities.

Cardiology/Cardiovascular Research

Verghese D, Bhat AG, Patlolla SH, Naidu SS, **Basir MB**, Cubeddu RJ, Navas V, Zhao DX, and Vallabhajosyula S. Outcomes in non-ST-segment elevation myocardial infarction complicated by in-hospital cardiac arrest based on management strategy. *Indian Heart J* 2023; Epub ahead of print. PMID: 37863393. Full Text

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BACKGROUND: There are limited data on in-hospital cardiac arrest (IHCA) complicating non-ST-segment-elevation myocardial infarction (NSTEMI) based on management strategy. METHODS: We used National Inpatient Sample (2000-2017) to identify adults with NSTEMI (not undergoing coronary artery bypass grafting) and concomitant IHCA. The cohort was stratified based on use of early (hospital day 0) or delayed (≥hospital day 1) coronary angiography (CAG), percutaneous coronary intervention (PCI), and medical management. Outcomes included incidence of IHCA, in-hospital mortality, adverse events, length of stay, and hospitalization costs. RESULTS: Of 6,583,662 NSTEMI admissions, 375,873 (5.7 %) underwent early CAG, 1,133,143 (17.2 %) received delayed CAG, 2,326,391 (35.3 %) underwent PCI, and 2,748,255 (41.7 %) admissions were managed medically. The medical management cohort was older, predominantly female, and with higher comorbidities. Overall, 63,085 (1.0 %) admissions had IHCA, and incidence of IHCA was highest in the medical management group (1.4 % vs 1.1 % vs 0.7 % vs 0.6 %, $p < 0.001$) compared to early CAG, delayed CAG and PCI groups, respectively. In adjusted analysis, early CAG (adjusted OR [aOR] 0.67 [95 % confidence interval {CI} 0.65-0.69]; $p < 0.001$), delayed CAG (aOR 0.49 [95 % CI 0.48-0.50]; $p < 0.001$), and PCI (aOR 0.42 [95 % CI 0.41-0.43]; $p < 0.001$) were associated with lower incidence of IHCA compared to medical management. Compared to medical management, early CAG (adjusted OR 0.53, CI: 0.49-0.58), delayed CAG (adjusted OR 0.34, CI: 0.32-0.36) and PCI (adjusted OR 0.19, CI: 0.18-0.20) were associated with lower in-hospital mortality (all $p < 0.001$). CONCLUSION: Early CAG and PCI in NSTEMI was associated with lower incidence of IHCA and lower mortality among NSTEMI-IHCA admissions.

Center for Health Policy and Health Services Research

Ahmedani BK, **Yeh HH**, Penfold RB, Simon GE, **Miller-Matero LR**, **Akinyemi E**, **Fallone M**, **Patel S**, **Beebani G**, Hooker SA, Owen-Smith A, Knowlton G, **Levin A**, Eke-Usim A, and Rossom RC. Psychotherapy Disruption Before and After the Transition to Virtual Mental Health Care Induced by the COVID-19 Pandemic. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 37817579. Full Text

Center for Health Policy and Health Services Research (Ahmedani, Yeh, Miller-Matero), Behavioral Health Services (Ahmedani, Miller-Matero, Akinyemi, Fallone, Patel, Beebani), and Public Health Sciences (Levin), Henry Ford Health, Detroit; Kaiser Permanente Washington Health Research Institute, Seattle (Penfold, Simon); HealthPartners Institute, Minneapolis (Hooker, Knowlton, Rossom); Center for Research and Evaluation, Kaiser Permanente Georgia, and Department of Health Policy and Behavioral Sciences, Georgia State University, Atlanta (Owen-Smith); Authority Health, Detroit (Eke-Usim).

OBJECTIVE: This study aimed to examine population-level disruption in psychotherapy before and after the rapid shift to virtual mental health care induced by the onset of the COVID-19 pandemic in the United States. METHODS: This retrospective study used electronic health record and insurance claims data from three U.S. health systems. The sample included 110,089 patients with mental health conditions who were members of the health systems' affiliated health plans and attended at least two psychotherapy visits from

June 14, 2019, through December 15, 2020. Data were subdivided into two 9-month periods (before vs. after COVID-19 onset, defined in this study as March 14, 2020). Psychotherapy visits were measured via health records and categorized as in person or virtual. Disruption was defined as a gap of >45 days between visits. RESULTS: Visits in the preonset period were almost exclusively in person (97%), whereas over half of visits in the postonset period were virtual (52%). Approximately 35% of psychotherapy visits were followed by a disruption in the preonset period, compared with 18% in the postonset period. Disruption continued to be less common (adjusted OR=0.45) during the postonset period after adjustment for visit, mental health, and sociodemographic factors. The magnitude of the difference in disruption between periods was homogeneous across sociodemographic characteristics but heterogeneous across psychiatric diagnoses. CONCLUSIONS: This study found fewer population-level disruptions in psychotherapy receipt after rapid transition to virtual mental health care following COVID-19 onset. These data support the continued availability of virtual psychotherapy.

Center for Health Policy and Health Services Research
Arias SA, Sperber K, Jones R, Taxman FS, Miller TR, Zylberfuden S, Weinstock LM, Brown GK, **Ahmedani B**, and Johnson JE. Managed Care Updates of Subscriber Jail Release to Prompt Community Suicide Prevention: Clinical Trial Protocol. *Res Sq* 2023; Epub ahead of print. PMID: 37841869. Full Text

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BACKGROUND: Recent jail detention is a marker for trait and state suicide risk in community-based populations. However, healthcare providers are typically unaware that their client was in jail and few post-release suicide prevention efforts exist. This protocol paper describes an effectiveness-implementation trial evaluating community suicide prevention practices triggered by advances in informatics that alert CareSource, a large managed care organization (MCO), when a subscriber is released from jail. METHODS: This randomized controlled trial investigates two evidence-based suicide prevention practices triggered by CareSource's jail detention/release notifications, in a partial factorial design. The first phase randomizes ~43,000 CareSource subscribers who pass through any Ohio jail to receive Caring Contact letters sent by CareSource or to Usual Care after jail release. The second phase (running simultaneously) involves a subset of ~6,000 of the 43,000 subscribers passing through jail who have been seen in one of 12 contracted behavioral health agencies in the 6 months prior to incarceration in a stepped-wedge design. Agencies will receive: (a) notifications of the client's jail detention/release, (b) instructions for re-engaging these clients, and (c) training in suicide risk assessment and the Safety Planning Intervention for use at re-engagement. We will track suicide-related and service linkage outcomes 6 months following jail release using claims data. CONCLUSIONS: This design allows us to rigorously test two intervention main effects and their interaction. It also provides valuable information on the effects of system-level change and the scalability of interventions using big data from a MCO to flag jail release and suicide risk. TRIAL REGISTRATION: The trial is registered at clinicaltrials.gov (NCT05579600). Registered 27 June, 2023, https://beta.clinicaltrials.gov/study/NCT05579600?cond=Suicide&term=Managed%20Care&rank=1.

Center for Health Policy and Health Services Research
Coleman KJ, Rossom RC, **Braciszewski JM**, Padilla A, Li X, Waters HC, Penfold RB, Simon GE, and Nau CL. Beyond clinical outcomes: Case control study of the role of race in disruptive life events for people with serious mental illness. *Gen Hosp Psychiatry* 2023; 85:80-86. PMID: 37844540. Full Text

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OBJECTIVE: To understand how race and serious mental illness (SMI) interact for disruptive life events defined as financial (bankruptcy and judgement filings), and non-financial (arrests). METHODS: Patients were adults with schizophrenia (SCZ; N = 16,159) or bipolar I disorder (BPI; N = 30,008) matched 1:1 to patients without SMI (non-SMI) from health systems in Michigan and Southern California during 1/1/2007 through 12/31/2018. The main exposure was self-reported race, and the outcome was disruptive life events aggregated by Transunion. We hypothesized that Black patients with SCZ or BPI would be the most likely to experience a disruptive life event when compared to Black patients without SMI, and all White or Asian patients regardless of mental illness. RESULTS: Black patients with SCZ had the least likelihood (37% lower) and Asian patients with BPI had the greatest likelihood (2.25 times higher) of experiencing a financial disruptive life event among all patients in the study. There was no interaction of race with either SCZ or BPI for experiencing an arrest. The findings did not support our hypotheses for patients with SCZ and partially supported them for patients with BPI. CONCLUSIONS: Clinical initiatives to assess social determinants of health should consider a focus on Asian patients with BPI.

Center for Health Policy and Health Services Research
Haley EN, **Loree AM**, **Maye M**, Coleman KJ, **Braciszewski JM**, **Snodgrass M**, Harry ML, **Carlin AM**, and **Miller-Matero LR**. Racial Differences in Psychiatric Symptoms, Maladaptive Eating, and Lifestyle Behaviors After Bariatric Surgery. *J Racial Ethn Health Disparities* 2023; Epub ahead of print. PMID: 37874488. Full Text

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There are several psychological and behavioral factors associated with poorer outcomes following bariatric surgery, yet it is unknown whether and how these factors may differ by race. In this cross-sectional study, individuals who underwent bariatric surgery from 2018 to 2021 and up to 4 years post-surgery were invited to complete an online survey. Psychiatric symptoms, maladaptive eating patterns, self-monitoring behaviors, and exercise frequency were examined. Participants (N = 733) were 87% women, 63% White, with a mean age of 44 years. Analyses of covariance demonstrated that White individuals endorsed greater anxiety symptoms (p =.01) and emotional eating due to depression (p = .01), whereas Black individuals endorsed greater depression severity (p = .02). Logistic regression analyses demonstrated that White individuals were more likely to experience loss of control eating (OR= 1.7, p = .002), grazing (OR= 2.53, p <.001), and regular self-weighing (OR= 1.41, p <.001) than Black individuals, and were less likely to skip meals (OR= .61, p = .04), or partake in nighttime eating (OR= .40, p <.001). There were no racial differences in binge eating, emotional eating due to anxiety or frustration, use of a food diary, or exercise. Thus, depressive symptoms, skipping meals, and nighttime eating may be important, modifiable intervention targets to optimize the benefits of bariatric surgery and promote equitable outcomes.

Center for Health Policy and Health Services Research
Miller-Matero LR, **Haley EN**, **Loree AM**, **Braciszewski JM**, **Maye M**, **Sehgal M**, and **Carlin AM**. Post-surgical psychiatric symptoms, maladaptive eating patterns, and lifestyle behaviors associated with weight recurrence after bariatric surgery. *Surg Obes Relat Dis* 2023; Epub ahead of print. PMID: 37923621. Full Text

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BACKGROUND: A significant proportion of patients who undergo bariatric surgery experience weight recurrence; however, the most important areas to target to prevent weight recurrence remain unknown. OBJECTIVES: The purpose was to examine whether psychiatric symptoms, maladaptive eating behaviors, and lifestyle factors were associated with weight recurrence. SETTING: Single healthcare system. METHODS: Individuals who underwent bariatric surgery were invited to complete a web-based survey in which they reported their current weight and completed measures of psychiatric symptoms, maladaptive eating behaviors, and lifestyle behaviors. Participants were included if they were at least 2 years postsurgery. Weight recurrence was measured from the 1-year follow-up to the survey date. RESULTS: Participants (n = 169) were predominantly female and White or Black, with a mean age of 45 years. The rate of significant weight recurrence was 23.1%. Those who underwent sleeve gastrectomy were more likely to experience weight recurrence (odds ratio [OR] = 12.99; P = .01). In bivariate analyses, anxiety and depressive symptoms, emotional eating, loss of control eating, binge eating, and night eating were associated with weight recurrence (P < .05). Those who did not eat mindfully, take 20 minutes to eat, or get adequate sleep were also more likely to have weight recurrence (P < .05). In a multivariate model, only a lack of mindful eating (OR = 4.84; P = .03) and inadequate sleep (OR = 7.30; P = .02) remained statistically significant predictors. CONCLUSION: Engaging in mindful eating and obtaining adequate sleep may protect against weight recurrence following bariatric surgery. Clinicians may want to screen and monitor these behaviors.

Center for Health Policy and Health Services Research
Miller-Matero LR, **Ross K**, **Arellano C**, **Zelenak L**, **DePascale E**, **Gavrilova L**, **Braciszewski JM**, **Hecht LM**, **Haley EN**, **Brescacin C**, and **Carlin AM**. Cannabis use following bariatric surgery is associated with anxiety and maladaptive eating. *Surg Obes Relat Dis* 2023; Epub ahead of print. PMID: 37863791. Full Text

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BACKGROUND: There are limited data regarding the association of cannabis use with outcomes after bariatric surgery. As such, it is challenging to know how to counsel patients using cannabis. OBJECTIVES: The purpose of this study was to examine whether postsurgical cannabis use was associated with psychiatric symptoms and maladaptive eating among individuals up to 4 years after bariatric surgery. SETTING: Single health system. METHODS: All patients who underwent bariatric surgery over a 4-year period were invited to participate. Participants (N = 765) completed questionnaires online regarding postsurgical cannabis use, psychiatric symptoms, and maladaptive eating. RESULTS: Any cannabis use after bariatric surgery was associated with increased likelihood of having elevated symptoms of anxiety (odds ratio [OR] = 1.88, P = .003; 37.8% versus 24.4%), increased likelihood of grazing behaviors (OR = 1.77, P = .01; 71.2% versus 58.2%), and higher scores for eating in response to

depression (P = .01; 12.13 versus 10.75). Weekly cannabis use was associated with loss of control eating (OR = 1.81, P = .04; 37.2% versus 24.7%), binge eating (OR = 2.16, P = .03; 20.0% versus 10.4%), and night eating behaviors (OR = 2.11, P = .01; 40.0% versus 24.0%). Cannabis use was not associated with depression (P > .05). CONCLUSIONS: Cannabis use after bariatric surgery was associated with anxiety symptoms and engaging in maladaptive eating behaviors. Frequent cannabis use (i.e., ≥1 per week) was associated with additional types of maladaptive eating. Clinicians involved in presurgical and postsurgical care may want to counsel patients currently using cannabis, especially those who are engaging in frequent use.

Center for Health Policy and Health Services Research
Miller-Matero LR, **Yaldo M**, Chohan S, **Zabel C**, **Patel S**, Chrusciel T, Salas J, Wilson L, Sullivan MD, **Ahmedani BK**, Lustman PJ, and Scherrer JF. Factors Associated with Interest in Engaging in Psychological Interventions for Pain Management. *Clin J Pain* 2023; Epub ahead of print. PMID: 37819213. Full Text

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OBJECTIVE: Engagement in evidence-based psychological interventions for pain management is low. Identifying characteristics associated with interest in interventions can inform approaches to increase uptake and engagement. The purpose of this study was to examine factors associated with interest in psychological interventions among persons with non-cancer pain receiving prescription opioids. METHODSPARTICIPANTS: with non-cancer pain and a new 30-90 day opioid prescription were recruited from two health systems. Participants (N=845) completed measures regarding pain, opioid use, psychiatric symptoms, emotional support, and interest in psychological interventions for pain management. RESULTS: There were 245 (29.0%) participants who reported high interest in psychological interventions for pain management. In bivariate analyses, variables associated with interest included younger age, female gender, greater pain severity, greater pain interference, greater number of pain sites, lower emotional support, depression, anxiety, and post-traumatic stress disorder (P<0.05). In a multivariate model, greater pain severity (OR=1.17; CI: 1.04-1.32), depression (OR=2.10; CI: 1.39-3.16), PTSD (OR=1.85; CI: 1.19-2.95), and lower emotional support (OR=0.69; CI: 0.5-0.97) remained statistically significant. DISCUSSION: The rate of interest in psychological interventions for pain management was low, which may indicate that patients initiating opioid treatment of chronic pain have low interest in psychological interventions. Greater pain severity and psychiatric distress were related to interest, and patients with these characteristics may especially benefit from psychological interventions. Providers may want to refer to psychological interventions prior to or when opioids are initiated. Additional work is needed to determine if this would reduce long-term opioid use.

Center for Health Policy and Health Services Research
Secrest S, **Miller-Matero LR**, Chrusciel T, Salas J, Sullivan MD, **Zabel C**, Lustman P, **Ahmedani B**, Carpenter RW, and Scherrer JF. Baseline Characteristics from a New Longitudinal Cohort of Patients with Non-cancer Pain and Chronic Opioid use in the United States. *J Pain* 2023; Epub ahead of print. PMID: 37907114. Request Article

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Retrospective cohort studies have consistently observed that long-term prescription opioid use is a risk factor for new major depressive episodes. However, prospective studies are needed to confirm these findings and to establish evidence for causation. The Prescription Opioids and Depression Pathways cohort study is designed for this purpose. The present report describes the baseline sample and associations between participant characteristics and odds of daily vs. non-daily opioid use. Second, we report associations between participant characteristics and odds of depression, dysthymia, anhedonia, and vital exhaustion. Patients with non-cancer pain were eligible if they started a new period of prescription opioid use lasting 30 to 90 days. Participants were 54.8 (SD±11.3) years of age, 57.3% female and 73% white race. Less than college education was more common among daily vs. non-daily opioid users (32.4% vs. 27.3%; p=0.0008), as was back pain (64.2% vs. 51.3%; p<0.0001), any non-opioid substance use disorder (12.8% vs. 4.8%; p<0.0001) and current smoking (30.7% vs. 18.4% p<0.0001). High pain interference (50.9% vs. 28.4%; p<0.0001) was significantly associated with depression, as was having more pain sites (6.9±3.6 vs. 5.7±3.6; p<0.0001), and benzodiazepine co-mediation (38.2% vs. 23.4%; p<0.0001). High pain interference was significantly more common among those with anhedonia (46.8% vs. 27.4%; p<0.0001) and more pain sites (7.0±3.7 vs. 5.6±3.6; p<0.0001) were associated with anhedonia. Having more pain sites (7.9±3.6 vs. 5.5±3.50; p<0.0001) was associated with vital exhaustion as was back pain (71.9% vs. 56.8%; p=0.0001) and benzodiazepine co-medication (42.8% vs. 22.8%; p<0.0001). Patients using prescription opioids for non-cancer pain have complex pain, psychiatric, and substance use disorder comorbidities. Longitudinal data will reveal whether long-term opioid therapy leads to depression or other mood disturbances such as anhedonia and vital exhaustion. PERSPECTIVE: This study reports baseline characteristics of a new prospective, non-cancer pain cohort study. Risk factors for adverse opioid outcomes were most common in those with depression and vital exhaustion and less common in dysthymia and anhedonia. Baseline data highlight the complexity of patients receiving long-term opioid therapy for non-cancer pain.

Center for Health Policy and Health Services Research

Wartko PD, Bobb JF, Boudreau DM, Matthews AG, McCormack J, Lee AK, Qiu H, Yu O, Hyun N, Idu AE, Campbell CI, Saxon AJ, Liu DS, Altschuler A, Samet JH, Labelle CT, Zare-Mehrjerdi M, Stotts AL, **Braciszewski JM**, Murphy MT, Dryden D, Arnsten JH, Cunningham CO, Horigian VE, Szapocznik J, Glass JE, Caldeiro RM, Phillips RC, Shea M, Bart G, Schwartz RP, McNeely J, Liebschutz JM, Tsui JI, Merrill JO, Lapham GT, Addis M, Bradley KA, Ghiroli MM, Hamilton LK, **Hu Y**, LaHue JS, **Loree AM**, Murphy SM, Northrup TF, Shmueli-Blumberg D, Silva AJ, Weinstein ZM, Wong MT, and Burganowski RP. Nurse Care Management for Opioid Use Disorder Treatment: The PROUD Cluster Randomized Clinical Trial. *JAMA Intern Med* 2023; Epub ahead of print. PMID: 37902748. Full Text

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IMPORTANCE: Few primary care (PC) practices treat patients with medications for opioid use disorder (OUD) despite availability of effective treatments. OBJECTIVE: To assess whether implementation of the Massachusetts model of nurse care management for OUD in PC increases OUD treatment with buprenorphine or extended-release injectable naltrexone and secondarily decreases acute care utilization. DESIGN, SETTING, AND PARTICIPANTS: The Primary Care Opioid Use Disorders Treatment (PROUD) trial was a mixed-methods, implementation-effectiveness cluster randomized clinical trial conducted in 6 diverse health systems across 5 US states (New York, Florida, Michigan, Texas, and Washington). Two PC clinics in each system were randomized to intervention or usual care (UC) stratified by system (5 systems were notified on February 28, 2018, and 1 system with delayed data use agreement on August 31, 2018). Data were obtained from electronic health records and insurance claims. An implementation monitoring team collected qualitative data. Primary care patients were included if they were 16 to 90 years old and visited a participating clinic from up to 3 years before a system's randomization date through 2 years after. INTERVENTION: The PROUD intervention included 3 components: (1) salary for a full-time OUD nurse care manager; (2) training and technical assistance for nurse care managers; and (3) 3 or more PC clinicians agreeing to prescribe buprenorphine. MAIN OUTCOMES AND MEASURES: The primary outcome was a clinic-level measure of patient-years of OUD treatment (buprenorphine or extended-release injectable naltrexone) per 10 000 PC patients during the 2 years postrandomization (follow-up). The secondary outcome, among patients with OUD prerandomization, was a patient-level measure of the number of days of acute care utilization during follow-up. RESULTS: During the baseline period, a total of 130 623 patients were seen in intervention

clinics (mean [SD] age, 48.6 [17.7] years; 59.7% female), and 159 459 patients were seen in UC clinics (mean [SD] age, 47.2 [17.5] years; 63.0% female). Intervention clinics provided 8.2 (95% CI, 5.4-∞) more patient-years of OUD treatment per 10 000 PC patients compared with UC clinics (P = .002). Most of the benefit accrued in 2 health systems and in patients new to clinics (5.8 [95% CI, 1.3-∞] more patient-years) or newly treated for OUD postrandomization (8.3 [95% CI, 4.3-∞] more patient-years). Qualitative data indicated that keys to successful implementation included broad commitment to treat OUD in PC from system leaders and PC teams, full financial coverage for OUD treatment, and straightforward pathways for patients to access nurse care managers. Acute care utilization did not differ between intervention and UC clinics (relative rate, 1.16; 95% CI, 0.47-2.92; P = .70). CONCLUSIONS AND RELEVANCE: The PROUD cluster randomized clinical trial intervention meaningfully increased PC OUD treatment, albeit unevenly across health systems; however, it did not decrease acute care utilization among patients with OUD. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03407638.

Center for Individualized and Genomic Medicine Research

Budu-Aggrey A, Kilanowski A, Sobczyk MK, Shringarpure SS, Mitchell R, Reis K, Reigo A, Mägi R, Nelis M, Tanaka N, Brumpton BM, Thomas LF, Sole-Navais P, Flatley C, Espuela-Ortiz A, Herrera-Luis E, Lominchar JVT, Bork-Jensen J, Marenholz I, Arnau-Soler A, Jeong A, Fawcett KA, Baurecht H, Rodriguez E, Alves AC, Kumar A, Sleiman PM, Chang X, Medina-Gomez C, Hu C, Xu CJ, Qi C, El-Heis S, Titcombe P, Antoun E, Fadista J, Wang CA, Thiering E, **Wu B**, Kress S, Kothalawala DM, Kadalayil L, Duan J, Zhang H, Hadebe S, Hoffmann T, Jorgenson E, Choquet H, Risch N, Njølstad P, Andreassen OA, Johansson S, Almqvist C, Gong T, Ullemar V, Karlsson R, Magnusson PKE, Szwajda A, Burchard EG, Thyssen JP, Hansen T, Kårhus LL, Dantoft TM, Jeanrenaud A, Ghauri A, Arnold A, Homuth G, Lau S, Nöthen MM, Hübner N, Imboden M, Visconti A, Falchi M, Bataille V, Hysi P, Ballardini N, Boomsma DI, Hottenga JJ, Müller-Nurasyid M, Ahluwalia TS, Stokholm J, Chawes B, Schoos AM, Esplugues A, Bustamante M, Raby B, Arshad S, German C, Esko T, Milani LA, Metspalu A, Terao C, Abuabara K, Løset M, Hveem K, Jacobsson B, Pino-Yanes M, Strachan DP, Grarup N, Linneberg A, Lee YA, Probst-Hensch N, Weidinger S, Jarvelin MR, Melén E, Hakonarson H, Irvine AD, Jarvis D, Nijsten T, Duijts L, Vonk JM, Koppelmann GH, Godfrey KM, Barton SJ, Feenstra B, Pennell CE, Sly PD, Holt PG, **Williams LK**, Bisgaard H, Bønnelykke K, Curtin J, Simpson A, Murray C, Schikowski T, Bunyavanich S, Weiss ST, Holloway JW, Min JL, Brown SJ, Standl M, and Paternoster L. European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation. *Nat Commun* 2023; 14(1):6172. PMID: 37794016. Full Text

Atopic dermatitis (AD) is a common inflammatory skin condition and prior genome-wide association studies (GWAS) have identified 71 associated loci. In the current study we conducted the largest AD GWAS to date (discovery N = 1,086,394, replication N = 3,604,027), combining previously reported cohorts with additional available data. We identified 81 loci (29 novel) in the European-only analysis (which all replicated in a separate European analysis) and 10 additional loci in the multi-ancestry analysis (3 novel). Eight variants from the multi-ancestry analysis replicated in at least one of the populations tested (European, Latino or African), while two may be specific to individuals of Japanese ancestry. AD loci showed enrichment for DNAse I hypersensitivity and eQTL associations in blood. At each locus we prioritised candidate genes by integrating multi-omic data. The implicated genes are predominantly in immune pathways of relevance to atopic inflammation and some offer drug repurposing opportunities.

Dermatology

Kwa M, Guttentag A, Chase L, van Meijgaard J, and **Lim HW**. Trends in price for topical corticosteroids from 2017 to 2021 and the opportunity for cost savings identifiable at the point of care: A retrospective cross-sectional study. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 37730020. Full Text

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BACKGROUND: Topical corticosteroids possess numerous generics and similar-strength substitutes. Affordability can impact obtaining the medication prescribed. OBJECTIVE: To determine recent trends in topical corticosteroid pricing and potential for cost saving. METHODS: A retrospective cross-sectional

study analyzing all prescriptions dispensed for topical corticosteroids from January 1, 2017 through December 31, 2021, using a US all-payer pharmacy-claims database and commercial coupon dataset, was performed. RESULTS: Two hundred thirty-seven unique drug products (≥1 claim) were identified. Factors that predicted for higher cost (P < .05) were branded products (105% more expensive than generics) and ultrapotent class (55% more expensive than low potency) while ointments predicted for lower cost (19% less expensive than creams). Cash prices remained relatively stable, except for ultrapotent branded topical corticosteroids (63% increase). Cost savings were available for both brand-to-generic ($14.75 per unit) and generic-to-generic ($6.82 per unit) switching. Coupon prices were consistently lower than cash prices (r = 0.89). LIMITATIONS: Contracted rates through insurance plans were not included. CONCLUSIONS: Topical corticosteroid prices over the past 5 years have stabilized, the exception being branded ultrapotent corticosteroids. Savings from switching among similar-strength substitutes remain significant despite price stabilization. Coupon prices mirror the hierarchy of cash prices and can help assess real-time costs.

Dermatology
Passeron T, **Lim HW**, Goh CL, Kang HY, Ly F, Morita A, Ocampo-Candiani J, Puig S, Schalka S, Wei L, Demessant AL, Le Floc'h C, Kerob D, Dreno B, and Krutmann J. Do regrets of parents about sun overexposure impact preventive measures applied on their children? *J Eur Acad Dermatol Venereol* 2023; Epub ahead of print. PMID: 37803519. Full Text

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Department of Dermatology, The General Hospital of Air Force PLA, Beijing, China.
La Roche-Posay International, Levallois-Perret, France.
Nantes University, Université Angers, INSERM, Immunology and New Concepts in ImmunoTherapy, INCIT, UMR 1302, Nantes, France.
IUF Leibniz Research Institute for Environmental Medicine, Duesseldorf, Germany.
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Dermatology
Patel A, and **Chaffins M**. Nodular elastosis in the setting of lichen sclerosus. *JAAD Case Rep* 2023; 41:107-109. PMID: 37920702. Full Text

Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.
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Dermatology
Rosales Santillan M, Guzman A, and Waldman AH. Industry Payments Comparison Between Female and Male Mohs Surgeons From 2015 to 2021. *Dermatol Surg* 2023; Epub ahead of print. PMID: 37910514. Full Text

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BACKGROUND: There are limited data on female Mohs surgeon industry relationships. OBJECTIVE: To evaluate industry payment activity between female and male Mohs surgeons. MATERIALS AND METHODS: A retrospective review of the U.S. Centers for Medicare and Medicaid Services open payments data was performed between 2015 and 2021 for Mohs surgeons in the United States. Gender, academic affiliation, practice region, annual total payment, cumulative payment, and industry payment type was collected. RESULTS: Male Mohs surgeons received higher mean total payments than female Mohs surgeons ($p = .04$), which persisted when data were stratified based on industry payment type and practice region. Both genders had similar median total payments ($p = .4$). Females in academic practice received higher mean total payments than those in private practice. Females experienced a significant lower mean total payment compared with males in the South ($p = .03$). CONCLUSION: High total payments received by male Mohs surgeons skewed the data, which is supported by a significant mean total payment difference despite a similar median total payment distribution. Female Mohs surgeons receiving the top payments may address this mean payment difference. Females seem to have higher payments if they practice in the Northeast and are in academics. Further studies are needed to evaluate this payment gap.

Dermatology

Zhang Y, Luo Y, Liu X, Kiupel M, Li A, Wang H, **Mi QS**, and Xiao H. NCOA5 Haploinsufficiency in Myeloid-Lineage Cells Sufficiently Causes Nonalcoholic Steatohepatitis and Hepatocellular Carcinoma. *Cell Mol Gastroenterol Hepatol* 2023; Epub ahead of print. PMID: 37734594. Full Text

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BACKGROUND & AIMS: The nuclear receptor coactivator 5 (NCOA5) is a putative type 2 diabetes susceptibility gene. NCOA5 haploinsufficiency results in the spontaneous development of nonalcoholic fatty liver disease (NAFLD), insulin resistance, and hepatocellular carcinoma (HCC) in male mice; however, the cell-specific effect of NCOA5 haploinsufficiency in various types of cells, including macrophages, on the development of NAFLD and HCC remains unknown. METHODS: Control and myeloid-lineage-specific Ncoa5 deletion (Ncoa5(ΔM/+)) mice fed a normal diet were examined for the development of NAFLD, nonalcoholic steatohepatitis (NASH), and HCC. Altered genes and signaling pathways in the intrahepatic macrophages of Ncoa5(ΔM/+) male mice were analyzed and compared with those of obese human individuals. The role of platelet factor 4 (PF4) in macrophages and the underlying mechanism by which PF4 affects NAFLD/NASH were explored in vitro and in vivo. PF4 expression in HCC patient specimens and prognosis was examined. RESULTS: Myeloid-lineage-specific Ncoa5 deletion sufficiently causes spontaneous NASH and HCC development in male mice fed a normal diet. PF4 overexpression in Ncoa5(ΔM/+) intrahepatic macrophages is identified as a potent mediator to trigger lipid accumulation in hepatocytes by inducing lipogenesis-promoting gene expression. The transcriptome of intrahepatic macrophages from Ncoa5(ΔM/+) male mice resembles that of obese human individuals. High PF4 expression correlated with poor prognosis of HCC patients and increased infiltrations of M2 macrophages, regulatory T cells, and myeloid-derived suppressor cells in HCCs. CONCLUSIONS: Our findings reveal a novel mechanism for the onset of NAFLD/NASH and HCC

initiated by NCOA5-deficient macrophages, suggesting the NCOA5-PF4 axis in macrophages as a potential target for developing preventive and therapeutic interventions against NAFLD/NASH and HCC.

Diagnostic Radiology

Chen Y, Wang Y, **Corrigan J**, and **Memon AB**. B-Cell Lymphoma Presenting With Seventh Cranial Nerve Palsy and Mononeuritis Multiplex: A Case Report and Comprehensive Literature Review. *Cureus* 2023; 15(9):e44983. PMID: 37822434. Full Text

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Diagnosing B-cell lymphoma-associated mononeuritis multiplex is challenging due to its rarity and the potential co-existence of other causes of mononeuritis multiplex. Here, we report a case of a 74-year-old male who initially presented with left cranial neuropathies followed by right-sided extremity weakness with hyporeflexia, right facial involvement, and subsequently asymmetric weakness and multifocal muscle wasting. Minor improvements were observed with multiple rounds of steroid treatment. The diffuse large B-cell lymphoma diagnosis was eventually established six months later upon a repeat mediastinal lymph node biopsy and cerebrospinal fluid cytology. A nerve biopsy demonstrated severe axonal neuropathy with loss of axons in all fascicles without evidence of vasculitis. A muscle biopsy showed atrophy in both type 1 and type 2 fibers. A presentation of mononeuritis multiplex warrants concern for B-cell lymphoma, mainly when other mechanisms of peripheral neuropathy are less likely.

Diagnostic Radiology

Lawrence RL, **Soliman SB**, Dalbøge A, Lohse K, and **Bey MJ**. Investigating the multifactorial etiology of supraspinatus tendon tears. *J Orthop Res* 2023; Epub ahead of print. PMID: 37814893. Full Text

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The purpose of this study was to develop a multivariable model to determine the extent to which a combination of etiological factors is associated with supraspinatus tendon tears. Fifty-four asymptomatic individuals (55 ± 4 years) underwent testing of their dominant shoulder. Diagnostic ultrasound was used to assess for a supraspinatus tendon tear. The etiological factors investigated included demographics (age and sex), tendon impingement during shoulder motion (via biplane videoradiography), glenohumeral morphology (via computed tomography imaging), family history of a tear (via self-report), occupational shoulder exposure (via shoulder job exposure matrix), and athletic exposure (via self-report). Univariate relationships between etiological predictors and supraspinatus tears were assessed using logistic regression and odds ratios (ORs), while multivariable relationships were assessed using classification and regression tree analysis. Thirteen participants (24.1%) had evidence of a supraspinatus tear. Individuals with a tear had a higher critical shoulder angle (OR 1.2, $p = 0.028$) and acromial index (OR 1.2, $p = 0.016$) than individuals without a tear. The multivariable model suggested that a tear in this cohort can be explained with acceptable accuracy (AUROC = 0.731) by the interaction between acromial index and shoulder occupational exposure: a tear is more likely in individuals with a high acromial index ($p < 0.001$), and in individuals with a low acromial index and high occupational exposure ($p < 0.001$). The combination of an individual's glenohumeral morphology (acromial index) and occupational shoulder exposure may be important in the development of supraspinatus tears.

Diagnostic Radiology

Morrison CW, Sanjasaz KN, **Nathanson SD**, **Raina-Hukku S**, **Pinkney DM**, and **Davenport AA**. Dedifferentiated endometrial carcinoma metastasis to axillary lymph node: a case report. *J Med Case Rep* 2023; 17(1):451. PMID: 37899461. Full Text

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BACKGROUND: We present an unusual case of a left axillary lymph node metastasis from a primary dedifferentiated endometrial carcinoma. This pattern of metastasis is likely the result of circulating tumor cells reaching the node through its arterial blood supply. CASE PRESENTATION: In this report, a 68-year-old white woman with a dedifferentiated endometrial carcinoma underwent a hysterectomy. She later developed an enlarged axillary lymph node due to metastatic dedifferentiated endometrial carcinoma, treated with chemotherapy and anti-programmed cell death protein 1 immunotherapy resulting in a complete clinical and radiological response. CONCLUSION: A review of the literature reveals the rarity of blood-borne lymph node metastasis, especially with uterine carcinoma. Immunotherapy has shown promising results in the treatment of some subtypes of metastatic uterine carcinoma.

Emergency Medicine

Marsh PL, Moore EE, Moore HB, **Bunch CM**, Aboukhaled M, **Condon SM, 2nd**, Al-Fadhl MD, Thomas SJ, Larson JR, Bower CW, Miller CB, Pearson ML, Twilling CL, Reser DW, Kim GS, Troyer BM, Yeager D, Thomas SG, Srikureja DP, **Patel SS**, Añón SL, Thomas AV, **Miller JB**, Van Ryn DE, Pamulapati SV, Zimmerman D, Wells B, Martin PL, Seder CW, Aversa JG, Greene RB, March RJ, Kwaan HC, Fulkerson DH, Vande Lune SA, Mollnes TE, Nielsen EW, Storm BS, and Walsh MM. Iatrogenic air embolism: pathoanatomy, thromboinflammation, endotheliopathy, and therapies. *Front Immunol* 2023; 14:1230049. PMID: 37795086. Full Text

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Iatrogenic vascular air embolism is a relatively infrequent event but is associated with significant morbidity and mortality. These emboli can arise in many clinical settings such as neurosurgery, cardiac surgery, and liver transplantation, but more recently, endoscopy, hemodialysis, thoracentesis, tissue biopsy, angiography, and central and peripheral venous access and removal have overtaken surgery and trauma as significant causes of vascular air embolism. The true incidence may be greater since many of these air emboli are asymptomatic and frequently go undiagnosed or unreported. Due to the rarity of vascular air embolism and because of the many manifestations, diagnoses can be difficult and require immediate therapeutic intervention. An iatrogenic air embolism can result in both venous and arterial emboli whose anatomic locations dictate the clinical course. Most clinically significant iatrogenic air emboli are caused by arterial obstruction of small vessels because the pulmonary gas exchange filters the more frequent, smaller volume bubbles that gain access to the venous circulation. However, there is a subset of patients with venous air emboli caused by larger volumes of air who present with more protean manifestations. There have been significant gains in the understanding of the interactions of fluid dynamics, hemostasis, and inflammation caused by air emboli due to in vitro and in vivo studies on flow dynamics of bubbles in small vessels. Intensive research regarding the thromboinflammatory changes at the level of the endothelium has been described recently. The obstruction of vessels by air emboli causes immediate pathoanatomic and immunologic and thromboinflammatory responses at the level of the endothelium. In this review, we describe those immunologic and thromboinflammatory responses at the level of the endothelium as well as evaluate traditional and novel forms of therapy for this rare and often unrecognized clinical condition.

Emergency Medicine

Naseem A, **Majed M**, **Abdallah S**, **Saleh M**, **Lirhoff M**, **Bazzi A**, and **Caldwell MT**. Exploring Muslim Women's Reproductive Health Needs and Preferences in the Emergency Department. *West J Emerg Med* 2023; 24(5):983-992. PMID: 37788041. Full Text

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Objective: We explored individual Muslim women's reproductive healthcare experiences, preferences, beliefs, and behaviors in the emergency department (ED) and in general. Methods: This was a qualitative study conducted at a community ED using semi-structured interviews with a piloted interview guide. We interviewed participants awaiting care in the ED with the following criteria: female gender; English or Arabic speaking; aged ≥18 years; and self-identified as Muslim. We conducted interviews in both English and Arabic until thematic saturation was reached. Transcripts were coded using an iteratively developed codebook, maintaining intercoder agreement greater than 80%. We used an inductive thematic analysis to identify themes, and results were interpreted in the context of interview language and patient's age. Results: We interviewed 26 Muslim-identified female ED patients. We found that cultural representation and sensitivity among ED staff mitigated discrimination and promoted inclusion for Muslim ED patients. However, assumptions about Muslim identity also impacted the participants' healthcare. Most participants endorsed a preference for a female clinician for their reproductive healthcare in general, but not necessarily for other areas of medicine. Clinician cultural concordance was not always preferred for participants in the ED due to fears about the loss of confidentiality. Marital status impacted beliefs about reproductive and sexual health in the context of Muslim identity. Overall, family planning was acceptable and encouraged in this patient population. Conclusion: The themes elucidated in this study may guide clinicians in developing culturally sensitive practices when providing reproductive healthcare to the Muslim population.

Emergency Medicine

Rowland GE, Roeckner A, Ely TD, Lebois LAM, van Rooij SJH, Bruce SE, Jovanovic T, House SL, Beaudoin FL, An X, Neylan TC, Clifford GD, Linnstaedt SD, Germine LT, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Musey PI, Jr., Hendry PL, Sheikh S, Jones CW, Punches BE, Kurz MC, Gentile NT, Hudak LA, Pascual JL, Seamon MJ, Harris E, Pearson C, Merchant RC, Domeier RM, Rathlev NK, Sergot P, Sanchez LD, Miller MW, Pietrzak RH, Joormann J, Pizzagalli DA, Sheridan JF, Smoller JW,

Harte SE, Elliott JM, Kessler RC, Koenen KC, McLean SA, Ressler KJ, Stevens JS, and Harnett NG. Prior Sexual Trauma Exposure Impacts Posttraumatic Dysfunction and Neural Circuitry Following a Recent Traumatic Event in the AURORA Study. *Biol Psychiatry Glob Open Sci* 2023; 3(4):705-715. PMID: 37881578. Full Text

BACKGROUND: Prior sexual trauma (ST) is associated with greater risk for posttraumatic stress disorder after a subsequent traumatic event; however, the underlying neurobiological mechanisms remain opaque. We investigated longitudinal posttraumatic dysfunction and amygdala functional dynamics following admission to an emergency department for new primarily nonsexual trauma in participants with and without previous ST. METHODS: Participants (N = 2178) were recruited following acute trauma exposure (primarily motor vehicle collision). A subset (n = 242) completed magnetic resonance imaging that included a fearful faces task and a resting-state scan 2 weeks after the trauma. We investigated associations between prior ST and several dimensions of posttraumatic symptoms over 6 months. We further assessed amygdala activation and connectivity differences between groups with or without prior ST. RESULTS: Prior ST was associated with greater posttraumatic depression ($F(1,1120) = 28.35$, $p = 1.22 \times 10(-7)$, $\eta(p)(2) = 0.06$), anxiety ($F(1,1113) = 17.43$, $p = 3.21 \times 10(-5)$, $\eta(p)(2) = 0.05$), and posttraumatic stress disorder ($F(1,1027) = 11.34$, $p = 7.85 \times 10(-4)$, $\eta(p)(2) = 0.04$) severity and more maladaptive beliefs about pain ($F(1,1113) = 8.51$, $p = .004$, $\eta(p)(2) = 0.02$) but was not related to amygdala reactivity to fearful versus neutral faces (all ps > .05). A secondary analysis revealed an interaction between ST and lifetime trauma load on the left amygdala to visual cortex connectivity (peak Z value: -4.41, corrected $p < .02$). CONCLUSIONS: Findings suggest that prior ST is associated with heightened posttraumatic dysfunction following a new trauma exposure but not increased amygdala activity. In addition, ST may interact with lifetime trauma load to alter neural circuitry in visual processing regions following acute trauma exposure. Further research should probe the relationship between trauma type and visual circuitry in the acute aftermath of trauma.

Endocrinology and Metabolism

Aleppo G, Gal RL, Raghinaru D, **Kruger D**, Beck RW, Bergenstal RM, **Cushman T**, Hood KK, Johnson ML, McArthur T, Bradshaw A, Olson BA, Oser SM, Oser TK, Kollman C, and Weinstock RS. Comprehensive Telehealth Model to Support Diabetes Self-Management. *JAMA Netw Open* 2023; 6(10):e2336876. PMID: 37792375. Full Text

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IMPORTANCE: As the number of patients with diabetes continues to increase in the United States, novel approaches to clinical care access should be considered to meet the care needs for this population, including support for diabetes-related technology. OBJECTIVE: To evaluate a virtual clinic to facilitate comprehensive diabetes care, support continuous glucose monitoring (CGM) integration into diabetes self-management, and provide behavioral health support for diabetes-related issues. DESIGN, SETTING, AND PARTICIPANTS: This cohort study was a prospective, single-arm, remote study involving adult participants with type 1 or type 2 diabetes who were referred through community resources. The study was conducted virtually from August 24, 2020, to May 26, 2022; analysis was conducted at the clinical coordinating center. INTERVENTION: Training and education led by a Certified Diabetes Care and Education Specialist for CGM use through a virtual endocrinology clinic structure, which included endocrinologists and behavioral health team members. MAIN OUTCOMES AND MEASURES: Main outcomes included CGM-measured mean glucose level, coefficient of variation, and time in range (TIR) of 70 to 180 mg/dL, time with values greater than 180 mg/dL or 250 mg/dL, and time with values less than 70 mg/dL or 54 mg/dL. Hemoglobin A1c was measured at baseline and at 12 and 24 weeks. RESULTS:

Among the 234 participants, 160 had type 1 diabetes and 74 had type 2 diabetes. The mean (SD) age was 47 (14) years, 123 (53%) were female, and median diabetes duration was 20 years. Median (IQR) CGM use over 6 months was 96% (91%-98%) for participants with type 1 diabetes and 94% (85%-97%) for those with type 2 diabetes. Mean (SD) hemoglobin A1c (HbA1c) in those with type 1 diabetes decreased from 7.8% (1.6%) at baseline to 7.1% (1.0%) at 3 months and 7.1% (1.0%) at 6 months (mean change from baseline to 6 months, -0.6%, 95% CI, -0.8% to -0.5%; P < .001), with an 11% mean TIR increase over 6 months (95% CI, 9% to 14%; P < .001). Mean HbA1c in participants with type 2 diabetes decreased from 8.1% (1.7%) at baseline to 7.1% (1.0%) at 3 months and 7.1% (0.9%) at 6 months (mean change from baseline to 6 months, -1.0%; 95% CI, -1.4% to -0.7%; P < .001), with an 18% TIR increase over 6 months (95% CI, 13% to 24%; P < .001). In participants with type 1 diabetes, mean percentage of time with values less than 70 mg/dL and less than 54 mg/dL decreased over 6 months by 0.8% (95% CI, -1.2% to -0.4%; P = .001) and by 0.3% (95% CI, -0.5% to -0.2%, P < .001), respectively. In the type 2 diabetes group, hypoglycemia was rare (mean [SD] percentage of time <70 mg/dL, 0.5% [0.6%]; and <54 mg/dL, 0.07% [0.14%], over 6 months). CONCLUSIONS AND RELEVANCE: Results from this cohort study demonstrated clinical benefits associated with implementation of a comprehensive care model that included diabetes education. This model of care has potential to reach a large portion of patients with diabetes, facilitate diabetes technology adoption, and improve glucose control.

Endocrinology and Metabolism

Yaseen A, and **Lahiri SW**. Health Care Provider Prescribing Habits and Barriers to Use of New Type 2 Diabetes Medications: A Single-System Survey Study. *Clin Diabetes* 2023; 41(4):490-501. PMID: 37849520. Request Article

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This survey study evaluated type 2 diabetes medication prescribing patterns of health care providers in different specialties and of different professional designations or levels of training at an academic health care system and sought to identify factors influencing medication choices and uncover barriers to prescribing glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors. High cost and the need for prior authorizations were reported as the main barriers to prescribing drugs in these two classes, along with a lack of experience among some specialists. Greater system support to decrease the administrative burden of prescribing newer medications and greater dialogue among the specialties caring for patients with cardiorenal comorbidities can improve prescribing of these drugs in accordance with clinical practice recommendations.

Gastroenterology

Gonzalez HC, and **Trudeau S**. COVID-19 + Cirrhosis = Excess Hospital Confinement, Excess Casualties. *Dig Dis Sci* 2023; Epub ahead of print. PMID: 37864740. Full Text

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Gastroenterology

Ichkhanian Y, **Nimri F**, **Salman MF**, **Harris K**, **Taha A**, **Fahad H**, and **Zuchelli T**. A challenging case of pancreaticogastric anastomotic stricture in a patient with surgically altered anatomy. *VideoGIE* 2023; 8(10):410-415. PMID: 37849772. Full Text

Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan.

Video 1EUS-guided gastro-jejunostomy using a lumen-apposing metal stent to access the surgical pancreaticogastric anastomotic site and perform EUS-guided de novo pancreatico-gastrostomy for the management of a postsurgical pancreaticogastric anastomotic stricture with pancreatic insufficiency.

Gastroenterology
Mayo MJ, Vierling JM, Bowlus CL, Levy C, Hirschfield GM, Neff GW, Galambos MR, **Gordon SC**, Borg BB, Harrison SA, Thuluvath PJ, Goel A, Shiffman ML, Swain MG, Jones DEJ, Trivedi P, Kremer AE, Aspinall RJ, Sheridan DA, Dörffel Y, Yang K, Choi YJ, and McWherter CA. Open-label, clinical trial extension: Two-year safety and efficacy results of seladelpar in patients with primary biliary cholangitis. *Aliment Pharmacol Ther* 2023; Epub ahead of print. PMID: 37904314. Full Text

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Liver Institute of Virginia, Bon Secours Mercy Health, Richmond and Newport News, Virginia, USA.
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Institute of Cellular Medicine and National Institute for Health Research (NIHR), Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne, UK.
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Department of Gastroenterology and Hepatology, University Hospital Zürich, Zürich, Switzerland.
Department of Gastroenterology and Hepatology, Portsmouth Hospitals University NHS Trust, Queen Alexandra Hospital, Portsmouth, UK.
Faculty of Health, University of Plymouth and South West Liver Unit, University Hospitals Plymouth NHS Trust, Plymouth, UK.
Medical Outpatient Department, Charité Universitätsmedizin, Berlin, Germany.
Biometrics, CymaBay Therapeutics, Inc, Newark, California, USA.
Research and Development, CymaBay Therapeutics, Inc, Newark, California, USA.

BACKGROUND: Seladelpar is a potent and selective peroxisome proliferator-activated receptor-δ agonist that targets multiple cell types involved in primary biliary cholangitis (PBC), leading to anti-cholestatic, anti-inflammatory and anti-pruritic effects. AIMS: To evaluate the long-term safety and efficacy of seladelpar in patients with PBC. METHODS: In an open-label, international, long-term extension study, patients with PBC completing seladelpar lead-in studies continued treatment. Seladelpar was taken orally once daily at doses of 5 or 10 mg with dose adjustment permitted for safety or tolerability. The primary analysis was for safety and the secondary efficacy analysis examined biochemical markers of cholestasis and liver injury. The study was terminated early due to the unexpected histological findings in a concurrent study for non-alcoholic steatohepatitis, which were subsequently found to predate treatment. Safety and efficacy data were analysed through 2 years. RESULTS: There were no serious treatment-related adverse events observed among 106 patients treated with seladelpar for up to 2 years. There

were four discontinuations for safety, one possibly related to seladelpar. Among 53 patients who completed 2 years of seladelpar, response rates increased from years 1 to 2 for the composite endpoint (alkaline phosphatase [ALP] <1.67 × ULN, ≥15% decrease in ALP, and total bilirubin ≤ULN) and ALP normalisation from 66% to 79% and from 26% to 42%, respectively. In those with elevated bilirubin at baseline, 43% achieved normalisation at year 2. CONCLUSIONS: Seladelpar was safe, and markedly improved biochemical markers of cholestasis and liver injury in patients with PBC. These effects were maintained or improved throughout the second year. CLINICALTRIALS: gov: NCT03301506; Clinicaltrialsregister.eu: 2017-003910-16.

Gastroenterology

Obri M, **Ichkhanian Y**, **Brown P**, **Almajed MR**, **Nimri F**, **Taha A**, **Agha Y**, **Jesse M**, **Singla S**, **Piraka C**, and **Zuchelli TE**. Full-thickness resection device for management of lesions involving the appendiceal orifice: Systematic review and meta-analysis. *Endosc Int Open* 2023; 11(9):E899-e907. PMID: 37810898. Full Text

Internal Medicine, Henry Ford Health System, Detroit, United States. RINGGOLD: 2971
Division of Gastroenterology, Henry Ford Health System, Detroit, United States. RINGGOLD: 2971
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Background and study aims Endoscopic resection of lesions involving the appendiceal orifice is technically challenging and is commonly referred for surgical resection. However, post-resection appendicitis is a concern. Many studies have varying rates of post-procedure appendicitis. We aim to report the rate of post-resection appendicitis by performing a systematic review and meta-analysis. Methods Studies that involved the use of a full-thickness resection device (FTRD) for management of appendiceal polyps were included. The primary outcome was appendicitis after FTRD and a subgroup analysis was performed on studies that only included FTRD performed at the appendiceal orifice. Results Appendicitis was encountered in 15% (95%CI: [11-21]) of the patients with 61% (95% CI: [44-76]) requiring surgical management. Pooled rates of technical success, histologic FTR, and histologic R0 resection in this sub-group (n=123) were 92% (95% CI: [85-96]), 98% (95% CI: [93-100]), and 72% (95% CI: [64-84%]), respectively. Post-resection histopathological evaluation revealed a mean resected specimen size of 16.8 ± 5.4 mm, with non-neoplastic pathology in 9 (7%), adenomas in 103 (84%), adenomas + high-grade dysplasia (HGD) in nine (7%), and adenocarcinoma in two (2%). The pooled rate for non-appendicitis-related surgical management (technical failure and/or high-risk lesions) was 11 % (CI: 7-17). Conclusions FTRD appears to be an effective method for managing appendiceal lesions. However, appendicitis post-resection occurs in a non-trivial number of patients and the R0 resection rate in appendiceal lesions is only 72%. Therefore, caution should be employed in the use of this technique, considering the relative risks of surgical intervention in each patient.

Hematology-Oncology

Carpenter ES, Kadiyala P, Elhossiny AM, Kemp SB, Li J, **Steele NG**, Nicolle R, Nwosu ZC, Freeman J, Dai H, Paglia D, Du W, Donahue K, Morales J, Medina-Cabrera PI, Bonilla ME, Harris L, The S, Gunchick V, Peterson N, Brown K, Mattea M, Espinoza CE, McGue J, Kabala SM, Baliira RK, Renollet NM, Mooney AG, Liu J, Bhalla S, Farida JP, Ko C, Machicado JD, Kwon RS, Wamsteker EJ, Schulman A, Anderson MA, Law R, Prabhu A, Coulombe PA, Rao A, Frankel TL, Bednar F, Shi J, Sahai V, and Pasca di Magliano M. KRT17High/CXCL8+ tumor cells display both classical and basal features and regulate myeloid infiltration in the pancreatic cancer microenvironment. *Clin Cancer Res* 2023; Epub ahead of print. PMID: 37851080. Full Text

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PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) is generally divided in two subtypes, classical and basal. Recently, single cell RNA sequencing has uncovered the co-existence of basal and classical cancer cells, as well as intermediary cancer cells, in individual tumors. The latter remains poorly understood; here, we sought to characterize them using a multimodal approach. EXPERIMENTAL DESIGN: We performed subtyping on a single cell RNA sequencing dataset containing 18 human PDAC samples to identify multiple intermediary subtypes. We generated patient-derived PDAC organoids for functional studies. We compared single cell profiling of matched blood and tumor samples to measure changes in the local and systemic immune microenvironment. We then leveraged longitudinally patient-matched blood to follow individual patients over the course of chemotherapy. RESULTS: We identified a cluster of KRT17-high intermediary cancer cells that uniquely express high levels of CXCL8 and other cytokines. The proportion of KRT17High/CXCL8+ cells in patient tumors correlated with intra-tumoral myeloid abundance, and, interestingly, high pro-tumor peripheral blood granulocytes, implicating local and systemic roles. Patient-derived organoids maintained KRT17High/CXCL8+cells and induced myeloid cell migration in an CXCL8-dependent manner. In our longitudinal studies, plasma CXCL8 decreased following chemotherapy in responsive patients, while CXCL8 persistence portended worse prognosis. CONCLUSIONS: Through single cell analysis of PDAC samples we identified KRT17High/CXCL8+ cancer cells as an intermediary subtype, marked by a unique cytokine profile and capable of influencing myeloid cells in the tumor microenvironment and systemically. The abundance of this cell population should be considered for patient stratification in precision immunotherapy.

Hematology-Oncology
Dorff T, Zengin Z, Henderson N, Ali A, **Nguyen C**, **Hwang C**, Barata PC, Bilen M, Graham L, Mo G, Kilari D, Tripathi A, Labriola M, Rothstein S, Garje R, Koshkin V, Patel V, Schweizer M, Armstrong A, McKay R, and Alva A. Clinical implications of AR alterations in advanced prostate cancer: A multi-institutional collaboration. *Res Sq* 2023; Epub ahead of print. PMID: 37609284. Full Text

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Duke University Medical Center.
Moores Cancer Center.
University of Michigan-Ann Arbor.

BACKGROUND: AR gene alterations can develop in response to pressure of testosterone suppression and androgen receptor targeting agents (ARTA). Despite this, the relevance of these gene alterations in the context of ARTA treatment and clinical outcomes remains unclear. METHODS: Patients with castration-resistant prostate cancer (CRPC) who had undergone genomic testing and received ARTA treatment were identified in the Prostate Cancer Precision Medicine Multi-Institutional Collaborative Effort (PROMISE) database. Patients were stratified according to the timing of genomic testing relative to the first ARTA treatment (pre-/post-ARTA). Clinical outcomes such as time to progression, PSA response, and overall survival were compared based on alteration types. RESULTS: In total, 540 CRPC patients who received ARTA and had tissue-based (n=321) and/or blood-based (n=244) genomic sequencing were identified. Median age was 62 years (range 39-90) at the time of the diagnosis. Majority were White

(72.2%) and had metastatic disease (92.6%) at the time of the first ARTA treatment. Pre-ARTA genomic testing was available in 24.8% of the patients, and AR mutations and amplifications were observed in 8.2% and 13.1% of the patients, respectively. Further, time to progression was longer in patients with AR amplifications (25.7 months) compared to those without an AR alteration (9.6 months; p=0.03). In the post-ARTA group (n=406), AR mutations and AR amplifications were observed in 18.5% and 35.7% of the patients, respectively. The most common mutation in post-ARTA group was L702H (9.9%). CONCLUSION: To our knowledge, this is the largest real-world clinicogenomics database-driven study exploring the development of ARalterations and their association with ARTA treatment outcomes. Our study showed that AR amplifications are associated with longer time to progression on first ARTA treatment. Further prospective studies are needed to optimize therapeutic strategies for patients with AR alterations.

Hematology-Oncology

Jiagge E, Jin DX, Newberg JY, Perea-Chamblee T, Pekala KR, Fong C, Waters M, Ma D, Dei-Adomakoh Y, Erb G, Arora KS, Maund SL, Njiraini N, Ntekim A, Kim S, Bai X, Thomas M, van Eeden R, Hegde P, Jee J, Chakravarty D, Schultz N, Berger MF, Frampton GM, Sokol ES, and Carrot-Zhang J. Tumor sequencing of African ancestry reveals differences in clinically relevant alterations across common cancers. *Cancer Cell* 2023; Epub ahead of print. PMID: 37890492. Full Text

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Cancer genomes from patients with African (AFR) ancestry have been poorly studied in clinical research. We leverage two large genomic cohorts to investigate the relationship between genomic alterations and AFR ancestry in six common cancers. Cross-cancer type associations, such as an enrichment of MYC amplification with AFR ancestry in lung, breast, and prostate cancers, and depletion of BRAF alterations are observed in colorectal and pancreatic cancers. There are differences in actionable alterations, such as depletion of KRAS G12C and EGFR L858R, and enrichment of ROS1 fusion with AFR ancestry in lung cancers. Interestingly, in lung cancer, KRAS mutations are less common in both smokers and non-smokers with AFR ancestry, whereas the association of TP53 mutations with AFR ancestry is only seen

in smokers, suggesting an ancestry-environment interaction that modifies driver rates. Our study highlights the need to increase representation of patients with AFR ancestry in drug development and biomarker discovery.

Hematology-Oncology

Nagaraj G, Vinayak S, Khaki AR, Sun T, Kuderer NM, Aboulafia DM, Acoba JD, Awosika J, Bakouny Z, Balmaceda NB, Bao T, Bashir B, Berg S, Bilen MA, Bindal P, Blau S, Bodin BE, Borno HT, Castellano C, Choi H, Deeken J, Desai A, Edwin N, Feldman LE, Flora DB, Friese CR, Galsky MD, Gonzalez CJ, Grivas P, Gupta S, Haynam M, Heilman H, Hershman DL, **Hwang C**, Jani C, Jhawar SR, Joshi M, Kaklamani V, Klein EJ, Knox N, Koshkin VS, Kulkarni AA, Kwon DH, Labaki C, Lammers PE, Lathrop KI, Lewis MA, Li X, Lopes GL, Lyman GH, Makower DF, Mansoor AH, Markham MJ, Mashru SH, McKay RR, Messing I, Mico V, Nadkarni R, Namburi S, Nguyen RH, Nonato TK, O'Connor TL, Panagiotou OA, Park K, Patel JM, Patel KG, Peppercorn J, Polimera H, Puc M, Rao YJ, Razavi P, Reid SA, Riess JW, Rivera DR, Robson M, Rose SJ, Russ AD, Schapira L, Shah PK, Shanahan MK, Shapiro LC, Smits M, Stover DG, Streckfuss M, Tachiki L, Thompson MA, Tolaney SM, Weissmann LB, Wilson G, Wotman MT, Wulff-Burchfield EM, Mishra S, French B, Warner JL, Lustberg MB, Accordino MK, and Shah DP. Clinical characteristics, racial inequities, and outcomes in patients with breast cancer and COVID-19: a COVID-19 and cancer consortium (CCC19) cohort study. *Elife* 2023; 12. PMID: 37846664. Full Text

Background: Limited information is available for patients with breast cancer (BC) and coronavirus disease 2019 (COVID-19), especially among underrepresented racial/ethnic populations. Methods: This is a COVID-19 and Cancer Consortium (CCC19) registry-based retrospective cohort study of females with active or history of BC and laboratory-confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection diagnosed between March 2020 and June 2021 in the US. Primary outcome was COVID-19 severity measured on a five-level ordinal scale, including none of the following complications, hospitalization, intensive care unit admission, mechanical ventilation, and all-cause mortality. Multivariable ordinal logistic regression model identified characteristics associated with COVID-19 severity. Results: 1,383 female patient records with BC and COVID-19 were included in the analysis, the median age was 61 years, and median follow-up was 90 days. Multivariable analysis revealed higher odds of COVID-19 severity for older age (aOR per decade, 1.48 [95% CI, 1.32 -1.67]); Black patients (aOR 1.74; 95 CI 1.24-2.45), Asian Americans and Pacific Islander patients (aOR 3.40; 95 CI 1.70 - 6.79) and Other (aOR 2.97; 95 CI 1.71-5.17) racial/ethnic groups; worse ECOG performance status (ECOG PS ≥2: aOR, 7.78 [95% CI, 4.83 - 12.5]); pre-existing cardiovascular (aOR, 2.26 [95% CI, 1.63 - 3.15])/pulmonary comorbidities (aOR, 1.65 [95% CI, 1.20 - 2.29]); diabetes mellitus (aOR, 2.25 [95% CI, 1.66 - 3.04]); and active and progressing cancer (aOR, 12.5 [95% CI, 6.89 - 22.6]). Hispanic ethnicity, timing and type of anti-cancer therapy modalities were not significantly associated with worse COVID-19 outcomes. The total all-cause mortality and hospitalization rate for the entire cohort was 9% and 37%, respectively however, it varied according to the BC disease status. Conclusions: Using one of the largest registries on cancer and COVID-19, we identified patient and BC related factors associated with worse COVID-19 outcomes. After adjusting for baseline characteristics, underrepresented racial/ethnic patients experienced worse outcomes compared to Non-Hispanic White patients. Funding: This study was partly supported by National Cancer Institute grant number P30 CA068485 to Tianyi Sun, Sanjay Mishra, Benjamin French, Jeremy L. Warner; P30-CA046592 to Christopher R. Friese; P30 CA023100 for Rana R McKay; P30-CA054174 for Pankil K. Shah and Dimpy P. Shah; and the American Cancer Society and Hope Foundation for Cancer Research (MRSG-16-152-01 -CCE) and P30-CA054174 for Dimpy P. Shah. REDCap is developed and supported by Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH). The funding sources had no role in the writing of the manuscript or the decision to submit it for publication. Clinical Trial Number: CCC19 registry is registered on ClinicalTrials.gov, NCT04354701.

Hematology-Oncology

Neslund-Dudas C, **Tang A**, **Alleman E**, **Zarins KR**, **Li P**, **Simoff MJ**, **Lafata JE**, Rendle KA, Hartman ANB, Honda SA, Oshiro C, Olaiya O, Greenlee RT, Vachani A, and Ritzwoller DP. Uptake of Lung Cancer Screening CT After a Provider Order for Screening in the PROSPR-Lung Consortium. *J Gen Intern Med* 2023; Epub ahead of print. PMID: 37783984. Full Text

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Institute for Health Research, Kaiser Permanente Colorado, Aurora, CO, USA.
Center for Integrated Healthcare Research, Kaiser Permanente Hawaii, Honolulu, HI, USA.
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Marshfield Clinic Research Institute, Marshfield, WI, USA.

BACKGROUND: Uptake of lung cancer screening (LCS) has been slow with less than 20% of eligible people who currently or formerly smoked reported to have undergone a screening CT. OBJECTIVE: To determine individual-, health system-, and neighborhood-level factors associated with LCS uptake after a provider order for screening. DESIGN AND SUBJECTS: We conducted an observational cohort study of screening-eligible patients within the Population-based Research to Optimize the Screening Process (PROSPR)-Lung Consortium who received a radiology referral/order for a baseline low-dose screening CT (LDCT) from a healthcare provider between January 1, 2015, and June 30, 2019. MAIN MEASURES: The primary outcome is screening uptake, defined as LCS-LDCT completion within 90 days of the screening order date. KEY RESULTS: During the study period, 18,294 patients received their first order for LCS-LDCT. Orders more than doubled from the beginning to the end of the study period. Overall, 60% of patients completed screening after receiving their first LCS-LDCT order. Across health systems, uptake varied from 41 to 87%. In both univariate and multivariable analyses, older age, male sex, former smoking status, COPD, and receiving care in a centralized LCS program were positively associated with completing LCS-LDCT. Unknown insurance status, other or unknown race, and lower neighborhood socioeconomic status, as measured by the Yost Index, were negatively associated with screening uptake. CONCLUSIONS: Overall, 40% of patients referred for LCS did not complete a LDCT within 90 days, highlighting a substantial gap in the lung screening care pathway, particularly in decentralized screening programs.

Hematology-Oncology

Ramanan S, **Singh H**, **Ahmed O**, **Zande M**, and **Trimble M**. A Rare Case of Splenic Infarct Secondary to Mobile Cardiac Echodensity. *Cureus* 2023; 15(10):e46434. PMID: 37927647. Full Text

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Lambl's excrescences (LE) are mobile filiform lesions, mostly found on the left-sided heart valves. Histologically, they have a mesenchymal origin with a single endothelial layer. They have the potential to detach, resulting in catastrophic thromboembolic events. Their rarity often leads to them being misdiagnosed as vegetations of endocarditis with patients failing to improve on conventional therapy. A 48-year-old female with a history of hypertension presented to the Emergency Department with a one-week history of sharp left upper quadrant pain. She was vitally stable; the only lab abnormality was revealed to be a mildly elevated white cell count. CT abdomen revealed a splenic infarct involving 25% of the parenchyma. Patients had no history of abdominal trauma, coagulation disorders, exogenous estrogen use or IV drug abuse. Subsequent investigations failed to reveal any cause of hypercoagulability. An extensive cardiac workup revealed no arrhythmias, but transesophageal echocardiogram showed a mobile echo density on the ventricular side of the aortic valve attached at the coaptation zone, approximately 2.7 cm long and 0.1 cm wide, suggesting a very prominent Lambl's excrescence. In the absence of any other findings, the patient's splenic infarct was determined to be secondary to an embolic event from the aortic valve lesion. Rivaroxaban was initiated and the patient subsequently improved. Existing literature describes most LEs as being asymptomatic and discovered incidentally on echocardiograms. This case illustrates the need to develop a criterion for prompt identification of LEs and differentiating them from the vegetations of endocarditis. It also brings forth the

question of prophylactic treatment of these lesions while highlighting the lack of guidelines regarding the management of embolic phenomena secondary to LE.

Hematology-Oncology
Rashidijahanabad Z, Ramadan S, O'Brien NA, Nakisa A, Lang S, **Crawford H**, Gildersleeve JC, and Huang X. Stereoselective Synthesis of Sialyl Lewis(a) Antigen and the Effective Anticancer Activity of Its Bacteriophage Qβ Conjugate as an Anticancer Vaccine. *Angew Chem Int Ed Engl* 2023; Epub ahead of print. PMID: 37781858. Full Text

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Sialyl Lewis(a) (sLe(a)), also known as cancer antigen 19-9 (CA19-9), is a tumor-associated carbohydrate antigen. The overexpression of sLe(a) on the surface of a variety of cancer cells makes it an attractive target for anticancer immunotherapy. However, sLe(a) -based anticancer vaccines have been under-explored. To develop a new vaccine, efficient stereoselective synthesis of sLe(a) with an amine-bearing linker was achieved, which was subsequently conjugated with a powerful carrier bacteriophage, Qβ. Mouse immunization with the Qβ-sLe(a) conjugate generated strong and long-lasting anti-sLe(a) IgG antibody responses, which were superior to those induced by the corresponding conjugate of sLe(a) with the benchmark carrier keyhole limpet hemocyanin. Antibodies elicited by Qβ-sLe(a) were highly selective toward the sLe(a) structure, could bind strongly with sLe(a) -expressing cancer cells and human pancreatic cancer tissues, and kill tumor cells through complement-mediated cytotoxicity. Furthermore, vaccination with Qβ-sLe(a) significantly reduced tumor development in a metastatic cancer model in mice, demonstrating tumor protection for the first time by a sLe(a) -based vaccine, thus highlighting the significant potential of sLe(a) as a promising cancer antigen.

Hematology-Oncology
Roy RV, Means N, Rao G, Asfa S, Madka V, Dey A, Zhang Y, Choudhury M, Fung KM, Dhanasekaran DN, Friedman JE, **Crawford HC**, Rao CV, Bhattacharya R, and Mukherjee P. Pancreatic Ubap2 deletion regulates glucose tolerance, inflammation, and protection from cerulein-induced pancreatitis. *Cancer Lett* 2023; 578:216455. PMID: 37865160. Full Text

Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; Department of Pathology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.
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Ubiquitin-binding associated protein 2 (UBAP2) is reported to promote macropinocytosis and pancreatic adenocarcinoma (PDAC) growth, however, its role in normal pancreatic function remains unknown. We addressed this knowledge gap by generating UBAP2 knockout (U2KO) mice under a pancreas-specific Cre recombinase (Pdx1-Cre). Pancreatic architecture remained intact in U2KO animals, but they demonstrated slight glucose intolerance compared to controls. Upon cerulein challenge to induce pancreatitis, U2KO animals had reduced levels of several pancreatitis-relevant cytokines, amylase and lipase in the serum, reduced tissue damage, and lessened neutrophil infiltration into the pancreatic tissue. Mechanistically, cerulein-challenged U2KO animals revealed reduced NF-κB activation compared to controls. In vitro promoter binding studies confirmed the reduction of NF-κB binding to its target molecules supporting UBAP2 as a new regulator of inflammation in pancreatitis and may be exploited as a therapeutic target in future to inhibit pancreatitis.

Hematology-Oncology
Steele NG, and **Hartway KM**. Multi-omics analysis of metastatic pancreatic cancer reveals an immunosuppressive landscape. *Med* 2023; 4(10):657-659. PMID: 37837960. Request Article

Henry Ford Pancreatic Cancer Center, Department of Surgery, Henry Ford Hospital, Detroit, MI 48202, USA; Department of Pathology, Wayne State University School of Medicine, Detroit, MI 48202, USA; Deparment of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824, USA. Electronic address: nsteele1@hfhs.org.
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Immune cell populations play key functional roles in tumor growth and metastasis, and multi-omic approaches can map cellular interactions to identify targets for highly immunosuppressive and treatment resistant cancers. In this issue of Med, Zhang et al.(1) investigate the immune cell landscape of advanced pancreatic cancer to understand the mechanisms underlying liver metastasis.

Hematology-Oncology
Udumula MP, **Singh H**, **Rashid F**, **Poisson L**, **Tiwari N**, **Dimitrova I**, **Hijaz M**, Gogoi R, **Swenor M**, **Munkarah A**, **Giri S**, and **Rattan R**. Intermittent fasting induced ketogenesis inhibits mouse epithelial ovarian cancer by promoting antitumor T cell response. *iScience* 2023; 26(10):107839. PMID: 37822507. Full Text

Department of Women's Health Services, Henry Ford Hospital and Henry Ford Cancer Institute, Detroit, MI, USA.
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In various cancer models, dietary interventions have been shown to inhibit tumor growth, improve anticancer drug efficacy, and enhance immunity, but no such evidence exists for epithelial ovarian cancer (EOC), the most lethal gynecologic cancer. The anticancer immune responses induced by 16-h intermittent fasting (IF) were studied in mice with EOC. IF consistently reduced metabolic growth factors and cytokines that stimulate tumor growth, creating a tumor-hostile environment. Immune profiling

showed that IF dramatically alters anti-cancer immunity by increasing CD4(+) and CD8(+) cells, Th1 and cytotoxic responses, and metabolic fitness. β-hydroxy butyrate (BHB), a bioactive metabolite produced by IF, partially imitates its anticancer effects by inducing CD8(+) effector function. In a direct comparison, IF outperformed exogenous BHB treatment in survival and anti-tumor immune response, probably due to increased ketogenesis. Thus, IF and one of its metabolic mediators BHB suppress EOC growth and sustain a potent anti-tumor T cell response.

Hospital Medicine

Gupta K, **Zahedi S**, **Kakar TS**, Khuttan A, Kalra R, and **Zweig BM**. Independent prognostic value of high-risk ventricular premature complexes during exercise or recovery in asymptomatic patients: A meta-analysis of observational studies. *Indian Heart J* 2023; Epub ahead of print. PMID: 37858721. Full Text

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INTRODUCTION: Ventricular premature contractions (VPCs) are a common finding during cardiac stress tests. The independent prognostic value of these findings in patients in asymptomatic patients is unclear. METHODS: We conducted a systematic review and meta-analysis of observational studies exploring the independent prognostic value of VPCs to predict all-cause mortality. The secondary outcome was cardiovascular (CV) mortality. We excluded studies that did not report outcomes after adjusting for ≥1 confounder. Random effect meta-analyses were used to predict cumulative hazard ratios. We stratified results based on VPC during exercise or recovery. RESULTS: We found 7 studies with 24,518 patients that met our inclusion criteria. Two studies reported all-cause mortality only, 1 study reported CV mortality only, rest 4 reported both. There was significant heterogeneity in the baseline population, definition of high-risk VPCs, and variables used in adjusted models. Using multivariable summary estimates from individual studies, only VPCs during exercise were associated with a higher risk of all-cause mortality (HR 1.27, 95 % CI 1.07, 1.48). Both VPCs during exercise and recovery were associated with a higher risk CV mortality (HR 1.69, 95 % CI 1.19, 2.20, I(2) = 17.6 % and 1.62, 95 % CI 1.25, 2.00, $p < 0.001$ for both). CONCLUSION: High-risk VPCs during exercise is associated with increased risk of all-cause and CV mortality, while those during recovery are associated with an increased risk of CV mortality only.

Hospital Medicine

Munroe ES, Heath ME, **Eteer M**, Gershengorn HB, Horowitz JK, Jones J, **Kaatz S**, Tamae Kakazu M, McLaughlin E, Flanders SA, and Prescott HC. Use and outcomes of peripheral vasopressors in early sepsis-induced hypotension across Michigan hospitals: a retrospective cohort study. *Chest* 2023; Epub ahead of print. PMID: 37898185. Full Text

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BACKGROUND: Vasopressors are traditionally administered via central access, but newer data suggest peripheral administration may be safe and avoid delays and complications associated with central line placement. RESEARCH QUESTION: How commonly are vasopressors initiated through peripheral IVs in routine practice? Is vasopressor initiation route associated with in-hospital mortality? STUDY DESIGN AND METHODS: This retrospective cohort study included adults hospitalized with sepsis (11/2020-9/2022) at 29 hospitals in the Michigan Hospital Medicine Safety Consortium, a Collaborative Quality Initiative sponsored by Blue Cross Blue Shield of Michigan. We assessed route of early vasopressor initiation, factors and outcomes associated with peripheral initiation, and timing of central line placement. RESULTS: 594 patients received vasopressors within 6 hours of hospital arrival and were included in this study. Peripheral vasopressor initiation was common (400/594, 67.3%). Patients with peripheral vs central initiation were similar; body mass index was the only patient factor independently associated with initiation route (aOR of peripheral initiation [per 1 kg/m(2) increase]: 0.98, 95%CI: 0.97-1.00, p=0.015). Hospital had a large impact on initiation route (median OR: 2.19, 95%CI: 1.31-3.07). Compared to central, peripheral initiation was faster (median 2.5 vs 2.7 hours from hospital arrival, p=0.002) but associated with less initial norepinephrine use (84.3% vs 96.8%, p=0.001). We found no independent association between initiation route and in-hospital mortality (32.3% vs 42.2%, aOR 0.66, 95%CI: 0.39-1.12). There was no documented tissue injury from peripheral vasopressors. Of patients with peripheral initiation, 135/400 (33.8%) never had a central line placed. INTERPRETATION: Peripheral vasopressor initiation was common across Michigan hospitals and had practical benefits, including expedited vasopressor administration and avoidance of central line placement in one-third of patients. However, there was wide practice variation not explained by patient case-mix and lower use of first-line norepinephrine with peripheral administration, suggesting additional standardization may be needed.

Infectious Diseases

Hardy ME, **Kenney RM**, **Tibbetts RJ**, **Shallal AB**, and **Veve MP**. Leveraging stewardship to promote ceftriaxone use in severe infections with low- and no-risk AmpC Enterobacterales. *Antimicrob Agents Chemother* 2023; Epub ahead of print. PMID: 37882541. Full Text

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AmpC β-lactamases are associated with development of ceftriaxone resistance despite initial in vitro susceptibility, but the risk of AmpC derepression is not equal among Enterobacterales. The purpose of this study was to evaluate the impact of an AmpC stewardship intervention on the definitive treatment of low- and no-risk Enterobacterales. This was an IRB-approved, single pre-test, post-test quasi-experiment at a 5-hospital system. An AmpC stewardship intervention was implemented in July 2022 and included prescriber education, the removal of microbiology comments indicating potential for ceftriaxone resistance on therapy, and the modification of a blood PCR comment for Serratia marcescens to recommend ceftriaxone. Adults ≥18 years pre-intervention (July 2021 to December 2021) and post-intervention (July 2022 to December 2022) who received ≥72 hours of inpatient definitive therapy and had non-urine cultures growing low- and no-risk organisms (S. marcescens, Providencia spp., Citrobacter koseri, Citrobacter amalonaticus, or Morganella morganii) were included. The primary endpoint was definitive treatment with ceftriaxone. A total of 224 patients were included; 115 (51%) in pre-intervention and 109 (49%) in post-intervention. Definitive ceftriaxone therapy was prescribed more frequently after intervention [6 (5%) vs 72 (66%), P < 0.001]. After adjustment for critical illness, patients in the post-group were more likely to receive definitive ceftriaxone (adjOR, 34.7; 95% CI, 13.9-86.6). The proportion of patients requiring retreatment was 18 (15%) and 11 (10%) for pre- and post-intervention patients (P = 0.22), and ceftriaxone resistance within 30 days occurred in 5 (4%) and 2 (2%) patients in the pre- and

post-group (P = 0.45). An antimicrobial stewardship intervention was associated with increased ceftriaxone prescribing and similar patient outcomes for low- and no-risk AmpC Enterobacterales.

Infectious Diseases

Surie D, Yuengling KA, DeCuir J, Zhu Y, Gaglani M, Ginde AA, Talbot HK, Casey JD, Mohr NM, Ghamande S, Gibbs KW, Files DC, Hager DN, Ali H, Prekker ME, Gong MN, Mohamed A, Johnson NJ, Steingrub JS, Peltan ID, Brown SM, Leis AM, Khan A, Hough CL, Bender WS, Duggal A, Wilson JG, Qadir N, Chang SY, Mallow C, Kwon JH, Exline MC, Lauring AS, Shapiro NI, Columbus C, **Vaughn IA**, **Ramesh M**, Safdar B, Halasa N, Chappell JD, Grijalva CG, Baughman A, Rice TW, Womack KN, Han JH, Swan SA, Mukherjee I, Lewis NM, Ellington S, McMorrow ML, Martin ET, and Self WH. Disease Severity of Respiratory Syncytial Virus Compared with COVID-19 and Influenza Among Hospitalized Adults Aged ≥60 Years - IVY Network, 20 U.S. States, February 2022-May 2023. *MMWR Morb Mortal Wkly Rep* 2023; 72(40):1083-1088. PMID: 37796753. Full Text

On June 21, 2023, CDC's Advisory Committee on Immunization Practices recommended respiratory syncytial virus (RSV) vaccination for adults aged ≥60 years, offered to individual adults using shared clinical decision-making. Informed use of these vaccines requires an understanding of RSV disease severity. To characterize RSV-associated severity, 5,784 adults aged ≥60 years hospitalized with acute respiratory illness and laboratory-confirmed RSV, SARS-CoV-2, or influenza infection were prospectively enrolled from 25 hospitals in 20 U.S. states during February 1, 2022-May 31, 2023. Multivariable logistic regression was used to compare RSV disease severity with COVID-19 and influenza severity on the basis of the following outcomes: 1) standard flow (<30 L/minute) oxygen therapy, 2) high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV), 3) intensive care unit (ICU) admission, and 4) invasive mechanical ventilation (IMV) or death. Overall, 304 (5.3%) enrolled adults were hospitalized with RSV, 4,734 (81.8%) with COVID-19 and 746 (12.9%) with influenza. Patients hospitalized with RSV were more likely to receive standard flow oxygen, HFNC or NIV, and ICU admission than were those hospitalized with COVID-19 or influenza. Patients hospitalized with RSV were more likely to receive IMV or die compared with patients hospitalized with influenza (adjusted odds ratio = 2.08; 95% CI = 1.33-3.26). Among hospitalized older adults, RSV was less common, but was associated with more severe disease than COVID-19 or influenza. High disease severity in older adults hospitalized with RSV is important to consider in shared clinical decision-making regarding RSV vaccination.

Internal Medicine

Abusuliman M, Mohamed AM, Mahmoud A, Beliani T, and Ismail-Sayed IM. Peritoneal Carcinoma Unveiling a Hidden Threat: A Case of Malignant Pericardial Effusion. *Cureus* 2023; 15(9):e46059. PMID: 37900376. Full Text

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Malignant pericardial effusion (MPE) is a slowly progressive and potentially clinically silent condition. Pericardial effusion can arise in oncology patients due to several factors, including disease spreading directly or metastatically, anticancer therapy side effects, or both. Solid and hematological malignancy metastasis more frequently involves the pericardium than primary tumors, with lung cancer being the most common metastatic tumor to involve the pericardium. While 5%-20% of all patients with metastatic neoplasms have pericardial involvement, MPE rarely appears with hemodynamic instability. Occasionally, MPE constitutes the initial manifestation of an underlying malignancy. Diagnosis and treatment require a multidisciplinary approach and a high degree of clinical suspicion. We present a case of a 59-year-old female with a history of peritoneal carcinoma who presented with persistent dyspnea on exertion following an episode of pneumonia that was treated with antibiotics. Physical examination and bedside point-of-care ultrasound (POCUS) revealed fluid in the pericardial sac. The cytological examination of the fluid revealed it to be of malignant origin, resulting from metastasis from gynecologic adenocarcinoma. Pericardiocentesis was done, and symptoms improved after fluid drainage.

Internal Medicine

Akce M, Farran B, Switchenko JM, Rupji M, Kang S, Khalil L, Ruggieri-Joyce A, Olson B, Shaib WL, Wu C, Alese OB, **Diab M**, Lesinski GB, and El-Rayes BF. Phase II trial of nivolumab and metformin in patients with treatment-refractory microsatellite stable metastatic colorectal cancer. *J Immunother Cancer* 2023; 11(10). PMID: 37852737. Full Text

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BACKGROUND: Preclinical studies showed metformin reduces exhaustion of tumor-infiltrating lymphocytes and potentiates programmed cell death protein-1 (PD-1) blockade. We hypothesized that metformin with nivolumab would elicit potent antitumor and immune modulatory activity in metastatic microsatellite stable (MSS) colorectal cancer (CRC). We evaluated this hypothesis in a phase II study. METHODS: Nivolumab (480 mg) was administered intravenously every 4 weeks while metformin (1000 mg) was given orally, two times per day following a 14-day metformin only lead-in phase. Patients ≥18 years of age, with previously treated, stage IV MSS CRC, and Eastern Cooperative Oncology Group 0-1, having received no prior anti-PD-1 agent were eligible. The primary endpoint was overall response rate with secondary endpoints of overall survival (OS) and progression-free survival (PFS). Correlative studies using paired pretreatment/on-treatment biopsies and peripheral blood evaluated a series of immune biomarkers in the tumor microenvironment and systemic circulation using ChipCytometry and flow cytometry. RESULTS: A total of 24 patients were enrolled, 6 patients were replaced per protocol, 18 patients had evaluable disease. Of the 18 evaluable patients, 11/18 (61%) were women and the median age was 58 (IQR 50-67). Two patients had stable disease, but no patients had objective response, hence the study was stopped for futility. Median OS and PFS was 5.2 months (95% CI (3.2 to 11.7)) and 2.3 months (95% CI (1.7 to 2.3)). Most common grade 3/4 toxicities: Anemia (n=2), diarrhea (n=2), and fever (n=2). Metformin alone failed to increase the infiltration of T-cell subsets in the tumor, but combined metformin and nivolumab increased percentages of tumor-infiltrating leukocytes (p=0.031). Dual treatment also increased Tim3+ levels in patient tissues and decreased naïve CD8+T cells (p=0.0475). CONCLUSIONS: Nivolumab and metformin were well tolerated in patients with MSS CRC but had no evidence of efficacy. Correlative studies did not reveal an appreciable degree of immune modulation from metformin alone, but showed trends in tumorous T-cell infiltration as a result of dual metformin and PD-1 blockade despite progression in a majority of patients.

Internal Medicine

Almajed MR, Almajed A, **Khan N**, **Obri MS**, and **Ananthasubramaniam K**. Systemic right ventricle complications in levo-transposition of the great arteries: A case report and review of literature. *World J Cardiol* 2023; 15(10):542-552. PMID: 37900900. Full Text

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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 in life. sRV dysfunction and remodeling predisposes patients to intracardiac thrombus (ICT) formation. CASE SUMMARY: A 40-year-old male with L-TGA presented with symptoms of acute decompensated heart failure. 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 showed a sRV ejection fraction of 40%, severe sTV regurgitation, and a newly identified sRV ICT. ICT was confirmed by ultrasound-enhancing agents and transesophageal echocardiography. Our patient was optimized with guideline-directed medical therapy and diuresis. Anticoagulation was achieved with a vitamin K antagonist (VKA) and he was later referred for evaluation by advanced heart failure and heart transplant services. CONCLUSION: Anticoagulation with VKA is the mainstay of treatment in the absence of conclusive data supporting direct oral anticoagulant use in ICT in patients with congenital heart disease. This case illustrates the natural history of L-TGA and highlights the importance of surveillance and monitoring with dedicated cardiac imaging to identify complications.

Internal Medicine

Ekeh L, **Ibrahim H**, **Askar F**, **Meysami A**, and Simmons BA. Cushing's syndrome of the orbit: congestive orbitopathy and optic neuropathy associated with steroids. *Orbit* 2023; 1-4. PMID: 37855748. Request Article

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A 56-year-old female with a history of chronic systemic steroid use for asthma control displayed orbital congestion, exophthalmos, a mild abduction deficit, and optic neuropathy. Laboratory workup was unrevealing. Neuroimaging showed increased orbital fat compartments, though the orbital fat was unremarkable on biopsy. The patient was diagnosed with iatrogenic Cushing's syndrome of the orbit and underwent orbital decompression. Early published literature declared this orbitopathy benign. However, newer cases describe more pathologic changes, suggesting the disease is diagnosed later and/or treatment is delayed.

Internal Medicine

Gupta K, **Zahedi S**, **Kakar TS**, Khuttan A, Kalra R, and **Zweig BM**. Independent prognostic value of high-risk ventricular premature complexes during exercise or recovery in asymptomatic patients: A meta-analysis of observational studies. *Indian Heart J* 2023; Epub ahead of print. PMID: 37858721. Full Text

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INTRODUCTION: Ventricular premature contractions (VPCs) are a common finding during cardiac stress tests. The independent prognostic value of these findings in patients in asymptomatic patients is unclear.

METHODS: We conducted a systematic review and meta-analysis of observational studies exploring the independent prognostic value of VPCs to predict all-cause mortality. The secondary outcome was cardiovascular (CV) mortality. We excluded studies that did not report outcomes after adjusting for ≥1 confounder. Random effect meta-analyses were used to predict cumulative hazard ratios. We stratified results based on VPC during exercise or recovery. RESULTS: We found 7 studies with 24,518 patients that met our inclusion criteria. Two studies reported all-cause mortality only, 1 study reported CV mortality only, rest 4 reported both. There was significant heterogeneity in the baseline population, definition of high-risk VPCs, and variables used in adjusted models. Using multivariable summary estimates from individual studies, only VPCs during exercise were associated with a higher risk of all-cause mortality (HR 1.27, 95 % CI 1.07, 1.48). Both VPCs during exercise and recovery were associated with a higher risk CV mortality (HR 1.69, 95 % CI 1.19, 2.20, I(2) = 17.6 % and 1.62, 95 % CI 1.25, 2.00, p < 0.001 for both). CONCLUSION: High-risk VPCs during exercise is associated with increased risk of all-cause and CV mortality, while those during recovery are associated with an increased risk of CV mortality only.

Internal Medicine
Ichkhanian Y, **Nimri F**, **Salman MF**, **Harris K**, **Taha A**, **Fahad H**, and **Zuchelli T**. A challenging case of pancreaticogastric anastomotic stricture in a patient with surgically altered anatomy. *VideoGIE* 2023; 8(10):410-415. PMID: 37849772. Full Text

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Video 1EUS-guided gastro-jejunostomy using a lumen-apposing metal stent to access the surgical pancreaticogastric anastomotic site and perform EUS-guided de novo pancreatico-gastrostomy for the management of a postsurgical pancreaticogastric anastomotic stricture with pancreatic insufficiency.

Internal Medicine
Memon A, Abdelghany A, **Abusuliman M**, Eldesouki M, Fatima M, Abdelhalim O, and Abosheaishaa H. Altered Mental Status on Top of Anaplasmosis-Induced Severe Rhabdomyolysis: A Rare Clinical Presentation. *Cureus* 2023; 15(9):e45020. PMID: 37829994. Full Text

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Human granulocytic anaplasmosis (HGA) is a disease caused by tick-borne infection of Anaplasma phagocytophilum. The typical symptoms are fever, malaise, and body aches accompanied by abnormal blood tests such as leukopenia, thrombocytopenia, and transaminitis. Some rare complications may occur, especially in patients living in heavily wooded areas, with a mean age of 70 years. We present a case of a 67-year-old male who was admitted for lower abdominal pain, fever, and diarrhea with derangement of his blood tests. Despite treatment, his condition deteriorated and complicated rhabdomyolysis and acute kidney dysfunction. Empiric treatment including doxycycline was initiated while waiting for the infection blood work results. PCR came back positive for HGA. Empiric therapy was narrowed down to doxycycline for 14 days, and the patient's condition began to improve gradually and steadily. Aggressive hydration markedly improved rhabdomyolysis and, in turn, kidney function. Our case underscores the importance of considering HGA in ambiguous clinical scenarios and highlights the value of early diagnosis, empiric treatment, and intravenous hydration, especially in the presence of rhabdomyolysis.

Internal Medicine

Obri M, **Ichkhanian Y**, **Brown P**, **Almajed MR**, **Nimri F**, **Taha A**, **Agha Y**, **Jesse M**, **Singla S**, **Piraka C**, and **Zuchelli TE**. Full-thickness resection device for management of lesions involving the appendiceal orifice: Systematic review and meta-analysis. *Endosc Int Open* 2023; 11(9):E899-e907. PMID: 37810898. Full Text

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Background and study aims Endoscopic resection of lesions involving the appendiceal orifice is technically challenging and is commonly referred for surgical resection. However, post-resection appendicitis is a concern. Many studies have varying rates of post-procedure appendicitis. We aim to report the rate of post-resection appendicitis by performing a systematic review and meta-analysis. Methods Studies that involved the use of a full-thickness resection device (FTRD) for management of appendiceal polyps were included. The primary outcome was appendicitis after FTRD and a subgroup analysis was performed on studies that only included FTRD performed at the appendiceal orifice. Results Appendicitis was encountered in 15% (95%CI: [11-21]) of the patients with 61% (95% CI: [44-76]) requiring surgical management. Pooled rates of technical success, histologic FTR, and histologic R0 resection in this sub-group (n=123) were 92% (95% CI: [85-96]), 98% (95% CI: [93-100]), and 72% (95% CI: [64-84%]), respectively. Post-resection histopathological evaluation revealed a mean resected specimen size of 16.8 ± 5.4 mm, with non-neoplastic pathology in 9 (7%), adenomas in 103 (84%), adenomas + high-grade dysplasia (HGD) in nine (7%), and adenocarcinoma in two (2%). The pooled rate for non-appendicitis-related surgical management (technical failure and/or high-risk lesions) was 11 % (CI: 7-17). Conclusions FTRD appears to be an effective method for managing appendiceal lesions. However, appendicitis post-resection occurs in a non-trivial number of patients and the R0 resection rate in appendiceal lesions is only 72%. Therefore, caution should be employed in the use of this technique, considering the relative risks of surgical intervention in each patient.

Internal Medicine

Ramanan S, **Singh H**, **Ahmed O**, **Zande M**, and **Trimble M**. A Rare Case of Splenic Infarct Secondary to Mobile Cardiac Echodensity. *Cureus* 2023; 15(10):e46434. PMID: 37927647. Full Text

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Lambl's excrescences (LE) are mobile filiform lesions, mostly found on the left-sided heart valves. Histologically, they have a mesenchymal origin with a single endothelial layer. They have the potential to detach, resulting in catastrophic thromboembolic events. Their rarity often leads to them being misdiagnosed as vegetations of endocarditis with patients failing to improve on conventional therapy. A 48-year-old female with a history of hypertension presented to the Emergency Department with a one-week history of sharp left upper quadrant pain. She was vitally stable; the only lab abnormality was revealed to be a mildly elevated white cell count. CT abdomen revealed a splenic infarct involving 25% of the parenchyma. Patients had no history of abdominal trauma, coagulation disorders, exogenous estrogen use or IV drug abuse. Subsequent investigations failed to reveal any cause of hypercoagulability. An extensive cardiac workup revealed no arrhythmias, but transesophageal echocardiogram showed a mobile echo density on the ventricular side of the aortic valve attached at the coaptation zone, approximately 2.7 cm long and 0.1 cm wide, suggesting a very prominent Lambl's excrescence. In the absence of any other findings, the patient's splenic infarct was determined to be secondary to an embolic event from the aortic valve lesion. Rivaroxaban was initiated and the patient subsequently improved. Existing literature describes most LEs as being asymptomatic and discovered incidentally on echocardiograms. This case illustrates the need to develop a criterion for prompt identification of LEs and differentiating them from the vegetations of endocarditis. It also brings forth the question of prophylactic treatment of these lesions while highlighting the lack of guidelines regarding the management of embolic phenomena secondary to LE.

Internal Medicine
Singh H, Yura T, and **Kak V**. Sporadic Creutzfeldt-Jakob Disease With COVID-19 Infection: A Case Report. *Cureus* 2023; 15(9):e45757. PMID: 37872927. Full Text

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Creutzfeldt-Jakob disease (CJD) is a rare and rapidly fatal neurological disease. Diagnosis is made through clinical features, imaging, electroencephalography, and cerebrospinal fluid analysis. Sporadic CJD accounts for the majority of cases and occurs due to somatic mutation in the gene or random structural change in the prion protein. Coronavirus disease 2019 (COVID-19) is known to cause neurodegeneration, and CJD acceleration is hypothesized due to systemic inflammatory response and prion misfolding. We present a 70-year-old lady with rapidly progressing dementia diagnosed as CJD, with the onset coinciding with COVID-19 infection.

Internal Medicine
Yaseen A, and **Lahiri SW**. Health Care Provider Prescribing Habits and Barriers to Use of New Type 2 Diabetes Medications: A Single-System Survey Study. *Clin Diabetes* 2023; 41(4):490-501. PMID: 37849520. Request Article

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This survey study evaluated type 2 diabetes medication prescribing patterns of health care providers in different specialties and of different professional designations or levels of training at an academic health care system and sought to identify factors influencing medication choices and uncover barriers to prescribing glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors. High cost and the need for prior authorizations were reported as the main barriers to prescribing drugs in these two classes, along with a lack of experience among some specialists. Greater system support to decrease the administrative burden of prescribing newer medications and greater dialogue among the specialties caring for patients with cardiorenal comorbidities can improve prescribing of these drugs in accordance with clinical practice recommendations.

Internal Medicine
Zimbrean PC, Rubman S, Andacoglu O, Bakhai D, Clifton E, Deng Y, Doshi M, Emamaullee J, Gan G, Holmes R, Jaber L, Jackson W, Joyce M, Kalil R, Kumar V, Laflen J, Lentine K, **Prashar R**, Winder GS, Yadav A, and Liapakis A. Psychosocial evaluation of living liver Donors- State of current practices in the US. *Liver Transpl* 2023; Epub ahead of print. PMID: 37861339. Full Text

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We surveyed living donor liver transplant (LDLT) programs in the United States to describe practices in the psychosocial evaluation of living donors focused on 1) composition of psychosocial team, 2) domains, workflow, and tools of the psychosocial assessment, 3) absolute and relative mental-health related contraindications to donation, and 4) post-donation psychosocial follow-up. We received 52 unique responses, representing 33 of 50 (66%) of active LDLT programs. Thirty-one (93.9%) provider teams included social workers, 22 (66.7%) psychiatrists, and 14 (42.4%) psychologists. Validated tools were rarely utilized but domains assessed were consistent. Respondents rated active alcohol (93.8%), cocaine (96.8%), and opioid (96.8%) use disorder, as absolute contraindications to donation. Active suicidality (97%), self-injurious behavior (90.9%), eating disorders (87.9%), psychosis (84.8%), non-adherence (71.9%), and inability to cooperate with the evaluation team (78.1%) were absolute contraindications to donation. There were no statistically significant differences in absolute psychosocial contraindications to liver donation between geographical areas or between large and small programs. Programs conduct post-donation psychosocial follow up (57.6%) or screening (39.4%) but routine follow-up of declined donors is rarely conducted (15.8%). Psychosocial evaluation of donor candidates is a multidisciplinary process. The structure of the psychosocial evaluation of donor is not uniform among programs though domains assessed are consistent. Psycho-social contraindications to living liver donation vary amongst the transplant programs. Mental health follow-up of donor candidates is not standardized.

Nephrology

Drawz PE, Lenoir KM, Rai NK, Rastogi A, Chu CD, Rahbari-Oskoui FF, Whelton PK, Thomas G, McWilliams A, Agarwal AK, Suarez MM, Dobre M, Powell J, Rocco MV, Lash JP, Oparil S, Raj DS, Dwyer J, Rahman M, **Soman S**, Townsend RR, Pemu P, Horwitz E, Ix JH, Tuot DS, Ishani A, and Pajewski NM. Effect of Intensive Blood Pressure Control on Kidney Outcomes: Long-Term Electronic Health Record-Based Post-trial Follow-Up of SPRINT. *Clin J Am Soc Nephrol* 2023; Epub ahead of print. PMID: 37883184. Full Text

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BACKGROUND: Intensive blood pressure (BP) lowering in SPRINT produced acute decreases in kidney function and higher risk for acute kidney injury. We evaluated the effect of intensive BP lowering on long-term changes in kidney function using trial and outpatient electronic health record (EHR) creatinine values. METHODS: SPRINT data were linked with EHR data from 49 (of 102) study sites. The primary outcome was the total slope of decline in estimated glomerular filtration rate (eGFR) for the intervention phase and the post-trial slope of decline during the observation phase using trial and outpatient EHR values. Secondary outcomes included a ≥30% decline in eGFR to <60ml/min/1.73m 2 and a ≥50% decline in eGFR or kidney failure among participants with baseline eGFR ≥60 and <60ml/min/1.73m 2 , respectively. RESULTS: EHR creatinine values were available for a median of 8.3 years for 3041 participants. The total slope of decline in eGFR during the intervention phase was -0.67 ml/min/1.73m 2 /year (95% CI -0.79 to -0.56) in the standard treatment group and -0.96 ml/min/1.73m 2 /year (95% CI -1.08 to -0.85) in the intensive treatment group (P <0.001). The slopes were not significantly different during the observation phase: -1.02 ml/min/1.73m 2 per year (95% CI -1.24 to -0.81) in the standard group and -0.85 ml/min/1.73m 2 per year (95% CI -1.07 to -0.64) in the intensive group. Among participants without chronic kidney disease (CKD) at baseline, intensive treatment was associated with higher risk of a ≥30% decline in eGFR during the intervention (hazard ratio (HR) 3.27, 95% CI 2.43, 4.40), but not during the post-intervention observation phase. In those with CKD at baseline, intensive treatment was associated with a higher hazard of eGFR decline only during the intervention phase (HR 1.95, 95% CI 1.03 to 3.70). CONCLUSIONS: Intensive BP lowering was associated with a steeper total slope of decline in eGFR and higher risk for kidney events during the intervention phase of the trial but not during the post-intervention observation phase.

Neurology

Bagić AI, **Bowyer SM**, Burgess RC, Funke ME, Lowden A, Mohamed IS, Wilson T, Zhang W, Zillgitt AJ, and Tenney JR. Role of optically pumped magnetometers in presurgical epilepsy evaluation: Commentary of the American Clinical Magnetoencephalography Society. *Epilepsia* 2023; Epub ahead of print. PMID: 37728519. Full Text

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One of the major challenges of modern epileptology is the underutilization of epilepsy surgery for treatment of patients with focal, medication resistant epilepsy (MRE). Aggravating this distressing failure to deliver optimum care to these patients is the underuse of proven localizing tools, such as magnetoencephalography (MEG), a clinically validated, non-invasive, neurophysiological method used to directly measure and localize brain activity. A sizable mass of published evidence indicates that MEG can improve identification of surgical candidates and guide pre-surgical planning, increasing the yield of SEEG and improving operative outcomes. However, despite at least 10 common, evidence supported,

clinical scenarios in MRE patients where MEG can offer non-redundant information and improve the pre-surgical evaluation, it is regularly used by only a minority of USA epilepsy centers. The current state of the art in MEG sensors employs SQUIDs, which require cooling with liquid helium to achieve superconductivity. This sensor technology has undergone significant generational improvement since whole head MEG scanners were introduced around in 1990s, but still has limitations. Further advances in sensor technology which may make ME G more easily accessible and affordable have been eagerly awaited, and development of new techniques should be encouraged. Of late, optically pumped magnetometers (OPMs) have received considerable attention, even prompting some potential acquisitions of new MEG systems to be put on hold, based on a hope that OPMs will usher in a new generation of MEG equipment and procedures. The development of any new clinical test used to guide intracranial EEG monitoring and/or surgical planning must address several specific issues. The goal of this commentary is to recognize the current state of OPM technology and to suggest a framework for it to advance in the clinical realm where it can eventually be deemed clinically valuable to physicians and patients. The American Clinical MEG Society (ACMEGS) strongly supports more advanced and less expensive technology and looks forward to continuing work with researchers to develop new sensors and clinical devices which will improve the experience and outcome for patients, and perhaps extend the role of MEG. However, currently, there are no OPM devices ready for practical clinical use. Based on the engineering obstacles and the clinical tradeoffs to be resolved, the assessment of experts suggests that there will most likely be another decade relying solely on "frozen SQUIDs" in the clinical MEG field.

Neurology

Chen Y, Wang Y, **Corrigan J**, and **Memon AB**. B-Cell Lymphoma Presenting With Seventh Cranial Nerve Palsy and Mononeuritis Multiplex: A Case Report and Comprehensive Literature Review. *Cureus* 2023; 15(9):e44983. PMID: 37822434. Full Text

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Diagnosing B-cell lymphoma-associated mononeuritis multiplex is challenging due to its rarity and the potential co-existence of other causes of mononeuritis multiplex. Here, we report a case of a 74-year-old male who initially presented with left cranial neuropathies followed by right-sided extremity weakness with hyporeflexia, right facial involvement, and subsequently asymmetric weakness and multifocal muscle wasting. Minor improvements were observed with multiple rounds of steroid treatment. The diffuse large B-cell lymphoma diagnosis was eventually established six months later upon a repeat mediastinal lymph node biopsy and cerebrospinal fluid cytology. A nerve biopsy demonstrated severe axonal neuropathy with loss of axons in all fascicles without evidence of vasculitis. A muscle biopsy showed atrophy in both type 1 and type 2 fibers. A presentation of mononeuritis multiplex warrants concern for B-cell lymphoma, mainly when other mechanisms of peripheral neuropathy are less likely.

Neurology

Kaur J, **Boyd E**, **Ding G**, **Zhang L**, **Luo H**, **Li Q**, **Li L**, **Wei M**, **Landschoot-Ward J**, **Chopp M**, **Zhang Z**, and **Jiang Q**. The Association between Glymphatic System and Perivascular Macrophages in Brain Waste Clearance. *Res Sq* 2023; Epub ahead of print. PMID: 37886481. Full Text

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The glymphatic system suggests the convective bulk flow of cerebrospinal fluid (CSF) through perivascular spaces and the interstitial spaces of the brain parenchyma for the rapid removal of toxic

waste solutes from the brain. However, the presence of convective bulk flow within the brain interstitial spaces is still under debate. We first addressed this argument to determine the involvement of the glymphatic system in brain waste clearance utilizing contrast-enhanced 3D T1-weighted imaging (T1WI), diffusion tensor imaging (DTI), and confocal microscopy imaging. Furthermore, perivascular macrophages (PVMs), which are immune cells located within perivascular spaces, have not been thoroughly explored for their association with the glymphatic system. Therefore, we investigated tracer uptake by PVMs in the perivascular spaces of both the arteries/arterioles and veins/venules and the potential association of PVMs in assisting the glymphatic system for interstitial waste clearance. Our findings demonstrated that both convective bulk flow and diffusion are responsible for the clearance of interstitial waste solutes from the brain parenchyma. Furthermore, our results suggested that PVMs play an important function in glymphatic system-mediated interstitial waste clearance. The glymphatic system and PVMs could be targeted to enhance interstitial waste clearance in patients with waste-associated neurological conditions and aging.

Neurology

Kaur J, **Ding G**, **Zhang L**, **Lu Y**, **Luo H**, **Li L**, **Boyd E**, **Li Q**, **Wei M**, **Zhang Z**, **Chopp M**, and **Jiang Q**. Imaging glymphatic response to glioblastoma. *Cancer Imaging* 2023; 23(1):107. PMID: 37904254. Full Text

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BACKGROUND: The glymphatic system actively exchanges cerebrospinal fluid (CSF) and interstitial fluid (ISF) to eliminate toxic interstitial waste solutes from the brain parenchyma. Impairment of the glymphatic system has been linked to several neurological conditions. Glioblastoma, also known as Glioblastoma multiforme (GBM) is a highly aggressive form of malignant brain cancer within the glioma category. However, the impact of GBM on the functioning of the glymphatic system has not been investigated. Using dynamic contrast-enhanced magnetic resonance imaging (CE-MRI) and advanced kinetic modeling, we examined the changes in the glymphatic system in rats with GBM. METHODS: Dynamic 3D contrast-enhanced T1-weighted imaging (T1WI) with intra-cisterna magna (ICM) infusion of paramagnetic Gd-DTPA contrast agent was used for MRI glymphatic measurements in both GBM-induced and control rats. Glymphatic flow in the whole brain and the olfactory bulb was analyzed using model-derived parameters of arrival time, infusion rate, clearance rate, and residual that describe the dynamics of CSF tracer over time. RESULTS: 3D dynamic T1WI data identified reduced glymphatic influx and clearance, indicating an impaired glymphatic system due to GBM. Kinetic modeling and quantitative analyses consistently indicated significantly reduced infusion rate, clearance rate, and increased residual of CSF tracer in GBM rats compared to control rats, suggesting restricted glymphatic flow in the brain with GBM. In addition, our results identified compromised perineural pathway along the optic nerves in GBM rats. CONCLUSIONS: Our study demonstrates the presence of GBM-impaired glymphatic response in the rat brain and impaired perineural pathway along the optic nerves. Reduced glymphatic waste clearance may lead to the accumulation of toxic waste solutes and pro-inflammatory signaling molecules which may affect the progression of the GBM.

Neurology

Suhail H, **Nematullah M**, **Rashid F**, **Sajad M**, **Fatma M**, **Singh J**, **Zahoor I**, **Cheung WL**, **Tiwari N**, **Ayasolla K**, Kumar A, **Hoda N**, **Rattan R**, and **Giri S**. An early glycolysis burst in microglia regulates mitochondrial dysfunction in oligodendrocytes under neuroinflammation. *iScience* 2023; 26(10):107921. PMID: 37841597. Full Text

Department of Neurology, Henry Ford Health System, Detroit, MI 48202, USA.
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Metabolism and energy processes governing oligodendrocyte function during neuroinflammatory disease are of great interest. However, how varied cellular environments affect oligodendrocyte activity during neuroinflammation is unknown. We demonstrate that activated microglial energy metabolism controls oligodendrocyte mitochondrial respiration and activity. Lipopolysaccharide/interferon gamma promote glycolysis and decrease mitochondrial respiration and myelin protein synthesis in rat brain glial cells. Enriched microglia showed an early burst in glycolysis. In microglia-conditioned medium, oligodendrocytes did not respire and expressed less myelin. SCENITH revealed metabolic derangement in microglia and O4-positive oligodendrocytes in endotoxemia and experimental autoimmune encephalitogenic models. The early burst of glycolysis in microglia was mediated by PDPK1 and protein kinase B/AKT signaling. We found that microglia-produced NO and itaconate, a tricarboxylic acid bifurcated metabolite, reduced mitochondrial respiration in oligodendrocytes. During inflammation, we discovered a signaling pathway in microglia that could be used as a therapeutic target to restore mitochondrial function in oligodendrocytes and induce remyelination.

Neurology
Udumula MP, **Singh H**, **Rashid F**, **Poisson L**, **Tiwari N**, **Dimitrova I**, **Hijaz M**, Gogoi R, **Swenor M**, **Munkarah A**, **Giri S**, and **Rattan R**. Intermittent fasting induced ketogenesis inhibits mouse epithelial ovarian cancer by promoting antitumor T cell response. *iScience* 2023; 26(10):107839. PMID: 37822507. Full Text

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In various cancer models, dietary interventions have been shown to inhibit tumor growth, improve anticancer drug efficacy, and enhance immunity, but no such evidence exists for epithelial ovarian cancer (EOC), the most lethal gynecologic cancer. The anticancer immune responses induced by 16-h intermittent fasting (IF) were studied in mice with EOC. IF consistently reduced metabolic growth factors and cytokines that stimulate tumor growth, creating a tumor-hostile environment. Immune profiling showed that IF dramatically alters anti-cancer immunity by increasing CD4(+) and CD8(+) cells, Th1 and cytotoxic responses, and metabolic fitness. β-hydroxy butyrate (BHB), a bioactive metabolite produced by IF, partially imitates its anticancer effects by inducing CD8(+) effector function. In a direct comparison, IF outperformed exogenous BHB treatment in survival and anti-tumor immune response, probably due to increased ketogenesis. Thus, IF and one of its metabolic mediators BHB suppress EOC growth and sustain a potent anti-tumor T cell response.

Neurology
Zhang L, **Luo H**, **Li C**, **Teng H**, **Powell B**, **Lu M**, **Chopp M**, and **Zhang ZG**. Treatment of stroke in aged male and female rats with Vepoloxamer and tPA reduces neurovascular damage. *Front Neurol* 2023; 14:1282736. PMID: 37869138. Full Text

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Stroke is a leading cause of death and disability worldwide, mainly affecting the elderly. Unfortunately, current treatments for acute ischemic stroke warrant improvement. To date, tissue plasminogen activator (tPA) is of limited use in stroke patients mainly due to its narrow therapeutic window and potential for hemorrhagic complication. The adjuvant treatment with Vepoloxamer, a purified amphipathic polymer has been shown to enhance the thrombolytic efficacy of tPA treatment in young adult male rats after embolic stroke. However, most stroke patients are aged; therefore, the current study investigated the therapeutic effect of the combined tPA and Vepoloxamer treatment in aged male and female rats subjected to embolic stroke. METHODS: Male and female Wistar rats at 18 months of age were subjected to embolic middle cerebral artery occlusion and treated either with monotherapy of tPA or Vepoloxamer, a combination of these two agents, or saline at 4 h after stroke onset. Neurological outcomes were evaluated with a battery of behavioral tests including adhesive removal, foot-fault, and modified neurological severity score tests at 1 and 7 days after stroke onset, followed by histopathological analysis of infarct volume. Residual clot size and vascular patency and integrity were analyzed. RESULTS: The combination treatment with Vepoloxamer and tPA significantly reduced infarct volume and neurological deficits in male and female rats compared to rats treated with saline and the monotherapies of tPA and Vepoloxamer. While Vepoloxamer monotherapy moderately reduced neurological deficits, monotherapies with tPA and Vepoloxamer failed to reduce infarct volume compared to saline treatment. Furthermore, the combination treatment with tPA and Vepoloxamer accelerated thrombolysis, reduced ischemia and tPA-potentiated microvascular disruption, and concomitantly improved cerebrovascular integrity and perfusion in the male ischemic rats. CONCLUSION: Combination treatment with tPA and Vepoloxamer at 4 h after stroke onset effectively reduces ischemic neurovascular damage by accelerating thrombolysis and reducing ischemia and tPA potentiated side effects in the aged rats. This funding suggests that the combination treatment with tPA and Vepoloxamer represents a promising strategy to potentially apply to the general population of stroke patients.

Neurosurgery
Fadel HA, **Pawloski JA**, and **Lee IY**. In Reply: Laser Interstitial Thermal Therapy for First-Line Treatment of Surgically Accessible Recurrent Glioblastoma: Outcomes Compared With a Surgical Cohort. *Neurosurgery* 2023; Epub ahead of print. PMID: 37819071. Full Text

Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA.

Neurosurgery
Field NC, **Entezami P**, Boulos AS, Dalfino J, and Paul AR. Artificial intelligence improves transfer times and ischemic stroke workflow metrics. *Interv Neuroradiol* 2023; Epub ahead of print. PMID: 37847774. Full Text

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INTRODUCTION: Rapid initiation of mechanical thrombectomy (MT) for the treatment of large-vessel occlusion (LVO) critically improves patient outcomes. Artificial intelligence algorithms aid in the identification of LVOs and improve door to puncture times as well as patient transfer times. OBJECTIVES: We aimed to determine whether the implementation of an LVO detection algorithm that provides immediate active notification to the thrombectomy team provider's cell phone would improve ischemic stroke workflow at our institution and aid in patient transfer from outlying hospitals when compared to our prior system of passive computed tomography perfusion software analysis and radiologist interpretation and notification. METHODS: A retrospective review of our institutional thrombectomy registry was performed for all patients who underwent MT between January 2020 and March 2022. Demographic, radiographic, and stroke workflow metrics and notification times were collected. Transfer times and stroke metrics were compared pre- and post-implementation of the Viz.ai (Viz.ai, San Francisco, California, USA) smartphone application. RESULTS: Two hundred sixty-two patients underwent MT during the study period. Door-to-puncture time decreased 15 min ($p = 0.009$) after the implementation of Viz.ai at our

Comprehensive Stroke Center. Transfer time from outside hospitals that implemented Viz.ai was reduced by 37 min (p = 0.04). There was no significant change in transfer time over the same time period in outlying hospitals that did not implement the Viz.ai software. CONCLUSION: Active notification of the neurosurgical team significantly reduces patient transfer time and initiation of MT.

Neurosurgery
Rahman A, **Janic B**, **Rahman T**, **Singh H**, **Ali H**, **Rattan R**, Kazi M, and **Ali MM**. Immunotherapy Enhancement by Targeting Extracellular Tumor pH in Triple-Negative Breast Cancer Mouse Model. *Cancers (Basel)* 2023; 15(20). PMID: 37894298. Full Text

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Triple-negative breast cancer (TNBC), as one of the most aggressive forms of breast cancer, is characterized by a poor prognosis and a very low rate of disease-free and overall survival. In recent years, immunotherapeutic approaches targeting T cell checkpoint molecules, such as cytotoxic lymphocyte antigen-4 (CTLA-4), programmed death1 (PD-1) or its ligand, programmed death ligand 1 (PD-L1), have shown great potential and have been used to treat various cancers as single therapies or in combination with other modalities. However, despite this remarkable progress, patients with TNBC have shown a low response rate to this approach, commonly developing resistance to immune checkpoint blockade, leading to treatment failure. Extracellular acidosis within the tumor microenvironment (also known as the Warburg effect) is one of the factors preventing immune cells from mounting effective responses and contributing to immunotherapy treatment failure. Therefore, reducing tumor acidity is important for increasing cancer immunotherapy effectiveness and this has yet to be realized in the TNBC environment. In this study, the oral administration of sodium bicarbonate (NaHCO(3)) enhanced the antitumor effect of anti-PD-L1 antibody treatment, as demonstrated by generated antitumor immunity, tumor growth inhibition and enhanced survival in 4T1-Luc breast cancer model. Here, we show that NaHCO(3) increased extracellular pH (pH(e)) in tumor tissues in vivo, an effect that was accompanied by an increase in T cell infiltration, T cell activation and IFN-γ, IL2 and IL12p40 mRNA expression in tumor tissues, as well as an increase in T cell activation in tumor-draining lymph nodes. Interestingly, these changes were further enhanced in response to combined NaHCO(3) + anti-PD-L1 therapy. In addition, the acidic extracellular conditions caused a significant increase in PD-L1 expression in vitro. Taken together, these results indicate that alkalizing therapy holds potential as a new tumor microenvironment immunomodulator and we hypothesize that NaHCO(3) can enhance the antitumor effects of anti-PD-L1 breast cancer therapy. The combination of these treatments may have an exceptional impact on future TNBC immunotherapeutic approaches by providing a powerful personalized medicine paradigm. Therefore, our findings have a great translational potential for improving outcomes in TNBC patients.

Obstetrics, Gynecology and Women's Health Services
Combs EL. Raising the Bar for Optimal Maternal Health. *J Obstet Gynecol Neonatal Nurs* 2023; 52(5):329-332. PMID: 37562459. Full Text

The Raising the Bar for Maternal Health Equity and Excellence initiative supports the implementation of transformative measures that address the underlying factors that contribute to the maternal health crisis.

Obstetrics, Gynecology and Women's Health Services
Moawad G, Youssef Y, Fruscalzo A, Faysal H, **Kheil M**, Pirtea P, Guani B, Ayoubi JM, and Feki A. The Present and the Future of Medical Therapies for Adenomyosis: A Narrative Review. *J Clin Med* 2023; 12(19). PMID: 37834773. Full Text

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Uterine Adenomyosis is a benign condition characterized by the presence of endometrium-like epithelial and stromal tissue in the myometrium. Several medical treatments have been proposed, but still, no guidelines directing the management of adenomyosis are available. While a hysterectomy is typically regarded as the definitive treatment for adenomyosis, the scarcity of high-quality data leaves patients desiring fertility with limited conservative options. Based on the available data, the levonorgestrel-IUD appears to offer the most favorable outcomes. Other treatments, including GnRH antagonists, dienogest, prolactin, and oxytocin modulators, show promise; however, further data are required to establish their efficacy definitively. Furthermore, there are many emerging therapies that have been developed that seem worthy of consideration in the near future. The aim of this narrative review was to explore the current medical treatments available for adenomyosis and to provide a glimpse of future therapies under assessment. For this scope, we performed a literature search on PubMed and Medline from incept to September 2022 using the keywords: "medical treatment", "non-steroidal anti-inflammatory", "progesterone intrauterine device", "dienogest", "combined oral contraceptives", "gonadotropin releasing hormone agonist", "gonadotropin releasing hormone antagonist", "danazol", "aromatase inhibitors", "ulipristal acetate", "anti-platelet therapy", "dopamine", "oxytocin antagonists", "STAT3", "KRAS", "MAPK", "micro-RNA", "mifepristone", "valproic acid", "levo-tetrahydropalamatine", and "andrographolide". The search was limited to articles in English, with subsequent screening of abstracts. Abstracts were screened to select relevant studies.

Obstetrics, Gynecology and Women's Health Services

Rahman A, **Janic B**, **Rahman T**, **Singh H**, **Ali H**, **Rattan R**, Kazi M, and **Ali MM**. Immunotherapy Enhancement by Targeting Extracellular Tumor pH in Triple-Negative Breast Cancer Mouse Model. *Cancers (Basel)* 2023; 15(20). PMID: 37894298. Full Text

Department of Neurosurgery, Henry Ford Hospital, Detroit, MI 48202, USA.
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Triple-negative breast cancer (TNBC), as one of the most aggressive forms of breast cancer, is characterized by a poor prognosis and a very low rate of disease-free and overall survival. In recent years, immunotherapeutic approaches targeting T cell checkpoint molecules, such as cytotoxic lymphocyte antigen-4 (CTLA-4), programmed death1 (PD-1) or its ligand, programmed death ligand 1 (PD-L1), have shown great potential and have been used to treat various cancers as single therapies or in combination with other modalities. However, despite this remarkable progress, patients with TNBC have shown a low response rate to this approach, commonly developing resistance to immune checkpoint blockade, leading to treatment failure. Extracellular acidosis within the tumor microenvironment (also known as the Warburg effect) is one of the factors preventing immune cells from mounting effective responses and contributing to immunotherapy treatment failure. Therefore, reducing tumor acidity is important for increasing cancer immunotherapy effectiveness and this has yet to be realized in the TNBC environment. In this study, the oral administration of sodium bicarbonate (NaHCO(3)) enhanced the antitumor effect of anti-PD-L1 antibody treatment, as demonstrated by generated antitumor immunity, tumor growth inhibition and enhanced survival in 4T1-Luc breast cancer model. Here, we show that NaHCO(3) increased extracellular pH (pH(e)) in tumor tissues in vivo, an effect that was accompanied by an increase in T cell infiltration, T cell activation and IFN-γ, IL2 and IL12p40 mRNA expression in tumor tissues, as well as an increase in T cell activation in tumor-draining lymph nodes. Interestingly, these changes were further enhanced in response to combined NaHCO(3) +

anti-PD-L1 therapy. In addition, the acidic extracellular conditions caused a significant increase in PD-L1 expression in vitro. Taken together, these results indicate that alkalizing therapy holds potential as a new tumor microenvironment immunomodulator and we hypothesize that NaHCO(3) can enhance the antitumor effects of anti-PD-L1 breast cancer therapy. The combination of these treatments may have an exceptional impact on future TNBC immunotherapeutic approaches by providing a powerful personalized medicine paradigm. Therefore, our findings have a great translational potential for improving outcomes in TNBC patients.

Obstetrics, Gynecology and Women's Health Services
Suhail H, **Nematullah M**, **Rashid F**, **Sajad M**, **Fatma M**, **Singh J**, **Zahoor I**, **Cheung WL**, **Tiwari N**, **Ayasolla K**, Kumar A, **Hoda N**, **Rattan R**, and **Giri S**. An early glycolysis burst in microglia regulates mitochondrial dysfunction in oligodendrocytes under neuroinflammation. *iScience* 2023; 26(10):107921. PMID: 37841597. Full Text

Department of Neurology, Henry Ford Health System, Detroit, MI 48202, USA.
Department of Ophthalmology/Kresge Eye Institute, Department of Anatomy and Cell Biology, Department of Immunology and Microbiology, Wayne State University, Detroit, MI, USA.
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Metabolism and energy processes governing oligodendrocyte function during neuroinflammatory disease are of great interest. However, how varied cellular environments affect oligodendrocyte activity during neuroinflammation is unknown. We demonstrate that activated microglial energy metabolism controls oligodendrocyte mitochondrial respiration and activity. Lipopolysaccharide/interferon gamma promote glycolysis and decrease mitochondrial respiration and myelin protein synthesis in rat brain glial cells. Enriched microglia showed an early burst in glycolysis. In microglia-conditioned medium, oligodendrocytes did not respire and expressed less myelin. SCENITH revealed metabolic derangement in microglia and O4-positive oligodendrocytes in endotoxemia and experimental autoimmune encephalitogenic models. The early burst of glycolysis in microglia was mediated by PDPK1 and protein kinase B/AKT signaling. We found that microglia-produced NO and itaconate, a tricarboxylic acid bifurcated metabolite, reduced mitochondrial respiration in oligodendrocytes. During inflammation, we discovered a signaling pathway in microglia that could be used as a therapeutic target to restore mitochondrial function in oligodendrocytes and induce remyelination.

Obstetrics, Gynecology and Women's Health Services
Swain M, **Miller M**, **Cannella C**, and **Daviskiba S**. Disparities in fertility preservation among patients diagnosed with female breast cancer. *J Assist Reprod Genet* 2023; Epub ahead of print. PMID: 37819551. Full Text

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PURPOSE: To investigate the association of specific patient factors with disparities in fertility preservation counseling and utilization of fertility preservation among patients ≤ 40 years old diagnosed with female breast cancer. METHODS: A retrospective chart review was conducted investigating patients diagnosed with breast cancer between January 2012 and December 2020 in a multi-site health system. Rates of fertility counseling and utilization of preservation services were compared based on age, race/ethnicity, parity, insurance type, and treatment site. RESULTS: Of the 6,783 patients diagnosed with female breast cancer, 306 (4.5%) were ≤ 40 years old at the time of diagnosis. There was no significant difference between Black or African American and White patients in rates of fertility counseling (12.1% vs 17.4%; $p = 0.285$) or pursuit of fertility preservation (3.3% vs 4.2%; $p = 0.508$), nor was a difference observed when compared by insurance type. However, younger patients (< 30 years of age), patients with 1 or no children, and patients treated in the more affluent county were more likely to undergo counseling and pursue fertility preservation than their matched counterparts. CONCLUSION: Age, parity, and location of breast cancer care may impact rates of fertility counseling and preservation among reproductive age

women diagnosed with breast cancer. Thus, further attention to age discrimination, a patient's desire for future fertility, need for standardization in fertility preservation counseling, and perhaps implementation of comprehensive fertility coverage mandates across all states could help to improve gaps in fertility counseling and fertility preservation.

Obstetrics, Gynecology and Women's Health Services

Udumula MP, **Singh H**, **Rashid F**, **Poisson L**, **Tiwari N**, **Dimitrova I**, **Hijaz M**, Gogoi R, **Swenor M**, **Munkarah A**, **Giri S**, and **Rattan R**. Intermittent fasting induced ketogenesis inhibits mouse epithelial ovarian cancer by promoting antitumor T cell response. *iScience* 2023; 26(10):107839. PMID: 37822507. Full Text

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In various cancer models, dietary interventions have been shown to inhibit tumor growth, improve anticancer drug efficacy, and enhance immunity, but no such evidence exists for epithelial ovarian cancer (EOC), the most lethal gynecologic cancer. The anticancer immune responses induced by 16-h intermittent fasting (IF) were studied in mice with EOC. IF consistently reduced metabolic growth factors and cytokines that stimulate tumor growth, creating a tumor-hostile environment. Immune profiling showed that IF dramatically alters anti-cancer immunity by increasing CD4(+) and CD8(+) cells, Th1 and cytotoxic responses, and metabolic fitness. β-hydroxy butyrate (BHB), a bioactive metabolite produced by IF, partially imitates its anticancer effects by inducing CD8(+) effector function. In a direct comparison, IF outperformed exogenous BHB treatment in survival and anti-tumor immune response, probably due to increased ketogenesis. Thus, IF and one of its metabolic mediators BHB suppress EOC growth and sustain a potent anti-tumor T cell response.

Ophthalmology and Eye Care Services

Cho J, Song M, Niziol LM, Heisler M, Resnicow K, Musch DC, Lee P, **Darnley-Fisch D**, and Newman-Casey PA. Patient-Centered Outcomes After a Medication Adherence Intervention: a Pilot Study. *J Glaucoma* 2023; 32(10):891-899. PMID: 37054438. Full Text

Department of Ophthalmology & Visual Sciences, University of Michigan Medical School, Ann Arbor, MI.
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PRCIS: Self-determination theory (SDT) guided behavioral interventions are effective in improving several patient-centered metrics, including glaucoma-related distress. However, whether improvement in patient-centered metrics can drive an improvement in medication-taking behavior remains to be seen.
OBJECTIVE: The 7-month Support, Educate, Empower (SEE) personalized glaucoma coaching program was previously shown to improve glaucoma medication adherence by 21 percent points. This study's goal was to assess the impact of the SEE program on self-determination theory (SDT) metrics and other patient-centered outcome measures. PARTICIPANTS AND METHODS: Glaucoma patients (≥40 y old, taking ≥1 medication) self-reporting poor medication adherence were recruited at the University of Michigan. Eight surveys (with 10 subscales) were completed before and after the 7-month SEE program.

Three surveys assessed changes in SDT (Treatment Self-regulation Questionnaire, Healthcare-Climate Questionnaire, Perceived Competence) while the others assessed participants' Glaucoma Knowledge, Glaucoma Medication Self-efficacy, Glaucoma-related distress, Perceived benefits, confidence asking and getting questions answered. RESULTS: Thirty-nine participants completed the SEE program. Significant improvements were in 7 subscales, including all three SDT tenets of competence (mean change =0.9, SD =±1.2, adjusted P =0.0002), autonomy (0.5, ±0.9, 0.044), and relatedness (P =0.002). Glaucoma-related distress (-2.0, ±3.2, 0.004), confidence in asking questions (1.1, ±2.0, 0.008), and confidence in getting questions answered (1.0, ±2.0, 0.009) also improved. Glaucoma-related distress was correlated with perceived competence (r =-0.56, adjusted P =0.005), and an increase in perceived competence was associated with a decrease in glaucoma-related distress (β=-0.43, 95% CI -0.67 - -0.20, adjusted P =0.007). CONCLUSIONS: The SEE program improved participants' autonomous motivation, perceived support, perceived competence, glaucoma-related distress, and competence. These results point to the promising potential of SDT-guided behavioral interventions in improving patient-centered metrics.

Ophthalmology and Eye Care Services
Ekeh L, **Ibrahim H**, **Askar F**, **Meysami A**, and Simmons BA. Cushing's syndrome of the orbit: congestive orbitopathy and optic neuropathy associated with steroids. *Orbit* 2023; 1-4. PMID: 37855748. Request Article

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A 56-year-old female with a history of chronic systemic steroid use for asthma control displayed orbital congestion, exophthalmos, a mild abduction deficit, and optic neuropathy. Laboratory workup was unrevealing. Neuroimaging showed increased orbital fat compartments, though the orbital fat was unremarkable on biopsy. The patient was diagnosed with iatrogenic Cushing's syndrome of the orbit and underwent orbital decompression. Early published literature declared this orbitopathy benign. However, newer cases describe more pathologic changes, suggesting the disease is diagnosed later and/or treatment is delayed.

Ophthalmology and Eye Care Services
Kasetty VM, and Marcus DM. Reply to Letter to the Editor: Endolaserless Vitrectomy With Aflibercept Monotherapy for Proliferative Diabetic Retinopathy-Related Vitreous Hemorrhage. *Ophthalmic Surg Lasers Imaging Retina* 2023; 54(10):610-611. PMID: 37847160. Request Article

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Orthopedics/Bone and Joint Center
Burdick GB, Beydoun RS, **Bell KL**, Fathima B, Pietroski AD, Warren JR, Wolterink TD, **Kasto JK**, **Sanii RY**, and **Muh S**. Time-to-Surgery and Short-Term Outcomes of Trimalleolar Ankle Fracture During the COVID-19 Pandemic. *Cureus* 2023; 15(8):e44478. PMID: 37791182. Full Text

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Introduction During the coronavirus disease 2019 (COVID-19) pandemic, a rapid and significant transformation in patient management occurred across the healthcare system in order to mitigate the spread of the disease and address resource constraints. Numerous surgical cases were either postponed or canceled, permitting only the most critical and emergent cases to proceed. The impact of these modifications on patient outcomes remains uncertain. The purpose of this study was to compare time-to-surgery and outcomes of open reduction and internal fixation for trimalleolar ankle fractures during the pandemic to a pre-pandemic group. We hypothesized that the pandemic group would have a prolonged time-to-surgery and worse outcomes compared to the pre-pandemic cohort. Materials and methods This retrospective cohort study was conducted within a single healthcare system, examining the treatment of trimalleolar ankle fractures during two distinct periods: April to July 2020 (COVID-19 group) and January to December 2018 (2018 group). Cases were identified using Current Procedural Terminology code 27822. Information on demographics, fracture characteristics, and outcomes was obtained through chart review. Outcomes analyzed included time-to-surgery, mean visual analog scale scores, ankle strength and range of motion, and complications. Results COVID-19 and 2018 groups consisted of 32 and 100 patients, respectively. No significant difference was observed in group demographics and comorbidities ($p > 0.05$). Fracture characteristics were similar between groups apart from tibiofibular syndesmosis injury, 62.5% (20/32) in COVID-19 vs 42.0% (42/100) in 2018 ($p = 0.03$). Time-to-surgery was not significantly different between the two groups (8.84 ± 6.78 days in COVID-19 vs 8.61 ± 6.02 days in 2018, $p = 0.85$). Mean visual analog scale scores, ankle strength, and ankle range of motion in plantarflexion were not significantly different between the two groups at three and six months postoperatively ($p > 0.05$). Dorsiflexion was significantly higher in the COVID-19 group at three months ($p = 0.03$), but not six months ($p = 0.94$) postoperatively. No significant difference in postoperative complication was seen between groups, 25.0% (8/32) COVID-19 group compared to 15.0% (15/100) 2018 group ($p = 0.11$). Conclusions Patients who underwent surgery during the early months of the COVID-19 pandemic did not experience prolonged time-to-surgery and had similar outcomes compared to patients treated prior to the pandemic.

Orthopedics/Bone and Joint Center

Goodrich E, Walcott Q, Dallman J, Crow H, and Templeton K. Bone Health in the Transgender Population. *JBJS Rev* 2023; 11(10). PMID: 37883596. Full Text

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» Transgender women are more susceptible to low bone mineral density (BMD) before initiating gender-affirming hormone therapy (GAHT), and while bone density initially improves with GAHT, it gradually declines while still remaining above baseline. Transgender women older than 50 years have a comparable fracture risk as age-matched cisgender women. Transgender men typically have normal or increased BMD before initiating and while receiving GAHT and are not at increased risk of fractures.» Transgender youth who receive puberty-blocking medications experience either no change or a slight decrease in BMD that returns to baseline after initiating GAHT.» It is important to abide by the International Society for Clinical Densitometry guidelines whenever ordering, performing, or reading a BMD scan for a gender-diverse patient.» There are no specific guidelines concerning vitamin D and calcium supplementation or the use of bisphosphonates in the transgender population, so the current recommendation is to abide by the guidelines for cisgender individuals.

Orthopedics/Bone and Joint Center

Lawrence RL, **Soliman SB**, Dalbøge A, Lohse K, and **Bey MJ**. Investigating the multifactorial etiology of supraspinatus tendon tears. *J Orthop Res* 2023; Epub ahead of print. PMID: 37814893. Full Text

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The purpose of this study was to develop a multivariable model to determine the extent to which a combination of etiological factors is associated with supraspinatus tendon tears. Fifty-four asymptomatic individuals (55 ± 4 years) underwent testing of their dominant shoulder. Diagnostic ultrasound was used to assess for a supraspinatus tendon tear. The etiological factors investigated included demographics (age and sex), tendon impingement during shoulder motion (via biplane videoradiography), glenohumeral morphology (via computed tomography imaging), family history of a tear (via self-report), occupational shoulder exposure (via shoulder job exposure matrix), and athletic exposure (via self-report). Univariate relationships between etiological predictors and supraspinatus tears were assessed using logistic regression and odds ratios (ORs), while multivariable relationships were assessed using classification and regression tree analysis. Thirteen participants (24.1%) had evidence of a supraspinatus tear. Individuals with a tear had a higher critical shoulder angle (OR 1.2, $p = 0.028$) and acromial index (OR 1.2, $p = 0.016$) than individuals without a tear. The multivariable model suggested that a tear in this cohort can be explained with acceptable accuracy (AUROC = 0.731) by the interaction between acromial index and shoulder occupational exposure: a tear is more likely in individuals with a high acromial index ($p < 0.001$), and in individuals with a low acromial index and high occupational exposure ($p < 0.001$). The combination of an individual's glenohumeral morphology (acromial index) and occupational shoulder exposure may be important in the development of supraspinatus tears.

Orthopedics/Bone and Joint Center

Mantebea H, Singh A, Badar F, Abdelmessih G, Sebastian TM, **Baker K**, Newton M, and Xia Y. Characteristics of distal femoral articular cartilage in 6 weeks posttraumatic osteoarthritis by a subcritical impact. *J Orthop Res* 2023; Epub ahead of print. PMID: 37874329. Full Text

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Traumatized knee greatly contributes to osteoarthritis (OA) of the knee in young adults. To intervene effectively before the onset of severe structural disruption, detection of the disease at the early onset is crucial. In this study, we put together the findings for the detection of OA from the femoral knee joint cartilage of the rabbit at 6 weeks posttrauma. Articular cartilage samples are taken from the impacted and nonimpacted joints at 0 week (serving as the control group) and at 6 weeks posttrauma by minimal force. The samples were imaged using microscopic magnetic resonance imaging (μMRI) at 11.7 μm/pixel and polarized light microscopy (PLM) at 1 μm/pixel. In addition, an inductively coupled plasma - optical emission spectrometry analysis was performed using the adjacent cartilage samples. The outcomes of this study demonstrate an increase in T2 values in 6 weeks samples compared to the 0 week samples by μMRI technique, indicating a general increase of tissue hydration within cartilage. PLM detects a decrease in the average thickness of the superficial zones in the posttraumatic osteoarthritis samples, significant in the impacted femurs. There was an average increasing trend of maximum retardation in the tide mark in comparison to the reported calcium concentration (mg/L) in impacted samples suggesting a possible rise in mineralization in the 6 weeks samples. Qualitatively, physical observation of the joint after 6 weeks showed signs of reddening in the anterior femur suggesting the disease process is a localized phenomenon. Through microscopic imaging, we are able to detect these changes at 6 weeks posttrauma qualitatively and quantitatively.

Otolaryngology – Head and Neck Surgery

Eide JG, **Mason W**, **Ray A**, **Carey J**, **Cook B**, and **Craig JR**. Systematic review of errors on beta-2 transferrin gel electrophoresis testing of rhinorrhea and otorrhea. *Int Forum Allergy Rhinol* 2023; Epub ahead of print. PMID: 37864574. Full Text

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BACKGROUND: Beta-2 transferrin (B2-Tf) gel electrophoresis (GE) is the preferred non-invasive diagnostic modality for confirming cerebrospinal fluid (CSF) in body fluids. While B2-Tf GE testing is highly sensitive and specific for CSF, false-positive (FP) and false-negative (FN) results can lead to diagnostic and therapeutic dilemmas. Several series have demonstrated potential causes of false B2-Tf GE results, but few studies have reported reasons for these errors. The purpose of this systematic review was to describe sources of B2-Tf GE errors. METHODS: A systematic review was performed by searching OVID, EMBASE, and Web of Science databases for B2-Tf GE studies. After applying exclusion criteria, original research studies directly addressing erroneous B2-Tf GE results underwent qualitative analysis. RESULTS: Of the 243 abstracts screened, 71 underwent full-text review and 18 studies reporting B2-Tf GE errors were included for analysis. There were 15 potential FPs, 12 actual FPs, 12 potential FNs, 19 actual FNs, and 14 indeterminate results. There were also 246 potentially indeterminate results from in vitro studies. Reasons for B2-Tf GE errors included serum transferrin alterations (n = 17; all potential), infection related (n = 13; 9 potential), orbital or salivary contamination (n = 2; 1 potential), and collection related (n = 255; 246 potential). There were 31 false or indeterminate results with unspecified reasons. There were no reported errors due to laboratory processing. CONCLUSIONS: Multiple potential or actual reasons for false or indeterminate results have been reported for B2-Tf GE testing of rhinorrhea and otorrhea. Future studies should explore reasons for B2-Tf testing errors and how these may affect clinical decision making.

Otolaryngology – Head and Neck Surgery
Goel RR, Jeranko M, **Jones L**, **Bishnoi A**, and **Meysami A**. Diagnostic Utility of Minor Salivary Gland Biopsy for Primary Sjögren Syndrome in Patients With Negative Anti-SSA Antibodies. *Cureus* 2023; 15(9):e46207. PMID: 37905256. Full Text

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BACKGROUND: Sjögren syndrome is a systemic autoimmune disease characterized by lacrimal and salivary gland inflammation resulting in dry eyes and mouth. Although it is a common disease, diagnosis can be challenging due to its heterogeneous presentation. A positive minor salivary gland biopsy is mandatory to fulfill the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for primary Sjögren syndrome in patients who are seronegative for anti-SSA/Ro antibodies. The objective of our study was to evaluate the validity of minor salivary gland biopsy for patients who are SSA antibody-negative yet are suspected of having primary Sjögren syndrome because of compelling symptoms. METHODS: We conducted a retrospective chart review of adult patients with a negative anti-SSA antibody test who underwent minor salivary gland biopsy to assess suspected Sjögren syndrome at Henry Ford Rheumatology Clinics between January 2005 and December 2019. Patient characteristics and clinical features are described. Sensitivity, specificity, positive predictive value, and negative predictive value are assessed. RESULTS: A total of 47 patients were included: 46 (97.9%) females and one (2.1%) male. The mean age was 57.2 ± 13.8 years. There were 14 (29.8%) patients who had a positive minor salivary gland biopsy result and 15 (31.9%) patients who had a final diagnosis of Sjögren syndrome. Minor salivary gland biopsy had 93.3% sensitivity (95% confidence interval (CI): 68%-99.8%), 100% specificity (95% CI: 89.1%-100%), 100% positive predictive value (95% CI: 76.8%-100%), and 97% negative predictive value (95% CI: 84.2%-99.9%). CONCLUSION: The diagnostic value of minor salivary gland biopsy is high for patients who do not have anti-SSA antibodies yet are suspected of having Sjögren syndrome. The results of the study support the consideration of routine minor salivary gland biopsy for identifying Sjögren syndrome in these patients.

Otolaryngology – Head and Neck Surgery
Pace-Asciak P, Russell J, Solorzano C, Berber E, **Singer M**, Shaha AR, Khafif A, Angelos P, Nixon I, and Tufano RP. The utility of parathyroid autofluorescence as an adjunct in thyroid and parathyroid surgery 2023. *Head Neck* 2023; Epub ahead of print. PMID: 37807364. Full Text

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Thyroid and parathyroid surgery requires careful dissection around the vascular pedicle of the parathyroid glands to avoid excessive manipulation of the tissues. If the blood supply to the parathyroid glands is disrupted, or the glands are inadvertently removed, temporary and/or permanent hypocalcemia can occur, requiring post-operative exogenous calcium and vitamin D analogues to maintain stable levels. This can have a significant impact on the quality of life of patients, particularly if it results in permanent hypocalcemia. For over a decade, parathyroid tissue has been noted to have unique intrinsic properties known as "fluorophores," which fluoresce when excited by an external light source. As a result, parathyroid autofluorescence has emerged as an intra-operative technique to help with identification of parathyroid glands and to supplement direct visualization during thyroidectomy and parathyroidectomy. Due to the growing body of literature surrounding Near Infrared Autofluorescence (NIRAF), we sought to review the value of using autofluorescence technology for parathyroid detection during thyroid and parathyroid surgery. A literature review of parathyroid autofluorescence was performed using PubMED. Based on the reviewed literature and expert surgeons' opinions who have used this technology, recommendations were made. We discuss the current available technologies (image vs. probe approach) as well as their limitations. We also capture the opinions and recommendations of international high-volume endocrine surgeons and whether this technology is of value as an intraoperative adjunct. The utility and value of this technology seems promising and needs to be further defined in different scenarios involving surgeon experience and different patient populations and conditions.

Pathology and Laboratory Medicine

Eide JG, **Mason W**, **Ray A**, **Carey J**, **Cook B**, and **Craig JR**. Systematic review of errors on beta-2 transferrin gel electrophoresis testing of rhinorrhea and otorrhea. *Int Forum Allergy Rhinol* 2023; Epub ahead of print. PMID: 37864574. Full Text

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BACKGROUND: Beta-2 transferrin (B2-Tf) gel electrophoresis (GE) is the preferred non-invasive diagnostic modality for confirming cerebrospinal fluid (CSF) in body fluids. While B2-Tf GE testing is highly sensitive and specific for CSF, false-positive (FP) and false-negative (FN) results can lead to diagnostic and therapeutic dilemmas. Several series have demonstrated potential causes of false B2-Tf GE results, but few studies have reported reasons for these errors. The purpose of this systematic review was to describe sources of B2-Tf GE errors. METHODS: A systematic review was performed by searching OVID, EMBASE, and Web of Science databases for B2-Tf GE studies. After applying exclusion criteria, original research studies directly addressing erroneous B2-Tf GE results underwent qualitative analysis. RESULTS: Of the 243 abstracts screened, 71 underwent full-text review and 18 studies reporting B2-Tf GE errors were included for analysis. There were 15 potential FPs, 12 actual FPs, 12 potential FNs, 19 actual FNs, and 14 indeterminate results. There were also 246 potentially indeterminate results from in vitro studies. Reasons for B2-Tf GE errors included serum transferrin alterations (n = 17; all potential), infection related (n = 13; 9 potential), orbital or salivary contamination (n = 2; 1 potential),

and collection related (n = 255; 246 potential). There were 31 false or indeterminate results with unspecified reasons. There were no reported errors due to laboratory processing. CONCLUSIONS: Multiple potential or actual reasons for false or indeterminate results have been reported for B2-Tf GE testing of rhinorrhea and otorrhea. Future studies should explore reasons for B2-Tf testing errors and how these may affect clinical decision making.

Pathology and Laboratory Medicine

Hardy ME, **Kenney RM**, **Tibbetts RJ**, **Shallal AB**, and **Veve MP**. Leveraging stewardship to promote ceftriaxone use in severe infections with low- and no-risk AmpC Enterobacterales. *Antimicrob Agents Chemother* 2023; Epub ahead of print. PMID: 37882541. Full Text

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AmpC β-lactamases are associated with development of ceftriaxone resistance despite initial in vitro susceptibility, but the risk of AmpC derepression is not equal among Enterobacterales. The purpose of this study was to evaluate the impact of an AmpC stewardship intervention on the definitive treatment of low- and no-risk Enterobacterales. This was an IRB-approved, single pre-test, post-test quasi-experiment at a 5-hospital system. An AmpC stewardship intervention was implemented in July 2022 and included prescriber education, the removal of microbiology comments indicating potential for ceftriaxone resistance on therapy, and the modification of a blood PCR comment for Serratia marcescens to recommend ceftriaxone. Adults ≥18 years pre-intervention (July 2021 to December 2021) and post-intervention (July 2022 to December 2022) who received ≥72 hours of inpatient definitive therapy and had non-urine cultures growing low- and no-risk organisms (S. marcescens, Providencia spp., Citrobacter koseri, Citrobacter amalonaticus, or Morganella morganii) were included. The primary endpoint was definitive treatment with ceftriaxone. A total of 224 patients were included; 115 (51%) in pre-intervention and 109 (49%) in post-intervention. Definitive ceftriaxone therapy was prescribed more frequently after intervention [6 (5%) vs 72 (66%), P < 0.001]. After adjustment for critical illness, patients in the post-group were more likely to receive definitive ceftriaxone (adjOR, 34.7; 95% CI, 13.9-86.6). The proportion of patients requiring retreatment was 18 (15%) and 11 (10%) for pre- and post-intervention patients (P = 0.22), and ceftriaxone resistance within 30 days occurred in 5 (4%) and 2 (2%) patients in the pre- and post-group (P = 0.45). An antimicrobial stewardship intervention was associated with increased ceftriaxone prescribing and similar patient outcomes for low- and no-risk AmpC Enterobacterales.

Pathology and Laboratory Medicine

Lockwood CM, Borsu L, **Cankovic M**, Earle JSL, Gocke CD, Hameed M, Jordan D, Lopategui JR, Pullambhatla M, Reuther J, Rumilla KM, Tafe LJ, Temple-Smolkin RL, Terraf P, and Tsimberidou AM. Recommendations for Cell-Free DNA Assay Validations: A Joint Consensus Recommendation of the Association for Molecular Pathology and the College of American Pathologists. *J Mol Diagn* 2023; Epub ahead of print. PMID: 37806433. Full Text

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Association for Molecular Pathology, Rockville, Maryland.
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Liquid Biopsy Working Group of the Clinical Practice Committee, Association for Molecular Pathology, Rockville, Maryland; Invitae, San Francisco, California.
Liquid Biopsy Working Group of the Clinical Practice Committee, Association for Molecular Pathology, Rockville, Maryland; Division of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota.
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Liquid Biopsy Working Group of the Clinical Practice Committee, Association for Molecular Pathology, Rockville, Maryland; Department of Investigational Cancer Therapeutics, Unit 455, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Diagnosing, selecting therapy for, and monitoring cancer in patients using a minimally invasive blood test represents a significant advance in precision medicine. Wide variability exists in how circulating tumor DNA (ctDNA) assays are developed, validated, and reported in the literature, which hinders clinical adoption and may negatively impact patient care. Standardization is needed for factors affecting ctDNA assay performance and reporting, including pre-analytical variables, analytical considerations, and elements of laboratory assay reporting. The Association for Molecular Pathology Clinical Practice Committee's Liquid Biopsy Working Group (LBxWG), including organizational representation from the American Society of Clinical Oncology and the College of American Pathologists, has undertaken a full-text data extraction of 1228 ctDNA publications that describe assays performed in patients with lymphoma and solid tumor malignancies. With an emphasis on clinical assay validation, the LBxWG has developed a set of 13 best practice consensus recommendations for validating, reporting, and publishing clinical ctDNA assays. Recommendations include reporting key pre-analytical considerations and assay performance metrics; this analysis demonstrates these elements are inconsistently included in publications. The LBxWG recommendations are intended to assist clinical laboratories with validating and reporting ctDNA assays and to ensure high-quality data are included in publications. It is expected that these recommendations will need to be updated as the body of literature continues to mature.

Pathology and Laboratory Medicine

Morrison CW, Sanjasaz KN, **Nathanson SD**, **Raina-Hukku S**, **Pinkney DM**, and **Davenport AA**. Dedifferentiated endometrial carcinoma metastasis to axillary lymph node: a case report. *J Med Case Rep* 2023; 17(1):451. PMID: 37899461. Full Text

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BACKGROUND: We present an unusual case of a left axillary lymph node metastasis from a primary dedifferentiated endometrial carcinoma. This pattern of metastasis is likely the result of circulating tumor cells reaching the node through its arterial blood supply. CASE PRESENTATION: In this report, a 68-year-old white woman with a dedifferentiated endometrial carcinoma underwent a hysterectomy. She later developed an enlarged axillary lymph node due to metastatic dedifferentiated endometrial carcinoma, treated with chemotherapy and anti-programmed cell death protein 1 immunotherapy resulting in a

complete clinical and radiological response. CONCLUSION: A review of the literature reveals the rarity of blood-borne lymph node metastasis, especially with uterine carcinoma. Immunotherapy has shown promising results in the treatment of some subtypes of metastatic uterine carcinoma.

Pathology and Laboratory Medicine
Patel A, and **Chaffins M**. Nodular elastosis in the setting of lichen sclerosus. *JAAD Case Rep* 2023; 41:107-109. PMID: 37920702. Full Text

Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.
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Pathology and Laboratory Medicine
Qadir H, Larik MO, and Iftekhar MA. Bombay Blood Group Phenotype Misdiagnosed As O Phenotype: A Case Report. *Cureus* 2023; 15(9):e45555. PMID: 37868503. Full Text

Department of Pathology, Henry Ford Health System, Detroit, USA.
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Bombay blood group is a rare type that was initially identified in the city of Bombay, India. It is characterized by the presence of serum antibodies anti-A, anti-B, and anti-H, which can cause agglutination in all blood groups within the ABO system. The clinical importance of the Bombay blood group lies in its inability to receive transfusions from other blood groups. In this case report, we present a case of a young male who was initially misdiagnosed as having an O phenotype, resulting in a hemolytic transfusion reaction. This case highlights the diagnostic and therapeutic challenges associated with rare blood phenotypes.

Pharmacy
August B, Matlob A, and Kale-Pradhan PB. Sulbactam-Durlobactam in the Treatment of Carbapenem-Resistant Acinetobacter baumannii Infections. *Ann Pharmacother* 2023; Epub ahead of print. PMID: 37817550. Full Text

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OBJECTIVE: To review the pharmacology, efficacy, and safety of intravenous sulbactam-durlobactam (SUL-DUR) in the treatment of carbapenem-resistant Acinetobacter baumannii (CRAB) infections. DATA SOURCES: PubMed databases and ClinicalTrials.gov were searched using the following terms: Sulbactam Durlobactam, ETX2514, Xacduro, Sulbactam-ETX2514, ETX2514SUL. STUDY SELECTION AND DATA EXTRACTION: Articles published in English between January 1985 and September 13, 2023, related to pharmacology, safety, efficacy, and clinical trials were reviewed. DATA SYNTHESIS: A phase II trial compared SUL-DUR with placebo with imipenem and cilastatin in both groups. Overall treatment success in the microbiological intention-to-treat analysis was reported in 76.6% of patients in the SUL-DUR group compared with 81% patients in the placebo group. A phase III trial compared SUL-DUR with colistin in adults with confirmed CRAB infections. Patients received either SUL-DUR or colistin and background therapy with imipenem-cilastatin. SUL-DUR was noninferior to colistin for 28-day all-cause mortality (19% vs 32.3%, treatment difference -13.2%; 95% CI [-30.0 to 3.5]). RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE IN COMPARISON TO EXISTING DRUGS: Clinicians have limited options to treat CRAB infections. SUL-DUR has demonstrated efficacy against CRAB in patients with pneumonia and may be considered a viable treatment option. Nonetheless, potential impact of concomitant imipenem-cilastatin as background therapy on clinical trial findings is unclear. Further studies are needed to elucidate the role of SUL-DUR alone or in combination with other active antimicrobials for the treatment of CRAB infections. CONCLUSIONS: SUL-DUR has shown to be predominantly noninferior

to alternative antibiotics in the treatment of pneumonias caused by CRAB, making it a viable treatment option. Further postmarketing data is needed to ascertain its role in other infections.

Pharmacy

Hardy ME, **Kenney RM**, **Tibbetts RJ**, **Shallal AB**, and **Veve MP**. Leveraging stewardship to promote ceftriaxone use in severe infections with low- and no-risk AmpC Enterobacterales. *Antimicrob Agents Chemother* 2023; Epub ahead of print. PMID: 37882541. Full Text

Department of Pharmacy, Henry Ford Hospital , Detroit, Michigan, USA.
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AmpC β-lactamases are associated with development of ceftriaxone resistance despite initial in vitro susceptibility, but the risk of AmpC derepression is not equal among Enterobacterales. The purpose of this study was to evaluate the impact of an AmpC stewardship intervention on the definitive treatment of low- and no-risk Enterobacterales. This was an IRB-approved, single pre-test, post-test quasi-experiment at a 5-hospital system. An AmpC stewardship intervention was implemented in July 2022 and included prescriber education, the removal of microbiology comments indicating potential for ceftriaxone resistance on therapy, and the modification of a blood PCR comment for Serratia marcescens to recommend ceftriaxone. Adults ≥18 years pre-intervention (July 2021 to December 2021) and post-intervention (July 2022 to December 2022) who received ≥72 hours of inpatient definitive therapy and had non-urine cultures growing low- and no-risk organisms (S. marcescens, Providencia spp., Citrobacter koseri, Citrobacter amalonaticus, or Morganella morganii) were included. The primary endpoint was definitive treatment with ceftriaxone. A total of 224 patients were included; 115 (51%) in pre-intervention and 109 (49%) in post-intervention. Definitive ceftriaxone therapy was prescribed more frequently after intervention [6 (5%) vs 72 (66%), P < 0.001]. After adjustment for critical illness, patients in the post-group were more likely to receive definitive ceftriaxone (adjOR, 34.7; 95% CI, 13.9-86.6). The proportion of patients requiring retreatment was 18 (15%) and 11 (10%) for pre- and post-intervention patients (P = 0.22), and ceftriaxone resistance within 30 days occurred in 5 (4%) and 2 (2%) patients in the pre- and post-group (P = 0.45). An antimicrobial stewardship intervention was associated with increased ceftriaxone prescribing and similar patient outcomes for low- and no-risk AmpC Enterobacterales.

Pharmacy

Marsh PL, Moore EE, Moore HB, **Bunch CM**, Aboukhaled M, **Condon SM, 2nd**, Al-Fadhl MD, Thomas SJ, Larson JR, Bower CW, Miller CB, Pearson ML, Twilling CL, Reser DW, Kim GS, Troyer BM, Yeager D, Thomas SG, Srikureja DP, **Patel SS**, Añón SL, Thomas AV, **Miller JB**, Van Ryn DE, Pamulapati SV, Zimmerman D, Wells B, Martin PL, Seder CW, Aversa JG, Greene RB, March RJ, Kwaan HC, Fulkerson DH, Vande Lune SA, Mollnes TE, Nielsen EW, Storm BS, and Walsh MM. Iatrogenic air embolism: pathoanatomy, thromboinflammation, endotheliopathy, and therapies. *Front Immunol* 2023; 14:1230049. PMID: 37795086. Full Text

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Iatrogenic vascular air embolism is a relatively infrequent event but is associated with significant morbidity and mortality. These emboli can arise in many clinical settings such as neurosurgery, cardiac surgery, and liver transplantation, but more recently, endoscopy, hemodialysis, thoracentesis, tissue biopsy, angiography, and central and peripheral venous access and removal have overtaken surgery and trauma as significant causes of vascular air embolism. The true incidence may be greater since many of these air emboli are asymptomatic and frequently go undiagnosed or unreported. Due to the rarity of vascular air embolism and because of the many manifestations, diagnoses can be difficult and require immediate therapeutic intervention. An iatrogenic air embolism can result in both venous and arterial emboli whose anatomic locations dictate the clinical course. Most clinically significant iatrogenic air emboli are caused by arterial obstruction of small vessels because the pulmonary gas exchange filters the more frequent, smaller volume bubbles that gain access to the venous circulation. However, there is a subset of patients with venous air emboli caused by larger volumes of air who present with more protean manifestations. There have been significant gains in the understanding of the interactions of fluid dynamics, hemostasis, and inflammation caused by air emboli due to in vitro and in vivo studies on flow dynamics of bubbles in small vessels. Intensive research regarding the thromboinflammatory changes at the level of the endothelium has been described recently. The obstruction of vessels by air emboli causes immediate pathoanatomic and immunologic and thromboinflammatory responses at the level of the endothelium. In this review, we describe those immunologic and thromboinflammatory responses at the level of the endothelium as well as evaluate traditional and novel forms of therapy for this rare and often unrecognized clinical condition.

Pharmacy

Mart MF, Gardner-Gray JM, and Ahmed S. Delirium and Long-Term Cognitive Impairment after Critical Illness. *ATS Sch* 2023; 4(3):387-388. PMID: 37795122. Full Text

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Pharmacy

Martirosov AL, Giuliano C, Shupp M, Channey S, and Kale-Pradhan PB. Zavegepant Intranasal Spray for Migraines. *Ann Pharmacother* 2023; Epub ahead of print. PMID: 37897226. Full Text

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OBJECTIVE: The objective is to review the pharmacology, efficacy, and safety of intranasal zavegepant in the acute treatment of migraine with or without aura. DATA SOURCE: PubMed, Embase database, and ClinicalTrials.gov were searched using the following terms: Zavzpret, Zavegepant, BHV-3500, and migraine. STUDY SELECTION AND DATA EXTRACTION: Articles published in English from January 2013 to September 2023 related to pharmacology, safety, efficacy, and clinical trials were assessed. DATA SYNTHESIS: In a phase 2/3 trial, zavegepant 10 and 20 mg were more effective than placebo on primary endpoints of freedom of pain (22.5%, 23.1%, and 15.5%, respectively), and freedom from most bothersome symptoms (MBSs) (41.9%, 47.9%, and 33.7%, respectively) 2 hours after treatment. The incidence of adverse effects for both doses was similar to placebo. In a phase 3 trial, zavegepant 10 mg was compared with placebo. Two hours after treatment, more patients in the zavegepant group achieved pain freedom (24% vs 15%) and relief from MBSs (40% vs 31%) compared with placebo. Common adverse events included dysgeusia (21% zavegepant vs 5% placebo) and nasal discomfort (5% zavegepant vs 1% placebo). RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE IN COMPARISON WITH EXISTING DRUGS: Zavegepant is indicated for acute treatment of migraine with or without aura in adults. Zavegepant method of administration and prompt relief of migraine symptoms may be an attractive alternative to triptans for those in need of relief. CONCLUSION: Zavegepant may be a convenient and useful acute treatment option for migraines with and without aura.

Plastic Surgery
Holland C, Shaffer L, Dobkin E, and **Hall J**. Coffee administration to promote return of bowel function after small bowel resection: A randomized, controlled trial. *Am J Surg* 2023; 226(2):156-160. PMID: 37003891. Full Text

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BACKGROUND: Prolonged ileus occurs in 10%-24% of patients undergoing abdominal surgery. Several trials have found coffee administration reduces postoperative ileus, but this has not been evaluated for small bowel resection. METHODS: Following small bowel resection, patients were randomized to caffeinated coffee or warm water three times a day until the time of first flatus or first bowel movement. Primary outcomes were time from end of procedure to: 1) nasogastric tube removal; and 2) when the discharge order was written. Outcomes were compared using Kaplan-Meier survival curves. RESULTS: Thirty-nine patients received coffee and 40 water. Median days to nasogastric tube removal was 3.4 for the coffee and 4.0 for the water groups ($p = 0.002$). Median days to discharge order was 6.7 for the coffee and 7.7 for the water groups ($p = 0.01$). CONCLUSION: Coffee was safe and decreased time to nasogastric tube removal and hospital stay in patients undergoing small bowel resection.

Public Health Sciences
Ahmedani BK, **Yeh HH**, Penfold RB, Simon GE, **Miller-Matero LR**, **Akinyemi E**, **Fallone M**, **Patel S**, **Beebani G**, Hooker SA, Owen-Smith A, Knowlton G, **Levin A**, Eke-Usim A, and Rossom RC. Psychotherapy Disruption Before and After the Transition to Virtual Mental Health Care Induced by the COVID-19 Pandemic. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 37817579. Full Text

Center for Health Policy and Health Services Research (Ahmedani, Yeh, Miller-Matero), Behavioral Health Services (Ahmedani, Miller-Matero, Akinyemi, Fallone, Patel, Beebani), and Public Health Sciences (Levin), Henry Ford Health, Detroit; Kaiser Permanente Washington Health Research Institute, Seattle (Penfold, Simon); HealthPartners Institute, Minneapolis (Hooker, Knowlton, Rossom); Center for

Research and Evaluation, Kaiser Permanente Georgia, and Department of Health Policy and Behavioral Sciences, Georgia State University, Atlanta (Owen-Smith); Authority Health, Detroit (Eke-Usim).

OBJECTIVE: This study aimed to examine population-level disruption in psychotherapy before and after the rapid shift to virtual mental health care induced by the onset of the COVID-19 pandemic in the United States. METHODS: This retrospective study used electronic health record and insurance claims data from three U.S. health systems. The sample included 110,089 patients with mental health conditions who were members of the health systems' affiliated health plans and attended at least two psychotherapy visits from June 14, 2019, through December 15, 2020. Data were subdivided into two 9-month periods (before vs. after COVID-19 onset, defined in this study as March 14, 2020). Psychotherapy visits were measured via health records and categorized as in person or virtual. Disruption was defined as a gap of >45 days between visits. RESULTS: Visits in the preonset period were almost exclusively in person (97%), whereas over half of visits in the postonset period were virtual (52%). Approximately 35% of psychotherapy visits were followed by a disruption in the preonset period, compared with 18% in the postonset period. Disruption continued to be less common (adjusted OR=0.45) during the postonset period after adjustment for visit, mental health, and sociodemographic factors. The magnitude of the difference in disruption between periods was homogeneous across sociodemographic characteristics but heterogeneous across psychiatric diagnoses. CONCLUSIONS: This study found fewer population-level disruptions in psychotherapy receipt after rapid transition to virtual mental health care following COVID-19 onset. These data support the continued availability of virtual psychotherapy.

Public Health Sciences

Burnett-Hartman AN, Powers JD, Hixon BP, Carroll NM, Frankland TB, Honda SA, Saia C, Rendle KA, Greenlee RT, **Neslund-Dudas C**, Zheng Y, Vachani A, and Ritzwoller DP. Development of an Electronic Health Record-Based Algorithm for Predicting Lung Cancer Screening Eligibility in the Population-Based Research to Optimize the Screening Process Lung Research Consortium. *JCO Clin Cancer Inform* 2023; 7:e2300063. PMID: 37910824. Full Text

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PURPOSE: Lung cancer screening (LCS) guidelines in the United States recommend LCS for those age 50-80 years with at least 20 pack-years smoking history who currently smoke or quit within the last 15 years. We tested the performance of simple smoking-related criteria derived from electronic health record (EHR) data and developed and tested the performance of a multivariable model in predicting LCS eligibility. METHODS: Analyses were completed within the Population-based Research to Optimize the Screening Process Lung Consortium (PROSPR-Lung). In our primary validity analyses, the reference standard LCS eligibility was based on self-reported smoking data collected via survey. Within one PROSPR-Lung health system, we used a training data set and penalized multivariable logistic regression using the Least Absolute Shrinkage and Selection Operator to select EHR-based variables into the prediction model including demographics, smoking history, diagnoses, and prescription medications. A separate test data set assessed model performance. We also conducted external validation analysis in a separate health system and reported AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy metrics associated with the Youden Index. RESULTS: There were 14,214 individuals with survey data to assess LCS eligibility in primary analyses. The overall performance for assigning LCS eligibility status as measured by the AUC values at the two health systems was 0.940 and 0.938. At the Youden Index cutoff value, performance metrics were as follows: accuracy, 0.855 and 0.895; sensitivity, 0.886 and 0.920; specificity, 0.896 and 0.850; PPV, 0.357 and 0.444; and NPV, 0.988 and 0.992. CONCLUSION: Our results suggest that health systems can use an EHR-derived multivariable prediction model to aid in the identification of those who may be eligible for LCS.

Public Health Sciences

Coronado GD, Anyane-Yeboa A, Byhoff E, Escaron AL, Sonik R, Talamantes E, and **Neslund-Dudas C**. Greater Investments in Safety Net Health Systems Can Help Diversify Participation in Clinical Trials and Research. *J Gen Intern Med* 2023; Epub ahead of print. PMID: 37884838. Full Text

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Public Health Sciences

Gonzalez HC, and **Trudeau S**. COVID-19 + Cirrhosis = Excess Hospital Confinement, Excess Casualties. *Dig Dis Sci* 2023; Epub ahead of print. PMID: 37864740. Full Text

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Public Health Sciences

Neslund-Dudas C, **Tang A**, **Alleman E**, **Zarins KR**, **Li P**, **Simoff MJ**, **Lafata JE**, Rendle KA, Hartman ANB, Honda SA, Oshiro C, Olaiya O, Greenlee RT, Vachani A, and Ritzwoller DP. Uptake of Lung Cancer Screening CT After a Provider Order for Screening in the PROSPR-Lung Consortium. *J Gen Intern Med* 2023; Epub ahead of print. PMID: 37783984. Full Text

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BACKGROUND: Uptake of lung cancer screening (LCS) has been slow with less than 20% of eligible people who currently or formerly smoked reported to have undergone a screening CT. OBJECTIVE: To determine individual-, health system-, and neighborhood-level factors associated with LCS uptake after a provider order for screening. DESIGN AND SUBJECTS: We conducted an observational cohort study of screening-eligible patients within the Population-based Research to Optimize the Screening Process (PROSPR)-Lung Consortium who received a radiology referral/order for a baseline low-dose screening CT (LDCT) from a healthcare provider between January 1, 2015, and June 30, 2019. MAIN MEASURES: The primary outcome is screening uptake, defined as LCS-LDCT completion within 90 days of the screening order date. KEY RESULTS: During the study period, 18,294 patients received their first order for LCS-LDCT. Orders more than doubled from the beginning to the end of the study period. Overall, 60% of patients completed screening after receiving their first LCS-LDCT order. Across health systems, uptake varied from 41 to 87%. In both univariate and multivariable analyses, older age, male sex, former

smoking status, COPD, and receiving care in a centralized LCS program were positively associated with completing LCS-LDCT. Unknown insurance status, other or unknown race, and lower neighborhood socioeconomic status, as measured by the Yost Index, were negatively associated with screening uptake. CONCLUSIONS: Overall, 40% of patients referred for LCS did not complete a LDCT within 90 days, highlighting a substantial gap in the lung screening care pathway, particularly in decentralized screening programs.

Public Health Sciences

Surie D, Yuengling KA, DeCuir J, Zhu Y, Gaglani M, Ginde AA, Talbot HK, Casey JD, Mohr NM, Ghamande S, Gibbs KW, Files DC, Hager DN, Ali H, Prekker ME, Gong MN, Mohamed A, Johnson NJ, Steingrub JS, Peltan ID, Brown SM, Leis AM, Khan A, Hough CL, Bender WS, Duggal A, Wilson JG, Qadir N, Chang SY, Mallow C, Kwon JH, Exline MC, Lauring AS, Shapiro NI, Columbus C, **Vaughn IA**, **Ramesh M**, Safdar B, Halasa N, Chappell JD, Grijalva CG, Baughman A, Rice TW, Womack KN, Han JH, Swan SA, Mukherjee I, Lewis NM, Ellington S, McMorrow ML, Martin ET, and Self WH. Disease Severity of Respiratory Syncytial Virus Compared with COVID-19 and Influenza Among Hospitalized Adults Aged ≥60 Years - IVY Network, 20 U.S. States, February 2022-May 2023. *MMWR Morb Mortal Wkly Rep* 2023; 72(40):1083-1088. PMID: 37796753. Full Text

On June 21, 2023, CDC's Advisory Committee on Immunization Practices recommended respiratory syncytial virus (RSV) vaccination for adults aged ≥60 years, offered to individual adults using shared clinical decision-making. Informed use of these vaccines requires an understanding of RSV disease severity. To characterize RSV-associated severity, 5,784 adults aged ≥60 years hospitalized with acute respiratory illness and laboratory-confirmed RSV, SARS-CoV-2, or influenza infection were prospectively enrolled from 25 hospitals in 20 U.S. states during February 1, 2022-May 31, 2023. Multivariable logistic regression was used to compare RSV disease severity with COVID-19 and influenza severity on the basis of the following outcomes: 1) standard flow (<30 L/minute) oxygen therapy, 2) high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV), 3) intensive care unit (ICU) admission, and 4) invasive mechanical ventilation (IMV) or death. Overall, 304 (5.3%) enrolled adults were hospitalized with RSV, 4,734 (81.8%) with COVID-19 and 746 (12.9%) with influenza. Patients hospitalized with RSV were more likely to receive standard flow oxygen, HFNC or NIV, and ICU admission than were those hospitalized with COVID-19 or influenza. Patients hospitalized with RSV were more likely to receive IMV or die compared with patients hospitalized with influenza (adjusted odds ratio = 2.08; 95% CI = 1.33-3.26). Among hospitalized older adults, RSV was less common, but was associated with more severe disease than COVID-19 or influenza. High disease severity in older adults hospitalized with RSV is important to consider in shared clinical decision-making regarding RSV vaccination.

Public Health Sciences

Swain M, **Miller M**, **Cannella C**, and **Daviskiba S**. Disparities in fertility preservation among patients diagnosed with female breast cancer. *J Assist Reprod Genet* 2023; Epub ahead of print. PMID: 37819551. Full Text

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PURPOSE: To investigate the association of specific patient factors with disparities in fertility preservation counseling and utilization of fertility preservation among patients ≤ 40 years old diagnosed with female breast cancer. METHODS: A retrospective chart review was conducted investigating patients diagnosed with breast cancer between January 2012 and December 2020 in a multi-site health system. Rates of fertility counseling and utilization of preservation services were compared based on age, race/ethnicity, parity, insurance type, and treatment site. RESULTS: Of the 6,783 patients diagnosed with female breast cancer, 306 (4.5%) were ≤ 40 years old at the time of diagnosis. There was no significant difference between Black or African American and White patients in rates of fertility counseling (12.1% vs 17.4%; p = 0.285) or pursuit of fertility preservation (3.3% vs 4.2%; p = 0.508), nor was a difference observed when compared by insurance type. However, younger patients (< 30 years of age), patients with 1 or no children, and patients treated in the more affluent county were more likely to undergo counseling and

pursue fertility preservation than their matched counterparts. CONCLUSION: Age, parity, and location of breast cancer care may impact rates of fertility counseling and preservation among reproductive age women diagnosed with breast cancer. Thus, further attention to age discrimination, a patient's desire for future fertility, need for standardization in fertility preservation counseling, and perhaps implementation of comprehensive fertility coverage mandates across all states could help to improve gaps in fertility counseling and fertility preservation.

Public Health Sciences
Udumula MP, **Singh H**, **Rashid F**, **Poisson L**, **Tiwari N**, **Dimitrova I**, **Hijaz M**, Gogoi R, **Swenor M**, **Munkarah A**, **Giri S**, and **Rattan R**. Intermittent fasting induced ketogenesis inhibits mouse epithelial ovarian cancer by promoting antitumor T cell response. *iScience* 2023; 26(10):107839. PMID: 37822507. Full Text

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In various cancer models, dietary interventions have been shown to inhibit tumor growth, improve anticancer drug efficacy, and enhance immunity, but no such evidence exists for epithelial ovarian cancer (EOC), the most lethal gynecologic cancer. The anticancer immune responses induced by 16-h intermittent fasting (IF) were studied in mice with EOC. IF consistently reduced metabolic growth factors and cytokines that stimulate tumor growth, creating a tumor-hostile environment. Immune profiling showed that IF dramatically alters anti-cancer immunity by increasing CD4(+) and CD8(+) cells, Th1 and cytotoxic responses, and metabolic fitness. β-hydroxy butyrate (BHB), a bioactive metabolite produced by IF, partially imitates its anticancer effects by inducing CD8(+) effector function. In a direct comparison, IF outperformed exogenous BHB treatment in survival and anti-tumor immune response, probably due to increased ketogenesis. Thus, IF and one of its metabolic mediators BHB suppress EOC growth and sustain a potent anti-tumor T cell response.

Public Health Sciences
Wise LA, Wang TR, Mikkelsen EM, Wesselink AK, Calafat AM, **Wegienka G**, Geller RJ, Coleman CM, Willis MD, Marsh EE, Schildroth S, Botelho JC, Messerlian-Lambert G, and Hatch EE. Per- and Polyfluoroalkyl Substances and Anti-Müllerian Hormone Concentrations in Two Preconception Cohort Studies. *Environ Health Perspect* 2023; 131(10):107703. PMID: 37882725. Full Text

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Public Health Sciences
Zhang L, **Luo H**, **Li C**, **Teng H**, **Powell B**, **Lu M**, **Chopp M**, and **Zhang ZG**. Treatment of stroke in aged male and female rats with Vepoloxamer and tPA reduces neurovascular damage. *Front Neurol* 2023; 14:1282736. PMID: 37869138. Full Text

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Stroke is a leading cause of death and disability worldwide, mainly affecting the elderly. Unfortunately, current treatments for acute ischemic stroke warrant improvement. To date, tissue plasminogen activator (tPA) is of limited use in stroke patients mainly due to its narrow therapeutic window and potential for hemorrhagic complication. The adjuvant treatment with Vepoloxamer, a purified amphipathic polymer has been shown to enhance the thrombolytic efficacy of tPA treatment in young adult male rats after embolic stroke. However, most stroke patients are aged; therefore, the current study investigated the therapeutic effect of the combined tPA and Vepoloxamer treatment in aged male and female rats subjected to embolic stroke. METHODS: Male and female Wistar rats at 18 months of age were subjected to embolic middle cerebral artery occlusion and treated either with monotherapy of tPA or Vepoloxamer, a combination of these two agents, or saline at 4 h after stroke onset. Neurological outcomes were evaluated with a battery of behavioral tests including adhesive removal, foot-fault, and modified neurological severity score tests at 1 and 7 days after stroke onset, followed by histopathological analysis of infarct volume. Residual clot size and vascular patency and integrity were analyzed. RESULTS: The combination treatment with Vepoloxamer and tPA significantly reduced infarct volume and neurological deficits in male and female rats compared to rats treated with saline and the monotherapies of tPA and Vepoloxamer. While Vepoloxamer monotherapy moderately reduced neurological deficits, monotherapies with tPA and Vepoloxamer failed to reduce infarct volume compared to saline treatment. Furthermore, the combination treatment with tPA and Vepoloxamer accelerated thrombolysis, reduced ischemia and tPA-potentiated microvascular disruption, and concomitantly improved cerebrovascular integrity and perfusion in the male ischemic rats. CONCLUSION: Combination treatment with tPA and Vepoloxamer at 4 h after stroke onset effectively reduces ischemic neurovascular damage by accelerating thrombolysis and reducing ischemia and tPA potentiated side effects in the aged rats. This funding suggests that the combination treatment with tPA and Vepoloxamer represents a promising strategy to potentially apply to the general population of stroke patients.

Pulmonary and Critical Care Medicine

Neslund-Dudas C, **Tang A**, **Alleman E**, **Zarins KR**, **Li P**, **Simoff MJ**, **Lafata JE**, Rendle KA, Hartman ANB, Honda SA, Oshiro C, Olaiya O, Greenlee RT, Vachani A, and Ritzwoller DP. Uptake of Lung Cancer Screening CT After a Provider Order for Screening in the PROSPR-Lung Consortium. *J Gen Intern Med* 2023; Epub ahead of print. PMID: 37783984. Full Text

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Center for Integrated Healthcare Research, Kaiser Permanente Hawaii, Honolulu, HI, USA.
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Marshfield Clinic Research Institute, Marshfield, WI, USA.

BACKGROUND: Uptake of lung cancer screening (LCS) has been slow with less than 20% of eligible people who currently or formerly smoked reported to have undergone a screening CT. OBJECTIVE: To determine individual-, health system-, and neighborhood-level factors associated with LCS uptake after a provider order for screening. DESIGN AND SUBJECTS: We conducted an observational cohort study of screening-eligible patients within the Population-based Research to Optimize the Screening Process (PROSPR)-Lung Consortium who received a radiology referral/order for a baseline low-dose screening CT (LDCT) from a healthcare provider between January 1, 2015, and June 30, 2019. MAIN MEASURES: The primary outcome is screening uptake, defined as LCS-LDCT completion within 90 days of the

screening order date. KEY RESULTS: During the study period, 18,294 patients received their first order for LCS-LDCT. Orders more than doubled from the beginning to the end of the study period. Overall, 60% of patients completed screening after receiving their first LCS-LDCT order. Across health systems, uptake varied from 41 to 87%. In both univariate and multivariable analyses, older age, male sex, former smoking status, COPD, and receiving care in a centralized LCS program were positively associated with completing LCS-LDCT. Unknown insurance status, other or unknown race, and lower neighborhood socioeconomic status, as measured by the Yost Index, were negatively associated with screening uptake. CONCLUSIONS: Overall, 40% of patients referred for LCS did not complete a LDCT within 90 days, highlighting a substantial gap in the lung screening care pathway, particularly in decentralized screening programs.

Radiation Oncology

Herr DJ, Moncion A, Griffith KA, Marsh R, Grubb M, Bhatt A, Dominello M, **Walker EM**, Narayana V, Abu-Isa E, Vicini FA, Hayman JA, and Pierce LJ. Factors Associated With Cardiac Radiation Dose Reduction After Hypofractionated Radiation Therapy for Localized, Left-Sided Breast Cancer in a Large Statewide Quality Consortium. *Int J Radiat Oncol Biol Phys* 2023; Epub ahead of print. PMID: 37797748. Full Text

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PURPOSE: Limiting cardiac radiation dose is important for minimizing long-term cardiac toxicity in patients with left-sided early-stage breast cancer. METHODS AND MATERIALS: Prospectively collected dosimetric data were analyzed for patients undergoing moderately hypofractionated radiation therapy to the left breast within the Michigan Radiation Oncology Quality Consortium from 2016 to 2022. The mean heart dose (MHD) goal was progressively tightened from ≤2 Gy in 2016 to MHD ≤ 1.2 Gy in 2018. In 2021, a planning target volume (PTV) coverage goal was added, and the goal MHD was reduced to ≤1 Gy. Multivariate logistic regression models were developed to assess for covariates associated with meeting the MHD goals in 2016 to 2020 and the combined MHD/PTV coverage goal in 2021 to 2022. RESULTS: In total, 4165 patients were analyzed with a median age of 64 years. Overall average cardiac metric compliance was 91.7%. Utilization of motion management increased from 41.8% in 2016 to 2020 to 46.5% in 2021 to 2022. Similarly, use of prone positioning increased from 12.2% to 22.2% in these periods. On multivariate analysis in the 2016 to 2020 cohort, treatment with motion management (odds ratio [OR], 5.20; 95% CI, 3.59-7.54; P < .0001) or prone positioning (OR, 3.21; 95% CI, 1.85-5.57; P < .0001) was associated with meeting the MHD goal, while receipt of boost (OR, 0.25; 95% CI, 0.17-0.39; P < .0001) and omission of hormone therapy (OR, 0.65; 95% CI, 0.49-0.88; P = .0047) were associated with not meeting the MHD goal. From 2021 to 2022, treatment with motion management (OR, 1.89; 95% CI, 1.12-3.21; P = .018) or prone positioning (OR, 3.71; 95% CI, 1.73-7.95; P = .0008) was associated with meeting the combined MHD/PTV goal, while larger breast volume (≥1440 cc; OR, 0.34; 95% CI, 0.13-0.91; P = .031) was associated with not meeting the combined goal. CONCLUSIONS: In our statewide consortium, high rates of compliance with aggressive targets for limiting cardiac dose were achievable without sacrificing target coverage.

Radiation Oncology

Rahman A, **Janic B**, **Rahman T**, **Singh H**, **Ali H**, **Rattan R**, Kazi M, and **Ali MM**. Immunotherapy Enhancement by Targeting Extracellular Tumor pH in Triple-Negative Breast Cancer Mouse Model. *Cancers (Basel)* 2023; 15(20). PMID: 37894298. Full Text

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Triple-negative breast cancer (TNBC), as one of the most aggressive forms of breast cancer, is characterized by a poor prognosis and a very low rate of disease-free and overall survival. In recent years, immunotherapeutic approaches targeting T cell checkpoint molecules, such as cytotoxic lymphocyte antigen-4 (CTLA-4), programmed death1 (PD-1) or its ligand, programmed death ligand 1 (PD-L1), have shown great potential and have been used to treat various cancers as single therapies or in combination with other modalities. However, despite this remarkable progress, patients with TNBC have shown a low response rate to this approach, commonly developing resistance to immune checkpoint blockade, leading to treatment failure. Extracellular acidosis within the tumor microenvironment (also known as the Warburg effect) is one of the factors preventing immune cells from mounting effective responses and contributing to immunotherapy treatment failure. Therefore, reducing tumor acidity is important for increasing cancer immunotherapy effectiveness and this has yet to be realized in the TNBC environment. In this study, the oral administration of sodium bicarbonate (NaHCO(3)) enhanced the antitumor effect of anti-PD-L1 antibody treatment, as demonstrated by generated antitumor immunity, tumor growth inhibition and enhanced survival in 4T1-Luc breast cancer model. Here, we show that NaHCO(3) increased extracellular pH (pH(e)) in tumor tissues in vivo, an effect that was accompanied by an increase in T cell infiltration, T cell activation and IFN-γ, IL2 and IL12p40 mRNA expression in tumor tissues, as well as an increase in T cell activation in tumor-draining lymph nodes. Interestingly, these changes were further enhanced in response to combined NaHCO(3) + anti-PD-L1 therapy. In addition, the acidic extracellular conditions caused a significant increase in PD-L1 expression in vitro. Taken together, these results indicate that alkalizing therapy holds potential as a new tumor microenvironment immunomodulator and we hypothesize that NaHCO(3) can enhance the antitumor effects of anti-PD-L1 breast cancer therapy. The combination of these treatments may have an exceptional impact on future TNBC immunotherapeutic approaches by providing a powerful personalized medicine paradigm. Therefore, our findings have a great translational potential for improving outcomes in TNBC patients.

Rheumatology

Ekeh L, **Ibrahim H**, **Askar F**, **Meysami A**, and Simmons BA. Cushing's syndrome of the orbit: congestive orbitopathy and optic neuropathy associated with steroids. *Orbit* 2023; 1-4. PMID: 37855748. Request Article

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A 56-year-old female with a history of chronic systemic steroid use for asthma control displayed orbital congestion, exophthalmos, a mild abduction deficit, and optic neuropathy. Laboratory workup was unrevealing. Neuroimaging showed increased orbital fat compartments, though the orbital fat was unremarkable on biopsy. The patient was diagnosed with iatrogenic Cushing's syndrome of the orbit and underwent orbital decompression. Early published literature declared this orbitopathy benign. However, newer cases describe more pathologic changes, suggesting the disease is diagnosed later and/or treatment is delayed.

Rheumatology

Goel RR, Jeranko M, **Jones L**, **Bishnoi A**, and **Meysami A**. Diagnostic Utility of Minor Salivary Gland Biopsy for Primary Sjögren Syndrome in Patients With Negative Anti-SSA Antibodies. *Cureus* 2023; 15(9):e46207. PMID: 37905256. Full Text

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BACKGROUND: Sjögren syndrome is a systemic autoimmune disease characterized by lacrimal and salivary gland inflammation resulting in dry eyes and mouth. Although it is a common disease, diagnosis can be challenging due to its heterogeneous presentation. A positive minor salivary gland biopsy is mandatory to fulfill the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for primary Sjögren syndrome in patients who are seronegative for anti-SSA/Ro antibodies. The objective of our study was to evaluate the validity of minor salivary gland biopsy for patients who are SSA antibody-negative yet are suspected of having primary Sjögren syndrome because of compelling symptoms. METHODS: We conducted a retrospective chart review of adult patients with a negative anti-SSA antibody test who underwent minor salivary gland biopsy to assess suspected Sjögren syndrome at Henry Ford Rheumatology Clinics between January 2005 and December 2019. Patient characteristics and clinical features are described. Sensitivity, specificity, positive predictive value, and negative predictive value are assessed. RESULTS: A total of 47 patients were included: 46 (97.9%) females and one (2.1%) male. The mean age was 57.2 ± 13.8 years. There were 14 (29.8%) patients who had a positive minor salivary gland biopsy result and 15 (31.9%) patients who had a final diagnosis of Sjögren syndrome. Minor salivary gland biopsy had 93.3% sensitivity (95% confidence interval (CI): 68%-99.8%), 100% specificity (95% CI: 89.1%-100%), 100% positive predictive value (95% CI: 76.8%-100%), and 97% negative predictive value (95% CI: 84.2%-99.9%). CONCLUSION: The diagnostic value of minor salivary gland biopsy is high for patients who do not have anti-SSA antibodies yet are suspected of having Sjögren syndrome. The results of the study support the consideration of routine minor salivary gland biopsy for identifying Sjögren syndrome in these patients.

Sleep Medicine

Schweitzer PK, Taranto-Montemurro L, Ojile JM, Thein SG, **Drake CL**, Rosenberg R, Corser B, Abaluck B, Sangal RB, and Maynard J. The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA): A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2023; Epub ahead of print. PMID: 37812772. Full Text

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RATIONALE: Obstructive sleep apnea (OSA) is a common sleep disorder for which the principal treatment option, continuous positive airway pressure, is often poorly tolerated. There is currently no approved pharmacotherapy for OSA. However, recent studies have demonstrated improvement in OSA with combined antimuscarinic and noradrenergic drugs. OBJECTIVES: The aim of this study was to evaluate the efficacy and safety of AD109, a combination of the novel antimuscarinic aroxybutynin and the norepinephrine reuptake inhibitor atomoxetine in the treatment of OSA. METHODS: Phase 2, randomized, double-blind, placebo-controlled, parallel-group, 4-week trial comparing AD109 2.5/75 mg, AD109 5/75 mg, atomoxetine 75 mg alone, and placebo (NCT05071612). MEASUREMENTS AND MAIN RESULTS: Of 211 randomized patients, 181 were included in the pre-specified efficacy analyses. Sleep was assessed by two baseline and two treatment polysomnograms. Apnea-hypopnea index (AHI(4), 4% desaturation criterion, primary outcome) was reduced from median (IQR) of 20.5 (12.3-27.2) to 10.8 (5.6-18.5) in the AD109 2.5/75 mg arm (-47.1%), from 19.4 (13.7-26.4) to 9.5 (6.1-19.3) in the 5/75 mg arm (-42.9%, both p<0.0001 vs placebo), and from 19.0 (11.8-28.8) to 11.8 (5.5-21.5) with atomoxetine alone (-38.8%, p<0.01 vs placebo). Placebo AHI(4) went from 20.1 (11.9 - 25.9) to 16.3 (11.1 - 28.9).

Subjectively, there was improvement in fatigue with AD109 2.5/75 (p<0.05 vs placebo and atomoxetine). Atomoxetine taken alone decreased total sleep time (p<0.05 vs AD109 and placebo). The most common adverse events were dry mouth, insomnia, and urinary hesitancy. CONCLUSIONS: AD109 showed clinically meaningful improvement in OSA, suggesting further development of the compound is warranted. Clinical trial registration available at www. CLINICALTRIALS: gov, ID: NCT05071612.

Sleep Medicine

Thiesse L, Staner L, Bourgin P, Comtet H, Fuchs G, Kirscher D, **Roth T**, Schaffhauser JY, Saoud JB, and Viola AU. Somno-Art Software identifies pathology-induced changes in sleep parameters similarly to polysomnography. *PLoS One* 2023; 18(10):e0291593. PMID: 37862307. Full Text

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Polysomnographic sleep architecture parameters are commonly used to diagnose or evaluate treatment of sleep disorders. Polysomnography (PSG) having practical constraints, the development of wearable devices and algorithms to monitor and stage sleep is rising. Beside pure validation studies, it is necessary for a clinician to ensure that the conclusions drawn with a new generation wearable sleep scoring device are consistent to the ones of gold standard PSG, leading to similar interpretation and diagnosis. This paper reports on the performance of Somno-Art Software for the detection of differences in sleep parameters between patients suffering from obstructive sleep apnea (OSA), insomniac or major depressive disorder (MDD) compared to healthy subjects. On 244 subjects (n = 26 healthy, n = 28 OSA, n = 66 insomniacs, n = 124 MDD), sleep staging was obtained from PSG and Somno-Art analysis on synchronized electrocardiogram and actimetry signals. Mixed model analysis of variance was performed for each sleep parameter. Possible differences in sleep parameters were further assessed with Mann-Whitney U-test between the healthy subjects and each pathology group. All sleep parameters, except N1+N2, showed significant differences between the healthy and the pathology group. No significant differences were observed between Somno-Art Software and PSG, except a 3.6±2.2 min overestimation of REM sleep. No significant interaction 'group'*'technology' was observed, suggesting that the differences in pathologies are independent of the technology used. Overall, comparable differences between healthy subjects and pathology groups were observed when using Somno-Art Software or polysomnography. Somno-Art proposes an interesting valid tool as an aid for diagnosis and treatment follow-up in ambulatory settings.

Surgery

Akabane S, **Miyake K**, Iwagami M, Tanabe K, and Takagi T. Machine learning-based prediction of postoperative mortality in emergency colorectal surgery: A retrospective, multicenter cohort study using Tokushukai medical database. *Heliyon* 2023; 9(9):e19695. PMID: 37810013. Full Text

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BACKGROUND: Although prognostic factors associated with mortality in patients with emergency colorectal surgery have been identified, an accurate mortality risk assessment is still necessary to determine the range of therapeutic resources in accordance with the severity of patients. We established machine-learning models to predict in-hospital mortality for patients who had emergency colorectal surgery using clinical data at admission and attempted to identify prognostic factors associated with in-hospital mortality. METHODS: This retrospective cohort study included adult patients undergoing emergency colorectal surgery in 42 hospitals between 2012 and 2020. We employed logistic regression and three supervised machine-learning models: random forests, gradient-boosting decision trees (GBDT), and multilayer perceptron (MLP). The area under the receiver operating characteristics curve (AUROC) was calculated for each model. The Shapley additive explanations (SHAP) values are also calculated to identify the significant variables in GBDT. RESULTS: There were 8792 patients who underwent emergency colorectal surgery. As a result, the AUROC values of 0.742, 0.782, 0.814, and 0.768 were obtained for logistic regression, random forests, GBDT, and MLP. According to SHAP values, age, colorectal cancer, use of laparoscopy, and some laboratory variables, including serum lactate dehydrogenase serum albumin, and blood urea nitrogen, were significantly associated with in-hospital mortality. CONCLUSION: We successfully generated a machine-learning prediction model, including GBDT, with the best prediction performance and exploited the potential for use in evaluating in-hospital mortality risk for patients who undergo emergency colorectal surgery.

Surgery
Albert RK, Jurkovich GJ, Connett J, Helgeson ES, Keniston A, Voelker H, Lindberg S, Proper JL, Bochicchio G, Stein DM, Cain C, Tesoriero R, Brown CVR, Davis J, Napolitano L, Carver T, Cipolle M, Cardenas L, Minei J, Nirula R, Doucet J, Miller PR, **Johnson J**, Inaba K, and Kao L. Sigh Ventilation in Patients With Trauma: The SiVent Randomized Clinical Trial. *Jama* 2023; Epub ahead of print. PMID: 37877609. Full Text

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Department of Surgery, University of Texas Southwestern, Dallas.
Department of Surgery, University of Utah, Salt Lake City.
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IMPORTANCE: Among patients receiving mechanical ventilation, tidal volumes with each breath are often constant or similar. This may lead to ventilator-induced lung injury by altering or depleting surfactant. The role of sigh breaths in reducing ventilator-induced lung injury among trauma patients at risk of poor outcomes is unknown. OBJECTIVE: To determine whether adding sigh breaths improves clinical outcomes. DESIGN, SETTING, AND PARTICIPANTS: A pragmatic, randomized trial of sigh breaths plus usual care conducted from 2016 to 2022 with 28-day follow-up in 15 academic trauma

centers in the US. Inclusion criteria were age older than 18 years, mechanical ventilation because of trauma for less than 24 hours, 1 or more of 5 risk factors for developing acute respiratory distress syndrome, expected duration of ventilation longer than 24 hours, and predicted survival longer than 48 hours. INTERVENTIONS: Sigh volumes producing plateau pressures of 35 cm H2O (or 40 cm H2O for inpatients with body mass indexes >35) delivered once every 6 minutes. Usual care was defined as the patient's physician(s) treating the patient as they wished. MAIN OUTCOMES AND MEASURES: The primary outcome was ventilator-free days. Prespecified secondary outcomes included all-cause 28-day mortality. RESULTS: Of 5753 patients screened, 524 were enrolled (mean [SD] age, 43.9 [19.2] years; 394 [75.2%] were male). The median ventilator-free days was 18.4 (IQR, 7.0-25.2) in patients randomized to sighs and 16.1 (IQR, 1.1-24.4) in those receiving usual care alone (P = .08). The unadjusted mean difference in ventilator-free days between groups was 1.9 days (95% CI, 0.1 to 3.6) and the prespecified adjusted mean difference was 1.4 days (95% CI, -0.2 to 3.0). For the prespecified secondary outcome, patients randomized to sighs had 28-day mortality of 11.6% (30/259) vs 17.6% (46/261) in those receiving usual care (P = .05). No differences were observed in nonfatal adverse events comparing patients with sighs (80/259 [30.9%]) vs those without (80/261 [30.7%]). CONCLUSIONS AND RELEVANCE: In a pragmatic, randomized trial among trauma patients receiving mechanical ventilation with risk factors for developing acute respiratory distress syndrome, the addition of sigh breaths did not significantly increase ventilator-free days. Prespecified secondary outcome data suggest that sighs are well-tolerated and may improve clinical outcomes. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02582957.

Surgery

Alkhaled L, **Al-Kurd A**, Butsch WS, Kashyap SR, and Aminian A. Diagnosis and management of post-bariatric surgery hypoglycemia. *Expert Rev Endocrinol Metab* 2023; 1-10. PMID: 37850227. Request Article

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INTRODUCTION: While bariatric surgery remains the most effective treatment for obesity that allows substantial weight loss with improvement and possibly remission of obesity-associated comorbidities, some postoperative complications may occur. Managing physicians need to be familiar with the common problems to ensure timely and effective management. Of these complications, postoperative hypoglycemia is an increasingly recognized complication of bariatric surgery that remains underreported and underdiagnosed. AREA COVERED: This article highlights the importance of identifying hypoglycemia in patients with a history of bariatric surgery, reviews pathophysiology and addresses available nutritional, pharmacological and surgical management options. Systemic evaluation including careful history taking, confirmation of hypoglycemia and biochemical assessment is essential to establish accurate diagnosis. Understanding the weight-dependent and weight-independent mechanisms of improved postoperative glycemic control can provide better insight into the causes of the exaggerated responses that lead to postoperative hypoglycemia. EXPERT OPINION: Management of post-operative hypoglycemia can be challenging and requires a multidisciplinary approach. While dietary modification is the mainstay of treatment for most patients, some patients may benefit from pharmacotherapy (e.g. GLP-1 receptor antagonist); Surgery (e.g. reversal of gastric bypass) is reserved for unresponsive severe cases. Additional research is needed to understand the underlying pathophysiology with a primary aim in optimizing diagnostics and treatment options.

Surgery

Bruschwein H, Chen G, Balliet W, Hart J, Canavan K, and **Jesse M**. Lessons learned: Development of an organ transplant caregiver educational resource. *Clin Teach* 2023; e13691. PMID: 37904630. Full Text

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BACKGROUND: Organ transplant lay caregivers perform an essential and complex role, but there is a paucity of comprehensive, accessible education regarding transplant caregiving. We sought to create a broad, multifaceted educational toolkit for transplant caregivers. Given the complexities of this population, we report on lessons learned by organising diverse stakeholder engagement to develop an educational resource covering the breadth and depth of organ transplantation. APPROACH: Following a call from organ transplant patients and caregivers, the American Society of Transplantation (AST) formed an Organ Transplant Caregiver Initiative with the aim to develop a comprehensive educational toolkit for transplant caregivers. The AST Organ Transplant Caregiver Toolkit was created through a shared, multi-step process involving transplant professionals and caregivers, who formed an education subcommittee to develop and refine content domains. The caregiver toolkit was reviewed with relevant external stakeholders and through an internal organisational review process. EVALUATION: Lessons learned included seeking guidance from others with experience creating similar resources, flexibility in project development, creativity in engaging stakeholders and routine communication between all entities involved. Insights gained contributed to the caregiver toolkit completion despite project challenges. IMPLICATIONS: The AST Organ Transplant Caregiver Toolkit can be utilised by health care professionals to educate and counsel transplant patients and caregivers. Lessons learned from the development of the caregiver toolkit can provide guidance to health care professionals and clinical teachers for the development of future education resources.

Surgery

Haley EN, **Loree AM**, **Maye M**, Coleman KJ, **Braciszewski JM**, **Snodgrass M**, Harry ML, **Carlin AM**, and **Miller-Matero LR**. Racial Differences in Psychiatric Symptoms, Maladaptive Eating, and Lifestyle Behaviors After Bariatric Surgery. *J Racial Ethn Health Disparities* 2023; Epub ahead of print. PMID: 37874488. Full Text

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There are several psychological and behavioral factors associated with poorer outcomes following bariatric surgery, yet it is unknown whether and how these factors may differ by race. In this cross-sectional study, individuals who underwent bariatric surgery from 2018 to 2021 and up to 4 years post-surgery were invited to complete an online survey. Psychiatric symptoms, maladaptive eating patterns, self-monitoring behaviors, and exercise frequency were examined. Participants (N = 733) were 87% women, 63% White, with a mean age of 44 years. Analyses of covariance demonstrated that White individuals endorsed greater anxiety symptoms (p =.01) and emotional eating due to depression (p = .01), whereas Black individuals endorsed greater depression severity (p = .02). Logistic regression analyses demonstrated that White individuals were more likely to experience loss of control eating (OR= 1.7, p = .002), grazing (OR= 2.53, p <.001), and regular self-weighing (OR= 1.41, p <.001) than Black individuals, and were less likely to skip meals (OR= .61, p = .04), or partake in nighttime eating (OR= .40, p <.001). There were no racial differences in binge eating, emotional eating due to anxiety or frustration, use of a food diary, or exercise. Thus, depressive symptoms, skipping meals, and nighttime eating may be important, modifiable intervention targets to optimize the benefits of bariatric surgery and promote equitable outcomes.

Surgery

Kahsai AW, Shah KS, Shim PJ, Lee MA, Shreiber BN, Schwalb AM, Zhang X, **Kwon HY**, Huang LY, Soderblom EJ, Ahn S, and Lefkowitz RJ. Signal transduction at GPCRs: Allosteric activation of the ERK MAPK by β-arrestin. *Proc Natl Acad Sci U S A* 2023; 120(43):e2303794120. PMID: 37844230. Request Article

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β-arrestins are multivalent adaptor proteins that bind active phosphorylated G protein-coupled receptors (GPCRs) to inhibit G protein signaling, mediate receptor internalization, and initiate alternative signaling events. β-arrestins link agonist-stimulated GPCRs to downstream signaling partners, such as the c-Raf-MEK1-ERK1/2 cascade leading to ERK1/2 activation. β-arrestins have been thought to transduce signals solely via passive scaffolding by facilitating the assembly of multiprotein signaling complexes. Recently, however, β-arrestin 1 and 2 were shown to activate two downstream signaling effectors, c-Src and c-Raf, allosterically. Over the last two decades, ERK1/2 have been the most intensely studied signaling proteins scaffolded by β-arrestins. Here, we demonstrate that β-arrestins play an active role in allosterically modulating ERK kinase activity in vitro and within intact cells. Specifically, we show that β-arrestins and their GPCR-mediated active states allosterically enhance ERK2 autophosphorylation and phosphorylation of a downstream ERK2 substrate, and we elucidate the mechanism by which β-arrestins do so. Furthermore, we find that allosteric stimulation of dually phosphorylated ERK2 by active-state β-arrestin 2 is more robust than by active-state β-arrestin 1, highlighting differential capacities of β-arrestin isoforms to regulate effector signaling pathways downstream of GPCRs. In summary, our study provides strong evidence for a new paradigm in which β-arrestins function as active "catalytic" scaffolds to allosterically unlock the enzymatic activity of signaling components downstream of GPCR activation.

Surgery

Miller-Matero LR, **Haley EN**, **Loree AM**, **Braciszewski JM**, **Maye M**, **Sehgal M**, and **Carlin AM**. Post-surgical psychiatric symptoms, maladaptive eating patterns, and lifestyle behaviors associated with weight recurrence after bariatric surgery. *Surg Obes Relat Dis* 2023; Epub ahead of print. PMID: 37923621. Full Text

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BACKGROUND: A significant proportion of patients who undergo bariatric surgery experience weight recurrence; however, the most important areas to target to prevent weight recurrence remain unknown. OBJECTIVES: The purpose was to examine whether psychiatric symptoms, maladaptive eating behaviors, and lifestyle factors were associated with weight recurrence. SETTING: Single healthcare system. METHODS: Individuals who underwent bariatric surgery were invited to complete a web-based survey in which they reported their current weight and completed measures of psychiatric symptoms, maladaptive eating behaviors, and lifestyle behaviors. Participants were included if they were at least 2

years postsurgery. Weight recurrence was measured from the 1-year follow-up to the survey date. RESULTS: Participants (n = 169) were predominantly female and White or Black, with a mean age of 45 years. The rate of significant weight recurrence was 23.1%. Those who underwent sleeve gastrectomy were more likely to experience weight recurrence (odds ratio [OR] = 12.99; P = .01). In bivariate analyses, anxiety and depressive symptoms, emotional eating, loss of control eating, binge eating, and night eating were associated with weight recurrence (P < .05). Those who did not eat mindfully, take 20 minutes to eat, or get adequate sleep were also more likely to have weight recurrence (P < .05). In a multivariate model, only a lack of mindful eating (OR = 4.84; P = .03) and inadequate sleep (OR = 7.30; P = .02) remained statistically significant predictors. CONCLUSION: Engaging in mindful eating and obtaining adequate sleep may protect against weight recurrence following bariatric surgery. Clinicians may want to screen and monitor these behaviors.

Surgery

Miller-Matero LR, **Ross K**, **Arellano C**, **Zelenak L**, **DePascale E**, **Gavrilova L**, **Braciszewski JM**, **Hecht LM**, **Haley EN**, **Brescacin C**, and **Carlin AM**. Cannabis use following bariatric surgery is associated with anxiety and maladaptive eating. *Surg Obes Relat Dis* 2023; Epub ahead of print. PMID: 37863791. Full Text

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BACKGROUND: There are limited data regarding the association of cannabis use with outcomes after bariatric surgery. As such, it is challenging to know how to counsel patients using cannabis. OBJECTIVES: The purpose of this study was to examine whether postsurgical cannabis use was associated with psychiatric symptoms and maladaptive eating among individuals up to 4 years after bariatric surgery. SETTING: Single health system. METHODS: All patients who underwent bariatric surgery over a 4-year period were invited to participate. Participants (N = 765) completed questionnaires online regarding postsurgical cannabis use, psychiatric symptoms, and maladaptive eating. RESULTS: Any cannabis use after bariatric surgery was associated with increased likelihood of having elevated symptoms of anxiety (odds ratio [OR] = 1.88, P = .003; 37.8% versus 24.4%), increased likelihood of grazing behaviors (OR = 1.77, P = .01; 71.2% versus 58.2%), and higher scores for eating in response to depression (P = .01; 12.13 versus 10.75). Weekly cannabis use was associated with loss of control eating (OR = 1.81, P = .04; 37.2% versus 24.7%), binge eating (OR = 2.16, P = .03; 20.0% versus 10.4%), and night eating behaviors (OR = 2.11, P = .01; 40.0% versus 24.0%). Cannabis use was not associated with depression (P > .05). CONCLUSIONS: Cannabis use after bariatric surgery was associated with anxiety symptoms and engaging in maladaptive eating behaviors. Frequent cannabis use (i.e., ≥1 per week) was associated with additional types of maladaptive eating. Clinicians involved in presurgical and postsurgical care may want to counsel patients currently using cannabis, especially those who are engaging in frequent use.

Surgery

Morrison CW, Sanjasaz KN, **Nathanson SD**, **Raina-Hukku S**, **Pinkney DM**, and **Davenport AA**. Dedifferentiated endometrial carcinoma metastasis to axillary lymph node: a case report. *J Med Case Rep* 2023; 17(1):451. PMID: 37899461. Full Text

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BACKGROUND: We present an unusual case of a left axillary lymph node metastasis from a primary dedifferentiated endometrial carcinoma. This pattern of metastasis is likely the result of circulating tumor cells reaching the node through its arterial blood supply. CASE PRESENTATION: In this report, a 68-year-old white woman with a dedifferentiated endometrial carcinoma underwent a hysterectomy. She later developed an enlarged axillary lymph node due to metastatic dedifferentiated endometrial carcinoma, treated with chemotherapy and anti-programmed cell death protein 1 immunotherapy resulting in a complete clinical and radiological response. CONCLUSION: A review of the literature reveals the rarity of blood-borne lymph node metastasis, especially with uterine carcinoma. Immunotherapy has shown promising results in the treatment of some subtypes of metastatic uterine carcinoma.

Surgery

Somerset AE, Wood MH, Bonham AJ, **Carlin AM**, Finks J, Ghaferi AA, and Varban OA. Association of program-specific variation in bariatric surgery volume for Medicaid patients and access to care: a tale of inequality? *Surg Endosc* 2023; 37(11):8570-8576. PMID: 37872428. Full Text

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BACKGROUND: Although patients with lower socioeconomic status are at higher risk of obesity, bariatric surgery utilization among patients with Medicaid is low and may be due to program-specific variation in access. Our goal was to compare bariatric surgery programs by percentage of Medicaid cases and to determine if variation in distribution of patients with Medicaid could be linked to adverse outcomes. METHODS: Using a state-wide bariatric-specific data registry that included 43 programs performing 97,207 cases between 2006 and 2020, we identified all patients with Medicaid insurance (n = 4780, 4.9%). Bariatric surgery programs were stratified into quartiles according to the percentage of Medicaid cases performed and we compared program-specific characteristics as well as baseline patient characteristics, risk-adjusted complication rates and wait times between top and bottom quartiles. RESULTS: Program-specific distribution of Medicaid cases varied between 0.69 and 22.4%. Programs in the top quartile (n = 11) performed 18,885 cases in total, with a mean of 13% for Medicaid patients, while programs in the bottom quartile (n = 11) performed 32,447 cases in total, with a mean of 1%. Patients undergoing surgery at programs in the top quartile were more likely to be Black (20.2% vs 13.5%, $p < 0.0001$), have diabetes (35.1% vs 29.5%, $p < 0.0001$), hypertension (55.1% vs 49.6%, $p < 0.0001$) and hyperlipidemia (47.6% vs 45.2%, $p < 0.0001$). Top quartile programs also had higher complication rates (8.4% vs 6.6%, $p < 0.0001$), extended length of stay (5.6% vs 4.0%, $p < 0.0001$), Emergency Department visits (8.1% vs 6.5%, $p < 0.0001$) and readmissions (4.7% vs 3.9%, $p < 0.0001$). Median time from initial evaluation to surgery date was also significantly longer among top quartile programs (200 vs 122 days, $p < 0.0001$). CONCLUSIONS: Bariatric surgery programs that perform a higher proportion of Medicaid cases tend to care for patients with greater disease severity who experience delays in care and also require more resource utilization. Improving bariatric surgery utilization among patients with lower socioeconomic status may benefit from insurance standardization and program-centered incentives to improve access and equitable distribution of care.

Surgery

Yaranov DM, Baldridge AS, Gonzalez M, Biglane JB, **Tanaka D**, Fischer W, Larkin C, Ullah R, Chaudhry SP, and Pham DT. Anticoagulation Bridging in Patients With Left Ventricular Assist Device: A Regional Analysis of HeartMate 3 Recipients. *Asaio j* 2023; Epub ahead of print. PMID: 37862687. Full Text

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Advances in left ventricular assist device technologies have led to an improvement in pump hemocompatibility and outcomes. Because of concerns of thromboembolic complications in prior generations of left ventricular assist devices, bridging with parenteral anticoagulants was routinely. Management strategies of subtherapeutic INRs and their effects on the current generation of devices deserve review. We performed analysis of the MOMENTUM 3 trial including 6 centers in the mid-America region. Patients with subtherapeutic INRs (INR < 2) occurring after the index admission underwent chart review to determine the management strategies taken by clinicians. Strategies were divided into two groups, bridging or nonbridging. Of the 225 patients included in the analysis, 130 (58%) patients had a total of 235 subtherapeutic international normalized ratio (INR) events. Most (n = 179, 76.2%) of these INRs were not bridged (n = 100 warfarin dose adjustment, n = 79 no change in warfarin dose). Among those INRs (n = 56, 23.8%) treated with bridging, approximately half (n = 30, 53.6%) were treated with subcutaneous agents and other half (n = 26, 46.4%) were treated with intravenous agents. There was no difference in individual outcomes or composite endpoints of death, rehospitalization, CVA, or bleeding events between the groups.

Urology

Kianian R, Carter M, Finkelshtein I, Eleswarapu SV, and **Kachroo N**. Application of Artificial Intelligence to Patient-Targeted Health Information on Kidney Stone Disease. *J Ren Nutr* 2023; Epub ahead of print. PMID: 37839591. Full Text

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OBJECTIVE: The American Medical Association (AMA) recommends health information to be written at a 6(th) grade level reading level. Our aim was to determine whether Artificial Intelligence (AI) can outperform the existing health information on kidney stone prevention and treatment. METHODS: The top 50 search results for "Kidney Stone Prevention" and "Kidney Stone Treatment" on Google, Bing, and Yahoo were selected. Duplicate webpages, advertisements, pages intended for health professionals such as science articles, links to videos, paid subscription pages, and links non-related to kidney stone prevention and/or treatment were excluded. Included pages were categorized into academic, hospital-affiliated, commercial, non-profit foundations, and other. Quality and readability of webpages were evaluated using validated tools, and the reading level was descriptively compared with ChatGPT generated health information on kidney stone prevention and treatment. RESULTS: 50 webpages on kidney stone prevention and 49 on stone treatment were included in this study. The reading level was determined to equate to that of a 10(th) to 12(th) grade student. Quality was measured as "fair" with no pages scoring "excellent" and only 20% receiving a "good" quality. There was no significant difference between pages from academic, hospital-affiliated, commercial, and non-profit foundation publications. The text generated by ChatGPT was considerably easier to understand with readability levels measured as low as 5(th) grade. CONCLUSIONS: The language used in existing information on kidney stone disease is of subpar quality and too complex to understand. Machine learning tools could in generating information that is comprehensible by the public.

Urology
Majdalany SE, **Yaguchi G**, **Bazzi M**, **Jamil ML**, **Dabaja AA**, and **Rambhatla A**. Peri-operative considerations for inflatable penile prosthesis: A same-day discharge pathway. *Urol Video J* 2023; 20. PMID: Not assigned. Full Text

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Urology
Xu AJ, Mishra K, **Shakir N**, and Zhao LC. A novel apparatus to assess intraoperative intrarenal pelvic pressure and associated clinical outcomes. *Urol Video J* 2023; 20. PMID: Not assigned. Full Text

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Objective: To design a simple, novel, economical apparatus which effectively provides reliable, real-time measurements of intrarenal pelvic pressure (IRPP) intraoperatively and to demonstrate clinical utility. Patients and Surgical Procedure: Patients undergoing robotic ureteral reconstruction from 10/2020 to 7/2021 for whom intraoperative IRPP measurement was conducted were included. Baseline opening pressure was noted with the pelvis completely drained. The kidney was intermittently drained when IRPP exceeded a certain threshold, returning the pressure to baseline. Relief of obstruction was defined as return of IRPP to physiologic value without further increases for the remainder of surgery. Demographic, intraoperative, and post-operative variables were collected and IRPP measurements extracted. Post-operative success was defined as resolution of obstruction by clinical symptoms and imaging. Results: Eleven patients met criteria including 4 (36.4%) men and 7 (63.6%) women. Median age and BMI was 61 years (range 14–23) and 26 kg/m2 (range 17.2–42), respectively. Six patients (54.5%) had undergone prior interventions. Ureteral reconstructive procedures included bilateral refluxing reimplants (2), unilateral reimplant with Boari flap (3), non-transecting reimplant (2), unilateral ileal ureter (1), bilateral ileal ureter (1), buccal ureteroplasty (1), and ureteroureterostomy (1). Median peak IRPP was 52 mmHg (range 27–59) and median nadir IRPP was 14 mmHg (range 1–24), with median decrease of 36 mmHg (range 26–84). At median follow-up of 120 days, all patients had successful repairs. Conclusions: Intraoperative measurement of IRPP can be utilized in patients with percutaneous nephrostomy tubes using readily available equipment. This measurement has the potential to ensure that ureteral obstruction is completely relieved and to prevent development of supraphysiologic IRPP during surgery.

Administration
Kattula MM, Steafo L, Corsi NJ, **Gutta RN**, and **Scher E**. BRASH SYNDROME: A CASE OF OCCULT BRADYCARDIAC SHOCK LEADING TO SYMPATHETIC OVERDRIVE. *J Gen Intern Med* 2023; 38:S434. Full Text

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CASE: A 58-year-old African American male with a past medical history of chronic diastolic heart failure, chronic kidney disease stage IV, and poorly controlled hypertension who presented following persistent bradycardia, and hypotensive readings at home. His antihypertensive regimen prior to arrival included Lisinopril, Nifedipine, Hydralazine, Isosorbid Mononitrate, and Carvedilol daily. On arrival, he was hemodynamically labile with a systolic blood pressure in the 90's, heart rate in the low 50's, and hypothermic to 33.8 degree Celsius. Initial lab work showed a creatinine of 3.56 (baseline of 2.80) and potassium of 6.4. A rapid EKG demonstrated sinus bradycardia, and CXR consistent with pulmonary edema. He was transferred to the MICU after initial management with calcium gluconate, Insulin, D50, Lokelma, and warming measures with a bear hugger. On arrival to the MICU, he required 4L via nasal cannula due to pulmonary edema and was aggressively diuresed with resolution of potassium disturbance. However, he was found to rebound and became increasingly hypertensive to 200s systolic without evidence of end organ damage. His blood pressure was medically managed on the floors and within 24 hours his kidney function neared baseline. He was discharged on a new regimen of antihypertensives, specifically with discontinuation of his beta blocker. IMPACT/DISCUSSION: The combination of bradycardia, renal failure, av nodal blockade, shock, and hyperkalemia creates a condition known as BRASH syndrome. Unfortunately, this is a cycle where one complication begets another in patients who take av nodal blocking agents and anti-hypertensives that cause hyperkalemia. There are different thoughts on whether it is renal failure or the combination of beta blockers and hyperkalemia that stimulates the cascade. Nonetheless, these components are interrelated and the cycle will continue if it's not identified and treated immediately, ultimately leading to multiorgan failure. What is unique to this case is the rare complication of hypertensive urgency as a result of sympathetic overdrive in response bradycardia causing reduced cardiac output. Furthermore, what is controversial is whether or not to restart medications that demonstrate improved mortality in patients with heart failure, yet may be the cause of this disease process. CONCLUSION: BRASH syndrome is unique because it's a continuum of a single disease, and therapy includes correction of hyperkalemia, fluid management, and vasopressor support when required. There is not enough data that shows if re-introducing these medications following resolution of BRASH syndrome is necessary and whether recurrence rates are significant in those who are restarted on these medications. Additionally, a rare complication that physicians should be aware of is the sympathetic drive that can lead to hypertensive urgency as a result of bradycardia causing reduced cardiac cardiac output.

Administration
Mattei L, **Miller M**, **Robb L**, **Polan R**, Gogoi R, and Morris R. The cost of convenience: Fellow and program director perspectives on the adequacy of virtual fellowship interviews as a replacement for in-person interviews (2317). *Gynecol Oncol* 2023; 176:S325-S326. Full Text

Objectives: Gynecologic oncology fellowship interviews have shifted to a virtual format in the wake of the COVID-19 pandemic. We assessed fellow and program director (PD) experiences with virtual and in-person fellowship interviewing and satisfaction with the subsequent match results. Methods: Surveys were designed and distributed via email to gynecologic oncology fellowship PDs and current fellows interviewed in either 2019 or 2020. Fellows and PDs were asked to reflect on their interview experiences and to indicate through five-level Likert scale questions and free text responses the adequacy of the interview process and the degree to which their interview experience was concordant with their current experience after the match. Results: We received 48 responses, 21 from fellows and 27 from program directors. PDs sent an average of 22 invitations per available position in 2019; 38% reported sending more invitations in 2020, with an average increase of 6 additional interviews per available position. Fellows who interviewed virtually applied to similar numbers of programs as those who interviewed in

person (39 vs 45, P = 0.32) but reported receiving significantly fewer invitations (19 vs 26, P = 0.035). Fellows who interviewed virtually spent significantly less money on average than those who interviewed in person ($83.33 vs $6833.33, P < 0.0001). Most PDs agreed or strongly agreed that they were able to assess candidates for fit and showcase their program's unique attributes (79.3% and 70.0%, respectively). However, only 53.3% agreed or strongly agreed that they were able to rank virtual applicants confidently. Most fellows felt similarly able to assess fit (90.4% overall, 91.6% virtual, 88.8% in-person) and rank with confidence (95.2% overall, 100% virtual, 88.8% in-person). Of the fellows who interviewed virtually, 83.3% agreed or strongly agreed that their current experiences were congruent with the impressions from their interview day. Similarly, 73.3% of PDs agreed or strongly agreed that their in-person experiences with their first-year fellows were congruent with their expectations of them based on their virtual interview. Fellow free text responses most commonly discussed themes relating to cost, ease of scheduling, and assessing program culture. PD themes not only included cost and applicant perceptions of programs but also emphasized the importance of social interaction. Conclusions: PDs and fellows who interviewed virtually report feeling satisfied with the virtual interview process, with the majority recommending that it be continued in the future. Issues of cost and the ability to assess program culture were the most commonly cited areas of concern among both fellows and program directors. Virtual interviewing with opportunities for in-person interaction or “second looks” has been proposed as a solution that may address the concerns identified in our survey.

Administration

Savard N, **Chami E**, **Salanger D**, **Gubler J**, **Dover C**, and **Weaver J**. Developing a Robust Leak Response Program. *Am J Infect Control* 2023; 51(7):S28. Full Text

Background: Aging infrastructure within a 100-year-old acute care hospital presents challenges that can often lead to an increase in leaks identified throughout the hospital in both clinical and non-clinical areas that increases the possibility of mold or other waterborne pathogens. In June 2021, the facility was tested even greater when a state of emergency was declared for following a rainstorm which overloaded the area's wastewater systems and further caused significant water damage to the Detroit-based hospital. An improved process was needed to identify and to reduce the occurrence of leaks throughout the hospital. Methods: After the 2021 flooding, the Infection Prevention team, in collaboration with hospital and Facility leadership, developed a leak response document that outlined the immediate expectations for the staff members who identify leaks, the Facility staff expectations, and how to properly report leaks and floods. In addition, a need was identified to better assess the flooring products used and develop a flooring recommendation document that identified the best flooring products that should be installed in areas that have a higher risk of leaks/flooding. Additionally, the Infection Prevention department invested in a moisture reader for room signoffs after leaks. Results: The leak response process and document were presented to all areas/departments throughout the facility. Additionally, the flooring product document was shared with facility design teams, who are now more integrated with Infection Prevention to work on which flooring products to select. Lastly, a process has been developed for room signoff after a known water intrusion. Conclusions: The detailed leak response process outlined and implemented has been improved response time in identifying and reporting leaks throughout the facility. The process in how to properly design and sign-off rooms has reduced the risk of mold growth and has improved room remediation time after a water intrusion event

Cardiology/Cardiovascular Research

Allana S, Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, **Alaswad K**, Jaffer F, Khatri J, Choi J, Krestyaninov O, Khelimskii D, Gorgulu S, Davies R, Benton S, Poommipanit P, Azzalini L, Chandwaney R, Rinfret S, Jaber W, Frizzell J, Jefferson B, Sandoval Y, Rangan B, and Brilakis E. TCT-334 Technical Analysis and Procedural Outcomes of Retrograde Approach to Chronic Total Occlusion Percutaneous Coronary Interventions: Insights From an International Multicenter Registry. *J Am Coll Cardiol* 2023; 82(17):B133-B134. Full Text

Background: Retrograde chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is associated with lower success and higher complication rates compared with antegrade approach. Methods: We examined baseline characteristics, procedural techniques and outcomes of 4,058 retrograde CTO PCIs performed at 44 centers between 2012 and 2023. Major adverse cardiac events

(MACE) included any of the following in-hospital events: death, myocardial infarction, repeat target-vessel revascularization, pericardiocentesis, cardiac surgery, and stroke. Results: The average J-CTO score was 3.1 ± 1.1. Retrograde crossing was successful in 60.5% and lesion crossing in 81.6% of cases. The collaterals pathways successfully used were septals in 62.0%, saphenous vein grafts in 17.4%, and epicardials in 19.1%. Epicardial collateral perforation was associated with significantly higher incidence of in-hospital MACE (14.0% vs 3.3%; P < 0.001) while there was no significant difference in in-hospital MACE with septal collateral perforation (2.3% vs 3.5%; P = 0.66). The technical and procedural success rates were 78.7% and 76.6%, respectively. When retrograde crossing failed, technical success was achieved in 50.3% of cases using an antegrade approach. In-hospital MACE was 3.5%. The coronary perforation rate was 9.5%. The incidence of in-hospital MACE with retrograde true lumen crossing, just marker antegrade crossing, conventional reverse controlled antegrade and retrograde tracking (CART), contemporary reverse CART, extended reverse CART, guide-extension reverse CART, and CART was 2.1%, 0.8%, 5.5%, 3.0%, 2.1%, 3.2%, and 4.1%, respectively; P = 0.01). Conclusion: Retrograde CTO PCI is utilized in cases with high lesion complexity and yields moderate success rates with 9.5% perforation and 3.5% peri-procedural MACE rates. Use of septal collateral was associated with the lowest risk of coronary perforation. Epicardial collateral perforation resulted in high rate of in hospital MACE. Among retrograde crossing strategies, retrograde true lumen puncture was the safest. Guide extension reverse CART has a good balance of feasibility and safety. There is need for improvement in efficacy and safety of retrograde CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Allana S, Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, Alexandrou M, Azzalini L, **Alaswad K**, Khatri J, Choi J, Jaffer F, Benton S, Davies R, Poommipanit P, Frizzell J, Khelimskii D, Gorgulu S, Krestyaninov O, Chandwaney R, Rinfret S, Jaber W, Jefferson B, Sandoval Y, Rangan B, and Brilakis E. TCT-338 “Tip in/Rendez-vous” Technique in Retrograde Chronic Total Occlusion Percutaneous Coronary Interventions: Insights From the PROGRESS CTO Registry. *J Am Coll Cardiol* 2023; 82(17):B135. Full Text

Background: After successful retrograde crossing, wire externalization is the default strategy. “Tip-in/rendez-vous” technique is an alternative strategy that is less frequently used. The aim of the study was to assess procedural strategies and outcomes of “tip-in/rendez-vous” technique in retrograde chronic total occlusion (CTO) percutaneous coronary intervention (PCI). Methods: We examined clinical and angiographic characteristics, procedural techniques, and outcomes of 2,456 CTO PCIs with successful retrograde crossing performed at 44 U.S. and non-U.S. centers between 2012 and 2023. In-hospital major adverse cardiac events (MACE) included any of the following in-hospital events: death, myocardial infarction, urgent repeat target-vessel revascularization, tamponade requiring pericardiocentesis or surgery, and stroke. Results: “Tip-in/rendez-vous” technique was performed in 73 (3.0%) cases and retrograde wire externalization in 2,383 (97.0%) cases. Compared with the CTO procedures with wire externalization, procedures requiring “tip-in/rendez-vous” required longer fluoroscopy times (86 [60, 118] minutes vs 74 [54, 99] minutes; P = 0.03], higher air kerma radiation dose (4.1 [2.4, 7.7] Gy vs 2.9 [1.7, 4.8] Gy; P = 0.001), and higher contrast volume (300 [185, 450] mL vs 230 [162, 320] mL; P = 0.002]. There was a trend toward lower technical success rate (94.5% vs 97.8%; P = 0.07) among lesions requiring “tip in/rendez-vous” technique. There were no significant differences in the overall procedural success rate (93.2% vs 94.8%; P = 0.53) and the rate of in-hospital MACE between the 2 groups (4.1% vs 3.4%; P = 0.74). Non-RCA target vessel, good distal landing zone, successful epicardial crossing, and proximal cap ambiguity were independently associated with higher likelihood of using “tip-in/rendez-vous” technique over wire externalization. Conclusion: “Tip-in/rendez-vous” technique is infrequently performed in retrograde CTO PCI. Compared with wire externalization, “tip-in/rendez-vous” technique in retrograde CTO PCI is associated with longer fluoroscopy times, higher air kerma radiation dose, higher contrast volume, and similar rates of technical and procedural success and in-hospital MACE. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Arora A, **Giustino G**, Sartori S, Feng Y, Tanner R, Vinayak M, Farooq A, Khan M, Dhulipala V, Salehi N, Mehran R, Kini A, and Sharma S. TCT-263 Percutaneous Coronary Intervention Risk Stratification: SYNTAX Score Versus Complex PCI Score. *J Am Coll Cardiol* 2023; 82(17):B103. Full Text

Background: The SYNTAX score is limited by complexity and inter-observer variability. However, the Complex PCI score is a simplified and accessible tool to risk stratify patients undergoing percutaneous coronary intervention (PCI), yet its ability to predict major adverse cardiac events (MACE) is less well studied. Methods: All patients undergoing PCI between 2015 and 2020 were included and SYNTAX scores calculated. The Complex PCI score assigns 1 point to: ≥3 vessel PCI, ≥3 stents, ≥3 lesions treated, a bifurcation with ≥2 stents, stent length ≥60 mm, and chronic total occlusion PCI. The ability of the both scores to predict MACE (all-cause mortality, myocardial infarction, and TVR) at 1 year was compared. Results: Among 16,037 patients, 86% (n = 13,709), 9.8% (n = 1,473), and 5.7% (n = 855) had a low (≤22), intermediate (23-32), and high (≥33) SYNTAX score, respectively. Complex PCI score of 0, 1, and ≥2 was seen in 59% (n = 8,860), 21.8% (n = 3,268), and 21.9% (n = 3,279) of patients, respectively. Higher MACE rate was seen in patients with an intermediate (HR: 2.11 [1.81-2.46]; P < 0.001) and high (HR: 3.70 [3.16-4.33]; P < 0.001) SYNTAX score compared with a low score. A Complex PCI score of 1 (HR: 1.50 [1.31-1.73]; P < 0.001) and ≥2 (HR: 2.05 [1.81-2.33]; P < 0.001) was associated with higher MACE rate compared with score of 0. The discriminator ability to predict MACE of each score was low but comparable. When Complex PCI variables were combined with the SYNTAX score, risk stratification ability improved (likelihood test ratio, P < 0.001). [Formula presented] Conclusion: Both SYNTAX and Complex PCI scores have similar but low discrimination ability in risk stratifying patients undergoing PCI. Further research is needed to develop an intuitive and accurate risk prediction tool. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Bharadwaj A, Truesdell A, Lemor A, Thompson J, Abu-Much A, Zhang Y, Schonning M, Redfors B, Cohen D, Witzke C, Matthews R, Dixon S, Lansky A, and **O'Neill W**. TCT-216 Defining High-Risk Percutaneous Coronary Intervention: Characteristics of Patients Undergoing Contemporary Percutaneous Coronary Intervention With Axial-Flow Mechanical Support. *J Am Coll Cardiol* 2023; 82(17):B83-B84. Full Text

Background: There is no universally accepted definition of high-risk percutaneous coronary intervention (HRPCI), nor is there consensus regarding when to use axial-flow mechanical circulatory support (MCS) during HRPCI. Expert opinions have suggested considering MCS in the presence of patient comorbidities, complex coronary anatomy, and adverse hemodynamics. Methods: Patients from 46 US centers who underwent Impella-supported HRPCI between 2017 and 2020 and were prospectively enrolled in the cVAD PROTECT III study were analyzed. Patient and procedural characteristics commonly cited as factors prompting use of MCS for HRPCI were classified as (A) complex coronary anatomical features, (B) medical comorbidities, and/or (C) adverse hemodynamic characteristics (Figure 1). Patients were analyzed to assess how many possessed 1, 2, or all 3 factors and, within each category, the number of individual features. Results: Of 1,237 patients, n = 1,020 (82.5%) patients had factors in groups A, B, and C, n = 20 (1.6%) in groups A and B, n = 69 (5.6%) in groups A and C, and n = 123 (9.9%) in groups B and C (Figure 1). No patients had medical comorbidities (B) only, only n = 5 (0.4%) patients had complex hemodynamic features (C) only, and no patients had complex coronary anatomy (A) only. Most patients had 2 or more features within each high-risk domain. [Formula presented] Conclusion: In this contemporary study, most patients undergoing Impella-assisted HRPCI possessed multiple medical comorbidities and multiple adverse hemodynamic and multiple complex coronary anatomical features, suggesting that the confluence of all 3 factors influence decision-making for use of MCS. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Brener M, Barker C, Davidson C, Narang A, Sharma R, Haeffele C, Yadav P, Thourani V, Kodali S, Hahn R, Makkar R, Makar M, Hausleiter J, Nabauer M, **O'Neill W**, **Wang DD**, Lindman B, Zahr F, Chadderdon S, Eleid M, Pislaru S, Mancilla M, Kemp L, Mollenkopf S, Ryan M, and Cohen D. TCT-720 Patient-

Reported Outcomes in Tricuspid Valve Intervention: Patient Preference Results From the TRISCEND II Trial. *J Am Coll Cardiol* 2023; 82(17):B289-B290. Full Text

Background: Validated patient reported outcome measures for tricuspid regurgitation (TR) are lacking. To address this knowledge gap, we assessed patient priorities for improvement during evaluation for treatment of TR. Methods: Participants in the prospective, multicenter TRISCEND II pivotal randomized trial, comparing outcomes of the EVOQUE transcatheter tricuspid valve replacement (TTVR) system (Edwards Lifesciences) plus optimal medical therapy (OMT) vs OMT alone for at least severe TR were administered a patient preference survey at baseline. Survey questions assessed patients' priorities for improvement in 6 symptoms (swelling in legs, ankles, and feet; fatigue; poor sleep; depression or anxiety; shortness of breath) and 6 activities (self-care; walking 1 block on level ground; climbing stairs; performing work, chores, or hobbies; recreational activities; and visiting family and friends). Results: 131 trial participants completed the survey correctly. For symptoms, participants most frequently prioritized improvement in shortness of breath (37.4%) and fatigue (23.7%) (see Table 1). For activities, patients prioritized self-care (54.2%) and ability to visit family/friends outside of the home (10.7%). Ongoing analyses will examine the relationship between patient preferences, changes in health status, and treatment assignment. [Formula presented] Conclusion: Among patients undergoing treatment for severe TR in the TRISCEND II RCT, improvements in dyspnea and independence were identified as key goals of therapy. The relationship between these goals and health status outcomes with TTVR vs medical therapy will be presented and will provide novel insights into the value of TTVR from the patient's perspective. Categories: STRUCTURAL: Valvular Disease: Tricuspid

Cardiology/Cardiovascular Research
Falah B, Tehrani B, Zhang Y, Abu-Much A, Cohen D, Redfors B, Acharya D, Garas S, Baron S, **Basir B**, Bharadwaj A, Lemor A, Truesdell A, **O'Neill W**, and Batchelor W. TCT-241 Clinical Characteristics and Outcomes of Impella-Supported High-Risk PCI in Patients Turned Down for Coronary Artery Bypass Graft Surgery: Insights From the cVAD PROTECT III Study. *J Am Coll Cardiol* 2023; 82(17):B94-B95. Full Text

Background: Impella-assisted percutaneous coronary intervention (PCI) is increasingly offered for patients deemed prohibitive risk for coronary artery bypass grafting (CABG), but limited data exist on the characteristics, reasons for turndown, and outcomes of these patients. Methods: Patients from the prospective, multicenter observational PROTECT III study who underwent Impella-assisted high-risk PCI were categorized into groups: CABG turndown by a cardiothoracic surgeon (CTS) or patients declining CABG despite surgical eligibility. Baseline characteristics and major adverse cardiovascular and cerebrovascular events (MACCE) at 30 and 90 days were assessed. Results: Of 1,235 patients, 791 evaluated for CABG were analyzed; 86.0% (n = 680) turned down by a CTS, and 14.0% (n = 111) declined surgery. Baseline characteristics are shown in Table 1. Comorbidities (40.4%; n = 275) and anatomical and hemodynamic reasons (24.0%, n = 163 for each) were the main factors for CTS turndown. Patients declining CABG showed no difference in 30-day MACCE compared with patients who declined surgery but had lower MACCE at 90 days (P = 0.02) (Figure 1). [Formula presented] [Formula presented] Conclusion: Results from PROTECT III reveal that patients who declined CABG had lower MACCE at 90 days. Further research is needed to enhance our understanding and risk stratification of patients with complex coronary disease undergoing evaluation for Impella-assisted high-risk PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Giustino G, Sartori S, Feng Y, Farhan S, Vogel B, Dhulipala V, Vinayak M, Mehran R, Kini A, Sharma S, and Tanner R. TCT-611 Clinical Outcomes After First Episode In-Stent Restenosis Percutaneous Coronary Intervention: Diabetics Versus Nondiabetics. *J Am Coll Cardiol* 2023; 82(17):B246. Full Text

Background: Diabetes mellitus is associated with an increased risk of in-stent restenosis (ISR) and major adverse cardiac events (MACE) after de novo lesion percutaneous coronary intervention (PCI). Whether diabetic patients undergoing PCI for ISR experience the same heighted risk for ISR and MACE is unknown. Methods: Patients with chronic coronary syndrome undergoing PCI between January 2015 and December 2021 for ISR at Mount Sinai Hospital were eligible for inclusion. The rate of MACE (all-cause death, myocardial infarction, and target lesion revascularization [TVR]) at 1-year follow-up was compared

between diabetic and nondiabetic patients in an adjusted HR (AHR) model. Results: A total of 3,153 patients (1,791 diabetic patients [56.7%]) underwent PCI for ISR during the study period. Diabetic patients were younger (66.4 ± 10.1 years vs 68 ± 11.3 years; P < 0.001) and more likely to be female (27.2% vs 19.8%; P < 0.001). Furthermore, diabetic patients were more likely to have previous coronary artery bypass grafting, chronic kidney disease, and anemia, and have a high SYNTAX score. The proportion of patients treated for bifurcations, chronic total occlusions, and type B2/C lesions was similar in both groups. At 1-year follow-up, there was no significant difference in the rate of MACE between diabetic and nondiabetic patients (22.4% vs 18.7%, AHR: 1.12; 95% CI [0.94-1.34]; P = 0.27). All-cause mortality (4.1% vs 2.0%, AHR: 1.71; 95% CI [1.03-2.82]; P = 0.036) was significantly higher in diabetic patients, but there was no difference in the rates of TVR (17.9% vs 16.0%; AHR: 1.07; 95% CI [0.88-1.31]; P = 0.486) and myocardial infarction (5.2% vs 3.6%; AHR: 1.18; 95% CI [0.80-1.75]; P = 0.406) between groups. Conclusion: Diabetic patients had a comparable risk of MACE to nondiabetic patients at 1-year follow-up, despite having more comorbidities. in contrast to studies on PCI for de novo lesions, diabetes does not appear to increase the risk of TVR after ISR PCI at medium-term follow-up. Categories: CORONARY: Stents: Drug-Eluting

Cardiology/Cardiovascular Research
Karacsonyi J, Stanberry L, Bergstedt S, Rempakos A, Kostantinis S, Simsek B, Alexandrou M, Allana S, Al-Ogaili A, **Alaswad K**, Krestyaninov O, Karmpaliotis D, Kirtane A, McEntegart M, Khatri J, Jaffer F, Poommipanit P, Choi J, Gorgulu S, Jaber W, Rinfret S, ElGuindy A, Rafeh NA, Goktekin O, Ungi I, Azzalini L, Rangan B, Mastrodemos O, Sandoval Y, Burke MN, and Brilakis E. TCT-607 Machine Learning for Predicting Major Adverse Cardiac Events in Percutaneous Coronary Intervention of Coronary Artery Chronic Total Occlusion. *J Am Coll Cardiol* 2023; 82(17):B244. Full Text

Background: Predicting major adverse cardiac events (MACE) in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) can assist with decision making and procedural planning. Methods: We analyzed 4,681 CTO PCIs from the PROGRESS-CTO (Prospective Global Registry for the Study of CTO intervention) registry performed between 2012 and 2022 at 42 centers. 8 machine learning (ML) methods were applied based on 32 parameters: multilayer perceptron (MLP) with decay model; support vector machine model; generalized additive model; MLP; extreme gradient boosting model; random forest model; Bayes GLM: Bayesian generalized linear model; and AvNNet: Neural Networks Using Model Averaging. The intervals were estimated using a bootstrap approach. The performance of the models was assessed using the receiver-operating characteristic curve. Results: The overall MACE rate was 1.9%. The median age of the patients was 65 years (57, 71 years). The data were divided into testing (n = 936) and training (n = 3,745) sets. The performance of the ML models on the testing set was as follows: MLP with decay model AUC 0.60; support vector machine model: 0.67; generalized additive model: 0.71; MLP: 0.65; extreme gradient boosting model: 0.44; random forest model: 0.60; Bayes GLM 0.72; AvNNet: 0.70. The AUC of the PROGRESS-CTO Complication logistic regression model was 0.675. The AUC of ML models and the Bayes-GLM method was found to have 50% of AUCs between 0.72 and 0.81, whereas the model built using linear logistic method had 50% of AUCs between 0.66 and 0.74 (Figure 1). [Formula presented] Conclusion: A machine learning-based model may improve the prediction of MACE in CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Lemor A, Shah T, Thompson J, Protty M, Mamas M, Kinnaird T, Bharadwaj A, Truesdell A, Zhang Y, Cohen D, Falah B, Redfors B, Baron S, Witzke C, Dixon S, Lansky A, **Basir B**, and **O'Neill W**. TCT-240 A-SMART-EF: A Novel Score to Predict Mortality in Patients Undergoing Impella-Assisted Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2023; 82(17):B93-B94. Full Text

Background: Predicting the risk of mortality before a high-risk percutaneous coronary intervention (PCI) is important for patient selection and shared decision-making. Using pre-procedural characteristics, we aimed to create a score to predict the 90-day mortality for these patients. Methods: The study included all patients enrolled in the prospective, multicenter, observational PROTECT III study of Impella-supported high-risk PCI from March 2017 to March 2022. Pre-procedural characteristics were analyzed using univariate and multivariable analysis. Variables with P values <0.1 were included in the risk score and

assigned an integer value based on their regression coefficient. Results: A total of 1,237 patients were included. Predictors of 90-day mortality included age >75 years, SYNTAX score ≥33, myocardial infarction on presentation, hemoglobin <12 mg/dL, glomerular filtration rate <60 mL/min/1.73 m2, tobacco use, and left ventricular ejection fraction <35%. The resulting A-SMART-EF (Age >75 years, SYNTAX score ≥33, Myocardial infarction, Anemia, Renal disease, Tobacco use, and Ejection Fraction <35%) risk score is calculated by assigning 1 point to each variable, except for SYNTAX ≥33 and left ventricular ejection fraction <35% (2 points each). Model discrimination (C-statistic 0.65) and calibration were reasonable. When the study population was stratified into low- and high-risk groups (A-SMART-EF score [0-5 vs 6-9]), 90-day mortality was 3 times higher in the high-risk group (6.6% vs 17.9%; HR: 0.35; 95% CI: 0.24-0.52; P < 0.0001). [Formula presented] Conclusion: The A-SMART-EF score is a novel risk assessment tool that can help predict 90-day mortality among patients undergoing Impella-assisted PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Mittal A, **Shukr BA**, **Behrendt R**, **Williams C**, **Piatak S**, **Craft S**, and **Willens D**. DESIGNING IMPLEMENTATION OF A SYSTEMWIDE EVIDENCE- BASED HEART FAILURE CARE PATHWAY. *J Gen Intern Med* 2023; 38:S658-S659. Full Text

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STATEMENT OF PROBLEM/QUESTION: After multistakeholder design of an inpatient, outpatient, and home heart failure (HF) care pathway, our regional health system needed implementation plans to drive uptake of key HF care steps. DESCRIPTION OF PROGRAM/INTERVENTION: Implementation plans are based on the AHRQ Learning Health System (LHS) framework and the Influencer change framework (Grenny, et al.). The LHS framework drives iterative care improvements via evidence application and ongoing learning from clinical performance data. The Influencer framework guides interventions that improve personal, structural, and social abilities and motivations to improve. The HF pathway included evidence-based interventions such as prescribing guideline directed medical therapy (GDMT), using universal healthliteracy appropriate patient education materials, and referring appropriate patients to cardiology, home-based care, or palliative care. Our implementation design team consisted of clinician-educators, residents, nurses, data analysts, an instructional designer, and a management engineer. Interventions include: 1) Driving buy-in by redesigning the pathway with facilitated teams of 100 clinicians and leaders from all disciplines and care venues; 2) Improving HF knowledge via education modules on our learning management system; 3) Audit and feedback of pathway uptake metrics; and 4) EMR tools to facilitate ordering of pathway steps. Education objectives are to update clinician knowledge on new HF nomenclature, GDMT, and descriptions of key steps in the HF care pathway. Rollout of these interventions is currently in progress. MEASURES OF SUCCESS: Clinician and executive qualitative feedback on content, usability, and design via unstructured interviews and our system wide HF governance structure. We will use the RE-AIM framework for evaluation of implementation. FINDINGS TO DATE: 1. The pathway design process engaged teams over 3 years despite competing priorities from COVID. 2. System wide education requires addressing differing resources across care settings and payors. 3. Defining which patients have HF by EMR data allowed real-time identification in hospitals, but challenges remain for outpatient and ED settings. 4. Specialty and location-based governance may be siloed, causing diffusion of ownership of implementation. KEY LESSONS FOR DISSEMINATION: Implementation plan design for the HF care pathway was successful due to: 1. Use of the AHRQ LHS and Influencer change frameworks facilitated more in-depth planning for spread and sustainability of clinical change. 2. Multi-stakeholder teams for sustained engagement across care siloes. 3. Executive sponsorship for system integration and local accountability. 4. Management engineer to coordinate multiple, diverse teams. 5. Instructional designer for effectiveness of education.

Cardiology/Cardiovascular Research

Nakhle A, **Jebaje ZA**, **Fadel R**, **Zakhour S**, **Brooks C**, **Longlade J**, **Basir B**, and **Alaswad K**. TCT-633 Presentation Management and Outcomes of Acute Right Ventricular Failure and Cardiogenic Shock After Right Ventricle Marginal Branch Occlusion During Chronic Total Occlusion Percutaneous Intervention. *J Am Coll Cardiol* 2023; 82(17):B254-B255. Full Text

Background: Cardiogenic shock (CS) complicating acute right ventricle (RV) branches occlusion during right coronary artery (RCA) chronic total occlusion percutaneous intervention (CTO PCI) is rare but life-threatening. The initial presentation is variable, and the diagnosis might be missed without invasive hemodynamic measurements. Methods: Among 1,415 CTO PCI procedures performed in 1,183 patients between September 13, 2014, and May 24, 2023, at our hospital, 10 patients had RV marginal branch occlusion complicated by CS. The baseline patient characteristics, procedural details, hemodynamics, management, and outcomes were retrospectively collected. Results: The incidence of CS caused by RV marginal branch occlusion after CTO PCI was 0.7% of all CTO PCIs and 1.32% of RCA CTO PCIs. The target vessel was the dominant RCA in all patients. 9 were men, 8 were White, 1 was Black, and 1 was Hispanic. 5 patients had a prior history of CABG, and 3 had end-stage renal disease requiring hemodialysis. None of the patients had baseline RV dysfunction. All procedures were performed under monitored anesthesia care, procedural success was achieved in 9 patients, the crossing technique was antegrade dissection and re-entry in 1 patient, and retrograde wiring with reverse controlled antegrade and retrograde tracking in 8 patients. Acute marginal branch occlusion occurred in all patients. 4 patients had coronary artery perforation, 2 developed tamponade requiring pericardiocentesis, and 2 had small RV free wall hematoma. Cardiac arrest was the initial presentation in 8 patients, profound RV failure requiring RV mechanical support was present in all patients, and 5 patients needed additional LV support. The mortality rate was 30% (3 patients). The mechanism of RV failure was occlusion of the acute marginal branches during the procedure in all patients. The average RV MCS support duration was 5.3 days. Conclusion: CS complicating RV marginal branches occlusion during RCA CTO PCI is associated with a 30% mortality rate. The initial presentation was cardiac arrest in 80%. All patients required RV MCS support. Early invasive hemodynamic measurement is necessary to make the diagnosis. Preservation of the RV marginal branches is essential to prevent this complication. Categories: CORONARY: Complex and Higher Risk Procedures for indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Pahuja M, **O'Neill W**, Karas RH, Moses J, Udelson J, Faraz H, and Kapur NK. Delaying Reperfusion Plus LV Unloading Reduces Infarct Size: A Per-Protocol-Analysis of the STEMI_DTU Pilot Study. *Cardiovasc Revasc Med* 2023; 53:S19. Full Text

Background: Myocardial infarct size (IS) and microvascular obstruction (MVO) are well-established prognostic markers in STEMI. The STEMI-DTU pilot trial was the first exploratory study to identify that LV unloading and delayed reperfusion was feasible. We now report new findings in patients from per-protocol cohort on the basis of magnitude of sum of precordial ST-segment elevation. Method: In a multicenter, prospective, randomized safety and feasibility trial, 50 patients with anterior STEMI to LV unloading using Impella CP were assigned into two different arms including immediate reperfusion (U-IR) versus delayed reperfusion after 30 minutes of unloading (U-DR). Cardiac magnetic resonance (CMR) imaging assessed infarct size normalized to the area at risk (IS/AAR) 3-5 days after PCI. Patients without CMR at 3-5 days, without PCI of a culprit LAD lesion and without STEMI were not per-protocol and thus excluded from this analysis. Results: 32 patients meeting all inclusion and exclusion criteria (U-IR,n=15; U-DR,n=17) were included in our analysis. Despite longer symptom-to-balloon times in the U-DR arm, IS/AAR was significantly lower with 30 minutes of delay to reperfusion in the presence of active LV unloading (47±16% vs 60±15%, p=0.02) and remained lower irrespective of the magnitude of precordial ΣSTE (Figure 1). MVO was not significantly different between groups (1.5±2.8% vs 3.5±4.8%,p=0.15), but significantly lower in the U-DR arm among patients with precordial ΣSTE>8mm (1.5±2.5% vs 5.6±5.3%, p=0.04). Conclusion: This analysis supports the paradigm-changing concept that when treated per protocol, 30 minutes of delay to reperfusion with active LV unloading may reduce infarct size irrespective of precordial STE magnitude. Ongoing STEMI-DTU Pivotal trial will provide us further information on these findings. [Formula presented]

Cardiology/Cardiovascular Research

Rempakos A, Alexandrou M, Mutlu D, Choi J, Khatri J, Davies R, Benton S, Gorgulu S, Jaffer F, Ybarra L, Azzalini L, Chandwaney R, Goktekin O, Bagur R, Rafeh NA, Khelimskii D, Rinfret S, Jaber W, Krestyaninov O, Nicholson W, Potluri S, Al-Azizi K, **Alaswad K**, Rangan B, Mastrodemos O, Allana S, Al-Ogaili A, Sandoval Y, Burke MN, Brilakis E, and Poommipanit P. TCT-427 Impact of Interventional

Collaterals on the Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2023; 82(17):B171-B172. Full Text

Background: The impact of interventional collaterals on the procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. Methods: We examined the clinical and angiographic characteristics and procedural outcomes of 11,205 patients who underwent 11,444 CTO PCIs at 45 U.S. and non-U.S. centers between 2012 and 2023. Results: Interventional collaterals were present in 6,553 (57%) CTO PCI cases. Compared with lesions with interventional collaterals, lesions without interventional collaterals had lower J-CTO score (2.3 ± 1.3 vs 2.4 ± 1.3; P < 0.001). In 126 (2.6%) cases, retrograde was the successful crossing strategy, despite the absence of interventional collaterals. Cases with interventional collaterals were more likely to require longer procedure (122 vs 100 min; P<0.001) and fluoroscopy (48 vs 36 min; P < 0.001) time. The presence of interventional collaterals was associated with higher technical (88.4% vs 84.1%; P < 0.001) and procedural (86.8% vs 83.2%; P < 0.001) success, but also slightly more major adverse cardiovascular events (MACE) (2.3% vs 1.5%; P = 0.004). Perforations were also more common in the presence of interventional collaterals (5.4 % vs 3.9%; P < 0.001). After adjusting for potential confounders, the presence of interventional collaterals was associated with higher technical success and no difference in MACE. [Formula presented] Conclusion: The presence of interventional collaterals is independently associated with higher rates of technical success in CTO PCI. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Rempakos A, Alexandrou M, Simsek B, Kostantinis S, Karacsonyi J, Mutlu D, Ybarra L, Bagur R, Choi J, Poommipanit P, Khatri J, Davies R, Benton S, Gorgulu S, Jaffer F, Chandwaney R, Jaber W, Rinfret S, Nicholson W, Azzalini L, Kerrigan J, Haddad E, **Alaswad K**, Krestyaninov O, Khelimskii D, Rafeh NA, Goktekin O, Rangan B, Mastrodemos O, Al-Ogaili A, Allana S, Burke MN, Sandoval Y, and Brilakis E. TCT-422 Trends and Outcomes of Antegrade Dissection and Re-Entry in Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2023; 82(17):B169-B170. Full Text

Background: The contemporary frequency and outcomes of antegrade dissection and re-entry (ADR) for chronic total occlusion (CTO) percutaneous coronary intervention (PCI) have received limited study. Methods: We examined the clinical and angiographic characteristics and procedural outcomes of 12,568 patients who underwent 12,841 CTO PCIs performed at 46 U.S. and non-U.S. centers between 2012 and 2023. Results: ADR was used in 2,385 (18.6%) of the procedures. ADR use declined from 37.9% in 2012 to 14.5% in 2022 (P < 0.001). Patients in whom ADR was used had a higher prevalence of comorbidities. CTOs treated with ADR were more likely to have complex angiographic characteristics and had higher mean J-CTO score (2.94 ± 1.11 vs 2.23 ± 1.26; P < 0.001). ADR cases had lower technical success (77.0% vs 89.3%; P < 0.001), and higher incidence of in-hospital major adverse cardiac events (MACE) (3.7% vs 1.6%; P < 0.001). The use of CrossBoss declined from 71% in 2012 to 1.4% in 2022 and was associated with higher technical success (87%) compared with wire-based techniques (73%). The Stingray device displayed higher technical success (86%) compared with subintimal tracking and re-entry (STAR) (74%) and limited antegrade subintimal tracking (LAST) (78%); however, its use has been decreasing, with STAR becoming the most used re-entry technique in 2022 (44% STAR vs 38% Stingray). [Formula presented] Conclusion: The use of ADR has been decreasing. ADR was used in more complex lesions and was associated with lower technical success and higher MACE, compared with non-ADR cases. There has been a decrease in Stingray use and an increase in the use of STAR for re-entry. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Riley R, Miller L, Davies R, **Alaswad K**, Doshi D, Jaffer F, Adusumalli S, Frizzell J, Kumar K, Patel M, Dakroub A, and Ali Z. TCT-155 Retrospective Multicenter Analysis of Intravascular Lithotripsy Use During Imaging-Guided Calcified Left Main Coronary Artery Percutaneous Coronary Interventions. *J Am Coll Cardiol* 2023; 82(17):B60. Full Text

Background: Data regarding the use of intravascular lithotripsy (IVL) to treat calcified left main coronary artery (LMCA) lesions are limited. This study aimed to evaluate short-term outcomes of IVL-assisted

LMCA PCI. Methods: This retrospective multicenter study enrolled patients who received intravascular imaging–guided, IVL-assisted PCI for severely calcified LMCA lesions. This was an all-comers study that included both acute and stable coronary artery disease (CAD). Clinical and procedural characteristics were obtained, including intravascular imaging results. Technical success was defined as successful stent deployment with <30% residual stenosis. Major adverse cardiac events (MACE) included death, myocardial infarction, and target vessel revascularization evaluated immediately after procedure and at 30-day follow-up. Results: Among 184 patients treated at 7 centers from 2019 to 2023, the majority (65.8%) were treated for acute coronary syndromes. IVL balloons were delivered in 100% of lesions and enabled 99.5% PCI technical success. Calcium fracture was identified in 82.4% of patients on post-PCI intravascular imaging. Pretreatment minimal luminal area increased significantly compared with post-PCI minimal stent area (MSA): 4.1 ± 1.3 to 9.3 ± 2.4 mm2 (P < 0.001). There was a direct correlation between the employed IVL balloon size and the resulting MSA (P = 0.002). In-hospital MACE was 4.4% and 30-day MACE was 8.8% (Table 1). In multivariate logistic regression, presentation with an acute myocardial infarction was the sole predictor of 30-day MACE, including all-cause death. [Formula presented] Conclusion: IVL-assisted PCI for calcified LMCA lesions was safe and resulted in excellent technical success rates, indicating its potential as a viable treatment approach in this challenging patient population. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Rommel KP, Bonnet G, Bellumkonda L, Zhang Y, Lansky A, Redfors B, Granada J, Bharadwaj A, **Basir B**, Patel R, **O'Neill W**, and Burkhoff D. TCT-214 Right Ventricular Function in Patients Undergoing Impella-Assisted High-Risk Percutaneous Coronary Intervention: Insights From the cVAD PROTECT III Study. *J Am Coll Cardiol* 2023; 82(17):B82-B83. Full Text

Background: Right ventricular dysfunction (RVD) is an important prognostic factor in several cardiac conditions. However, the impact of RVD on the clinical outcome of patients undergoing Impella-assisted high-risk percutaneous coronary intervention is unknown. Methods: Patients from the prospective, multicenter PROTECT III study were stratified according to the presence of RVD, defined as fractional area change <35%, tricuspid annular plane systolic excursion <17 mm, or S wave of the lateral tricuspid annulus <9.5 cm/s. Endpoints were in-hospital outcomes, 90-day major adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke, repeat revascularization), and 1-year mortality. Results: Of 239 patients who underwent RV function assessment, 124 had RVD. Lower left ventricular ejection fraction, higher blood urea nitrogen levels, and more severe RV dilatation were independently associated with RVD. The completeness of revascularization and in-hospital mortality did not differ significantly between patients with and without RVD. However, 90-day major adverse cardiac and cerebrovascular event rates were higher in patients with RVD, and RVD was a robust predictor of 1-year mortality with multivariable Cox regression analyses (Figure 1). [Formula presented] Conclusion: In the PROTECT III cohort of patients undergoing Impella-assisted high-risk percutaneous coronary intervention, RVD was associated with more advanced biventricular failure. Left ventricular support with Impella facilitated effective revascularization, even among those with concomitant RVD. Nevertheless, RVD was associated with unfavorable long-term prognoses. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Stephan J, **Almajed MR**, **Parsons AJ**, **Gregerson S**, and **Swanson B**. SECONDARY BACTERIAL PERICARDITIS WITH CARDIAC TAMPONADE AFTER ENDOBRONCHIAL ULTRASOUND WITH TRANSBRONCIAL NEEDLE ASPIRATION. *J Gen Intern Med* 2023; 38:S529. Full Text

J. Stephan, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 44-year-old male without signficant past medical history underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for an incidentally identified subcarinal mass. He later presented with pleuritic chest pain and shortness of breath. CT imaging demonstrated enlargement of the subcarinal mass with a trace pericardial effusion. The patient was planned to undergo repeat EBUS-TBNA, however, he quickly developed hemodynamic instability. Echocardiogram revealed a pericardial effusion with evidence of tamponade. Emergent pericardiocentesis was performed with

placement of a pericardial drain, purulent fluid was obtained. Videoassisted thoracoscopic surgery (VATS) was performed with mediastinal washout and pericardial window. Fluid cultures returned positive for S. aureus and Capnocytophaga. IMPACT/DISCUSSION: Bacterial pericarditis is a rare cause of pericarditis; in cases of secondary bacterial pericarditis, Staphylococcus Aureus is the most commonly implicated bacteria. Pericarditis is a known procedural complication of EBUS-TBNA. Given our patient's hemodynamic instability in the setting of cardiac tamponade, emergent pericardiocentesis was indicated. VATS was selected as the treatment modality of choice over subxiphoid pericardotomy, the standard of care, in order to achieve optimal source control by marsupialization of the bronchogenic cyst and completion of a mediastinal washout. Infectious disease was consulted given the atypical growth of Capnocytophaga and S. Aureus for which he was initially treated with Vancomycin and Piperacillin-Tazobactam then transitioned to Amoxicillin- Clavulanate to complete a 6-week treatment course. It was determined that Capnocytophagia was likely introduced to the patient's respiratory system by his dog licking the patient's face. Colchicine was administered for treatment of pericarditis in line with the current guideline recommendations. CONCLUSION: We present an uncommon case of Capnocytophaga bacterial pericarditis leading to cardiac tamponade. The occurrence of pericarditis after EBUS-TBNA is well-documented and clinicians should have a high index of suspicion in patients who become hemodynamically unstable within 3 months of the procedure. In cases of post-procedural bacterial pericarditis, it is important to take a multidisciplinary approach to determine the best treatment course.

Clinical Quality and Safety
Mittal A, **Shukr BA**, **Behrendt R**, **Williams C**, **Piatak S**, **Craft S**, and **Willens D**. DESIGNING IMPLEMENTATION OF A SYSTEMWIDE EVIDENCE- BASED HEART FAILURE CARE PATHWAY. *J Gen Intern Med* 2023; 38:S658-S659. Full Text

A. Mittal, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

STATEMENT OF PROBLEM/QUESTION: After multistakeholder design of an inpatient, outpatient, and home heart failure (HF) care pathway, our regional health system needed implementation plans to drive uptake of key HF care steps. DESCRIPTION OF PROGRAM/INTERVENTION: Implementation plans are based on the AHRQ Learning Health System (LHS) framework and the Influencer change framework (Grenny, et al.). The LHS framework drives iterative care improvements via evidence application and ongoing learning from clinical performance data. The Influencer framework guides interventions that improve personal, structural, and social abilities and motivations to improve. The HF pathway included evidence-based interventions such as prescribing guideline directed medical therapy (GDMT), using universal healthliteracy appropriate patient education materials, and referring appropriate patients to cardiology, home-based care, or palliative care. Our implementation design team consisted of clinician-educators, residents, nurses, data analysts, an instructional designer, and a management engineer. Interventions include: 1) Driving buy-in by redesigning the pathway with facilitated teams of 100 clinicians and leaders from all disciplines and care venues; 2) Improving HF knowledge via education modules on our learning management system; 3) Audit and feedback of pathway uptake metrics; and 4) EMR tools to facilitate ordering of pathway steps. Education objectives are to update clinician knowledge on new HF nomenclature, GDMT, and descriptions of key steps in the HF care pathway. Rollout of these interventions is currently in progress. MEASURES OF SUCCESS: Clinician and executive qualitative feedback on content, usability, and design via unstructured interviews and our system wide HF governance structure. We will use the RE-AIM framework for evaluation of implementation. FINDINGS TO DATE: 1. The pathway design process engaged teams over 3 years despite competing priorities from COVID. 2. System wide education requires addressing differing resources across care settings and payors. 3. Defining which patients have HF by EMR data allowed real-time identification in hospitals, but challenges remain for outpatient and ED settings. 4. Specialty and location-based governance may be siloed, causing diffusion of ownership of implementation. KEY LESSONS FOR DISSEMINATION: Implementation plan design for the HF care pathway was successful due to: 1. Use of the AHRQ LHS and Influencer change frameworks facilitated more in-depth planning for spread and sustainability of clinical change. 2. Multi-stakeholder teams for sustained engagement across care siloes. 3. Executive sponsorship for system integration and local accountability. 4. Management engineer to coordinate multiple, diverse teams. 5. Instructional designer for effectiveness of education.

Clinical Quality and Safety

Savard N, and **Chami E**. Leveraging Electronic Medical Records During a Candida Auris Investigation. *Am J Infect Control* 2023; 51(7):S46. Full Text

Background: In March 2022, the first patient with Candida auris (C. auris) infection was identified as having had a recent admission at a large tertiary care hospital. The patient had a lengthy hospitalization that included care on multiple units and had additionally had roommates during the encounter. Subsequent cases of C. auris colonization were also identified. C. auris is an emerging fungus that can spread in healthcare settings on contaminated surfaces or from person-to-person contact. Based on the size of the exposure, innovative solutions were needed to develop an efficient way to identify and follow-up with possible exposures and to rule out cases of C. auris colonization. Methods: The electronic medical records were used to create flags for rule-out and confirmed cases of C. auris. Patients identified as a possible exposure had a rule-out flag added to charts to immediately alert staff throughout the health system to isolate and screen for C. auris. Patients were identified using a custom hospital trace report and added to a custom patient list. In-house testing was implemented that was also added an infection flag and isolation order upon test order. Results: Of the 55 eligible patients that had been identified as possible exposures to patients with C. auris, 32 (58%) have had a readmission since the original exposure. All 32 patients were identified at the point of readmission and properly isolated and screened upon admission. Conclusions: By leveraging the electronic medical records system to identify and track possible exposures, at-risk patients were able to be immediately isolated and screened upon readmission at any of the system healthcare facilities. The quick response led to safer care by placing the patient in appropriate isolation precautions and allowed for appropriate environmental cleaning to prevent environmental contamination of C. auris, which removed the ability of further exposures.

Clinical Quality and Safety

Savard N, **Chami E**, **Salanger D**, **Gubler J**, **Dover C**, and **Weaver J**. Developing a Robust Leak Response Program. *Am J Infect Control* 2023; 51(7):S28. Full Text

Background: Aging infrastructure within a 100-year-old acute care hospital presents challenges that can often lead to an increase in leaks identified throughout the hospital in both clinical and non-clinical areas that increases the possibility of mold or other waterborne pathogens. In June 2021, the facility was tested even greater when a state of emergency was declared for following a rainstorm which overloaded the area's wastewater systems and further caused significant water damage to the Detroit-based hospital. An improved process was needed to identify and to reduce the occurrence of leaks throughout the hospital. Methods: After the 2021 flooding, the Infection Prevention team, in collaboration with hospital and Facility leadership, developed a leak response document that outlined the immediate expectations for the staff members who identify leaks, the Facility staff expectations, and how to properly report leaks and floods. In addition, a need was identified to better assess the flooring products used and develop a flooring recommendation document that identified the best flooring products that should be installed in areas that have a higher risk of leaks/flooding. Additionally, the Infection Prevention department invested in a moisture reader for room signoffs after leaks. Results: The leak response process and document were presented to all areas/departments throughout the facility. Additionally, the flooring product document was shared with facility design teams, who are now more integrated with Infection Prevention to work on which flooring products to select. Lastly, a process has been developed for room signoff after a known water intrusion. Conclusions: The detailed leak response process outlined and implemented has been improved response time in identifying and reporting leaks throughout the facility. The process in how to properly design and sign-off rooms has reduced the risk of mold growth and has improved room remediation time after a water intrusion event

Dermatology

Draelos Z, Tanghetti E, **Gold LS**, Kircik L, Bhatia N, Zeichner J, and Sugarman J. 43390 Dermal Irritation, Sensitization, and Safety of Fixed-Dose Triple-Combination Clindamycin Phosphate 1.2%/Benzoyl Peroxide 3.1%/Adapalene 0.15% Gel in Healthy Participants. *J Am Acad Dermatol* 2023; 89(3):AB33. Full Text

IDP-126 polymeric mesh gel (clindamycin phosphate 1.2%/benzoyl peroxide [BPO] 3.1%/adapalene 0.15%) is the first triple-combination, fixed-dose topical acne product in development and addresses major acne pathophysiological processes. IDP-126 demonstrated superior efficacy to vehicle and component dyads, with good safety/tolerability in a phase 2 study of patients with moderate-to-severe acne [1]. Two phase 1, randomized, evaluator-blinded, within-participant, dermal safety studies enrolled healthy participants aged ≥18 years (N=234, repeat insult patch test [RIPT]; N=45, cumulative irritation patch test [CIPT]). Patches were applied to the upper back multiple times over 6-8 weeks (RIPT) or every 24 hours for 21 days (CIPT). Patches contained: IDP-126 gel, vehicle gel, saline 0.9% (RIPT/CIPT), sodium lauryl sulfate (SLS) 0.5% (CIPT), or branded BPO 2.5%/adapalene 0.3% gel (CIPT). Participants in each study received all treatments. Endpoints comprised sensitization potential (RIPT), mean cumulative/total irritation scores, and treatment-emergent adverse events (TEAEs). Overall, irritation with IDP-126 was moderate and not clinically significant. CIPT: IDP-126 was “moderately irritating” (mean score: 1.29), which was significantly less irritating than BPO/adapalene (1.96; P<0.001), statistically similar to SLS (1.17), and more irritating than saline or vehicle (~0.30; P<0.001). RIPT: no participants had investigator- confirmed sensitization to any treatments. In both studies, no TEAEs were related to treatment. In two phase 1 studies, fixed-dose, triple-combination clindamycin phosphate 1.2%/ BPO 3.1%/adapalene 0.15% polymeric mesh gel had moderate irritancy and no confirmed sensitization in healthy participants. Additionally, IDP-126 demonstrated significantly less irritation versus commercially available, branded BPO 2.5%/adapalene 0.3% gel. IDP-126 demonstrated good safety/tolerability, mirroring the phase 2 study results.

Dermatology

Gao D, Swetter S, Hawryluk E, Geller A, and Beaulieu D. 42099 Analysis of utilization of sun-protective behavior among national SPOT Skin Cancer® program screenees from 2018 to 2019. *J Am Acad Dermatol* 2023; 89(3):AB4. Full Text

Information on sun-protective behaviors, including use of sunscreen and sun-protective clothing, of screening participants (“screenees”) with the American Academy of Dermatology’s (AAD) SPOT Skin Cancer® screening program is currently lacking. Information on trends in sun-protective behavior may help elucidate disparities on such behaviors between screenees, thereby informing where resources could be optimized for those presenting for dermatologic care. Records from 116,595 screenees were analyzed from 2018-2019, including demographic information (income per $10,000, age, sex, race, highest level of education completed, U.S. region of residence), self-reported tendency to sunburn, and self-reported sun-protective behavior. Most screenees were at least 30 years (88.6%), White (86.3%), female (61.8%), and completed at least a college education (69.6%). Lower zip code level income per $10,000 increments was associated with less sun-protective behavior (adjusted odds ratio [aOR]=0.95, P<0.001). Males were more likely than females to report less sun-protective behavior (aOR=1.53, P<0.001). Black, Hispanic, and Asians were more likely than Whites to have rarely/never used sun-protective behavior (aOR=2.86, 2.09, 2.85, 1.66 respectively, all P<0.001). Screenees with a highest attained level of elementary, high school, or college education were more likely to report less sun-protective behaviors than those with a graduate degree (aOR=1.84, 1.74, 1.13 respectively, all P<0.001). Midwest and South screenees utilized sun-protective behaviors less often than those from the Northeast (aOR=1.09, P=0.003, aOR=0.010, P=0.010, respectively). Resources regarding sun-protective behaviors could be optimized toward lower-income males with less education, particularly those from the Midwest or South. A major limitation is screenee self-selection and self-reporting.

Dermatology

Ghannoum M, Gamal A, Kadry A, Del Rosso J, Bunick C, **Gold LS**, Kircik L, and Harper J. 43405 Avoiding the Danger of Rising Resistance in Cutibacterium acnes: Criticality of Benzoyl Peroxide and Antibiotic Fixed Combinations. *J Am Acad Dermatol* 2023; 89(3):AB20. Full Text

Antibiotic resistance is a global concern, with several countries reporting >50% of Cutibacterium acnes (C. acnes) strains as resistant to certain antibiotics [1,2]. Combination formulations with multiple antibiotics/antimicrobials may reduce the risk of resistance, especially with prolonged use [3,4]. This four-part study tested susceptibility of 31 C. acnes clinical strains to antibiotics alone or in combination with benzoyl peroxide (BPO). All antibiotics tested—clindamycin, doxycycline, erythromycin, and

minocycline—had similar activity against most C. acnes strains tested, as assessed by minimum inhibitory concentration (MIC) ranges determined using epsilometer tests. Susceptibility was highly strain dependent, as some C. acnes strains had elevated MIC—an indication of resistance—against different antibiotics. C. acnes susceptibility to single-drug antibiotics and fixed-dose BPO combinations (branded/in-development) was then determined by measuring zone of inhibition using agar diffusion method, with larger diameter indicating increased bacterial inhibition. Interestingly, for 6 C. acnes strains that had no inhibitory zone with clindamycin alone, formulations with BPO enhanced activity against the same isolates (range: 0.8-2.2 cm with 3.1% BPO/1.2% clindamycin/0.15% adapalene, 5% BPO/1.2% clindamycin, or 3.75% BPO/1.2% clindamycin). Additional analyses are currently evaluating the potential synergistic effect of combining BPO and clindamycin and testing the development of C. acnes resistance following repeated bacterial growth exposed to a single antibiotic (clindamycin or minocycline) versus combinations with BPO. Overall, antibiotic susceptibility was highly strain dependent and antibiotic formulations with BPO exhibited enhanced activity against less susceptible C. acnes strains. Fixed combinations of BPO with an antibiotic may improve antimicrobial activity and protect against resistance development.

Dermatology
Gold LS, Kircik L, Werschler W, Baldwin H, Callender V, Green L, Sadick N, Sugarman J, Draelos Z, Tanghetti E, and Neal B. 43374 Impact of Age or Sex on Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel in Participants with Moderate-to-Severe Acne. *J Am Acad Dermatol* 2023; 89(3):AB54. Full Text

IDP-126 polymeric mesh gel (clindamycin phosphate 1.2%/benzoyl peroxide [BPO] 3.1%/adapalene 0.15%) is the first triple-combination, fixed-dose acne topical in development. IDP-126 demonstrated superior efficacy to vehicle and component dyads, with good safety/tolerability in a phase 2[1] and two phase 3 studies [2,3] of moderate-to-severe acne. This post hoc analysis evaluated effect of age or sex on efficacy/safety of IDP-126 using pooled data from two phase 3 (N=183; N=180), double-blind, randomized, 12-week studies[2,3]. Participants aged ≥9 years with moderate-to-severe acne were randomized 2:1 to once-daily IDP-126 gel or vehicle gel. Data were analyzed by age (pediatric [9-17 years]: n=178; adult [≥18 years]: n=185) or sex (females: n=212; males: n=151). Endpoints included ≥2-grade reduction from baseline in Evaluator's Global Severity Score and clear/almost clear skin (treatment success) and least-squares mean percent change from baseline in inflammatory/noninflammatory lesion counts. Treatment-emergent adverse events (TEAEs) were also assessed. At week 12, over half of pediatric and almost half of adult IDP-126-treated participants achieved treatment success (52.7% and 45.9%, respectively) versus one-fourth with vehicle (24.0% and 23.5%; P<0.01, both). Results by sex were similar (IDP-126 vs vehicle: females: 53.7% vs 23.0%; males: 43.1% vs 24.6%; P<0.05, both). IDP-126 provided >70% reductions in inflammatory/noninflammatory lesions in all subgroups versus vehicle (41%-63%; P≤0.001, all). Differences between sex or age groups were not statistically significant. Most TEAEs were of mild-moderate severity in all groups. Fixed-dose, triple-combination IDP-126 gel was efficacious and well tolerated, regardless of age or sex, with approximately half of participants with moderate-to-severe acne achieving clear/almost clear skin.

Dermatology
Novice M, **Novice T**, Guzman N, Goyert J, Hester T, Dejonckheere M, Wu J, Jeruss J, and Burness M. 43451 Identifying patient characteristics that contribute to a successful scalp cooling experience: a mixed methods study. *J Am Acad Dermatol* 2023; 89(3):AB175. Full Text

Background: Chemotherapy-induced alopecia (CIA) is a highly distressing treatment side- effect. Despite scalp cooling therapy's (SCT) well-demonstrated efficacy for reducing CIA, SCT use in the United States is limited. Our study seeks to understand factors that influence SCT use and QOL outcomes to guide patient counseling. Methods: This retrospective study utilizes a convergent mixed methods design consisting of a 29-question survey and a 1:1 virtual interview with cancer patients who either used or did not use SCT between 2010 to 2020. Results: Twenty-seven breast cancer patients participated: 14 (51.9%) used SCT and 13 (48.1%) did not. Participants who defined their SCT as successful (71.4%) shared the following characteristics: strong motivation to keep their hair (e.g., work), dedicated support system, "why not try" mentality, and a realistic definition of SCT success (e.g., enough to maintain privacy

about treatment). QOL impact of hair preservation during and post- chemotherapy, respectively, was as follows (scale of -50 to +50): +42.0 and +41.1 for the 8/14 who used SCT with >50% hair preservation; +26 and +27.5 for the 2/14 who used SCT with >25% hair preservation; -14 and +0 for the 4/14 who used SCT and kept <25%; and-34 and -20 for the 12/13 who did not use SCT and lost>75% of hair. Common QoL benefits included increased privacy, improved emotional well-being, and easier transition to the survivorship period. Conclusion: We identified specific characteristics that contribute to a successful SCT experience. These characteristics can guide providers regarding educational approaches for patients during the SCT decision-making process.

Dermatology

Reilly C, Hoopes R, Trupiano N, Young K, Yousif J, and **Novice T**. 43772 Sk(in depth): staying up-to-date with the latest dermatology research. *J Am Acad Dermatol* 2023; 89(3):AB223. Full Text

Background: Introduction Regularly scheduled email newsletters have shown to be effective in helping students stay up-to-date on research. Thus we created Sk(in depth), a bimonthly newsletter summarizing the latest dermatology research from high impact journals. With medical students as the target audience, we create and deliver issues directly to subscribers' email inboxes. Our goal is to distribute easily accessible and succinct research summaries to medical students in an engaging and effective manner. Methods: To date, we have 234 subscribers and analyzed data from four recent issues. Open rate was obtained through our email delivery agent, MailChimp. Each issue includes recap questions that assess knowledge from a prior issue; responses to these multiple-choice questions were analyzed. Results On average, 64.6% of subscribers opened our last four newsletters. Of subscribers participating, 57.5% correctly answer recap questions. Limitations Recap questions are made by our team and may not be accurate ways to measure information retention. Participants may have researched answers before submitting responses. Conclusion To our knowledge, Sk(in depth) is the first dermatology- focused newsletter to efficiently deliver novel research findings to medical students. Over half of subscribers open our newsletter, indicating that this format is engaging to medical students. The majority of subscribers participating in quiz questions answer correctly, suggesting that a curated newsletter may be an effective way for students to learn and retain information. Our findings indicate that a regularly emailed newsletter may help reduce the barriers for medical trainees in staying up-to-date with current dermatology research.

Emergency Medicine

Koerber S, **Huynh D**, **Farrington S**, **Springer K**, **Patel M**, and **Manteuffel J**. 190 Health Disparities in Emergency Department Administration of Buprenorphine for Treatment of Opioid Use Disorder. *Ann Emerg Med* 2023; 82(4):S87. Full Text

Objectives: Buprenorphine use in the emergency department contributes to decreased frequency of opioid overdose, reduced emergency room visits, and decreased associated health care costs. However, racial and ethnic disparities in buprenorphine prescription contribute to fewer prescriptions of buprenorphine for Black and Hispanic patients when compared to White patients. The objectives of our study were to 1) examine whether buprenorphine administration in an urban emergency department varies by patient demographics including race and ethnicity; and 2) examine other structural determinants of health to expand upon why these differences may exist. Methods: This is a retrospective analysis of electronic health records from patients who presented to the emergency room at Henry Ford Hospital between January 1, 2021, and December 31, 2021. Included patients were 18 years of age or older and screened positive for opioid use disorder (OUD) in the emergency room at Henry Ford Hospital. Area deprivation index (ADI) was determined based on patients' documented street addresses to serve as a proxy for measuring income, education, employment, and housing quality. Univariate and multivariate analyses were conducted using SAS 9.4. Statistical significance was set at $p<0.05$. The institutional IRB approved this study. Results: There were 1082 patients included in our final analysis. Patients had a mean age of 48.1 years and were largely male (n=721, 66.8%). The majority of patients were Black (n=682, 63.0%), had Medicaid insurance (n=667, 61.6%), and were from the most disadvantaged ADI group (n=624, 62.7%). Patients that received buprenorphine had on average longer length of stay (LOS) with a mean of 844.2 minutes ($p=0.016$). Patients who identified as Black or Other Race were less likely to receive buprenorphine, and patients who identified as White were more likely to receive buprenorphine ($p=0.021$). After adjusting for age, LOS, sex, insurance type, and ADI, Black patients were less likely to

receive buprenorphine as compared to White patients (p=0.0237). There were no significant differences found when comparing ADI among those who received buprenorphine. There were no differences among demographics for patients receiving buprenorphine for first-time induction compared to those receiving a maintenance dose. Conclusions: Our study demonstrates that the majority of patients at risk of opioid use disorder in our hospital sample were patients who were Black, male, had Medicaid insurance, and were from the most disadvantaged communities. However, White patients were still more likely to receive buprenorphine in our ED for treatment of OUD after controlling for other structural determinants of health. Limitations include the inherent inability of electronic medical records to accurately document a patient's identified race and ethnicity. Future studies should include prospective analyses that better capture the very complex relationships of unconscious bias in medicine and structural determinants of health. Furthermore, we can utilize multifaceted education and training for ED providers and advocate for systemic changes at the hospital and policy level. Equitable administration of buprenorphine in the ED can contribute to decreased health disparities in the treatment of OUD.

Emergency Medicine

Nassereddine H, **Cook B**, **Klausner H**, **Gunaga S**, **Morton T**, **Tuttle J**, **Mohammed H**, **Husain A**, **McCord J**, and **Miller J**. 208 Diagnostic Performance of Cardiac Stress Testing Following Exclusion of Acute Myocardial Infarction With a 0/1-Hour, High-Sensitivity Cardiac Troponin Protocol. *Ann Emerg Med* 2023; 82(4):S94-S95. Full Text

Background: Rapid exclusion of acute myocardial infarction (AMI) is critical for patients presenting to emergency departments (EDs) with chest pain or other anginal equivalents. High-sensitivity cardiac troponin (hs-cTn) protocols have been widely adopted in the United States for this purpose. These protocols allow for early identification and exclusion of patients with AMI using a 0 and 1-hour hs-cTn measurement. However, little is known about the use of cardiac stress testing in patients who ruled-out for AMI within 1 hour with very low hs-cTn values. This study analyzed the diagnostic performance of cardiac stress tests in this population. Methods: We performed a secondary analysis of the RACE-IT trial, a stepped-wedge cluster randomized trial performed across 9 EDs in a large metropolitan health system from July 2020 through March 2021. The eligibility criteria for the trial mirrored the real-world use of hs-cTn testing, including both patients complaining of chest pain and/or other anginal equivalents. All adults with a hs-cTnI and electrocardiogram (ECG) completed in the ED were enrolled, while patients with ST-segment elevation AMI, trauma, or pregnancy were excluded. In the interventional arm of the trial, AMI 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. The trial followed all patients through 30 days to assess for AMI or death and captured all cardiac testing. We compared stress testing results to invasive coronary imaging with or without revascularization. Results: 10,444 study patients (43.61%) ruled out for AMI in the ED within 1 hour and were included in this analysis. There were 320 (3.0%) patients who had a stress test within 30 days, with few ischemic findings (25, 0.24%) or revascularization procedures (5, 0.05%). The positive predictive value of stress testing in this population to identify the need for revascularization was 10.1% (95% CI 2.8% - 29.4%). Table 1 displays the proportion of ischemic stress tests and overall test performance in this population. The rate of 30-day death or AMI was low (17, 0.20%) among those discharged from the ED or placed in observation (n=8,553). Conclusions: Our study highlights the infrequent use and low diagnostic yield of stress testing in patients who have been ruled out for AMI within 1 hour using an accelerated hs-cTn protocol in the ED. [Formula presented]

Emergency Medicine

Patel M, **Marshall D**, **Manteuffel J**, **Miller J**, **Krieger S**, **Rammal JA**, **Loszewski C**, **Nassereddine H**, **Tuttle J**, and **Almri Y**. 411 Emergency Department and Hospital Utilization After Emergency Department-Initiated Buprenorphine for Opioid Use Disorder. *Ann Emerg Med* 2023; 82(4):S179-S180. Full Text

Objectives: The opioid crisis in the United States is a public health emergency. Emergency department (ED)-initiated buprenorphine with referral to ongoing care is an effective method to treat patients with opioid use disorder (OUD). While ED-initiated buprenorphine has been shown to be cost-effective, there is a paucity of data examining ED and hospital utilization after ED-initiated buprenorphine with referral to ongoing care. Our objective was to quantify ED and hospital utilization before and after ED-initiation of buprenorphine and referral to ongoing care. We hypothesized that patients would use the ED and be

hospitalized at a lower rate after receiving ED- initiated buprenorphine and referral to ongoing care. Methods: We performed a retrospective chart review using health information exchange data of patients who were treated in our ED with buprenorphine beginning March 1, 2020 through December 31, 2021. Patients were included if there was documentation of referral to ongoing care after receiving ED-initiated buprenorphine. Patients were excluded if they received a home dose medication or were not referred to ongoing care. We quantified the number of ED visits and medical hospitalizations in the 1 year before and after the initial ED-initiated buprenorphine treatment visit. Analysis includes descriptive statistics and McNemar's test to compare the proportion of patients pre or post ED-initiated buprenorphine that had ≥1 ED visit. Results: We identified 129 patients that were treated with ED-initiated buprenorphine and met the inclusion criteria. Total ED visits were reduced or zero in 76 (58.9%) of the patients after ED-initiated buprenorphine. Total hospitalizations were reduced or zero in 97 (75.2%) of the patients after ED-initiated buprenorphine. The odds ratio (OR) estimate of a patient having ≥1 ED visits following ED-initiated buprenorphine was lower (OR 0.57, 95% CI 0.26 – 1.16), though this did not meet statistical significance (p=0.096). Similarly, the odds of a patient having ≥1 admission was lower (OR 0.70, 95% CI 0.34 – 1.38) but did not meet statistical significance (p=0.262). Conclusions: In this retrospective chart review, the majority our patients visited the ED less and were admitted to hospital less after ED-initiated buprenorphine and referral to ongoing care. At this point in the data collection the study is underpowered to determine a significant difference. Further study is needed to quantify healthcare resource utilization after intervention with ED-initiated buprenorphine.

Emergency Medicine

Vajda P, **Klausner H**, **Betham B**, **Wanis N**, and **Goubert R**. 404 Emergency Department Length of Stay, Patient Boarding, Door-to-Doctor Time, and Percent of Patients Left Without Completing Service to Evaluate if There Is Any Correlation Among These Metrics. *Ann Emerg Med* 2023; 82(4):S176. Full Text

Background: There was a dramatic loss of ED volume during the early phase of the pandemic (March 2020 – September 2020). ED visit volumes remain below pre-pandemic levels yet our ED is struggling with increased overcrowding and patient boarding. We looked at these metrics to see if they correlate with each other. We believe objective data showing increased LOS and boarding serves as a justification for requests to hospital administration for more resources (physicians, nurses, technicians) despite reduced annual ED visit volume. The data also suggest that there may be lost revenue from patients who leave without completing service. Objectives: Retrospective study evaluating Emergency Department (ED) length of stay (LOS), patient boarding, door to doctor time, and percent of patients left without completing service (LWCS) to evaluate if there is any correlation among these metrics. Methods: Data was collected prospectively from Electronic Medical Records (EPIC) from January 2019 to December 2022. There is an Inflow Statistics Board Function in EMR which was used to obtain desired numbers during this period. We examined the following metrics – average Emergency Department Length of Stay (ED LOS), average Inpatient and Observation Boarding time, average Door to Doctor time – (in minutes), and LWCS as a percentage of ED volume. This study was evaluated by our hospital's IRB and deemed exempt and not human subject research. Results: The total annual number of patients seen in our ED is slowly increasing from the intra-pandemic numbers. In 2019, pre-pandemic ED volume averaged 8285 patients per month. ED volume declined to 4200 patients per month in the early pandemic (April and May 2020). Overall volume for 2020 was 6568 patients per month. Monthly ED volume was7137 and 6577 in 2021 and 2022, respectively. Inpatient and Observation Boarding numbers more than doubled from 419 minutes in 2019 to 950 minutes in summer of 2021. Average ED LOS increased from 430 minutes in 2019 to 576 minutes in 2021, and to 676 minutes in 2022. Patient percentage of LWCS was closely correlated to LOS and Boarding time in minutes. The higher the LOS, the higher the percent of LWCS. LWCS in 2019, 2020, 2021, and 2022 was 6.47%, 5.70%, 11.82%, and 16.12%, respectively. Average boarding times from 2019 to 2022 were 419, 328, 617, and 742 minutes. The same correlation was found between LOS and Boarding time and Door to Doctor time – the longer LOS meant also increased time of Door to Doctor from approximately 60 minutes in 2019, 2020 and early 2021 to average of 180 minutes in late 2021 and 2022. The data is summarized in the chart below. Conclusions: There is a direct correlation between an increase in LOS and Boarding time and the increase in percent of patients who LWCS. The same is true for LOS and Boarding time versus Door to Doc time. These statistics can be used by ED leadership to inform hospital administration of the increased need for more resources in the form of hiring additional medical staff. Increased Door to Doctor time also directly correlates with % of LWCS.

Decreasing Boarding/LOS/Door to Doc times should decrease % of LWCS patients and thus will assist in capturing lost revenue. This extra revenue may offset the investments used for hiring additional staff.

Emergency Medicine

Wanis N, **Rammal JA**, **Nassereddine H**, **Almri Y**, **Beyer M**, **Berger D**, **Sandoval S**, **Miller J**, **Otero R**, and **Klausner H**. 370 Accuracy of Clinical Assessment in Predicting Source of Infection for Septic Patients in the Emergency Department. *Ann Emerg Med* 2023; 82(4):S163-S164. Full Text

Background: Many sepsis cases are first encountered in the Emergency Department (ED), and it is essential to identify and assess the severity of patient illnesses as well as their mortality risks as soon as possible after they present to the ED. The Sepsis Core Measure requires that clinicians rapidly screen patients and administer antimicrobial treatment within 3 hours of identification of severe sepsis and septic shock. Although much research has been done on the importance of early fluid administration, antimicrobial initiation, and hemodynamic resuscitation of septic patients, less is known about clinician ability to diagnose or predict the presumptive source of a septic patient's clinical syndrome. Despite limitations in patient presentation and physical findings, clinicians must make a scientific judgment for the potential source of infection and initiate appropriate therapy swiftly. Objectives: To evaluate the predictive ability of clinicians to determine the likely source or site of infection leading to severe sepsis and septic shock. Methods: This was a prospective observational trial. Data was collected at an urban tertiary care medical center ED from September 2017 to December 2019. Data was collected with the assistance of undergraduate research associates. Results: There were 111 patients included in the analysis, 62 (55.9%) were female, 89 (80.2%) were Black, and the mean age was 53.1 (SD 19.2) years. A high proportion had diabetes (36.9%) and hypertension (54.1%). The median time from patient arrival to treating clinician survey was 2 [IQR 1, 3] hours. The median time to antibiotic administration was 4 [IQR 2, 5] hours. Median ED length of stay was 8 [IQR 6, 12] hours. The accuracy of clinician suspicion for the source of infection was modest: 70.0% (95% CI 60.0 - 78.2%) for skin and soft tissue or abdominal sources, 82.2% (95% CI 74.7 - 89.6%) for urinary, and 42.3% (95% CI 32.6 - 52.3%) for pneumonia. In 8 cases of bacteremia, antibiotics were initiated for all patients. Conclusions: In conclusion, this study provides insight into the clinical characteristics and outcomes of a cohort of patients with suspected sepsis in an ED. The majority of patients were Black and had comorbidities such as diabetes and hypertension. Overall hospital mortality was low, and the accuracy of clinician suspicion for the source of infection was variable. The highest clinician suspicion accuracy was observed for urinary infections, followed by skin and soft tissue or abdominal sources. In such patients, clinical suspicion is a valuable tool in rapid identification of infection sources as it enables swift administration of treatment specific to the source of infection. In contrast, the accuracy for diagnosing pneumonia was particularly low so clinician suspicion is of much less utility in such cases. This highlights the need for improved diagnostic tools and protocols to aid clinicians in accurately identifying the source of infection in patients with suspected sepsis. The study also highlights potential areas for improvement in care, such as reducing the time to antibiotic administration. Addressing these issues could lead to superior, more targeted treatments for patients, ultimately improving outcomes and reducing the risk of morbidity and mortality associated with sepsis.

Gastroenterology

Chaudhary AJ, **Rahim A**, **Khan MZ**, **Denha E**, and Michel A. A UNIQUE CASE OF AUTOIMMUNE HEPATITIS PRESENTING AFTER A 5-DAY COURSE OF NITROFURANTOIN FOR UNCOMPLICATED URINARY TRACT INFECTION. *J Gen Intern Med* 2023; 38:S430. Full Text

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CASE: An 84-year-old African American woman with a history of type 2 diabetes mellitus presented with postprandial right upper quadrant sharp shooting abdominal pain with associated nausea and vomiting. She reported taking nitrofurantoin 100 mg tablets twice daily for five days for a recent UTI. Denied taking herbal remedies or unprescribed supplements. Never smoked or drank excessive alcohol. Initial blood tests revealed elevated liver biochemistry with bilirubin 7.6 mg/dL, alanine transaminase 343 IU/L, aspartate aminotransferase 261 IU/L, and alkaline phosphatase 135 U/L. Her coagulation screen, full blood count, electrolytes, and renal function were normal. Viral hepatitis profile was negative. Toxicology

labs were negative for acetylsalicylic acid (ASA), acetaminophen, and alcohol. Abdominal imaging was unremarkable. Immunological tests revealed positive smooth muscle antibodies with a titer of 95 units: normal IgA and IgG levels and low IgM. Double-stranded DNA antibodies, anti-mitochondrial antibodies, and anti-microsomal antibodies were not detected. A liver biopsy was performed which showed acute hepatitis with moderate necroinflammatory activity consistent with AIH and drug-induced liver injury (DILI). IMPACT/DISCUSSION: Several viruses and drugs have been reported to have caused autoimmune liver disease. One of the drugs is nitrofurantoin which is commonly prescribed due to its low cost, high efficacy, and minimal antimicrobial resistance. Acute liver injury from nitrofurantoin has a prevalence of ~0.3/100,000 prescriptions, while chronic nitrofurantoin liver injury is estimated to be one in 1500. AIH is more common in females than males, with a ratio of 3.6:1. Acute hepatotoxicity is drug-induced liver injury immediately after exposure; chronic nitrofurantoin use is associated with chronic AIH. Our case is unique as the patient developed AIH three weeks after a 5-day course of nitrofurantoin for an uncomplicated UTI. The patient never had elevated liver function tests, a negative viral hepatitis profile, and any history of autoimmune disease or alcohol abuse. Our case was not a DILI, as these usually occur immediately after exposure or when the patient is actively taking the medication. We hypothesize that nitrofurantoin is associated with the development of AIH and the formation of antibodies (in our case, anti-smooth muscle antibodies). It may not only be a dose-related immune response that needs months of constant exposure to be evident; it might be related to nitrofurantoin acting as an antigen, possibly an idiosyncratic reaction. Treatment with steroids improved the LFT and symptoms within days which is also evidence in favor of AIH. CONCLUSION: In patients with recently treated UTI with nitrofurantoin who presents with acute elevation of LFTs within a few weeks, always take into consideration nitrofurantoin-induced AIH. Moreover, treatment with steroids should begin if the antibodies come out positive.

Gastroenterology

Claasen MPAW, **Ivanics T**, Montalvá E, Citterio D, Beumer BR, Dhote A, Adam R, Mazzaferro V, Ijzermans JNM, Sapisochin G, and Polak WG. Post-transplant recurrence patterns after liver transplantation for hepatocellular carcinoma: an international multicenter study. *Transplantation* 2023; 107(9):51. Full Text

M.P.A.W. Claasen, Erasmus MC Transplant Institute, University Medical Centre Rotterdam, Department of Surgery, Division of HPB and Transplant Surgery, Rotterdam, Netherlands

Background: Recurrence after liver transplantation (LT) for hepatocellular carcinoma (HCC) adversely affects post-LT survival. Data on whether certain groups can achieve acceptable survival post-recurrence is limited, especially for patients with lung-only metastasis. We sought to analyse post-LT recurrence patterns in patients transplanted for HCC and to map post-transplant outcomes for patients with lung-only metastasis. Methods: A large international multicenter cohort of patients transplanted for HCC between 2000-2022 was collected. Outcomes evaluated were overall survival (OS) and recurrence-free survival (RFS). Results: A total of 2,583 patients from five different centers were included in the study, of whom 369 (14%) developed recurrence post-LT. Five- and ten-years RFS were 69.9% and 58.4%, respectively. The first site of recurrence included liver-only (n=106 [28.7%]), lung-only (n=66 [17.9%]), bone (n=45 [12.2%]), adrenal gland-only (n=21 [5.7%]), peritoneal-only (n=18 [4.9%]), lymph nodes-only (n=16 [4.3%]), other single-site (n=17 [4.6%]), and multi-organ (n=73 [19.8%]). Overall 1-, 3-, 5-years post-LT and post-recurrence survival in patients that recurred was low (post-LT: 85.1%, 53.3%, 33.2%; post-recurrence: 55.8%, 22.7%, 14.0%). Patients with lung-only metastasis showed better outcomes than average with a 1-, 3-, 5-year OS post-LT of 94.0%, 64.4%, 40.9% and a 1-, 3-, 5-year OS post-recurrence of 76.4%, 40.3%, 24.0%. Thirtytwo (48%) of the patients with lung-only recurrence were treated with surgical resection, of whom 6 received additional treatment. Lung-only recurrent patients receiving surgical resection as singletreatment (n=26) showed significantly better OS post-LT (1-,3-,5-year: 100%, 88.0%, 66.2% vs. 89.7%, 47.9%, 22.6%,$p<0.01$) and post-recurrence (1-,3-,5-year: 96.2%, 60.4%, 53.7% vs. 62.2%, 24.5%, 0%,$p<0.01$) than patients receiving non-surgical or combined treatments (n=39). Conclusions: Post-LT recurrence often manifests as single-sited lesions, with liver and lung being the most common sites. Overall survival after recurrence is low, with patients with lung-only recurrence showing better than average survival. When treated with surgical resection, patients with lung-only metastasis can achieve acceptable long-term survival.

Gastroenterology

Ivanics T, **Jafri SM**, **Muszkat Y**, **Rizzari M**, **Abouljoud M**, **Yoshida A**, and **Nagai S**. A risk factor analysis of donor-specific factors on one- and threeyear post-transplant mortality after multi visceral transplantation. *Transplantation* 2023; 107(9):210-211. Full Text

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

Background: Patients undergoing combined liver and intestine transplantation (multi visceral transplantation [MVT]) represent a particularly vulnerable patient population. These patients have specific quality requirements for suitable donors. We sought to evaluate the effects of various marginal donor qualities on posttransplant outcomes in MVT patients. Methods: The Organ Procurement and Transplantation Network/ United Network for Organ Sharing database was used to identify all adult recipients of liver and intestine listed between 01/01/2010 and 01/25/2021. Outcomes included 1- and 3-year post-transplant patient survival and mortality. Results: A total of 268 MVTs were identified. Of these, 232 were intestine-liver-pancreas, 32 were intestine-liver-kidney, and four were intestine-liver. Of the MVTs, donor age >40 was present in 36/268(13%), donor body mass index(BMI)>30 in 10/268(4%), donor diabetes 1/268(0%), any donor pressor requirement in 108/268(40%), and multiple donor pressor requirements in 11/268(4%). The 1- and 3-year survival for donor age <40 vs. ≥40 was 65.8% vs. 52.1%;p=0.13 and 50.1%vs.48.9%;p=0.53. Similarly, the 1- and 3-year survival for no donor pressor requirement vs. donor pressor requirement were 61.9%vs.67.5%;p=0.61 and 45.8% vs. 57.0%;p=0.24, respectively. The 1-year survival for various cold ischemia cutoffs were ≤6.50hr 64.4%vs.6.51-7.56hr 63.9%vs.7.57-8.79hr 69.8% vs. ≥8.80hr 57.6%;p=0.50 and 3-year survival for the various cutoffs were ≤6.50hr 50.4%vs.6.51-7.56hr 54.0%vs.7.57-8.79hr 47.0% vs. ≥8.80hr 47.9%;p=0.83(Figure 1). Conclusions: Donors with older age(>40yo), high BMI, and/or multiple pressor requirements were not often used for MVT probably due to its careful donor selection. While no statistically significant donor-specific risk factors were noted to be associated with posttransplant mortality, older donor age(>40yo) and longer CIT(≥8.8hr) tended to worsen short-term outcome(1-year survival). Within this context, to maintain appropriate outcomes, the choice of MVT donors should be selective. There may a room to expand donor pool/donor selection criteria in MVT without adversely impacting outcomes.

Gastroenterology

Summers B, Segovia M, Horslen S, Weiner J, Schiano T, Mavis A, Ganoza A, and **Jafri MS**. Use of anti-inflammatory biologics agents after intestine transplantation - a multicenter survey. *Transplantation* 2023; 107:72. Full Text

B. Summers, Henry Ford Hospital, Detroit, United States

Introduction: Intestinal transplantation (IT) is a therapeutic option for patients with intestinal failure. A barrier to the success of IT is the significant risk of rejection and possible for disease recurrence in the patient's graft. A potential option for treating rejection refractory to mainstays of treatment and for managing disease recurrence are anti-inflammatory biologic agents. This survey was conducted to describe the utilization of these agents in IT centers in the United States Methods: A survey was conducted with questions pertaining to the utilization of biologics in IT in regard to agents used, dosing, infectious prophylaxis, duration, indication, outcomes, adverse effects, and barriers to use. The survey was distributed among centers in the United States via email database. Results: A total of 6 centers responded to the survey. Three centers treated adult population only; two pediatric and one both. The most utilized biologic was infliximab, then vedolizumab, and then some minimal usage of ustekinumab and adalimumab. For indications, most biologics were being used for refractory rejection and some minimal usage for Crohn's disease recurrence and nonspecific ulceration. Infectious prophylaxis use varied among the reported centers: 2 centers did not utilize prophylaxis, 2 used prophylaxis for bacterial, mold and fungal organisms, 1 specifically Pneumocystis jiroveci, and 2 others focused on Pneumocystis jiroveci and Cytomegalovirus. Most centers administered agents anywhere between 1-18 months and 4-6 doses. A center reported over 36 months in the case of 1 patient for inflammatory bowel disease. Only 1 center reported utilizing tumor necrosis factor (TNF) alpha levels to assist with dosing. Outcomes of reported biopsy results were predominantly some improvement and a reported 50% incidence of graft loss due to inefficacy. Lastly, biologics were well tolerated with 1 report of infusion reactions and

infections being the more common adverse event. The only barriers reported to initiating therapy was the need for prior authorizations by 3 centers. Conclusion: This survey provided insight into the practice of using anti-inflammatory biologics in intestinal transplantation. Their utilization appears to have some consistencies as far as agents used and indications for utilization. However, practices differ when it comes to infectious prophylaxis and TNF- alpha levels. As with most novel therapies, insurance approval can lead to barriers with use. Biologics have been proven to be useful agents for specific indications after IT but more guidance and data are needed to streamline utilization and provide data to support use for insurance approval.

Hematology-Oncology
Gadgeel SM, Mok TSK, Peters S, Nadal E, Han JY, Alatorre Alexander JA, Leighl N, Sriuranpong V, Pérol M, Castro GD, de Marinis F, Tan DSW, Paul S, Assaf ZJ, MacLennan M, Lohmann TO, Slade M, Mathisen MS, Bhagawati-Prasad V, and Dziadziuszko R. 1361P Alectinib for treatment-naïve advanced ALK+ NSCLC selected via blood-based NGS: Updated analyses of outcomes, circulating tumour (ct)DNA and biomarker subgroups from BFAST Cohort A. *Ann Oncol* 2023; 34:S782-S783. Request Abstract

Background: BFAST (NCT03178552) is an ongoing global, open-label, multicohort study assessing the activity of therapies in patients (pts) with advanced/metastatic NSCLC harbouring actionable genetic alterations identified in ctDNA via NGS. In a previous analysis of the BFAST ALK+ NSCLC cohort, a high overall response rate (ORR) was reported in pts treated with alectinib. We present updated data with longer follow-up, and exploratory correlative ctDNA and biomarker analyses. Methods: Pts aged ≥18 years with treatment-naïve stage III/IV NSCLC had comprehensive genomic profiling via NGS on ctDNA at screening. Pts with ALK fusions (ALK+) received alectinib 600 mg twice daily. Primary endpoint: investigator (INV)-assessed ORR; key secondary endpoints: INV-assessed progression-free survival (PFS), duration of response (DOR), overall survival (OS), safety. Blood samples for exploratory analyses were collected every 2 cycles during treatment, and at disease progression if feasible. Results: The cohort included 87 ALK+ pts; median survival follow-up was 52.0 months (range 2.6–62.6). At data cutoff (24 Feb 2023), 34 (39.1%) pts remain on alectinib. Median PFS data for the overall population and per subgroup are presented in the table. In the overall population, ORR was 89.7% (95% CI 81.3–95.2); median DOR was 35.1 months (95% CI 24.8–49.7); 48-month OS rate was 58.3% (95% CI 47.8–68.7). Most pts (93%) had complete clearance of ctDNA (no ALK fusion reads) by Cycle 3 Day 1. Pts without ALK clearance had poor PFS (7.1 months; 95% CI 5.6–NE). No new safety signals were identified. Conclusions: BFAST is the first trial with mature clinical data using prospective blood-based NGS screening of ALK to select pts for treatment with alectinib. PFS data were consistent with the ALEX study. Concurrent TP53 mutation and high baseline ctDNA levels were associated with poorer prognosis; ctDNA clearance was associated with better outcomes. [Formula presented] Clinical trial identification: NCT03178552.

Hematology-Oncology
Gadgeel SM, Zhang Q, Lin H, Fajardo O, Trinh H, Arndorfer S, Kong S, Rahman A, Li S, Archer VR, and Gainor JF. 1388P Real-world prognostic value of RET fusions in advanced non-small cell lung cancer (aNSCLC). *Ann Oncol* 2023; 34:S795-S796. Request Abstract

Background: RET fusions are found in 1–2% of patients (pts) with NSCLC. RET inhibitors (RETi) have recently been approved for RET fusion-positive (RET+) aNSCLC, but the prognostic value of RET fusions is unclear. This study aimed to describe the overall survival (OS) of pts with RET+ or RET wild-type (RET-WT: no RET alterations) NSCLC using real-world data from two large databases. Methods: This was a retrospective, observational study using US-based data from 1) a nationwide Flatiron Health–Foundation Medicine NSCLC clinico-genomic de-identified database (FH-FMI CGDB) and 2) a nationwide longitudinal electronic health record-derived FH de-identified database (FH). Pts with aNSCLC diagnosed between 1 Jan 2011 and 31 Dec 2021 (CGDB) or 30 Sep 2022 (FH) with known RET fusion status were included. Pts with other actionable gene alterations or previous treatment with RETi or a clinical study drug in any line were excluded. The primary objective was to compare the OS of pts with RET-WT vs RET+ aNSCLC in 1) all pts (index date: date of advanced diagnosis) and 2) pts who received first-line (1L) chemotherapy plus cancer immunotherapy (index date: start of 1L therapy). Hazard ratios (HRs) for left-truncated OS (to account for immortal time from index to RET testing) were adjusted for confounding variables using a

multivariate Cox proportional regression model. Results: Overall, 45 (CGDB) and 60 (FH) pts with RET+ aNSCLC, and 5,890 (CGDB) and 16,566 (FH) pts with RET-WT aNSCLC were included in the analysis. Pts with RET+ NSCLC tended to be younger (<65 yrs old: 51% vs 33%), less frequently smokers (8% vs 47%), and less commonly had KRAS (7% vs 34%) and TP53 (42% vs 72%) mutations than RET-WT pts. In CGDB and FH, there was no significant difference in OS between RET-WT and RET+ pts (Table). Conclusions: Data from this real-world study using two large databases show that pts with RET+ aNSCLC do not have a different prognosis than pts with RET-WT aNSCLC. These data suggest that RET fusions have no prognostic value in aNSCLC. [Formula presented]

Hematology-Oncology
Hamid O, **Weise A**, Lewis KD, Kim TM, McKean M, Lakhani NJ, Kaczmar J, Papadopoulos KP, Chen S, Mani J, and Gullo G. 43001 Phase 1 study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma: Expansion cohort analysis. *J Am Acad Dermatol* 2023; 89(3):AB207. Full Text

Background: Concurrent blockade of LAG-3 may enhance efficacy of anti-programmed cell death-1 (PD-1) therapies. We present updated safety and efficacy data from the Phase 1 study in patients with advanced melanoma treated with anti–LAG-3 (fianlimab) 1600 mg + anti–PD-1 (cemiplimab) 350 mg intravenously every 3 weeks for 12 months. Methods: We included patients with advanced melanoma who were anti–PD-1/PD-L1-naive (expansion cohorts [EC] 6 and 15; enrolled sequentially) or anti–PD-1/PD-L1-experienced within 3 months of screening (EC7). Results: As of July 1, 2022, data cutoff date, 80 patients in EC6+EC15 (40 each) and 15 in EC7 received fianlimab + cemiplimab. For EC6+EC15 and EC7 respectively, median age was 69.0 and 59.0 years, 60.0% and 46.7% were male, and 90.0% and 60.0% were White. Median treatment duration was 30.9 weeks (EC6+EC15) and 9.0 weeks (EC7). Grade 2:3 treatment-emergent adverse events (TEAEs) occurred in 40.0% (EC6+EC15) and 46.7% (EC7) of patients. Serious TEAEs occurred in 28.8% (EC6+EC15) and 33.3% (EC7) of patients. The investigator-assessed ORR was 63.8% (7 complete responses; 44 partial responses) in EC6+EC15 and 13.3% in EC7. Kaplan-Meier estimation of median progression free survival was 24.0 months (95% confidence interval [CI]: 9.9–not evaluable) in EC6+EC15 and 1.5 months (95% CI: 1.3–7.7) in EC7. Median duration of response has not been reached in these cohorts. Conclusion: Fianlimab + cemiplimab demonstrated high clinical activity among patients with anti–PD-1/PD-L1-naive advanced melanoma across sequential ECs with a similar safety profile to cemiplimab monotherapy.

Hematology-Oncology
Kattula MM, Steafo L, Corsi NJ, **Gutta RN**, and **Scher E**. BRASH SYNDROME: A CASE OF OCCULT BRADYCARDIAC SHOCK LEADING TO SYMPATHETIC OVERDRIVE. *J Gen Intern Med* 2023; 38:S434. Full Text

M.M. Kattula, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 58-year-old African American male with a past medical history of chronic diastolic heart failure, chronic kidney disease stage IV, and poorly controlled hypertension who presented following persistent bradycardia, and hypotensive readings at home. His antihypertensive regimen prior to arrival included Lisinopril, Nifedipine, Hydralazine, Isosorbid Mononitrate, and Carvedilol daily. On arrival, he was hemodynamically labile with a systolic blood pressure in the 90's, heart rate in the low 50's, and hypothermic to 33.8 degree Celsius. Initial lab work showed a creatinine of 3.56 (baseline of 2.80) and potassium of 6.4. A rapid EKG demonstrated sinus bradycardia, and CXR consistent with pulmonary edema. He was transferred to the MICU after initial management with calcium gluconate, Insulin, D50, Lokelma, and warming measures with a bear hugger. On arrival to the MICU, he required 4L via nasal cannula due to pulmonary edema and was aggressively diuresed with resolution of potassium disturbance. However, he was found to rebound and became increasingly hypertensive to 200s systolic without evidence of end organ damage. His blood pressure was medically managed on the floors and within 24 hours his kidney function neared baseline. He was discharged on a new regimen of antihypertensives, specifically with discontinuation of his beta blocker. IMPACT/DISCUSSION: The combination of bradycardia, renal failure, av nodal blockade, shock, and hyperkalemia creates a condition known as BRASH syndrome. Unfortunately, this is a cycle where one complication begets another in

patients who take av nodal blocking agents and anti-hypertensives that cause hyperkalemia. There are different thoughts on whether it is renal failure or the combination of beta blockers and hyperkalemia that stimulates the cascade. Nonetheless, these components are interrelated and the cycle will continue if it's not identified and treated immediately, ultimately leading to multiorgan failure. What is unique to this case is the rare complication of hypertensive urgency as a result of sympathetic overdrive in response bradycardia causing reduced cardiac output. Furthermore, what is controversial is whether or not to restart medications that demonstrate improved mortality in patients with heart failure, yet may be the cause of this disease process. CONCLUSION: BRASH syndrome is unique because it's a continuum of a single disease, and therapy includes correction of hyperkalemia, fluid management, and vasopressor support when required. There is not enough data that shows if re-introducing these medications following resolution of BRASH syndrome is necessary and whether recurrence rates are significant in those who are restarted on these medications. Additionally, a rare complication that physicians should be aware of is the sympathetic drive that can lead to hypertensive urgency as a result of bradycardia causing reduced cardiac cardiac output.

Hematology-Oncology

Patel MR, Doi T, Koyama T, Falchook GS, Friedman CF, Piha-Paul SA, Gutierrez M, Awad MM, **Mattour AH**, Satoh T, Okamoto N, Singh J, Yoshizuka N, Qian M, Qian X, Tran BP, Dosunmu O, Lu P, and Johnson ML. Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with advanced solid tumors: Updated clinical and biomarker results from a phase I/II study. *Ann Oncol* 2023; 34:S481-S482. Request Abstract

Background: I-DXd is a novel B7-H3–directed antibody–drug conjugate that leverages the clinically validated deruxtecan (DXd) technology with a plasma-stable linker and potent topoisomerase I inhibitor payload. Here we present a follow-up analysis (7 mo since last report) of an ongoing phase 1/2 trial that includes heavily pretreated patients with castration-resistant prostate cancer (CRPC), esophageal squamous cell carcinoma (ESCC), squamous non-small cell lung cancer (sqNSCLC), and small cell lung cancer (SCLC). DOR, OS, and B7-H3 correlations with response are reported for the first time for CRPC, ESCC, and sqNSCLC. Methods: Efficacy and safety were analyzed in patients treated with I-DXd at 4.8 to 16.0 mg/kg. Response was evaluated in patients with ≥2 postbaseline scans or discontinuation for any reason. Fourteen patients with CRPC lacked measurable target lesions at baseline (BL) and were excluded from ORR analysis. B7-H3 level was evaluated retrospectively as patients were not pre-selected by BL expression. Results: As of 31 Jan 2023, 8 patients remained on treatment. Safety data were consistent with previous reports. I-DXd still demonstrated promising ORR results, including in an updated sample size for sqNSCLC (Table). Even in this heavily pretreated population, I-DXd exhibited durable response and encouraging early OS (Table), although further follow-up is needed. B7-H3 expression was moderate to high in most patients; no correlation was observed between response and B7-H3 level, and an update will be presented at the congress. [Formula presented] Conclusions: I-DXd continues to demonstrate a manageable safety profile and promising antitumor activity with encouraging DOR and OS in these heavily pretreated patients, which warrants further clinical evaluation across multiple indications. Clinical trial identification: NCT04145622.

Hematology-Oncology

Sridhar S, O'Donnell PH, Flaig TW, Rosenberg JE, Hoimes CJ, Milowsky MI, Srinivas S, George S, McKay RR, Petrylak DP, Coelho Barata PM, **Hwang C**, Cruz-Correa M, Iafolla M, McKean M, Dreicer R, Brancato S, Lukas JJ, Yu Y, and Moon H. 2365MO Study EV-103 cohort L: Perioperative treatment w/ enfortumab vedotin (EV) monotherapy in cisplatin (cis)-ineligible patients (pts) w/ muscle invasive bladder cancer (MIBC). *Ann Oncol* 2023; 34:S1203. Request Abstract

Background: Current SOC for pts w/ MIBC is neoadjuvant cis-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection (RC+PLND). For pts who are cis-ineligible, SOC is RC+PLND alone but adjuvant therapy may be recommended. Due to high rates of recurrence in cis-ineligible pts, an urgent unmet need remains. Neoadjuvant EV showed promising antitumor activity in MIBC (pathological CR [pCR] of 36%, pathological downstaging [pDS] of 50%) in EV-103 Cohort H (Petrylak 2022). Cohort L examines a perioperative approach. Methods: Cohort L enrolled pts who are cis-ineligible w/ previously untreated MIBC (cT2-T4aN0M0 or cT1-T4aN1M0) who are medically fit for and agree to undergo curative intent RC+PLND within 12 wks. Pts received 3 cycles of neoadjuvant EV

(1.25mg/kg) on Days 1 and 8 of each 3-week cycle followed by RC+PLND and then 6 cycles of adjuvant EV (1.25 mg/kg) on Days 1 and 8 of every 3 week cycle starting 8 weeks post-RC. Primary endpoint is pathological CR (pCR) per central pathology review; secondary endpoints include pathological downstaging (pDS) rate per central pathology review, safety and tolerability. Here we present initial results from the neoadjuvant/RC+PLND phase + 30 days post surgery. Results: 52 pts were enrolled. 51 pts were treated w/ EV in the neoadjuvant phase w/ a median of 3 cycles; 42 pts (82.4%) completed RC+PLND. One pt achieved clinical CR and elected not to undergo RC+PLND and was excluded from pCR and pDS analyses; 17/50 (34.0%) pts had a pCR. pDS was seen in 21/50 (42.0%) pts. In the neoadjuvant/RC+PLND phase, of 51 treated pts most common EV-related TEAEs were fatigue (52.9%), rash maculo-papular (31.4%), and nausea (29.4%). 39.2% of pts had an EV-related TEAE ≥ grade 3; 31.4% pf pts had a RC-related TEAE ≥ grade 3. No surgeries were delayed due to EV-related TEAEs. One pt (2.0%) experienced an EV-related death (Stevens-Johnson syndrome) before surgery. Conclusions: EV continues to show promising activity and was tolerable in cis-ineligible pts w/ MIBC in this ongoing trial. Both the efficacy and safety profiles were consistent with previously reported data from Cohort H. These data support the ongoing phase 3 trials evaluating EV + pembrolizumab in MIBC. Clinical trial identification: EudraCT 2018-001527-39; Release Date: Amendment 11, 15-Feb-2023.

Hospital Medicine

Paje D, O'Malley M, Bernstein SJ, McLaughlin E, Horowitz JK, **Kaatz S**, Flanders S, and Chopra V. DOES A CATHETER-TO-VEIN RATIO >45% INCREASE PICCRELATED VENOUS THROMBOEMBOLISM? *J Gen Intern Med* 2023; 38:S333-S334. Full Text

D. Paje, Department of Internal Medicine, University of Michigan Michigan Medicine, Ann Arbor, MI, United States

BACKGROUND: Practice guidelines recommend a catheter-to-vein ratio (CVR) of less than 45% to reduce the risk of peripherally inserted central catheter (PICC) associated venous thromboembolism (VTE). We evaluated whether a CVR of >45% increases the risk of VTE and catheter occlusion in patients receiving PICCs. METHODS: From August 2020 to April 2022, trained abstractors collected demographic and clinical data on patients receiving PICCs while admitted at 52 hospitals participating in the Michigan Hospital Medicine Safety Consortium. Patients were followed until PICC removal, death, or 30 days following placement, whichever came first. Primary outcomes included image confirmed symptomatic VTE (including upper extremity deep venous thrombosis and pulmonary embolism) and catheter occlusion. PICC placements with CVR >45% were compared to those with CVR ≤45%. The association between CVR >45% and primary outcomes was also assessed after PICC placements were stratified according to catheter thickness. Comparisons used Chi-square tests for categorical variables and t-tests and Wilcoxon rank-sum tests for continuous variables. RESULTS: A total of 6,630 PICCs with documented CVR and catheter size were included in the analysis. Of these, 470 (7.1%) had CVR >45% and 6,160 (92.9%) had CVR ≤45%. The PICC catheter sizes were mostly 4-French (66.5%; N=4,406) and 5-French (32.6%; N=2,163); and median dwell time was 25 days (interquartile range, 9 to 30 days). Overall, catheter occlusion occurred in 433 (6.5%) PICCs and VTE in 120 (1.8%). PICCs with CVR>45% had similar rates of complications when compared to CVR ≤45%: catheter occlusion, 7.7% vs 6.4% (p=0.304); and VTE, 1.9% vs 1.8% (p=0.860). When stratified by catheter thickness, the rates of both complications were also similar between both groups. Overall, 5-French compared to 4-French catheters had higher rates of catheter occlusion, 11.0% vs 4.2% (p<.001) and VTE, 3.1% vs 1.2% (p<.001). CONCLUSIONS: In our analysis, CVR of >45% was not associated with PICC-related VTE or catheter occlusion. However, increasing catheter thickness was associated with a higher risk of VTE and catheter occlusion. Further studies are needed to identify the optimal catheter-to-vein ratio to predict PICC-related complications, and to assess the effect of catheter thickness on such association.

Hospital Medicine

Paje D, O'Malley M, Bernstein SJ, McLaughlin E, Horowitz JK, Quinn M, **Kaatz S**, Flanders S, and Chopra V. COMPARING PICC PLACEMENT BY VASCULAR ACCESS NURSES VERSUS INTERVENTIONAL RADIOLOGISTS. *J Gen Intern Med* 2023; 38:S332. Full Text

D. Paje, Internal Medicine, University of Michigan, Ann Arbor, MI, United States

BACKGROUND: The placement of peripherally inserted central catheters (PICCs) is increasingly performed primarily by vascular access nurses (VAN) in United States hospitals. Despite the increased use of these specially trained clinicians, little is known about the patient and device characteristics of the PICCs they placed compared to those placed by interventional radiology (IR) providers. While there is some evidence that VAN device placements are associated with low devicerelated complication rates, comparison to IR specialists cannot be made without accounting for likely differences in patient and device selection. In this study, we describe the patient and device characteristics of PICC placements by these two groups. METHODS: From January 2013 to November 2022, trained abstractors collected data on patients receiving PICCs while hospitalized at 13 hospitals participating in the Michigan Hospital Medicine Safety Consortium. At these hospitals PICCs are routinely placed by both VAN and IR providers. Patient and device characteristics of PICC placements by VAN were compared to those placed by IR. Device selection measures included preference for single-lumen devices, avoidance of short dwell times (less than 5 days), and avoidance of PICCs in patients with eGFR <45 ml/min/1.73m2. Patients were followed until PICC removal, for 30 days following PICC placement or death, whichever occurred first. Chi-square tests were used to compare categorical variables and t-tests and Wilcoxon rank-sum tests for continuous variables. Associations between patient characteristics and placements by VAN or IR were also assessed using mixed-effects logistic regression models, accounting for hospital-level clustering. RESULTS: A total of 25,276 PICCs placements were analyzed. Of these, 17,963 (71.1%) were placed by VAN and 7,314 (28.9%) by IR. Patient characteristics varied greatly across provider types. Compared to PICCs placed by VAN, those placed by IR were more likely to be in patients with renal failure (34.1% vs 31.5%; p<0.01), paralysis (6.4% vs. 3.9%; p<0.01), a history of breast cancer (4.1% vs. 2.4%; p<0.01) and another central venous catheter already in place (13.2% vs. 10.4%; p<0.01). IR-placed PICCs were less likely to be single-lumen devices (37.3% vs. 51.2%; p<0.01), were more frequently removed within 5 days (21.2% vs. 17.0%; p<0.01) and had a higher proportion of patients with eGFR <45 ml/min/1.73m2 (16.6% vs 11.0%; p<0.01). CONCLUSIONS: We found significant differences in patient and device characteristics when comparing vascular access nurse and interventional radiologist PICC placements. Because of these differences in patient and device selection and their established correlation with PICC-related outcomes, methods such as target-trial emulation are needed to evaluate the true association between catheter outcomes and these two provider types.

Hospital Medicine

Paje D, O'Malley M, McLaughlin E, Horowitz JK, Bernstein SJ, Flanders S, **Kaatz S**, and Chopra V. CAN THE MICHIGAN PICC-DVT RISK SCORE PREDICT MIDLINE-DVT? *J Gen Intern Med* 2023; 38:S331. Full Text

D. Paje, Department of Internal Medicine, University of Michigan Michigan Medicine, Ann Arbor, MI, United States

BACKGROUND: The Michigan PICC-DVT Risk Score (MRS) identified five predictors for deep venous thrombosis (DVT) associated with peripherally inserted central catheters (PICCs): presence of another central venous catheter (CVC), elevated white blood cell (WBC) count, active cancer, multiple catheter lumens, and history of venous thromboembolism (VTE). We sought to determine if these risk factors can also predict DVT in patients receiving midlines, which are shorter peripherally inserted devices associated with a similar risk of DVT as PICCs. METHODS: From 12/2016 to 07/2022, trained abstractors collected demographic and clinical data on patients receiving midlines at 64 hospitals participating in the Michigan Hospital Medicine Safety Consortium, a collaborative quality initiative funded by Blue Cross Blue Shield of Michigan. Patients were followed until midline removal, death, or 30 days post device insertion, whichever came first. The primary outcome was image-confirmed symptomatic upper extremity DVT (UE-DVT). Patient and device characteristics of midline placements with a UE-DVT were compared to those without a UE-DVT. All comparisons used Chi-square tests for categorical variables and t-tests and Wilcoxon rank-sum tests for continuous variables. We evaluated the association between MRS predictors and DVT in midline recipients using a mixed-effects logistic regression model that accounted for hospital-level clustering. Model discrimination was assessed through area under the curve (AUC) receiver operating characteristic analysis. RESULTS: A total of 19,334 midlines were included. UE-DVT occurred in 218 (1.13%). All MRS predictors were more common in midlines with a UE-DVT than those without: presence

of another CVC (19.7% vs 10.4%; p<0.01), elevated WBC count (38.0% vs 29.0%; p<0.01), active cancer (9.2% vs 5.7%; p=0.026), double-lumen midline (11.9% vs 8.2%; p<0.01), and history of VTE (24.8% vs 18.9%; p=0.03). After multivariable adjustment and accounting for hospitallevel clustering, only two MRS predictors for PICC-DVT were found to be predictive of DVT in midlines: presence of another CVC (odds ratio [OR] 1.85; 95% CI: 1.28-2.69) and WBC >12 k/microliter at time of insertion (OR 1.44; 95% CI: 1.06-1.94). Model calibration was driven by hospital-level variation more than predictor variables. The AUC was 0.732 when the predicted probability of an event included the random-effects for hospitals, but only 0.599 when hospital-level effects were removed. CONCLUSIONS: The MRS provides low predictive power for midline-associated DVT. Based on the low rate of midline-associated DVT in our sample, the poor predictive power could be a result of infrequent outcome, or it could be an indication of other patient and device characteristics driving DVT events in the midline population. A larger sample size may be necessary to develop an independent risk score for determining predictors of midline-associated DVT.

Infectious Diseases
Chaudhary AJ, Haider M, Khalid Y, **Jamil M**, **Samad M**, and **Brar I**. A RARE CASE OF FEBRILE LYMPHADENOPATHY PRESENTING AS ASEPTIC MENINGITIS. *J Gen Intern Med* 2023; 38:S416-S417. Full Text

A.J. Chaudhary, Internal Medicine, Henry Ford Health System, Detroit, MI, United States

CASE: 42-year-old female presented with a painful enlarged neck lymph node(LN), fever, night sweats, back pain, vomiting & rash(palm & soles) for three days. Patient was recently hospitalized, three weeks ago, for similar symptoms & treated for aseptic meningitis with clinical improvement. Currently, physical exam revealed tachycardia & palpable tender right cervical LN. Labs revealed anemia (Hb:8.8g/dl), leukopenia (WBC:2700/mm3), & elevated LFTs (AST:117, AST:53, ALP:214). Infectious workup including blood cultures, urinalysis, Quantiferon TB, aspergillus galactomannan, Histoplasma antigen, Blastomyces antigen, pneumocystis jiroveci IgG, Brucella (igG, IgM), Bartonella hensella (IgM, IgG), Q fever (IgG, IgM), syphilis serology, Francisella tularensis (IgG, IgM), Fungitell, VZV IgM, EBV IgM, CMV IgM, Hepatitis B, C & HIV were negative. Autoimmune labs revealed antinuclear antibody (Ab) of 1:320, dsDNA Ab, anti-histone Ab, anti- LKM Ab titer, antimitochondrial M2 Ab, anti-RNP Ab, antiSM Ab, anti-Ro & anti-La Ab were negative. C3 & C4 were within normal limits. CT scan of the chest abdomen pelvis demonstrated cervical lymphadenopathy with 2.5 cm in the largest dimension. The patient underwent a lymph node biopsy revealing benign necrotizing lymphadenitis with no evidence of lymphoma or metastatic process. She received high-dose steroids with clinical improvement. IMPACT/DISCUSSION: Kikuchi Fujimoto disease (KFD), an uncommon differential in febrile lymphadenopathy, resembles systemic lupus erythematosus(SLE) lymphadenitis, viral infections, bacterial adenitis & malignant lymphomas. Autoimmune & infectious workup was grossly negative. Histopathology differentiates KFD from lymphomas. KFD is a diagnosis of exclusion. Our patient was recently treated for aseptic meningitis, which is also an atypical presentation of KFD. Rash is common in KFD, although rash involving palms & soles is also seen in syphilis, coxsackie A virus & rickettsia but the remainder of the findings were less convincing for any of these infections. CONCLUSION: Kikuchi Fujimoto disease (KFD), a.k.a histiocytic necrotizing lymphadenitis, is a benign, self-limiting disease with unclear etiology & acute-subacute onset. It is more common in young, females & Asians. Symptoms include fever & lymphadenopathy, mostly posterior cervical group. Lymph nodes (LN) are painful, tender & swollen. Less frequent symptoms include nausea, vomiting & B-symptoms(chills, night sweats, weight loss). Atypical presentations include skin involvement & aseptic meningitis. Lab work may reveal cytopenia, elevated inflammatory markers & elevated liver function tests(LFTs). Diagnosis requires a lymph node biopsy. Management is conservative & steroids are used in severe cases.

Infectious Diseases
Savard N, and **Chami E**. Leveraging Electronic Medical Records During a Candida Auris Investigation. *Am J Infect Control* 2023; 51(7):S46. Full Text

Background: In March 2022, the first patient with Candida auris (C. auris) infection was identified as having had a recent admission at a large tertiary care hospital. The patient had a lengthy hospitalization that included care on multiple units and had additionally had roommates during the encounter.

Subsequent cases of C. auris colonization were also identified. C. auris is an emerging fungus that can spread in healthcare settings on contaminated surfaces or from person-to-person contact. Based on the size of the exposure, innovative solutions were needed to develop an efficient way to identify and follow-up with possible exposures and to rule out cases of C. auris colonization. Methods: The electronic medical records were used to create flags for rule-out and confirmed cases of C. auris. Patients identified as a possible exposure had a rule-out flag added to charts to immediately alert staff throughout the health system to isolate and screen for C. auris. Patients were identified using a custom hospital trace report and added to a custom patient list. In-house testing was implemented that was also added an infection flag and isolation order upon test order. Results: Of the 55 eligible patients that had been identified as possible exposures to patients with C. auris, 32 (58%) have had a readmission since the original exposure. All 32 patients were identified at the point of readmission and properly isolated and screened upon admission. Conclusions: By leveraging the electronic medical records system to identify and track possible exposures, at-risk patients were able to be immediately isolated and screened upon readmission at any of the system healthcare facilities. The quick response led to safer care by placing the patient in appropriate isolation precautions and allowed for appropriate environmental cleaning to prevent environmental contamination of C. auris, which removed the ability of further exposures.

Infectious Diseases

Savard N, **Chami E**, **Salanger D**, **Gubler J**, **Dover C**, and **Weaver J**. Developing a Robust Leak Response Program. *Am J Infect Control* 2023; 51(7):S28. Full Text

Background: Aging infrastructure within a 100-year-old acute care hospital presents challenges that can often lead to an increase in leaks identified throughout the hospital in both clinical and non-clinical areas that increases the possibility of mold or other waterborne pathogens. In June 2021, the facility was tested even greater when a state of emergency was declared for following a rainstorm which overloaded the area's wastewater systems and further caused significant water damage to the Detroit-based hospital. An improved process was needed to identify and to reduce the occurrence of leaks throughout the hospital. Methods: After the 2021 flooding, the Infection Prevention team, in collaboration with hospital and Facility leadership, developed a leak response document that outlined the immediate expectations for the staff members who identify leaks, the Facility staff expectations, and how to properly report leaks and floods. In addition, a need was identified to better assess the flooring products used and develop a flooring recommendation document that identified the best flooring products that should be installed in areas that have a higher risk of leaks/flooding. Additionally, the Infection Prevention department invested in a moisture reader for room signoffs after leaks. Results: The leak response process and document were presented to all areas/departments throughout the facility. Additionally, the flooring product document was shared with facility design teams, who are now more integrated with Infection Prevention to work on which flooring products to select. Lastly, a process has been developed for room signoff after a known water intrusion. Conclusions: The detailed leak response process outlined and implemented has been improved response time in identifying and reporting leaks throughout the facility. The process in how to properly design and sign-off rooms has reduced the risk of mold growth and has improved room remediation time after a water intrusion event

Internal Medicine

Almajed MR, **Kochhar P**, **Ibrahim AM**, **Nachawati D**, and **Mohammed M**. BROKEN HEART AND BROKEN FEET: TAKOTSUBO CARDIOMYOPATHY IN THE SETTING OF ACCIDENTAL HYPOTHERMIA AND FROSTBITE. *J Gen Intern Med* 2023; 38:S435. Full Text

M.R. Almajed, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 58-year-old man presented on a snowy winter night with severe bilateral foot pain for one week in addition to shortness of breath and bilateral lower limb swelling for several days. He was experiencing unstable housing and often slept without adequate shelter or heating. On examination, he was normothermic, tachycardic, hypertensive, and tachypneic. He had bilateral pitting pedal edema and his feet were erythematous and blistered, consistent with frostbite from environmental injury. Workup was notable for an elevated creatine phosphokinase consistent with rhabdomyolysis. High-sensitivity troponin was high at 75 ng/L, it rapidly increased to 2355 and peaked at 7649 within ten hours of presentation.

Brain natriuretic peptide was high at 135 pg/mL. Electrocardiogram showed anterolateral t-wave inversions. Throughout this course, the patient denied chest pain. Given the laboratory and electrocardiogram abnormalities, acute coronary syndrome was suspected and the patient was treated with antiplatelets, statin, and intravenous heparin. Transthoracic echocardiogram demonstrated a left ventricular (LV) ejection fraction of 21% with aneurysmal LV wall deformity. Invasive coronary angiography had no evidence of coronary artery disease. Repeat echocardiogram showed severe hypokinesis of the middle and distal LV wall segments with preserved basal wall motion. In the context of the clinical presentation, these echocardiographic findings supported the diagnosis of stress cardiomyopathy, termed Takotsubo Cardiomyopathy (TCM). The patient was treated with guidelinedirected medical therapy (GDMT) for heart failure with beta-blockers, angiotensin II receptor blockers, and diuretics after which he clinically recovered. IMPACT/DISCUSSION: TCM is an entity in which left ventricle (LV) dilation and ballooning, notably in the apex, results in a decline in systolic function that manifests as heart failure. It is classically described in the setting of emotional stress, although, recent literature suggests that this condition is underdiagnosed and frequently occurs after physical and physiological stress. Pathophysiology is uncertain but the surge in stress- associated hormones has been implicated in myocardial toxicity. This case offers an atypical presentation for TCM. The diagnosis warrants extensive workup including ischemic evaluation to rule out common causes of heart failure. Diagnostic criteria includes LV regional wall motion abnormalities that exceed a single vascular distribution, evidence of myocardial injury, and the absence of significant coronary artery disease. Management consists of medical optimization with GDMT. Most patients recover well with low mortality rates. CONCLUSION: Internists should be aware of TCM and consider it in patients experiencing significant stress who present with features of heart failure and laboratory testing suggestive of myocardial injury. This case highlights the different triggers for stress response, whether emotional, physical, or physiological.

Internal Medicine

Almajed MR, **Kochhar P**, **Khan N**, and **Entz A**. HEPATITIS C CIRRHOSIS, HEPATITIS B SUPERIMPOSED INFECTION, AND THE EMERGENCE OF AN ACUTE PORTAL VEIN THROMBOSIS. *J Gen Intern Med* 2023; 38:S474. Full Text

M.R. Almajed, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 65-year-old man presented with generalized fatigue for one month. His history was notable for liver cirrhosis secondary to hepatitis C, treated and in sustained virologic response. Patient was alert and oriented and exam was notable for scleral icterus, abdominal distension, and bilateral leg swelling. Workup showed new liver profile abnormalities with AST 467, ALT 470, and total bilirubin 10.9; his MELD-Na score was 26. Hepatitis C RNA was undetectable. Hepatitis B surface antigen and core antibody were positive, surface antibody was negative, and DNA level was 1,481,240. Ultrasonography with doppler and CT liver demonstrated patent vasculature. Patient was diagnosed with decompensated liver disease in the setting of active hepatitis B infection and was treated with Entecavir. Patient initially responded to treatment and had improvement in his symptoms and laboratory abnormalities, however, five days after presentation he became confused with hepatic encephalopathy. Infectious workup was unremarkable and he did not improve after empiric antibiotics, lactulose, and rifaximin. His liver profile worsened with AST 1147, ALT 407, total bilirubin 42.3; MELD-Na score increased to 39. He was escalated to the ICU where a repeat ultrasonography with doppler demonstrated an interval absence of color flow visualization in the main, right, and left portal veins indicative of acute portal vein thrombosis (PVT). Management with intravenous heparin resulted in improvement in laboratory markers. IMPACT/DISCUSSION: PVT involves occlusion of the portal vein by a thrombus and occurs in the setting of prothrombotic states or decompensated liver disease. Acute PVT presents with abdominal pain, fever, or gastrointestinal bleeding but is often asymptomatic. Chronic PVT results in portal hypertension which causes ascites and varices. Diagnosis is made with abdominal ultrasonography with doppler imaging, CT, or MRI. Management for patients with acute PVT involves anticoagulation to promote recanalization, although the indication for anticoagulation in chronic PVT remains unclear. This case offers a unique presentation of acute PVT that developed within several days of a hospitalization for decompensated liver disease, as proven by the interval absence of portal venous flow on repeat imaging. Despite the workup on initial presentation being negative for PVT, reconsideration of differentials after the change in our patient's

clinical status led to the diagnosis. Active hepatitis B infection was likely the initial trigger for the patient's cirrhosis decompensation and presentation; the subsequent coagulopathy and alteration in the portal blood flow triggered the development of an acute PVT. CONCLUSION: Patients with cirrhosis are at risk for both prothrombotic and antithrombotic complications. Superimposed infections with hepatitis viruses and abnormal flow through the hepatic portal system increase the risk for PVT. This case demonstrates the importance of reevaluating cases to reduce anchoring bias.

Internal Medicine

Brosious M, **Goodman BD**, and **Muhammad NI**. A DIAGNOSTIC DILEMMA COMPLICATED BY SAMPLING BIAS: MUCINOUS ADENOCARCINOMA WITH SUPERIMPOSED CRYPTOCOCCAL INFECTION. *J Gen Intern Med* 2023; 38:S393. Full Text

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CASE: A 66-year-old male with history of type 2 diabetes mellitus and coronary artery disease presented with subacute shortness of breath and pleuritic chest pain. He was recently evaluated at an outside hospital for these symptoms and transferred for additional advanced evaluation. Chest radiograph revealed a right- sided pneumothorax, and chest computed tomography (CT) scan was significant for a large right-sided hydropneumothorax and extensive pulmonary cavitary lesions bilaterally. Multiple samples of the pleural fluid were collected without significant findings. Prior to transfer, multiple biopsies of the cavitary lung lesions were obtained without yielding a diagnosis. On the fifth bronchoscopy, pathology results revealed adenocarcinoma with mucinous features and fungal cultures were significant for cryptococcus neoformans. The mucinous adenocarcinoma origin was unable to be identified on pathology, but a CT scan of the abdomen and pelvis showed an atrophic pancreas, but no definitive masses. Carbohydrate antigen 19-9 was significantly elevated. This, in conjunction with the CT findings, make a pancreatic origin the most likely source. IMPACT/DISCUSSION: Pulmonary cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or Cryptococcus gattii. This infection is known to occur in immunocompetent or immunocompromised patients. More severe disease is often seen with immunocompromised hosts, and those with malignancy are at increased risk for cryptococcosis. The findings on chest radiograph or chest CT for pulmonary cryptococcosis and metastatic disease to the lungs are similar. For this reason, it is important to obtain biopsies and cultures of areas of concern when the definitive diagnosis remains in question to determine a diagnosis and treat accordingly. This case also highlights the phenomenon of sampling bias. Sampling bias occurs when a sample is collected in such a way that it fails to collect a representative sample and systematically favors one outcome over another. In total, the patient had five bronchoscopies with biopsies before a final histological diagnosis was made. It is of paramount importance to emphasize the need of obtaining an adequate tissue sample from multiple sites in order to attain the highest yield for a quick and accurate diagnosis. One exam finding that made the diagnosis more difficult was that the patient did not have visual evidence of a lesion while performing the bronchoscopy. A retrospective study from 2008 of patients with a diagnosis of lung cancer showed that the diagnostic yield of non-visible lesions via biopsy is 25%. CONCLUSION: Cryptococcosis is a fungal infection that can lead to pulmonary manifestations which can mimic lung cancer on imaging. The diagnosis of lung cancer can be difficult due to sampling bias. In order to increase the diagnostic yield of a biopsy, an adequate sample size from multiple sites should be obtained.

Internal Medicine

Bugazia S, and Boshnaf M. 1739P Lung cancer mortality patterns of tobacco users in the United States: A 21-year analysis (1999-2020). *Ann Oncol* 2023; 34:S944. Request Abstract

Background: According to the American Cancer Society, lung cancer is the leading cause of cancer-related deaths globally, and tobacco use is the 1ry cause of the disease. The association between tobacco use and lung cancer is well recognized, with smoking cigarettes accounting for approximately 85% of all lung cancer cases. Despite significant public health efforts to reduce tobacco use, it remains a prevalent issue, with an estimated 14% of the U.S. adult population being current smokers. Therefore, there is a continued need to investigate the relationship between tobacco use and lung cancer to better establish public health interventions and policies that can reduce the burden of this deadly disease.

Methods: Using the CDC multiple causes of death database (ICD-10 revision codes), we identified all patients with history of tobacco use who died of lung cancer (C34.x registered as the underlying cause of death) in Caucasian, African American, Asian, American Indian races, between 1999 and 2020 in the United States. Age-adjusted mortality rates were calculated per 1,000,000 persons (PMP), standardized to the U.S. census data from 1999, and stratified by gender. Results: Between 1999 and 2020, 1,084,140 deaths were due to lung cancer in persons with history of tobacco use (age-adjusted mortality= 144.6 PMP). We identified a total of 970,370 Caucasian, 96,001 African American, 11,279 Asian, and 6,490 American Indian deaths in each population (total age-adjusted mortality was 151.5 PMP, 129.5 PMP, 38.3 PMP, and 117.7, respectively). Over 21 years, age-adjusted mortality increased by 782% in Caucasians (19.5 PMP in 1999 to 152.4 PMP in 2020), 575% in African Americans (21.2 PMP in 1999 to 121.9 PMP in 2020), 724% in Asians (5 PMP in 1999 to 36.2 PMP in 2020), and 351% in American Indians (27.2 PMP in 1999 to 95.5 PMP in 2020). Conclusions: The study's results show a significant and consistent rise in the mortality rates of tobacco-related lung cancer among all ethnicities, ranging from 351% in American Indians to 782% in Caucasians. These findings emphasize the urgent need for effective public health interventions and policies that can address the destructive impact of tobacco use on lung cancer mortality across all racial groups in the U.S. Legal entity responsible for the study: The authors. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

Internal Medicine

Chaudhary AJ, Haider M, Khalid Y, **Jamil M**, **Samad M**, and **Brar I**. A RARE CASE OF FEBRILE LYMPHADENOPATHY PRESENTING AS ASEPTIC MENINGITIS. *J Gen Intern Med* 2023; 38:S416-S417. Full Text

A.J. Chaudhary, Internal Medicine, Henry Ford Health System, Detroit, MI, United States

CASE: 42-year-old female presented with a painful enlarged neck lymph node(LN), fever, night sweats, back pain, vomiting & rash(palm & soles) for three days. Patient was recently hospitalized, three weeks ago, for similar symptoms & treated for aseptic meningitis with clinical improvement. Currently, physical exam revealed tachycardia & palpable tender right cervical LN. Labs revealed anemia (Hb:8.8g/dl), leukopenia (WBC:2700/mm3), & elevated LFTs (AST:117, AST:53, ALP:214). Infectious workup including blood cultures, urinalysis, Quantiferon TB, aspergillus galactomannan, Histoplasma antigen, Blastomyces antigen, pneumocystis jiroveci IgG, Brucella (igG, IgM), Bartonella hensella (IgM, IgG), Q fever (IgG, IgM), syphilis serology, Francisella tularensis (IgG, IgM), Fungitell, VZV IgM, EBV IgM, CMV IgM, Hepatitis B, C & HIV were negative. Autoimmune labs revealed antinuclear antibody (Ab) of 1:320, dsDNA Ab, anti-histone Ab, anti- LKM Ab titer, antimitochondrial M2 Ab, anti-RNP Ab, antiSM Ab, anti-Ro & anti-La Ab were negative. C3 & C4 were within normal limits. CT scan of the chest abdomen pelvis demonstrated cervical lymphadenopathy with 2.5 cm in the largest dimension. The patient underwent a lymph node biopsy revealing benign necrotizing lymphadenitis with no evidence of lymphoma or metastatic process. She received high-dose steroids with clinical improvement. IMPACT/DISCUSSION: Kikuchi Fujimoto disease (KFD), an uncommon differential in febrile lymphadenopathy, resembles systemic lupus erythematosus(SLE) lymphadenitis, viral infections, bacterial adenitis & malignant lymphomas. Autoimmune & infectious workup was grossly negative. Histopathology differentiates KFD from lymphomas. KFD is a diagnosis of exclusion. Our patient was recently treated for aseptic meningitis, which is also an atypical presentation of KFD. Rash is common in KFD, although rash involving palms & soles is also seen in syphilis, coxsackie A virus & rickettsia but the remainder of the findings were less convincing for any of these infections. CONCLUSION: Kikuchi Fujimoto disease (KFD), a.k.a histiocytic necrotizing lymphadenitis, is a benign, self-limiting disease with unclear etiology & acute-subacute onset. It is more common in young, females & Asians. Symptoms include fever & lymphadenopathy, mostly posterior cervical group. Lymph nodes (LN) are painful, tender & swollen. Less frequent symptoms include nausea, vomiting & B-symptoms(chills, night sweats, weight loss). Atypical presentations include skin involvement & aseptic meningitis. Lab work may reveal cytopenia, elevated inflammatory markers & elevated liver function tests(LFTs). Diagnosis requires a lymph node biopsy. Management is conservative & steroids are used in severe cases.

Internal Medicine

Chaudhary AJ, **Rahim A**, **Khan MZ**, **Denha E**, and Michel A. A UNIQUE CASE OF AUTOIMMUNE HEPATITIS PRESENTING AFTER A 5-DAY COURSE OF NITROFURANTOIN FOR UNCOMPLICATED URINARY TRACT INFECTION. *J Gen Intern Med* 2023; 38:S430. Full Text

A.J. Chaudhary, Internal Medicine, Henry Ford Health System, Detroit, MI, United States

CASE: An 84-year-old African American woman with a history of type 2 diabetes mellitus presented with postprandial right upper quadrant sharp shooting abdominal pain with associated nausea and vomiting. She reported taking nitrofurantoin 100 mg tablets twice daily for five days for a recent UTI. Denied taking herbal remedies or unprescribed supplements. Never smoked or drank excessive alcohol. Initial blood tests revealed elevated liver biochemistry with bilirubin 7.6 mg/dL, alanine transaminase 343 IU/L, aspartate aminotransferase 261 IU/L, and alkaline phosphatase 135 U/L. Her coagulation screen, full blood count, electrolytes, and renal function were normal. Viral hepatitis profile was negative. Toxicology labs were negative for acetylsalicylic acid (ASA), acetaminophen, and alcohol. Abdominal imaging was unremarkable. Immunological tests revealed positive smooth muscle antibodies with a titer of 95 units: normal IgA and IgG levels and low IgM. Double-stranded DNA antibodies, anti-mitochondrial antibodies, and anti-microsomal antibodies were not detected. A liver biopsy was performed which showed acute hepatitis with moderate necroinflammatory activity consistent with AIH and drug-induced liver injury (DILI). IMPACT/DISCUSSION: Several viruses and drugs have been reported to have caused autoimmune liver disease. One of the drugs is nitrofurantoin which is commonly prescribed due to its low cost, high efficacy, and minimal antimicrobial resistance. Acute liver injury from nitrofurantoin has a prevalence of ~0.3/100,000 prescriptions, while chronic nitrofurantoin liver injury is estimated to be one in 1500. AIH is more common in females than males, with a ratio of 3.6:1. Acute hepatotoxicity is drug-induced liver injury immediately after exposure; chronic nitrofurantoin use is associated with chronic AIH. Our case is unique as the patient developed AIH three weeks after a 5-day course of nitrofurantoin for an uncomplicated UTI. The patient never had elevated liver function tests, a negative viral hepatitis profile, and any history of autoimmune disease or alcohol abuse. Our case was not a DILI, as these usually occur immediately after exposure or when the patient is actively taking the medication. We hypothesize that nitrofurantoin is associated with the development of AIH and the formation of antibodies (in our case, anti-smooth muscle antibodies). It may not only be a dose-related immune response that needs months of constant exposure to be evident; it might be related to nitrofurantoin acting as an antigen, possibly an idiosyncratic reaction. Treatment with steroids improved the LFT and symptoms within days which is also evidence in favor of AIH. CONCLUSION: In patients with recently treated UTI with nitrofurantoin who presents with acute elevation of LFTs within a few weeks, always take into consideration nitrofurantoin-induced AIH. Moreover, treatment with steroids should begin if the antibodies come out positive.

Internal Medicine

Geletu A, **Gardner-Gray JM**, and **Roche M**. GITELMAN SYNDROME PRESENTING AS CARDIAC ARREST. *J Gen Intern Med* 2023; 38:S470. Full Text

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CASE: A 43 year-old-female with a history of cardiac arrest, seizure, and cerebral aneurysm was admitted to the medical ICU for cardiac arrest. A few hours before her presentation patient had a seizure followed by cardiac arrest. On EMS arrival, her rhythm revealed ventricular fibrillation. She was shocked and received amiodarone with a successful return of spontaneous circulation. On arrival to the ED, she was emergently intubated for respiratory distress. EKG revealed prolonged QTc to 707 ms. Labs revealed severe hypokalemia, hypomagnesemia, hypochloremia, and metabolic alkalosis. Given the second episode of cardiac arrest in a setting of profound hypokalemia in a patient with no known history of tubulopathy, eating disorder, or diuretic use, her presentation was concerning for underlying genetic renal tubular disease. Further workup revealed urine potassium of 198 mg/dL and creatinine of 27 mg/ dL with a K/Cr ratio of 7.3, suggesting renal loss of potassium. At this point, the top differential included Gitelman or Bartter syndrome. So urine calcium, chloride, and magnesium were obtained to aid in differentiating between Gitelman and Bartter phenotypes. Urine electrolytes revealed hypocalciuria with calcium (8.3 mg/dL), creatinine (34 mg/dL), and the ratio of urine Ca: Cr <0.7, which confirmed Gitelman's phenotype.

While admitted, electrolytes were repleted and put on potassium-sparing agents with stabilization of electrolytes. She later underwent successful placement of dual chamber ICD and was discharged. And she remained symptom-free. IMPACT/DISCUSSION: Gitelman syndrome (GS) is characterized by renal potassium and magnesium wasting with concomitant metabolic alkalosis and hypocalciuria. Diagnosis is usually clinical with workup revealing electrolyte abnormalities. Its clinical features range from nonspecific symptoms to life-threatening sudden cardiac arrest and seizures, which makes its diagnosis challenging. Management of GS involves close monitoring, life-long supplementation of potassium and magnesium, and cardiac risk stratification to prevent fatal arrhythmias. Our case again demonstrates the importance of accurate diagnosis. Had this patient been accurately diagnosed with GS, she could have had close follow-up and undergone cardiac stratification before her discharge, potentially preventing a second out-ofhospital cardiac arrest. Current guidelines for Implantable Cardioverter Defibrillator (ICD) placement for managing cardiac arrhythmias do not indicate ICD placement for cases with a reversible cause of the arrhythmia. Our case suggests that ICD could be beneficial for the secondary prevention of fatal arrhythmia in patients with Gitelman syndrome. CONCLUSION: The broad differential for electrolyte derangements and the relatively rare nature of Gitelman syndrome make its diagnosis challenging. As it can lead to fatal cardiac arrhythmias, accurate diagnosis can lead to life-saving interventions.

Internal Medicine

Ibrahim AM, **Almajed MR**, and **Brar I**. BRUCELLA OSTEOMYELITIS IN A TRAVELER TO THE UNITED STATES. *J Gen Intern Med* 2023; 38:S435. Full Text

A.M. Ibrahim, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: An 84-year-old male presented with a two-month history of intermittent fevers, malaise, weight loss, difficulty ambulating, and bowel and bladder incontinence. Before the onset of these symptoms, he had been independent in mobility with normal bowel and bladder function. On initial assessment, the patient had unremarkable vital signs and was afebrile. Examination was notable for tenderness over the lower lumbar spine with decreased strength, but normal sensation in the bilateral lower extremities. Workup was notable for a leukocytosis to 13.2 K/uL with elevated CRP 9.9 mg/dL and ESR 86 mm/ hr. Given the neurological findings, spinal MRI was performed and showed osteomyelitis at the C5-6 and L4-5 levels. CT-guided bone biopsy was obtained, and antibiotics were initiated with Vancomycin and Piperacillin-Tazobactam. Despite coverage with broad-spectrum antibiotics, the patient developed persistent fevers with a maximum temperature of 102.5 F. Blood and bone biopsy cultures later returned with concern for Brucella. Subsequent testing was remarkable for Brucella IgM of 1.56 and Brucella Antibody titer of 1:80, suggestive of active Brucella infection. Further elicitation of history noted that the patient was a shepherd in Yemen, where he had traveled from about 4 months ago; he had daily contact with sheep and cattle and would often consume unpasteurized milk. Given the diagnosis of Brucellosis, antibiotics were adjusted to Doxycycline and Rifampin, which he was treated with for six months. He had significant clinical improvement and followed up with Infectious Disease clinic. IMPACT/DISCUSSION: Brucellosis is a zoonotic infection with reservoirs typically including cattle, dogs, sheep, and goats. It is usually transmitted via ingestion of unpasteurized dairy products or undercooked meat from infected animals, inhalation of aerosols, and contact of broken skin or mucous membranes with animal tissues, bodily fluids, and placentas. At-risk populations include slaughterhouse workers, shepherds, and veterinarians. Brucellosis is rarely seen in the US, with 100-200 annual cases. Our case demonstrates the varying and often nonspecific presentation of Brucellosis, which can mimic other diseases, including osteomyelitis, tuberculosis, malignancy, and meningitis. Although Brucellosis is very rare in the US, it should be considered on the differential in patients presenting with fevers, back pain, and night sweats, especially in travelers. It also underlines the importance of thorough history taking, including travel and occupational history, as it can give clues to aid in diagnosis and management. CONCLUSION: -Recognize the importance of thorough history taking, including travel and occupational history, especially in patients presenting with infectious symptoms -Being aware of the signs and symptoms of Brucellosis, as well as general management -Although Brucellosis is rarely seen in the US, keeping it on the differential, especially in patients who have lived or recently traveled abroad.

Internal Medicine

Kattula MM, Steafo L, Corsi NJ, **Gutta RN**, and **Scher E**. BRASH SYNDROME: A CASE OF OCCULT BRADYCARDIAC SHOCK LEADING TO SYMPATHETIC OVERDRIVE. *J Gen Intern Med* 2023; 38:S434. Full Text

M.M. Kattula, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 58-year-old African American male with a past medical history of chronic diastolic heart failure, chronic kidney disease stage IV, and poorly controlled hypertension who presented following persistent bradycardia, and hypotensive readings at home. His antihypertensive regimen prior to arrival included Lisinopril, Nifedipine, Hydralazine, Isosorbid Mononitrate, and Carvedilol daily. On arrival, he was hemodynamically labile with a systolic blood pressure in the 90's, heart rate in the low 50's, and hypothermic to 33.8 degree Celsius. Initial lab work showed a creatinine of 3.56 (baseline of 2.80) and potassium of 6.4. A rapid EKG demonstrated sinus bradycardia, and CXR consistent with pulmonary edema. He was transferred to the MICU after initial management with calcium gluconate, Insulin, D50, Lokelma, and warming measures with a bear hugger. On arrival to the MICU, he required 4L via nasal cannula due to pulmonary edema and was aggressively diuresed with resolution of potassium disturbance. However, he was found to rebound and became increasingly hypertensive to 200s systolic without evidence of end organ damage. His blood pressure was medically managed on the floors and within 24 hours his kidney function neared baseline. He was discharged on a new regimen of antihypertensives, specifically with discontinuation of his beta blocker. IMPACT/DISCUSSION: The combination of bradycardia, renal failure, av nodal blockade, shock, and hyperkalemia creates a condition known as BRASH syndrome. Unfortunately, this is a cycle where one complication begets another in patients who take av nodal blocking agents and anti-hypertensives that cause hyperkalemia. There are different thoughts on whether it is renal failure or the combination of beta blockers and hyperkalemia that stimulates the cascade. Nonetheless, these components are interrelated and the cycle will continue if it's not identified and treated immediately, ultimately leading to multiorgan failure. What is unique to this case is the rare complication of hypertensive urgency as a result of sympathetic overdrive in response bradycardia causing reduced cardiac output. Furthermore, what is controversial is whether or not to restart medications that demonstrate improved mortality in patients with heart failure, yet may be the cause of this disease process. CONCLUSION: BRASH syndrome is unique because it's a continuum of a single disease, and therapy includes correction of hyperkalemia, fluid management, and vasopressor support when required. There is not enough data that shows if re-introducing these medications following resolution of BRASH syndrome is necessary and whether recurrence rates are significant in those who are restarted on these medications. Additionally, a rare complication that physicians should be aware of is the sympathetic drive that can lead to hypertensive urgency as a result of bradycardia causing reduced cardiac cardiac output.

Internal Medicine

Khan N, **Almajed MR**, **Kochhar P**, and **Entz A**. IATROGENIC OBSTRUCTIVE JAUNDICE AND CHOLANGITIS SECONDARY TO POST-ERCP HEMOBILIA. *J Gen Intern Med* 2023; 38:S477. Full Text

N. Khan, Internal Medicine, Henry Ford Health System, Detroit, MI, United States

CASE: A 67-year-old female presented acutely with abdominal pain associated with nausea and vomiting. Her history is notable for newly diagnosed liver cirrhosis of unknown etiology and diverticulitis status post colectomy. Upon presentation, patient was alert and oriented. On examination, she was febrile with jaundice and generalized abdominal tenderness. Workup demonstrated leukocytosis of 14.3, hemoglobin at baseline of 8.7, AST 39, ALT 16, ALP 341, and total bilirubin 0.9. CT abdomen showed moderate ascites with distended gallbladder and wall thickening. Abdominal US and HIDA scan were consistent with acute cholecystitis. Given poor surgical candidacy, patient underwent ERCP that demonstrated choledocholithiasis and biliary papillary stenosis with patent cystic duct. Stent was placed in the common bile duct to maintain patency due to the presence of papillary edema. She had clinical and laboratory improvement afterwards. Patient subsequently developed a fever with persistent RUQ pain. She had worsening hyperbilirubinemia to 4.0 and recurrence of leukocytosis to 14.0. Hemoglobin was stable around 8.0. She was started on antibiotics for cholangitis. Repeat ERCP showed that the previously

placed biliary stent was occluded with a clot secondary to a post-sphincterotomy bleed. This warranted stent removal and replacement with a fully covered metal stent. Cystogram following procedure revealed a patent cystic duct. She had clinical improvement with decrease in bilirubin to 2.2 after which she was discharged. IMPACT/DISCUSSION: ERCP is a diagnostic and therapeutic tool for the management of biliary and pancreatic diseases. It involves navigating an endoscope through the upper gastrointestinal tract and traversing the major duodenal papilla to access biliary and pancreatic ductal systems. This instrumentation is responsible for complications that include pancreatitis, cholangitis, hemorrhage, or perforation. This case offers a rare complication of ERCP involving biliary obstruction secondary to post-ERCP bleeding with subsequent cholangitis. Bleeding after this procedure is typically associated with a decrease in hemoglobin, hemodynamic instability, or overt signs of hemobilia which our patient did not demonstrate. Localized bleeding at the common bile duct resulted in a clot that completely occluded the recently placed stent, resulting in an iatrogenic biliary obstruction. Management of this complication involves repeat ERCP for stent retrieval, bleeding control, and biliary drainage after which laboratory and clinical parameters improve. CONCLUSION: Internists should be aware of the potential complications that occur in the immediate period after ERCP. Changes in a patient's exam or laboratory values including cholestatic markers and complete blood count should prompt re-evaluation with imaging or repeat ERCP when indicated. This case highlights the clinical presentation and management for iatrogenic biliary obstruction secondary to biliary stent clotting after ERCP.

Internal Medicine

Kochhar P, and **Sueng LFN**. ARGE SUBCLINICAL ABSCESS OF A FORGOTTEN FAILED RENAL ALLOGRAFT. *J Gen Intern Med* 2023; 38:S591. Full Text

P. Kochhar, Internal Medicine, Henry Ford Health System, Detroit, MI, United States

CASE: 39 year old female with a history of left nephrectomy in 2009, end-stage renal disease due to obstructive uropathy from neurogenic bladder, status post kidney transplant in 2016 with subsequent failure in 2020. She started peritoneal dialysis that year. She had residual urine production, for which she used intermittent straight catheterization. She was admitted for severe symptomatic anemia. Vitals were within normal limits. The examination was remarkable for subtle pain in the right lower quadrant. Complete blood count revealed a white count of 14.2 and hemoglobin of 6.0 mg/dL. Incidentally, the nursing staff noted cloudy urine with a very dense consistency during her straight catheterization. Dipstick urinalysis was unable to be fully processed due to the dense consistency of her urine but showed 149 RBCs, 182 WBCs, and many bacteria. Computed Tomography Abdomen showed a 7 cm large gas and fluid collection with no normal identifiable renal parenchyma consistent with necrosis of her kidney allograft. Abscess culture grew Actinomyces species and she was started on Ertapenem. The transplant surgery team was consulted but did not recommend transplantectomy due to poor surgical candidacy. A percutaneous drain was placed to achieve source control. She was eventually discharged with long-term oral antibiotic therapy with Augmentin. IMPACT/DISCUSSION: 1 in 5 patients with renal transplantation will have allografts that fail in 5 years, and more than one in two will have graft failure by 10 years. Potential complications of failed allografts include infections, malignancy, bone disease, and cardiovascular disease. Among these, infections remain the leading cause of complications following a kidney transplant. These can occur early post-transplant, during peak immunosuppression, and late onset. The latter occurs 6-12 months following transplant and includes community-acquired pneumonia, upper respiratory infections, and urinary infections, which are by far the most common. In patients with urinary infections, the clinical presentation can range from asymptomatic bacteriuria or pyuria to pyelonephritis and sepsis. In patients with failed transplants and recurrent urinary tract infections or sepsis, transplantectomy should be considered. This patient had multiple previous episodes of pyelonephritis with positive cultures for ESBL and VRE organisms. Patient could not recall if transplantectomy was discussed during her prior infection episodes. Her presentation was subtle despite the large abscess in the graft. This patient's symptoms were initially attributed to severe anemia and she did not exhibit any clear infectious symptoms. CONCLUSION: This case illustrates potential infectious complications of a failed kidney allograft. Transplantectomy should be discussed in patients with failed allograft and recurrent bacterial infections, and immunosuppression should be weaned accordingly. Diagnosis of renal allograft complications can be challenging due to atypical or subclinical presentations.

Internal Medicine

McBride P, **Andrews T**, **Gregerson S**, and **Trahan T**. A CASE OF DRESS IN THE SETTING OF RIFAXIMININDUCED BODILY FLUID DISCOLORATION. *J Gen Intern Med* 2023; 38:S373-S374. Full Text

P. McBride, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 59-year-old male with decompensated alcohol-induced liver cirrhosis was transferred to our facility for liver transplant evaluation. At the preceding facility, he presented with acute hepatic encephalopathy and was started on Lactulose 20g tid and Rifaximin 550mg. At our facility, he developed a fever of 101.1F and diffuse erythematous papules with confluence over the bilateral chest, shoulders, neck and head. The patient also developed bright-orange bodily fluid discoloration. CT abdomen/pelvis demonstrated diffuse inflammatory lymphadenopathy. A complete blood count demonstrated absolute eosinophilia. Dermatology performed punch biopsy showing superficial perivascular and interface dermatitis with eosinophils. Rifaximin was discontinued at this time, and Solumedrol 100 mg IV was initiated. Bodily fluid discoloration resolved 3 days after cessation of Rifaximin. On day 15, the rash was entirely resolved and rifaximin was restarted for severe hepatic encephalopathy. Yellow secretions appeared in the next several days and Rifaximin was again discontinued, with resolution of symptoms. IMPACT/DISCUSSION: Hepatic encephalopathy is a neuropsychiatric manifestation of advanced liver disease in result of inadequate hepatic clearance of toxins, namely, hyperammonemia. Pharmacological treatment relies on decreasing production and augmenting ammonia clearance. Rifaximin, a rifamycin derivative, is standard in pharmacological management of hepatic encephalopathy. Since FDA approval for liver disease in 2010, adverse effects of rifaximin use have been largely benign. Mechanistically, rifaximin's negligible systemic absorption likely prevents the side effect profile displayed in other rifamycin products. However, this case describes discoloration of bodily fluids and DRESS syndrome, both of which are well documented complications with rifampin use. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is DRESS secondary to Rifaximin is an exceedingly rare phenomenon. In most patients, symptoms will appear 2-8 weeks after initiation of drug therapy. Systemic symptoms can include fever, lymphadenopathy and rash. CONCLUSION: It is important to identify drug reactions in the hospitalized patient swiftly to avoid iatrogenic complications as the necessary intervention is cessation of inciting agent. Rifamycin antibiotics, such as Rifampin, rarely have been associated with DRESS Syndrome; few, if any, cases have ever been described of Rifaximin inducing DRESS Syndrome.

Internal Medicine

McBride P, **Mahmood S**, and **Parikh S**. PERICARDIAL TAMPONADE IN THE SETTING OF CHRONIC MYELOGENOUS LEUKEMIA. *J Gen Intern Med* 2023; 38:S513. Full Text

P. McBride, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 65-year-old female with a history of CML, DMII, HTN, and HLD presented for subacute exertional dyspnea which became progressive. She had orthopnea in the absence of chest pain/fevers. She was on Imatinib for 1 month prior to presentation for newly diagnosed CML. ECG showed electrical alternans, BNP was 50 pg/mL, and troponin was 6 ng/L. TTE demonstrated an EF of 60-65% with a large pericardial effusion and signs of right ventricular diastolic collapse. Pericardial drain had 400 mL output. Repeat TTE showed resolution of effusion. She was discharged on colchicine 0.6 mg daily and ibuprofen 600mg tid. Imatinib was held. 2 weeks later, she presented for progressive dyspnea. TTE demonstrated a moderately sized pericardial effusion. The patient had repeat pericardiocentesis, requiring a pericardial window. Pericardial biopsy showed chronic pericarditis without malignant cells. Cytology of the pericardial fluid was negative for malignancy. Patient was given colchicine .6mg bid and Ibuprofen 600mg tid at discharge. Hematology/Oncology decided to start patient on Bosutinib. At follow up 2 months later (5 months after symptom onset), patient was asymptomatic IMPACT/DISCUSSION: Subacute cardiac tamponade is more subtle presentation than acute tamponade. Tyrosine kinase inhibitors can cause severe fluid retention. Severe fluid retention (pleural effusion, pericardial effusion, pulmonary edema, and ascites) was reported in 1.3% of newly diagnosed CML patients taking Imatinib and in 2-6% of other adult CML patients taking Imatinib. The medication was discontinued at initial presentation, but the effusion recurred. In general, most side effects are reversible with temporarily interrupting or stopping therapy.

Correct dosing/duration of agents is essential for adequate treatment. Aspirin is dosed at 600-975mg tid-qid. Ibuprofen is dosed at 400- 800mg tid. Both medications are given for 1-2 weeks initially, and 2-4 weeks if recurrence of symptoms. Colchicine is dosed 0.5-0.6 mg bid for up to 3 months (6 months for recurrence). The patient was asymptomatic prior to diagnosis of CML, making it interesting that biopsy 6 weeks after symptom onset showed chronic pericarditis. Chronic pericarditis is defined as inflamation lasting 3 months or more. Of note, high-dose steroids have been associated with higher recurrence rates of pericarditis. CONCLUSION: Pericardial tamponade/effusion secondary to tyrosine kinase inhibitors is a previously described entity that can present as a subacute process without classic signs and symptoms of acute tamponade/ pericarditis. Traditionally, cessation of the drug was thought to be enough to prevent recurrence. Colchicine, Aspirin, or Ibuprofen are first-line agents. Steroids should generally be avoided. It is unclear if these traditional therapies are successful in treating chronic effusions associated with immunotherapy/malignancy.

Internal Medicine

Mittal A, **Shukr BA**, **Behrendt R**, **Williams C**, **Piatak S**, **Craft S**, and **Willens D**. DESIGNING IMPLEMENTATION OF A SYSTEMWIDE EVIDENCE- BASED HEART FAILURE CARE PATHWAY. *J Gen Intern Med* 2023; 38:S658-S659. Full Text

A. Mittal, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

STATEMENT OF PROBLEM/QUESTION: After multistakeholder design of an inpatient, outpatient, and home heart failure (HF) care pathway, our regional health system needed implementation plans to drive uptake of key HF care steps. DESCRIPTION OF PROGRAM/INTERVENTION: Implementation plans are based on the AHRQ Learning Health System (LHS) framework and the Influencer change framework (Grenny, et al.). The LHS framework drives iterative care improvements via evidence application and ongoing learning from clinical performance data. The Influencer framework guides interventions that improve personal, structural, and social abilities and motivations to improve. The HF pathway included evidence-based interventions such as prescribing guideline directed medical therapy (GDMT), using universal healthliteracy appropriate patient education materials, and referring appropriate patients to cardiology, home-based care, or palliative care. Our implementation design team consisted of clinician-educators, residents, nurses, data analysts, an instructional designer, and a management engineer. Interventions include: 1) Driving buy-in by redesigning the pathway with facilitated teams of 100 clinicians and leaders from all disciplines and care venues; 2) Improving HF knowledge via education modules on our learning management system; 3) Audit and feedback of pathway uptake metrics; and 4) EMR tools to facilitate ordering of pathway steps. Education objectives are to update clinician knowledge on new HF nomenclature, GDMT, and descriptions of key steps in the HF care pathway. Rollout of these interventions is currently in progress. MEASURES OF SUCCESS: Clinician and executive qualitative feedback on content, usability, and design via unstructured interviews and our system wide HF governance structure. We will use the RE-AIM framework for evaluation of implementation. FINDINGS TO DATE: 1. The pathway design process engaged teams over 3 years despite competing priorities from COVID. 2. System wide education requires addressing differing resources across care settings and payors. 3. Defining which patients have HF by EMR data allowed real-time identification in hospitals, but challenges remain for outpatient and ED settings. 4. Specialty and location-based governance may be siloed, causing diffusion of ownership of implementation. KEY LESSONS FOR DISSEMINATION: Implementation plan design for the HF care pathway was successful due to: 1. Use of the AHRQ LHS and Influencer change frameworks facilitated more in-depth planning for spread and sustainability of clinical change. 2. Multi-stakeholder teams for sustained engagement across care siloes. 3. Executive sponsorship for system integration and local accountability. 4. Management engineer to coordinate multiple, diverse teams. 5. Instructional designer for effectiveness of education.

Internal Medicine

Nguyen CO, **Gregerson S**, **Shams S**, **Buckley J**, and **McBride P**. A CASE OF BACLOFEN ENCEPHALOPATHY IN RENAL INSUFFICIENCY. *J Gen Intern Med* 2023; 38:S369-S370. Full Text

C.O. Nguyen, Wayne State University, School of Medicine, Detroit, MI, United States

CASE: A 64-year-old woman with a history of type 2 diabetes on long-term insulin complicated by gastroparesis, essential hypertension, and chronic kidney disease G5/A3 not on hemodialysis presented to the pain clinic 2 weeks prior to presentation for polyneuropathy and muscle spasms. She was prescribed gabapentin 100 mg three times daily and baclofen 5 mg 1-2 tablets three times daily. Two weeks after initiating baclofen, our patient fell at her home and was seen by family with bilateral shaking of upper extremities. Per family, the patient was confused but denied hitting her head or losing consciousness. She was brought to the Emergency Department for suspicion of stroke. The patient presented disoriented, lethargic and non-verbal with no focal deficits. Her presenting blood pressure was 215/98. She was admitted to the medical intensive care unit for hypertensive emergency with acute encephalopathy requiring continuous intravenous antihypertensive medication. Her physical exam demonstrated global encephalopathy but no focal neurological deficit. Her labs were significant for creatinine 3.96 (baseline 3.2) µmol/l. A brain computerized tomography (CT) without IV contrast showed stable chronic bilateral encephalomalacia in the cerebellar hemispheres with no acute intracranial abnormalities. Given her acute kidney injury superimposed on chronic kidney disease and persistent confusion despite resolution of hypertensive emergency, baclofen-induced encephalopathy was diagnosed. The patient underwent urgent hemodialysis with complete resolution of encephalopathy after the first 3.5h session. The patient underwent a second 4h hemodialysis session and was discharged 48 hours later with baseline mentation. IMPACT/DISCUSSION: Encephalopathy is a broad differential diagnosis including toxometabolic, infectious, traumatic, environmental and pharmacologic etiologies. Baclofen is a GABA agonist and acts through inhibition of pre-synaptic motor neurons to teat spasticity, pain, muscular rigidity, and spasms. As baclofen is primarily excreted by the kidneys, most cases of baclofen toxicity have been reported in dialysisdependent patients, usually 2-3 days to 6 weeks following ingestion of the drug. Intoxication signs and symptoms include seizures, autonomic disturbances, respiratory depression, and altered consciousness CONCLUSION: In patients with severe chronic kidney disease, baclofen should be avoided if possible. If baclofen cannot be avoided, it is important to initiate at low, renally-adjusted dosages. If toxicity is suspected, hemodialysis is an appropriate treatment to reduce clearance time and alleviate clinical symptoms.

Internal Medicine

Patel K, and **Omar J**. LOW DOSE ORAL MINOXIDIL CAUSING PERIPHERAL EDEMA AND RAPID WEIGHT GAIN. *J Gen Intern Med* 2023; 38:S592. Full Text

K. Patel, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: 54 year old female with history of hepatic hemangioma, migraines and recently diagnosed alopecia presented to clinic with bilateral upper and lower extremity swelling. She was seen by Dermatology one month prior to presentation and was started on oral Minoxidil 1.25 mg daily for her alopecia. Since then, she has noticed rapid weight gain of 20 pounds over one month, increased peripheral swelling bilaterally with associated leg pain. She has also had intermittent headaches that are different than her usual migraines. She denied chest pain, shortness of breath, palpitations. BNP was mildly elevated. Other lab work including TSH, urinalysis and liver profile was unremarkable. Imaging including CT head, CT PE, lower extremity dopplers, and echocardiogram were also unremarkable. She was trialed with a loop diuretic without improvement in symptoms despite sufficient urine output. Minoxidil was held and her symptoms improved significantly. IMPACT/DISCUSSION: Lower extremity edema is a common complaint that can have profound clinical impact on a patient. A chronic presentation is typically more common in the outpatient setting and is often the result of venous insufficiency. Less common is an acute to subacute presentation of which the most common etiologies typically include acute heart failure exacerbation, acute nephrotic syndrome, and bilateral deep vein thrombosis. Newly initiated medications should always be considered as a cause with dihydropyridine calcium channel blockers being the most commonly seen culprit. Side effects are often seen with a dose dependent relationship. Minoxidil produces vasodilation mediated by cyclic AMP, primarily effecting arteriolar smooth muscle. Although Minoxidil is indicated for use in hypertension, it is more commonly used for dermatological conditions such as androgenetic alopecia. Topical minoxidil is the most frequent formulation but oral minoxidil can also be used. Side effects are minimal but the most common include hypotension, headaches, and hypertrichosis. Peripheral edema is rare, particularly with low doses but is reversible with discontinuation and can be further aided by concurrent diuretic use. CONCLUSION: Rapid onset peripheral edema is

often related to acute heart failure, nephrotic syndrome or DVT. Although life-threatening causes should be quickly ruled out, a clinician should also consider medication side effects that could be contributing. Oral minoxidil is less frequently used than topical but significant side effects such as headaches, hypertrichosis, hypotension, and more rarely peripheral edema can occur. Discontinuation reverses the peripheral edema and a low dose loop diuretic can provide additional benefit.

Internal Medicine

Samad M, **Oudeif A**, **Mohammed M**, and **Chaudhary AJ**. DOES A NEGATIVE TEMPORAL ARTERY BIOPSY RULE OUT GIANT CELL ARTERITIS WITH LARGE VESSEL INVOLVEMENT? *J Gen Intern Med* 2023; 38:S456. Full Text

M. Samad, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 61-year-old female presented with initial symptoms of abdominal pain, nausea, vomiting, and weight loss. ESR, CRP, and WBC were elevated, and CT imaging revealed abdominal aortitis with retroperitoneal fibrosis and involvement of bilateral iliac arteries. The patient was initiated on high dose corticosteroids and had a negative workup for systematic vasculitis and infectious etiology during her hospital course. She continued an oral steroid regiment once discharged but discontinued her mediation five weeks later. Days after this, the patient presented to the ED with unilateral headache, blurry vision, and left upper limb claudication. Lab values and CT imaging were repeated which showed minimal change from prior admission. Clinical symptoms indicated giant cell arteritis and a temporal artery biopsy was pursued which was negative. The patient received IV corticosteroids, and she reported improvement in her symptoms, including her visual disturbances. She was transitioned to her initial high dose oral corticosteroid regiment and discharged home. IMPACT/DISCUSSION: Small and large vessel vasculitis in giant cell arteritis is more rare than small vessel involvement alone. This case highlights that temporal artery biopsy in a patient with large and small vessel disease has limited sensitivity. Furthermore, prior glucocorticoid treatment modifies the sensitivity of a temporal artery biopsy in addition to other features of the test. This case emphasizes the diagnostic challenge of giant cell arteritis and the limited differential diagnoses for aortitis. Prompt treatment, while indicated, can complicate the investigation, making it difficult to distinguish if the aortic inflammation is part of an idiopathic or systemic process. The diagnosis of giant cell arteritis is critical to appropriate treatment and management with chronic high dose steroids. CONCLUSION: Giant Cell Arteritis with small vessel involvement is generally diagnosed through temporal artery biopsy. However, when the disease involves both small and large vessels and treatment is initiated prior to biopsy, this can influence the diagnostic sensitivity of the biopsy, making the diagnosis challenging.

Internal Medicine

Stephan J, **Almajed MR**, **Parsons AJ**, **Gregerson S**, and **Swanson B**. SECONDARY BACTERIAL PERICARDITIS WITH CARDIAC TAMPONADE AFTER ENDOBRONCHIAL ULTRASOUND WITH TRANSBRONCIAL NEEDLE ASPIRATION. *J Gen Intern Med* 2023; 38:S529. Full Text

J. Stephan, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

CASE: A 44-year-old male without signficant past medical history underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for an incidentally identified subcarinal mass. He later presented with pleuritic chest pain and shortness of breath. CT imaging demonstrated enlargement of the subcarinal mass with a trace pericardial effusion. The patient was planned to undergo repeat EBUS-TBNA, however, he quickly developed hemodynamic instability. Echocardiogram revealed a pericardial effusion with evidence of tamponade. Emergent pericardiocentesis was performed with placement of a pericardial drain, purulent fluid was obtained. Videoassisted thoracoscopic surgery (VATS) was performed with mediastinal washout and pericardial window. Fluid cultures returned positive for S. aureus and Capnocytophaga. IMPACT/DISCUSSION: Bacterial pericarditis is a rare cause of pericarditis; in cases of secondary bacterial pericarditis, Staphylococcus Aureus is the most commonly implicated bacteria. Pericarditis is a known procedural complication of EBUS-TBNA. Given our patient's hemodynamic instability in the setting of cardiac tamponade, emergent pericardiocentesis was indicated. VATS was selected as the treatment modality of choice over subxiphoid pericardotomy, the standard of

care, in order to achieve optimal source control by marsupialization of the bronchogenic cyst and completion of a mediastinal washout. Infectious disease was consulted given the atypical growth of Capnocytophaga and S. Aureus for which he was initially treated with Vancomycin and Piperacillin-Tazobactam then transitioned to Amoxicillin- Clavulanate to complete a 6-week treatment course. It was determined that Capnocytophagia was likely introduced to the patient's respiratory system by his dog licking the patient's face. Colchicine was administered for treatment of pericarditis in line with the current guideline recommendations. CONCLUSION: We present an uncommon case of Capnocytophaga bacterial pericarditis leading to cardiac tamponade. The occurrence of pericarditis after EBUS-TBNA is well-documented and clinicians should have a high index of suspicion in patients who become hemodynamically unstable within 3 months of the procedure. In cases of post-procedural bacterial pericarditis, it is important to take a multidisciplinary approach to determine the best treatment course.

Neurology

Chehade H, Tedja R, **Zhang Y**, **Fox A**, **Millman M**, Gogoi R, Anderson M, Rutherford T, **Zhang Z**, **Chopp M**, Mor G, and Alvero A. Adipose-derived exosomal miR-421 induces epigenetic reprogramming in ovarian cancer cells by targeting CBX7 (2291). *Gynecol Oncol* 2023; 176:S310. Full Text

Objectives: Chromobox protein homolog 7 (CBX7), a member of the Polycomb repressor complex, is a potent epigenetic regulator and gene silencer. Our group previously reported that CBX7 functions as a tumor suppressor in ovarian cancer cells, and its loss accelerated the formation of carcinomatosis and drove tumor progression in an ovarian cancer mouse model. The goal of this study was to identify specific signaling pathways in the ovarian tumor microenvironment that can downregulate CBX7. Adipocytes are an integral component of the peritoneal cavity and the ovarian tumor microenvironment. Given its known pro-tumor functions, we hypothesized that the adipose microenvironment might be a main regulator of CBX7 expression. We report the characterization of exosomes derived from adiposities that regulate OC cell differentiation by releasing mir-421, a major regulator of CBX7 expression. Methods: Normal omentum was collected from female patients undergoing surgery for either benign or malignant conditions (age range: 30–80), and adipose-conditioned media (ACM) were obtained from these organ cultures. Human ovarian cancer cells used in this study include ATCC ovarian cancer (A2780, OVCA432, OVCAR3) and in-house cell lines (R182). Exosomes were isolated by serial centrifugation. Size and granularity were characterized using Nanosight, and cellular origin was determined using Exoview. mRNA and protein levels were determined by qPCR and western blot, respectively. Transfections were performed using a Lipofectamine transfection reagent. Results: Exosomes isolated from ACM decrease CBX7 protein levels without affecting its mRNA. These exosomes were characterized by higher expression of CD36 (adipocyte marker) compared to CD11b (macrophage marker) and showed a characteristic pattern of higher granularity suggesting a more complex cargo. Furthermore, they showed high levels of mir-421. Pre-treatment of ovarian cancer cells with the endocytosis inhibitor, nystatin, before culturing with ACM or exosomes, abolished the effect on CBX7. Furthermore, treatment of OC cells with anti-mir-421, but not control anti-mir, prior to the addition of adipose-derived exosomes abolished the effect on CBX7 expression. The direct binding of mir-421 to CBX7 3' UTR was demonstrated by a significant decrease in luciferase activity when CBX7 3' UTR plasmid was co-transfected with mir-421 ($P = 0.0005$, compared to control miRNA). Conclusions: We identified adipose-derived exosomal mir-421 as a specific signaling pathway in the ovarian tumor microenvironment that can downregulate CBX7 and induce an epigenetic change in ovarian cancer cells, which can drive disease progression. These findings open new venues to determine the value of targeting mir-421 to curtail ovarian cancer progression.

Neurology

Gilbert MR, Omuro A, Yuan Y, Mendoza T, Wall K, Grajkowska E, Vera E, Reyes J, Aldape K, Penas-Prado M, **Walbert T**, **Mikkelsen T**, Weathers S, Weathers S, O'Brien B, DeGroot J, Puduvalli V, Pentsova E, DeAngelis L, DeAngelis L, Kaley T, Gavrilovic I, Batchelor T, Batchelor T, Batchelor T, and Armstrong TS. PHASE 2 TRIAL OF CARBOPLATIN AND BEVACIZUMAB FOR RECURRENT ADULT EPENDYMOMA. A CERN STUDY. *Neuro-Oncology* 2023; 25:ii7. Full Text

M.R. Gilbert, NIH, Bethesda, MD, United States

BACKGROUND: Most adults with ependymoma undergo tumor resection at the time of diagnosis, which may be followed by radiation. At recurrence, re-resection and/or (re)-irradiation may be given, however, there are few established chemotherapy treatments. A previous retrospective report of 8 patients treated with carboplatin and bevacizumab showed a high response rate with 6 patients demonstrating an imaging response (Green, Neurology 2009). We sought to further investigate this regimen with a prospective trial. MATERIAL AND METHODS: We performed a prospective phase 2 study in the CERN Adult Clinical Trials Network. Adult patients with recurrent or progressive ependymoma were enrolled to receive carboplatin (AUC =4-5) every 4 weeks for up to 6 cycles and bevacizumab at 10mg/kg every 2 weeks for one year, with the option to continue until progression or toxicity. The primary endpoint was 12-month PFS rate and >50% defined efficacy. Serial symptom burden measurement at baseline and at the time of disease evaluation using MD Anderson Symptom Inventory-brain tumor (MDASI-BT) or MDASI-Spine patient-reported outcomes (PROs) were used to evaluate the clinical impact of PFS. RESULTS: A total of 22 patients with median age of 45 years were accrued and treated; 11 were women. WHO grade was 3 in 13 patients and grade 2 in 9 patients (3 with myxopapillary ependymoma) Ten patients had only spinal cord disease, 3 had both spinal cord and brain involvement and 9 patients had brain involvement alone (6 supratentorial, 3 infratentorial). Previous treatments included radiotherapy in all 22 patients and alkylating chemotherapy in 9 patients. Treatment was well tolerated with expected myelotoxicities and hypertension. The Kaplan-Meier calculated 12-Month PFS rate was 76.4% (95%CI 52.2%, 89.4%), median PFS = 18 months (95%CI 12.2, +∞). There were 2 partial responses (9.1%). Brain tumor responders (objective response or stable disease) showed reduction while non-responders had an increase in both neurologic and cognitive symptoms but similar report of other symptoms. Spine tumor responders and non-responders both showed worsening disease-related symptoms; autonomic symptoms worsened in responders. Activity related interference worsened for all patients. CONCLUSION: This treatment regimen was safe and met the primary efficacy endpoint of 12-month PFS rate. The improvement in disease-related symptoms in brain tumor patients supports that the achieved disease stability was clinically meaningful, but the increased activity-related interference suggests that treatment-associated symptoms may impact work, general activity, and walking ability during treatment. Improvements in spine tumor disease-associated symptoms were not seen. A confirmatory trial is warranted to further investigate the findings and to determine if there are differences in response amongst ependymoma subtypes and tumor location.

Neurology

Varelas P, Kananneh M, Brady P, Holden D, **Mehta C**, Ata A, Abdelhak T, Greer D, and **Rehman M**. Absence of Diabetes Insipidus in Brain Dead patients secondary to renal insufficiency. *Neurocrit Care* 2023; 39(1):S37. Full Text

P. Varelas, Albany Medical College, United States

Background & Purpose Critics of brain death allege that up to 50% of brain dead (BD) patients have residual brain function based on the absence of central diabetes insipidus (DI), which suggests remaining hypothalamic/pituitary function. We hypothesized that different degrees of renal dysfunction may impact the presence of DI in BD patients. Methods All adult patients declared BD over 12 years at Henry Ford Hospital were evaluated. DI was diagnosed by polyuria (>300 ml urine output for 2 or more consecutive hours), low urine specific gravity (< 1.005) and increasing serum sodium. Renal function was assessed by the estimated glomerular filtration rate (eGFR), calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation (validated for ages > 18). 192/266 BD patients were included in the analysis after excluding those with missing data, < 18-years-old or on vasopressin infusions (for hypotension). 122 (63.5%) developed DI. The proportion with DI decreased significantly with decreasing eGFR: for eGFR > 60ml/min, DI was present in 77.2%; for eGFR 15-60ml/min in 54.5%, and for eGFR < 15ml/min in 32% ($p < 0.001$). There were 14 patients with eGFR <9.7 ml/min (all with serum creatinine > 7.1 mg/dL); none experienced DI. Using logistic regression, for every 10 ml/min increase in eGFR the odds of DI increased by 1.2 times (95% CI: 1.10 to 1.32, $p < 0.001$) Conclusion Presence of hypothalamic/pituitary function (based on the absence of DI) is less common than previously thought in BD patients, as kidney dysfunction significantly impacts DI development. DI is observed less frequently in BD patients who have renal injury, and some patients with severe renal dysfunction never develop DI.

Renal dysfunction should be accounted for when considering the presence or absence of DI in brain death.

Neurology
Weller M, Alexander B, Berry D, Blondin N, Buxton M, Cavenee W, Colman H, De Groot J, De La Fuente M, Ducray F, Ellingson B, Gordon G, Hyddmark EMV, Khasraw M, Lassman A, Lee E, Lim M, Mellinghoff I, **Mikkelsen T**, Perry J, Sulman E, Tanner K, Wen P, Wick A, Yung A, and Cloughesy T. UPDATE ON GBM AGILE: A GLOBAL, PHASE 2/3 ADAPTIVE PLATFORM TRIAL TO EVALUATE MULTIPLE REGIMENS IN NEWLY DIAGNOSED AND RECURRENT GLIOBLASTOMA. *Neuro-Oncology* 2023; 25:ii79-ii80. Full Text

M. Weller, University Hospital Zurich, Zürich, Switzerland

BACKGROUND: GBM AGILE (Glioblastoma Adaptive, Global, Innovative Learning Environment) is a biomarker based, multi-arm, international, seamless Phase 2/3 platform trial designed to rapidly identify experimental therapies that improve overall survival and confirm efficacious experimental therapies and associated biomarker signatures to support new drug approvals and registration. GBM AGILE is a collaboration between academic investigators, patient organizations and industry to support new drug applications for newly diagnosed (ND) and recurrent GBM. METHODS: The primary objective of GBM AGILE is to identify therapies that effectively improve the overall survival in patients with ND or recurrent GBM. Bayesian response adaptive randomization is used within subtypes of the disease to assign participants to investigational arms based on their performance. New experimental therapies are added as information about promising new drugs is identified, while therapies are removed as they complete their evaluation. GBM AGILE has screened over 1400 patients and enrollment rates are 3 to 4 times greater than traditional GBM trials, with active sites averaging 0.75 to 1 patients/site/month. There are 41 active sites in the US, 4 active sites in Canada and 3 active sites in Europe with a total of 15 sites planned for Switzerland, France and Germany. Expansion to Australia is currently underway. GBM AGILE operates under a Master Protocol which allows multiple drugs from different pharmaceutical/ biotech companies to be evaluated simultaneously and/or over time against a common control. Along with an adaptive trial design, shared control arm and operational processes to serve the goal of helping patients receive optimal care in a fast and efficient manner, GBM AGILE incorporates new design and operational elements to enhance efficiencies, including more recently dose finding and enhanced safety management components. The dose finding phase allows for an initial evaluation of the experimental study drug in combination with radiotherapy and temozolomide, and/or lomustine in a limited number of patients at a select number of study sites within the trial in order to ensure that there are no critical safety signals before expansion to a larger subset of patients for enhanced safety monitoring followed by broader inclusion of the combination at all global study sites. The investigational drugs that have employed the dose finding phase and enhanced safety monitoring process have tolerable safety profile with toxicities that are monitorable, reversible, and not related to the control arm treatments. Through the use of improved and flexible processes, GBM AGILE continues to serve as a global trial that supports the efficient and rapid incorporation and evaluation of new experimental therapies for patients with GBM.

Neurosurgery
Gilbert MR, Omuro A, Yuan Y, Mendoza T, Wall K, Grajkowska E, Vera E, Reyes J, Aldape K, Penas-Prado M, **Walbert T**, **Mikkelsen T**, Weathers S, Weathers S, O'Brien B, DeGroot J, Puduvalli V, Pentsova E, DeAngelis L, DeAngelis L, Kaley T, Gavrilovic I, Batchelor T, Batchelor T, Batchelor T, and Armstrong TS. PHASE 2 TRIAL OF CARBOPLATIN AND BEVACIZUMAB FOR RECURRENT ADULT EPENDYMOMA. A CERN STUDY. *Neuro-Oncology* 2023; 25:ii7. Full Text

M.R. Gilbert, NIH, Bethesda, MD, United States

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MATERIAL AND METHODS: We performed a prospective phase 2 study in the CERN Adult Clinical Trials Network. Adult patients with recurrent or progressive ependymoma were enrolled to receive carboplatin (AUC =4-5) every 4 weeks for up to 6 cycles and bevacizumab at 10mg/kg every 2 weeks for one year, with the option to continue until progression or toxicity. The primary endpoint was 12-month PFS rate and >50% defined efficacy. Serial symptom burden measurement at baseline and at the time of disease evaluation using MD Anderson Symptom Inventory-brain tumor (MDASI-BT) or MDASI-Spine patient-reported outcomes (PROs) were used to evaluate the clinical impact of PFS. RESULTS: A total of 22 patients with median age of 45 years were accrued and treated; 11 were women. WHO grade was 3 in 13 patients and grade 2 in 9 patients (3 with myxopapillary ependymoma) Ten patients had only spinal cord disease, 3 had both spinal cord and brain involvement and 9 patients had brain involvement alone (6 supratentorial, 3 infratentorial). Previous treatments included radiotherapy in all 22 patients and alkylating chemotherapy in 9 patients. Treatment was well tolerated with expected myelotoxicities and hypertension. The Kaplan-Meier calculated 12-Month PFS rate was 76.4% (95%CI 52.2%, 89.4%), median PFS = 18 months (95%CI 12.2, +∞). There were 2 partial responses (9.1%). Brain tumor responders (objective response or stable disease) showed reduction while non-responders had an increase in both neurologic and cognitive symptoms but similar report of other symptoms. Spine tumor responders and non-responders both showed worsening disease-related symptoms; autonomic symptoms worsened in responders. Activity related interference worsened for all patients. CONCLUSION: This treatment regimen was safe and met the primary efficacy endpoint of 12-month PFS rate. The improvement in disease-related symptoms in brain tumor patients supports that the achieved disease stability was clinically meaningful, but the increased activity-related interference suggests that treatment-associated symptoms may impact work, general activity, and walking ability during treatment. Improvements in spine tumor disease-associated symptoms were not seen. A confirmatory trial is warranted to further investigate the findings and to determine if there are differences in response amongst ependymoma subtypes and tumor location.

Neurosurgery

Holden D, Lakos L, **Entezami P**, Quinlan M, and Thibodeau R. Safety of Intravenous Cangrelor Administered Within 24 hours of Thrombolytics in Patients With Ischemic Stroke and Acute Stenting. *Neurocrit Care* 2023; 39(1):S173. Full Text

D. Holden, Albany Medical Center, United States

Background & Purpose Thrombolytics, mechanical thrombectomy, and carotid stenting are frequently utilized for the treatment of acute ischemic stroke. It is recommended not to utilize antithrombotic agents in the immediate 24- hour period after thrombolytic administration for acute ischemic stroke due to perceived bleeding risk. When acute stent placement is needed within 24 hours of thrombolytic administration, antiplatelet agents are needed intra-procedure and post-procedure. Cangrelor is increasingly utilized during acute neuroendovascular stenting but the safety of using cangrelor in the immediate period after thrombolytic administration due to the need for stent placement has not been well studied. Methods Patients who presented with acute ischemic stroke who received a thrombolytic and underwent stent placement and received intravenous cangrelor within 24 hours were retrospectively reviewed. Demographics, procedure details/indications, cangrelor dose, and bleeding outcomes were collected. The European Cooperative Acute Stroke Study (ECASS) and the Heidelberg classification systems were utilized to categorize the severity of intracranial hemorrhage. Results A total of 15 patients met the inclusion criteria. All patients received alteplase and underwent mechanical thrombectomy and required stent placement. Five patients had intracranial hemorrhages that were categorized as Heidelberg hemorrhagic infarction class la or ECASS hemorrhagic infarction class 1. No patients had symptomatic intracranial hemorrhage or an intracranial hemorrhage that demonstrated confluence in the infarction bed or mass effect. Conclusion The utilization of intravenous cangrelor within 24 hours of thrombolytic administration post ischemic stroke in patients who require acute stenting appears to be safe. Comparative studies with a control population are needed to confirm these findings.

Neurosurgery

Kocakavuk E, Johnson KC, **Sabedot TS**, Reinhardt HC, **Noushmehr H**, and Verhaak RGW. HEMIZYGOUS CDKN2A DELETION CONFERS WORSE SURVIVAL OUTCOMES IN IDH-MUTANT GLIOMAS. *Neuro-Oncology* 2023; 25:ii8. Full Text

E. Kocakavuk, Yale School of Medicine, New Haven, CT, United States

BACKGROUND: The tumor suppressor gene CDKN2A is frequently deactivated in cancer. Homozygous CDKN2A deletion is a Grade 4 defining criterion for IDH-mutant gliomas. However, the prognostic value of hemizygous CDKN2A deletions is unclear. We assessed CNV profiles of 1238 initial and 479 recurrent IDHmut gliomas to evaluate the association of CDKN2A hemizygous deletions with overall survival (OS) outcomes. MATERIAL AND METHODS: The GLASS primary/recurrent glioma dataset was used to infer CDKN2A status with DNAseq (n=210) and DNA methylation array (n=100) data. Validation was conducted using DFCI, MSKCC, TCGA and DKFZ cohorts. RESULTS: Longitudinal analyses of IDH-mutant gliomas without 1p-/19q-codeletion showed significant increases in CDKN2A homozygous deletion from n=6 to n=23 (5% to 20%, P=0.0001, Fisher's-exact test) and hemizygous deletion from n=19 to n=34 (17% to 30%, P=0.002) at recurrence. CDKN2A hemizygous deletions were significantly associated with poor OS at initial diagnosis (P<0.0001, logrank test) and recurrence (P<0.0001), remaining significant in multivariable cox regression model that accounted for age, treatment with radiotherapy and/or alkylating agents, and 1p/19q-codeletion status: HR 2.40 (95%-CI: 1.31-4.37, P=0.004). Validation in independent datasets confirmed increased frequencies of CDKN2A hemizygous deletions in recurrent cases as well as the association between CDKN2A hemizygous deletion and worse OS in IDHmut gliomas. Using the DKFZ DNA methylation profiling dataset we further confirmed that CDKN2A status can be accurately assessed through DNAseq and DNA methylation array profiling. CONCLUSION: CDKN2A hemizygous deletion is associated with significantly worse OS in initial and recurrent IDHmut gliomas. Similar to CDKN2A homozygous deletion, CDKN2A hemizygous deletion is enriched in post-treatment, recurrent IDHmut gliomas, confirming the value of CDKN2A status (re-)assessment in recurrences. Our results highlight the importance of incorporating CDKN2A status in diagnostic workup to inform prognosis and treatment strategies, revealing the previously unrecognized prognostic value of hemizygous CDKN2A deletions.

Obstetrics, Gynecology and Women's Health Services

Andres S, **Shu M**, Kent A, Greenberg D, and Danakas G. Multimodal pain management after robotic-assisted total laparoscopic hysterectomy reduces postoperative opioid use and pain scores (1180). *Gynecol Oncol* 2023; 176:S123-S124. Full Text

Objectives: The standard of care for pain management after laparoscopic hysterectomy is non-specific; however, in light of the ongoing opioid epidemic, a transition to non-opioid pain medication regimens is desired by both physicians and patients. This study aimed to create a non-opioid multimodal pain regimen for women undergoing robotic hysterectomy to minimize postoperative opioid usage. Methods: Forty-nine adult women undergoing robotic-assisted total laparoscopic hysterectomy (RATLH) with a single surgeon at an academic-affiliated community hospital were enrolled in this prospective pilot study with retrospective controls. Full institutional IRB approval was obtained, and this study was registered in National Clinical Trials. In the intervention arm (n = 10, enrolled from November 2020 through May 2022), women received a multimodal pain medication regimen, including gabapentin, acetaminophen, celecoxib, ketorolac, a paracervical block with 0.5% ropivacaine, 0.5% ropivacaine at all robotic port sites and an opioid, such as oxycodone or hydrocodone, if needed. Control arm participants (n = 39, underwent surgery from November 2018 through December 2019) received a postoperative regimen of acetaminophen, ketorolac, ibuprofen, and an opioid, such as oxycodone or hydrocodone. Primary outcomes included total opioid pain medications required between 0 and 3 h (h) and 3-24 h postoperatively in morphine milligram equivalents (MME). Secondary outcomes included pain scores (numerical rating score 1–10), length of stay (LOS) (hours), operative time (minutes), estimated blood loss (EBL), and return to the office or emergency department (ED) due to postoperative pain within two weeks of hospital discharge. Results were analyzed using $\chi 2$ tests, t-tests, and Mann-Whitney U tests. Results: Demographics were similar between the intervention and control groups, with no difference between age, body mass index, and prior surgeries. Intraoperative characteristics were similar when

comparing resected uterine weight, concomitant oophorectomy, and the number of robotic ports utilized. A statistically significant decrease in opioid usage was noted in the intervention group. The intervention group used 62% less MMEs 0-3 h postoperatively (2.0 vs 5.3 mean MME, P < 0.05) and 98% less MMEs 3-24 h postoperatively (0.2 vs 12.3 mean MME, P < 0.05). Pain scores were similar between cases and controls at 0-3 h (3.8 vs 5.1, P = 0.26); however, the scores significantly decreased at 3-24 h (1.8 vs 5.4, P < 0.05) postoperatively. Mean LOS was decreased in the intervention group (12.0 h vs 35.8 h, P < 0.05). There was no difference in EBL, operative time, or return office and ED visits for postoperative pain between groups. Conclusions: A multimodal pain protocol integrated through the perioperative period, using gabapentin, acetaminophen, celecoxib, ketorolac, and local anesthetic injection at port sites and paracervical block, results in decreased opioid use and pain scores throughout the postoperative course.

Orthopedics/Bone and Joint Center

Burdick G, **Fathima B**, **Gaudiani M**, **Wolterink T**, **Haan J**, **Kasto J**, **Kolowich P**, **Muh S**, and **Castle J**. Arthroscopic rotator cuff repair with bioinductive patch achieves equivalent patientreported outcomes at 1 year. *Orthop J Sports Med* 2023; 11(7). Full Text

G. Burdick

Objectives: To compare patient reported outcomes, range of motion (ROM), and complications of patients undergoing arthroscopic rotator cuff repair (RCR) augmented with a bioinductive patch compared to standard repair. Methods: A retrospective review of patients undergoing primary arthroscopic rotator cuff repair with and without bioinductive bovine collagen patch augmentation for supraspinatus/infraspinatus tears from 2016 to 2021 at a single institution was performed. Patients were excluded based on the following criteria: age <18 years, open or mini-open rotator cuff repair, prior surgery of the affected shoulder (except diagnostic arthroscopy), rheumatological disease, active infection, or cancer. Patients who underwent RCR augmented with a collagen patch were matched 1:1 to those undergoing standard rotator cuff repair based on tear thickness and size. The electronic medical record was used to obtain patient demographics, range of motion (ROM), and assess for complications. MRI or ultrasound was used to confirm tear and classify size using the DeOrio and Cofield classification of small (<1cm), medium (1-3cm), large (3-5cm), and massive (>5cm). In addition, Patient Reported Outcome Information System (PROMIS) scores were recorded at preoperative, 6 weeks, 3 months, 6 months, and 1 year postoperative time points. Results: Fifty-four patients underwent RCR with patch augmentation and were matched to 54 controls. No significant differences were found between groups in terms of age (56.7 ± 9.0 patch vs. 59.3 ± 8.5 years control, p=0.12), sex, smoking, diabetes, degenerative vs. traumatic tears (50% vs. 50.9%, p=1.0), partial vs. full thickness (38.9% vs. 25.5%, p=0.2), as well as tear size (p=0.8). ROM in forward flexion (FF) and abduction (ABD) were significantly increased at 1 year compared to controls (FF 162 +/- 22 vs. 148 +/- 26 degrees, p<0.01; ABD 137 +/- 37 vs. 117 +/- 40, p=0.047). No differences were seen for PROMIS- UE, but PROMIS-PI scores were significantly lower in the patch group at 6 months (55.2 +/- 8.0 vs. 61.9 +/- 2.0, p<0.01) and 1 year (56.0 +/- 7.5 vs. 62.1 +/- 3.6, p<.01). The patch group had 7 retears compared to 0 controls (13.0% vs 0%, 2/7 for subscapularis tears not augmented) and 1 biceps tenodesis rupture, with 5 requiring revision surgery. Conclusions: Bioinductive patch augmentation for RCR demonstrated increased ROM, but equivalent physical function after 1 year.

Orthopedics/Bone and Joint Center

Castle J, **Wolternik T**, **Sprys-Tellner T**, **Haan J**, **Gasparro M**, **Lynch T**, and **Gaudiani M**. Analysis of National Hockey League Player Performance After Concussion and Financial Costs Associated with Implementation of an Updated Concussion Protocol: A Retrospective Comparative Study. *Orthop J Sports Med* 2023; 11(7). Full Text

J. Castle

Objectives: Background: An updated National Hockey League (NHL) concussion protocol (NHLCP) was established in the 2016-2017 season to mitigate the negative outcomes of sportrelated concussions. However, few studies on the effects of implementing the NHLCP have been performed. Purpose: To define concussion incidence and investigate differences in NHL player performance after a concussion during periods before and after implementation of the NHLCP and to assess the financial impact on NHL

teams associated with NHLCP implementation. We hypothesized that concussion incidence would increase and player performance would remain the same after NHLCP implementation. Methods: A retrospective review of NHL players who sustained a concussion before (2000-2001 to 2015-2016 seasons) and after (2016-2017 to 2020-2021 seasons) implementation of the NHLCP (pre- NHLCP and post-NHLCP groups). For each group, multiple performance metrics 30 days, 1 season, and 3 seasons before and after concussion were compared for both groups. Return to play, total concussion cost, and association of return to play with cost were investigated with regression analysis. Results: For both groups, no significant differences in standard performance were observed during the 30-day and 1-season time periods before and after concussion. Mean return to play was significantly higher in the pre-NHLCP than in the post-NHLCP group (20.1 vs 15.7 days; P=0.022). Mean adjusted player salary was not different between groups, but mean adjusted replacement player salary was significantly higher in the post-NHLCP group ($744,505 vs $896,942; P= 0.032). Mean cost of time missed did not differ between groups. Mean return to play time significantly decreased over the entire study period 2000-2021 (R2=0.335, P=0.005), and mean return to play time was positively associated with cost (R2=0.215, P=0.030). Conclusions: Concussion incidence did not change after implementation of the updated NHLCP, but players had significantly less missed time from injury after protocol implementation. Changes in player performance 30 days and 1 year before and after concussion injury were not different before and after NHLCP implementation. (Table Presented).

Otolaryngology – Head and Neck Surgery

Ghanem AI, **Gilbert M**, **Keller C**, **Gardner G**, **Mayerhoff R**, and **Siddiqui F**. Definitive and Salvage Radiotherapy Compared to Other Modalities for Laryngeal Carcinoma in Situ. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e583. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): We sought to analyze survival endpoints for laryngeal carcinoma in situ (CIS) undergoing definitive radiotherapy (RT) compared to other modalities. Materials/Methods: Usingour prospectively maintained head and neck cancer database, we identified laryngeal CIS patients treated between 6/2001 and 12/2021. We excluded low-grade dysplasia, CIS with any synchronous invasive squamous cell carcinoma (SCC) within 3 months of the initial CIS biopsy and cases with inadequate follow up. Patients were offered either definitive RT, CO2/KTP laser ablation, photodynamic therapy (PDT) or any sort of therapeutic excision. After first line treatment, follow-up includes visits every 3-6 months with laryngoscopy and biopsies as appropriate. For recurrent CIS beyond 6 months of first line treatment, we reported salvage therapies received and long-term outcomes were reported. Using Kaplan-Meier curves and log-rank test we investigated recurrence free (RFS), progression to invasive SCC free (IFS) and overall (OS) survival across treatment groups. Patients managed with salvage RT were compared to first line RT recipients. Results: Atotal of 85 CIS cases were included: median age 65 years (IQR: 55-74), 73 males (85%) and 70 white (82.4%). 86% had a history of smoking with median pack year of 38 (IQR: 20-55) and 66% had a history of alcohol use. CIS was glottic in most of the cases (90.6%: 66% unilateral, 21% bilateral & 13% involved commissure); with only 9.4% in the supraglottic region. RT was used in 49.4% (n = 42) after biopsy (55%) or surgery (45%) with median dose of 63 Gy/28 fractions, mainly by 3D conformal RT (76%). The remaining 50.6% (n = 43) got therapeutic excision alone (commonly microflap excision) (46.5%), CO2/KTP laser (32.6%) or PDT (20.9%). Demographics and clinicopathological details were non-different between RT and non-RT patients except for Charlson comorbidity index: median 2 (IQR 1-3) in non-RT vs 1 (IQR 0-2) in 1ry RT; p = 0.007. After a median follow-up of 4.8 years (IQR 3.5), 51.8% had recurrent disease, 21.2% progressed to invasive SCC and 9.4% had laryngectomies mainly for invasive SCC after RT. First line RT had improved 2-(83% vs 39%) and 5-(74% vs 22%) year RFS vs non-RT therapies (p<0.001). Nevertheless, 2- and 5-year IFS (89% vs 98% and 80% vs 79%) and OS (92% vs 93% and 81% vs 77%) were non-significant among both (p>0.05 for all). Among non-RT cases with CIS recurrences, 12/35 (34%) had salvage RT. Following RT, salvage RT patients had similar 2- and 5-year RFS (81% vs 83% and 81% vs 74%) and IFS (81% vs 89% and 81% vs 80%) compared to first line RT (p>0.05 for all). All cases with CIS recurrences were salvaged successfully with 100% living with no CIS at latest follow-up. Conclusion: Laryngeal CIS can be treated with a wide range of modalities including 1ry RT which has better recurrence free survival. Nevertheless,

non-RT recurrent CIS can be salvaged successfully with many options including RT with equivalent long-term results.

Otolaryngology – Head and Neck Surgery

Zari H, **Juras A**, **Chen C**, **Veasey K**, **Craig J**, **Carey JL**, and **Cook BC**. Sensitivity and Specificity of Beta-2 Transferrin Gel Electrophoresis With Immunofixation for Evaluating Nasal Cerebrospinal Fluid Leaks. *Clin Chem* 2023; 69:i243-i244. Full Text

H. Zari, Henry Ford Health, Detroit, MI, United States

BACKGROUND: Cerebrospinal fluid (CSF) rhinorrhea usually presents as unilateral clear thin nasal drainage, is caused by a direct communication from the subarachnoid space to the sinonasal cavities and can lead to intracranial infection, pneumocephalus, or death. Diagnosing CSF rhinorrhea can be challenging. While the gold standard for CSF leak confirmation is surgical exploration, testing nasal fluid for beta-2 transferrin (B2Tf) via agarose gel electrophoresis followed by immunofixation (AGEI) remains the initial non-invasive CSF confirmatory test of choice. However, AGEI requires subjective interpretation of immune-stained protein bands. Multiple studies have reported high sensitivity and specificity of B2Tf AGEI (90-100%), but other studies have shown wider ranges from 70-100%. Due to small sample sizes and methodologic differences between studies, comparing results between studies is problematic. The purpose of this study was to assess the sensitivity and specificity of B2Tf AGEI in confirming or excluding CSF rhinorrhea in patients with unilateral clear thin nasal drainage, and to determine the inter-reviewer variability of AGEI interpretation. METHODS: This was a retrospective observational study of patients who had B2Tf AGEI performed on their unilateral clear nasal drainage from 2020 through 2022. A pathologist and four trained medical laboratory scientists conducted visual reviews of archived gels and their results were compared to the documented CSF rhinorrhea status. Results were also compared to the original test results documented in patients' charts. Sensitivity and specificity, and inter-reviewer agreement were assessed for B2Tf AGEI confirming or excluding CSF rhinorrhea. The gold standard for confirming CSF rhinorrhea was surgical exploration. The gold standard for excluding CSF rhinorrhea included either negative surgical exploration or rhinorrhea resolution after medical therapy aimed at treating rhinitis or rhinosinusitis. RESULTS: Sensitivity and specificity varied for the five reviewers and documented test results, with sensitivities ranging from 65.0 to 86.0% (mean ± SD, 73.0 ± 5.7) and specificities from 61.4 to 88.6% (84.1 ± 11.0). The false positive rate was 8.7%, and false negative rate was 13.9%. Sensitivity and specificity for the documented test results ranging from 57.1 to 82.1% (mean ± SD, 72.1, 9.3) and specificities from 75.0 to 97.26% (91.6 ± 9.4). The abilities of the reviewers to reliability identify a CSF leak was moderate, with kappa statistics ranging from 0.313 to 0.646 (weighted average 62.2, 4.0). Two of the four reviewers demonstrated substantial to almost perfect agreement to the expert reviewer, with the other two demonstrating moderate agreement. CONCLUSIONS: B2Tf AGEI demonstrated lower sensitivity and specificity than some previous reports, however this study had a larger sample size and very well-defined clinical standards for CSF and non-CSF rhinorrhea. While false results were present in 9 to 14% of cases, the test is non-invasive, and is helpful in stratifying patients into those more or less likely to have CSF rhinorrhea. There was also substantial inter-reviewer variability, highlighting the challenges of subjective interpretation of this testing modality. Larger prospective studies would be helpful to more accurately determine the diagnostic accuracy of B2Tf AGEI, as well as explore practices to help limit inter-reviewer variability.

Pathology and Laboratory Medicine

Copeland JR, **Guerriero J**, and **Cook BC**. More Timely Patient Care Amidst Healthcare Staffing Shortages, Reducing Blood Specimen Tube Barcode Errors for Continuous Flow in an Automated Laboratory System. *Clin Chem* 2023; 69:i62. Full Text

J.R. Copeland, Henry Ford Health, Detroit, MI, United States

BACKGROUND: The Core Laboratory at Henry Ford Hospital utilizes total laboratory automation to support chemistry, hematology and coagulation analyzers, processing approximately 10 000 specimens daily. Testing and reporting delays can occur when the system encounters a specimen tube barcode error. Specimens will stop moving and causes approximately a 2-minute per error production pause while

the error is resolved. This induces congestion for all other specimens in line behind the error. The seemingly trivial minutes of congestion leads to a domino effect, resulting in reduced line productivity, a temporary limit of testing capacity and prolonged TATs. The laboratory receives specimen tubes with labels generated from over 600 printers. The system encounters 200-250 errors daily associated with barcode read failures of various types. Errors account for an estimated loss of ~320 h of staff productivity per month. METHODS: Automation line error files, manually recorded data from lab staff, observations of automation line errors occurring in real time, data from a printer maintenance blitz and barcode printer service requests were used in root cause analysis. Three progressive Kaizens events were organized in 2022 to induce rapid process change through focused chartering of events and actions. A probing study designed to induce controlled defects and stoppages helped recognize where congestion on the line was occurring. Simulation of barcode application errors allowed an understanding of the impact of label application. Staff and line productivity loss analysis predicted the potential opportunity of error reduction. RESULTS: Fifty-five percent of the barcode errors were caused by improper label application and 45% were poor print quality of the barcode on the label. Of the label application defects, 55% were caused by the label being placed upside-down, of which 34% were caused by the label format used by our Emergency Department. Print quality issues such as faded or pitted printing labels accounted for 45% of errors. The printer preventive maintenance blitz successfully reduced print quality errors by 30%. Converting to a more robust printer in two high-volume areas resulted in zero print quality errors over three months. Barcode label format changes were 100% effective in eliminating upside-down as a root cause. CONCLUSION: Elimination of barcode line errors can recover 2.0 FTEs in three divisions per month, while increasing automation line productivity and a cost approximately $150 000 per year in work delays and unnecessary rework. The Kaizen approach to problem-solving allowed for rapid brainstorming amongst multiple teams. Altered label format allowed built-in engineering control by mistake-proofing the process and making label positioning irrelevant. Identification of areas where high volumes of labels were being printed and replacing those printers with more robust printers reduced service calls and eliminated printer causal factors since these printers require less hands-on maintenance. Finally, instituting preventative label printer maintenance and total quality management reduces or prevents errors associated with print quality. Sustaining mechanisms include continued real-time data documentation and communication of defects, collaboration with colleagues in Nursing for further root cause analysis of barcode application defects.

Pathology and Laboratory Medicine

Ghanem AI, **Gilbert M**, **Keller C**, **Gardner G**, **Mayerhoff R**, and **Siddiqui F**. Definitive and Salvage Radiotherapy Compared to Other Modalities for Laryngeal Carcinoma in Situ. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e583. Full Text

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clinicopathological details were non-different between RT and non-RT patients except for Charlson comorbidity index: median 2 (IQR 1-3) in non-RT vs 1 (IQR 0-2) in 1ry RT; p = 0.007. After a median follow-up of 4.8 years (IQR 3.5), 51.8% had recurrent disease, 21.2% progressed to invasive SCC and 9.4% had laryngectomies mainly for invasive SCC after RT. First line RT had improved 2-(83% vs 39%) and 5-(74% vs 22%) year RFS vs non-RT therapies (p<0.001). Nevertheless, 2- and 5-year IFS (89% vs 98% and 80% vs 79%) and OS (92% vs 93% and 81% vs 77%) were non-significant among both (p>0.05 for all). Among non-RT cases with CIS recurrences, 12/35 (34%) had salvage RT. Following RT, salvage RT patients had similar 2- and 5-year RFS (81% vs 83% and 81% vs 74%) and IFS (81% vs 89% and 81% vs 80%) compared to first line RT (p>0.05 for all). All cases with CIS recurrences were salvaged successfully with 100% living with no CIS at latest follow-up. Conclusion: Laryngeal CIS can be treated with a wide range of modalities including 1ry RT which has better recurrence free survival. Nevertheless, non-RT recurrent CIS can be salvaged successfully with many options including RT with equivalent long-term results.

Pathology and Laboratory Medicine

Nassereddine H, **Cook B**, **Klausner H**, **Gunaga S**, **Morton T**, **Tuttle J**, **Mohammed H**, **Husain A**, **McCord J**, and **Miller J**. 208 Diagnostic Performance of Cardiac Stress Testing Following Exclusion of Acute Myocardial Infarction With a 0/1-Hour, High-Sensitivity Cardiac Troponin Protocol. *Ann Emerg Med* 2023; 82(4):S94-S95. Full Text

Background: Rapid exclusion of acute myocardial infarction (AMI) is critical for patients presenting to emergency departments (EDs) with chest pain or other anginal equivalents. High-sensitivity cardiac troponin (hs-cTn) protocols have been widely adopted in the United States for this purpose. These protocols allow for early identification and exclusion of patients with AMI using a 0 and 1-hour hs-cTn measurement. However, little is known about the use of cardiac stress testing in patients who ruled-out for AMI within 1 hour with very low hs-cTn values. This study analyzed the diagnostic performance of cardiac stress tests in this population. Methods: We performed a secondary analysis of the RACE-IT trial, a stepped-wedge cluster randomized trial performed across 9 EDs in a large metropolitan health system from July 2020 through March 2021. The eligibility criteria for the trial mirrored the real-world use of hs-cTn testing, including both patients complaining of chest pain and/or other anginal equivalents. All adults with a hs-cTnI and electrocardiogram (ECG) completed in the ED were enrolled, while patients with ST-segment elevation AMI, trauma, or pregnancy were excluded. In the interventional arm of the trial, AMI 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. The trial followed all patients through 30 days to assess for AMI or death and captured all cardiac testing. We compared stress testing results to invasive coronary imaging with or without revascularization. Results: 10,444 study patients (43.61%) ruled out for AMI in the ED within 1 hour and were included in this analysis. There were 320 (3.0%) patients who had a stress test within 30 days, with few ischemic findings (25, 0.24%) or revascularization procedures (5, 0.05%). The positive predictive value of stress testing in this population to identify the need for revascularization was 10.1% (95% CI 2.8% - 29.4%). Table 1 displays the proportion of ischemic stress tests and overall test performance in this population. The rate of 30-day death or AMI was low (17, 0.20%) among those discharged from the ED or placed in observation (n=8,553). Conclusions: Our study highlights the infrequent use and low diagnostic yield of stress testing in patients who have been ruled out for AMI within 1 hour using an accelerated hs-cTn protocol in the ED. [Formula presented] Yes, authors have interests to disclose Disclosure: Beckman Coulter Consultant/Advisor Beckman Coulter Disclosure: Beckman Coulter Grant Support Beckman Coulter Disclosure: Beckman Coulter Grant Support Beckman Coulter

Pathology and Laboratory Medicine

Stezar L, **Elhady R**, **Zari H**, **Winston-McPherson G**, **Carey J**, and **Cook B**. Reference Intervals for Serum Free Light Chains when Ruling out Monoclonal Gammopathies in Subjects with Normal or Minimally Variant Electrophoretic Findings. *Clin Chem* 2023; 69:i163-i164. Full Text

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

BACKGROUND: Serum free light chains (SFLC) analysis for detection and initial diagnosis of monoclonal gammopathies (MC) is a critical tool in the comprehensive assessment of risk and in management of

established disease. Our reference intervals (RIs) for SFLC were based on the seminal report by Katzmann. Recent literature indicates with current analytic platforms and reagent formulations, significantly different RIs might be more appropriate. METHODS: The study sought to establish RIs for the population typically evaluated for possible MC and was expected to include acute/chronic inflammation, polyclonal elevations of gamma-globulins, hypogammaglobulinemia and chronic liver disease. The reference population inclusion criteria were: serum submitted for a serum monoclonal protein evaluation and SPE (±IFIX); lacked any direct or indirect evidence of a MC; normal or minimally variant SPE pattern; no prior history of leukemia, lymphoma, myeloma or MGUS; normal eGFR (CKD1-2 or >60 mL/min). CKD-EPI calculation was based only on IDMS-standardized creatinine measurements without race modifiers. Of the 202 cases encountered over 15 days, 135 met the inclusion criteria. Specimens were tested using a Binding Site Optilite system. RESULTS: The mean subject age was 62 years. There was a mild female predominance (80 females vs 55 males) and females tended to be younger than males (58 vs 68 years). Two approaches used to establish the central 95% interval (mean ± 2SD and ranked-order analysis for 2.5 and 97.5 percentiles) yielded similar limits for SFLC and SFLC ratio (Table). These results agree well with recent reports from others. CONCLUSION: As international guideline prognostic thresholds for SFLCR in plasma cell neoplasia are based upon the original Binding Site free light chain analysis, we will maintain those RIs, adding an appended comment to all SFLC reports to indicate for screening purposes, the HFH laboratory-established SFLC ratio interval is 0.8-1.9:1.

Pathology and Laboratory Medicine

Zari H, **Juras A**, **Chen C**, **Veasey K**, **Craig J**, **Carey JL**, and **Cook BC**. Sensitivity and Specificity of Beta-2 Transferrin Gel Electrophoresis With Immunofixation for Evaluating Nasal Cerebrospinal Fluid Leaks. *Clin Chem* 2023; 69:i243-i244. Full Text

H. Zari, Henry Ford Health, Detroit, MI, United States

BACKGROUND: Cerebrospinal fluid (CSF) rhinorrhea usually presents as unilateral clear thin nasal drainage, is caused by a direct communication from the subarachnoid space to the sinonasal cavities and can lead to intracranial infection, pneumocephalus, or death. Diagnosing CSF rhinorrhea can be challenging. While the gold standard for CSF leak confirmation is surgical exploration, testing nasal fluid for beta-2 transferrin (B2Tf) via agarose gel electrophoresis followed by immunofixation (AGEI) remains the initial non-invasive CSF confirmatory test of choice. However, AGEI requires subjective interpretation of immune-stained protein bands. Multiple studies have reported high sensitivity and specificity of B2Tf AGEI (90-100%), but other studies have shown wider ranges from 70-100%. Due to small sample sizes and methodologic differences between studies, comparing results between studies is problematic. The purpose of this study was to assess the sensitivity and specificity of B2Tf AGEI in confirming or excluding CSF rhinorrhea in patients with unilateral clear thin nasal drainage, and to determine the inter-reviewer variability of AGEI interpretation. METHODS: This was a retrospective observational study of patients who had B2Tf AGEI performed on their unilateral clear nasal drainage from 2020 through 2022. A pathologist and four trained medical laboratory scientists conducted visual reviews of archived gels and their results were compared to the documented CSF rhinorrhea status. Results were also compared to the original test results documented in patients' charts. Sensitivity and specificity, and inter-reviewer agreement were assessed for B2Tf AGEI confirming or excluding CSF rhinorrhea. The gold standard for confirming CSF rhinorrhea was surgical exploration. The gold standard for excluding CSF rhinorrhea included either negative surgical exploration or rhinorrhea resolution after medical therapy aimed at treating rhinitis or rhinosinusitis. RESULTS: Sensitivity and specificity varied for the five reviewers and documented test results, with sensitivities ranging from 65.0 to 86.0% (mean ± SD, 73.0 ± 5.7) and specificities from 61.4 to 88.6% (84.1 ± 11.0). The false positive rate was 8.7%, and false negative rate was 13.9%. Sensitivity and specificity for the documented test results ranging from 57.1 to 82.1% (mean ± SD, 72.1, 9.3) and specificities from 75.0 to 97.26% (91.6 ± 9.4). The abilities of the reviewers to reliability identify a CSF leak was moderate, with kappa statistics ranging from 0.313 to 0.646 (weighted average 62.2, 4.0). Two of the four reviewers demonstrated substantial to almost perfect agreement to the expert reviewer, with the other two demonstrating moderate agreement. CONCLUSIONS: B2Tf AGEI demonstrated lower sensitivity and specificity than some previous reports, however this study had a larger sample size and very well-defined clinical standards for CSF and non-CSF rhinorrhea. While false

results were present in 9 to 14% of cases, the test is non-invasive, and is helpful in stratifying patients into those more or less likely to have CSF rhinorrhea. There was also substantial inter-reviewer variability, highlighting the challenges of subjective interpretation of this testing modality. Larger prospective studies would be helpful to more accurately determine the diagnostic accuracy of B2Tf AGEI, as well as explore practices to help limit inter-reviewer variability.

Public Health Sciences

Bhatnagar AR, **Ghanem AI**, **Li P**, and **Elshaikh MA**. The Prognostic Impact of Substantial Lymphovascular Space Invasion in Women with FIGO Stage I Uterine Endometrioid Carcinoma with Pathologically Negative Nodal Evaluation. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S132. Full Text

A.R. Bhatnagar, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Substantiallymphovascular space invasion (LVSI) is an important predictor of lymph node involvement in women with endometrial carcinoma. However, its prognostic significance in women with stage I who had pathologic negative nodal evaluation (PNNE) was not fully evaluated. We aimed to evaluate the prognostic significance of substantial LVSI on recurrence-free (RFS), disease-specific (DSS) and overall survival (OS) in women with FIGO stage I uterine endometrioid adenocarcinoma (EC). Materials/Methods: Our uterine cancer database was queried for women with stage I EC who had a hysterectomy and PNNE at our institution between 1/1990 and 11/2022. Postoperatively, patients were managed with observation or adjuvant radiation therapy (RT) with pelvic external beam RT or vaginal cuff brachytherapy (VB). Women with synchronous malignancies and those who received adjuvant chemotherapy were excluded. Pathologic specimens were retrieved and LVSI was quantified by Gynecology pathologists (none, focal or substantial). Patients' demographics, surgical and pathologic variables were analyzed. Predictors of RFS, DSS and OS using univariate (UVA) and multivariate analysis (MVA) were studied. Results: One thousand fifty-two patients were identified with a median age of 63 years and median follow-up of 9.7 years. Median number of examined lymph node (LN) were 9 (range 4-18). 907 patients (86.2%) had no LVSI, 87 (8.3%) had focal and 58 (5.5%) had substantial LVSI. In patients with focal LVSI, 32.2% received pelvic RT and 39.1% received VB. In patients with substantial LVSI, 20.7% received pelvic RT and 58.6% received VB.Recurrence was diagnosed in 86 patients (8.2%). While any LVSI was associated with tumor recurrence, there was no significant difference for the site of initial recurrence between patients with focal vs. substantial LVSI. 5-year RFS was 93.3% (95% CI 91.5-95.1), 76.8% (67.2-87.7) and 79.1% (67.6-95.3) for no, focal and substantial LVSI. The 5-year DSS was 97.6% (96.5-98.7), 83.5% (75-93.1), and 90% (81.8-99.9); and 5-year OS was 90.7% (88.7-92.8), 72.8% (62.9-84.2) and 86% (76.2-97.2), respectively. Independent predictors of worse 5-year RFS and DSS include any LVSI, age > 60 years, higher tumor grade. Independent predictors of worse 5- year OS include any LVSI, age > 60, high comorbidity burden, and higher tumor grade. Conclusion: Our large data suggest similar recurrence-free, disease specific and OS for women with stage I uterine endometrioid carcinoma who had pathologically negative nodal evaluation and substantial or focal LVSI. There was no significant difference for the site of initial recurrence between patients with focal or substantial LVSI. Multi-institutional pooled analyses may be needed to validate our results.

Public Health Sciences

Chai W, and **Tao MH**. Associations of Serum Lipid-Soluble Micronutrients With Hepatic Steatosis Among Adults in the United States. *Curr Dev Nutr* 2023; 7. Full Text

Objectives: Research suggests lipid-soluble micronutrients may be beneficial to chronic disease treatment and prevention. This study examined associations of serum lipid-soluble micronutrients (α- and γ-tocopherols, 25-hydroxy-vitamin D [25(OH) D], retinol, and carotenoids) and hepatic steatosis among adults in the United States utilizing the 2017–2018 National Health and Nutrition Examination Survey. Methods: The analysis included 4779 adults aged ≥20 years who completed the transient elastography examination. A threshold value of 302 dB/m was selected to identify participants with steatosis (S > S1, 5% steatosis). Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated using logistic regressions adjusting for relevant covariates. Results: The age-adjusted prevalence of steatosis was

28.0%. Higher serum α-tocopherol (highest vs. lowest quartile: OR=1.63, 95%CI=1.07–2.48, Ptrend=0.02) and γ-tocopherol (highest vs. lowest quartile: OR=2.42, 95%CI=1.80–3.24, Ptrend <0.0001) levels were associated with increased odds of steatosis. Higher serum 25(OH)D levels were associated with reduced odds of steatosis (highest vs. lowest quartile: OR=0.53, 95%CI=0.38–0.75, Ptrend=0.002). Inverse associations with steatosis were also observed for carotenoids such as α-carotene (Ptrend<0.0001), β-carotene (Ptrend<0.0001), and α-cryptoxanthin (Ptrend=0.025) in the serum. Conclusions: Our results suggest potential protective associations of serum lipid-soluble micronutrients such as 25(OH)D and carotenoids with steatosis. The positive associations between tocopherols and steatosis may indicate inflammation associated with steatosis as it was reported γ-tocopherol rises in response to inflammation. Funding Sources: N/A.

Public Health Sciences

Koerber S, **Huynh D**, **Farrington S**, **Springer K**, **Patel M**, and **Manteuffel J**. 190 Health Disparities in Emergency Department Administration of Buprenorphine for Treatment of Opioid Use Disorder. *Ann Emerg Med* 2023; 82(4):S87. Full Text

Objectives: Buprenorphine use in the emergency department contributes to decreased frequency of opioid overdose, reduced emergency room visits, and decreased associated health care costs. However, racial and ethnic disparities in buprenorphine prescription contribute to fewer prescriptions of buprenorphine for Black and Hispanic patients when compared to White patients. The objectives of our study were to 1) examine whether buprenorphine administration in an urban emergency department varies by patient demographics including race and ethnicity; and 2) examine other structural determinants of health to expand upon why these differences may exist. Methods: This is a retrospective analysis of electronic health records from patients who presented to the emergency room at Henry Ford Hospital between January 1, 2021, and December 31, 2021. Included patients were 18 years of age or older and screened positive for opioid use disorder (OUD) in the emergency room at Henry Ford Hospital. Area deprivation index (ADI) was determined based on patients' documented street addresses to serve as a proxy for measuring income, education, employment, and housing quality. Univariate and multivariate analyses were conducted using SAS 9.4. Statistical significance was set at p<0.05. The institutional IRB approved this study. Results: There were 1082 patients included in our final analysis. Patients had a mean age of 48.1 years and were largely male (n=721, 66.8%). The majority of patients were Black (n=682, 63.0%), had Medicaid insurance (n=667, 61.6%), and were from the most disadvantaged ADI group (n=624, 62.7%). Patients that received buprenorphine had on average longer length of stay (LOS) with a mean of 844.2 minutes (p=0.016). Patients who identified as Black or Other Race were less likely to receive buprenorphine, and patients who identified as White were more likely to receive buprenorphine (p=0.021). After adjusting for age, LOS, sex, insurance type, and ADI, Black patients were less likely to receive buprenorphine as compared to White patients (p=0.0237). There were no significant differences found when comparing ADI among those who received buprenorphine. There were no differences among demographics for patients receiving buprenorphine for first-time induction compared to those receiving a maintenance dose. Conclusions: Our study demonstrates that the majority of patients at risk of opioid use disorder in our hospital sample were patients who were Black, male, had Medicaid insurance, and were from the most disadvantaged communities. However, White patients were still more likely to receive buprenorphine in our ED for treatment of OUD after controlling for other structural determinants of health. Limitations include the inherent inability of electronic medical records to accurately document a patient's identified race and ethnicity. Future studies should include prospective analyses that better capture the very complex relationships of unconscious bias in medicine and structural determinants of health. Furthermore, we can utilize multifaceted education and training for ED providers and advocate for systemic changes at the hospital and policy level. Equitable administration of buprenorphine in the ED can contribute to decreased health disparities in the treatment of OUD.

Public Health Sciences

Mittal A, **Shukr BA**, **Behrendt R**, **Williams C**, **Piatak S**, **Craft S**, and **Willens D**. DESIGNING IMPLEMENTATION OF A SYSTEMWIDE EVIDENCE- BASED HEART FAILURE CARE PATHWAY. *J Gen Intern Med* 2023; 38:S658-S659. Full Text

A. Mittal, Internal Medicine, Henry Ford Hospital, Detroit, MI, United States

STATEMENT OF PROBLEM/QUESTION: After multistakeholder design of an inpatient, outpatient, and home heart failure (HF) care pathway, our regional health system needed implementation plans to drive uptake of key HF care steps. DESCRIPTION OF PROGRAM/INTERVENTION: Implementation plans are based on the AHRQ Learning Health System (LHS) framework and the Influencer change framework (Grenny, et al.). The LHS framework drives iterative care improvements via evidence application and ongoing learning from clinical performance data. The Influencer framework guides interventions that improve personal, structural, and social abilities and motivations to improve. The HF pathway included evidence-based interventions such as prescribing guideline directed medical therapy (GDMT), using universal healthliteracy appropriate patient education materials, and referring appropriate patients to cardiology, home-based care, or palliative care. Our implementation design team consisted of clinician-educators, residents, nurses, data analysts, an instructional designer, and a management engineer. Interventions include: 1) Driving buy-in by redesigning the pathway with facilitated teams of 100 clinicians and leaders from all disciplines and care venues; 2) Improving HF knowledge via education modules on our learning management system; 3) Audit and feedback of pathway uptake metrics; and 4) EMR tools to facilitate ordering of pathway steps. Education objectives are to update clinician knowledge on new HF nomenclature, GDMT, and descriptions of key steps in the HF care pathway. Rollout of these interventions is currently in progress. MEASURES OF SUCCESS: Clinician and executive qualitative feedback on content, usability, and design via unstructured interviews and our system wide HF governance structure. We will use the RE-AIM framework for evaluation of implementation. FINDINGS TO DATE: 1. The pathway design process engaged teams over 3 years despite competing priorities from COVID. 2. System wide education requires addressing differing resources across care settings and payors. 3. Defining which patients have HF by EMR data allowed real-time identification in hospitals, but challenges remain for outpatient and ED settings. 4. Specialty and location-based governance may be siloed, causing diffusion of ownership of implementation. KEY LESSONS FOR DISSEMINATION: Implementation plan design for the HF care pathway was successful due to: 1. Use of the AHRQ LHS and Influencer change frameworks facilitated more in-depth planning for spread and sustainability of clinical change. 2. Multi-stakeholder teams for sustained engagement across care siloes. 3. Executive sponsorship for system integration and local accountability. 4. Management engineer to coordinate multiple, diverse teams. 5. Instructional designer for effectiveness of education.

Public Health Sciences

Tao M, and Chai W. Association of Magnesium Status With Hepatic Fibrosis Differs by Race/Ethnicity in Adults: National Health and Nutrition Examination Survey (NHANES) 2017 to 2020. *Curr Dev Nutr* 2023; 7. Full Text

Objectives: Magnesium plays an important role in multiple metabolic disorders including diabetes, and is linked with the liver function. There are disparities in hepatic fibrosis risk based on sex and race/ethnicity in the US population. However, very few studies have examined whether the association between magnesium intake and liver fibrosis is similar across different racial/ethnic groups or between women and men. Methods: Utilizing data from the NHANES 2017 to March 2020, 6,972 participants aged 20 years and older who completed the transient elastography examination were analyzed. The median liver stiffness of 8.2 kPa was used to identify subjects with significant fibrosis (≥F2). Intakes of magnesium and calcium were determined from 24-hour dietary recalls and supplement interviews. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Interaction between magnesium intake and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), and between magnesium intake and gender, were examined, followed by stratified analyses. Results: The age-adjusted prevalence of significant fibrosis (≥F2) was 9.92% for non-Hispanic Whites, 9.02% for non- Hispanic Blacks, 10.52% for Hispanics, 6.57% for non-Hispanic Asians, and 19.15% for Others. After adjustment for confounders, total energy and calcium intake, a higher total magnesium intake was associated with decreased odds of significant fibrosis (OR: 0.89; 95% CI: 0.79, 1.00) comparing highest vs. lowest tertile (ptrend=0.04). Among non-Hispanic Blacks, total magnesium intake was associated with lower odds of significant fibrosis in males but not in females (p-interaction<0.01). The inverse association between total magnesium intake and significant fibrosis was found in female non-Hispanic Whites (p-interaction= 0.09). Conclusions: We found that higher magnesium intake was associated with reduced

risk of significant fibrosis in adults, and this inverse association might be dependent on gender and race/ethnicity. Further studies are needed to confirm the findings. Funding Sources: No.

Pulmonary and Critical Care Medicine

Nguyen CO, **Gregerson S**, **Shams S**, **Buckley J**, and **McBride P**. A CASE OF BACLOFEN ENCEPHALOPATHY IN RENAL INSUFFICIENCY. *J Gen Intern Med* 2023; 38:S369-S370. Full Text

C.O. Nguyen, Wayne State University, School of Medicine, Detroit, MI, United States

CASE: A 64-year-old woman with a history of type 2 diabetes on long-term insulin complicated by gastroparesis, essential hypertension, and chronic kidney disease G5/A3 not on hemodialysis presented to the pain clinic 2 weeks prior to presentation for polyneuropathy and muscle spasms. She was prescribed gabapentin 100 mg three times daily and baclofen 5 mg 1-2 tablets three times daily. Two weeks after initiating baclofen, our patient fell at her home and was seen by family with bilateral shaking of upper extremities. Per family, the patient was confused but denied hitting her head or losing consciousness. She was brought to the Emergency Department for suspicion of stroke. The patient presented disoriented, lethargic and non-verbal with no focal deficits. Her presenting blood pressure was 215/98. She was admitted to the medical intensive care unit for hypertensive emergency with acute encephalopathy requiring continuous intravenous antihypertensive medication. Her physical exam demonstrated global encephalopathy but no focal neurological deficit. Her labs were significant for creatinine 3.96 (baseline 3.2) µmol/l. A brain computerized tomography (CT) without IV contrast showed stable chronic bilateral encephalomalacia in the cerebellar hemispheres with no acute intracranial abnormalities. Given her acute kidney injury superimposed on chronic kidney disease and persistent confusion despite resolution of hypertensive emergency, baclofen-induced encephalopathy was diagnosed. The patient underwent urgent hemodialysis with complete resolution of encephalopathy after the first 3.5h session. The patient underwent a second 4h hemodialysis session and was discharged 48 hours later with baseline mentation. IMPACT/DISCUSSION: Encephalopathy is a broad differential diagnosis including toxometabolic, infectious, traumatic, environmental and pharmacologic etiologies. Baclofen is a GABA agonist and acts through inhibition of pre-synaptic motor neurons to teat spasticity, pain, muscular rigidity, and spasms. As baclofen is primarily excreted by the kidneys, most cases of baclofen toxicity have been reported in dialysisdependent patients, usually 2-3 days to 6 weeks following ingestion of the drug. Intoxication signs and symptoms include seizures, autonomic disturbances, respiratory depression, and altered consciousness CONCLUSION: In patients with severe chronic kidney disease, baclofen should be avoided if possible. If baclofen cannot be avoided, it is important to initiate at low, renally-adjusted dosages. If toxicity is suspected, hemodialysis is an appropriate treatment to reduce clearance time and alleviate clinical symptoms.

Radiation Oncology

Bayley C, Quirk S, Braun J, Sun L, Smith W, Quon HC, **Thind K**, and Martell K. Erectile Dysfunction Pharmacotherapy Utilization after 60Gy in 20 Fractions Volumetric Modulated Arc Therapy to the Prostate. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e367. Full Text

C. Bayley, Department of Oncology, Division of Radiation Oncology, Tom Baker Cancer Center, University of Calgary, Calgary, AB, Canada

Purpose/Objective(s): To determine which factors predict for worsening erectile function after highly conformal, modestly hypofractionated radiotherapy to the prostate. Materials/Methods: All patients who received 60Gy in 20 fractions, volumetric modulated arc therapy to the prostate across 4 centers over 9 years were included in this study. The provincial electronic medical record was interrogated to identify any new prescriptions for erectile dysfunction (ED) medication, any change in prescription of ED medication or any permanent discontinuance of ED medication persisting beyond 6 months post completion of any androgen deprivation therapy. The penile bulb, penile crux and penile shaft structures were retrospectively contoured. A Youden receiver-operator-curve analysis, logistic regression, and neural network based interpretable machine learning analysis were then used to determine dependencies between worsening ED and clinical factors including mean doses to these structures. Results: Two-hundred-twelve patients with median (inter-quartile-range) follow-up of 3.6 (3.2-4.4) years were identified.

Median age was 72 (67-76) years. 104 (49%) patients received androgen deprivation therapy. Prior to treatment, 52 (25%) patients were on ED medication: 20 (9%) on sildenafil, 28 (13%) on tadalafil and 4 (8%) on vardenafil. Median PTV volume was 158.9 (129.8-192.1) cc. Median penile bulb, penile crux and penile shaft volumes were 4.7 (3.6-6.2) cc, 6.5 (5.1-8.5) cc and 93.3 (80.6-106.2) cc, respectively. PTV V95 was 99.8 (99.5-99.9)%. Mean doses to penile bulb, penile crux and penile shaft were 2094.8 (1306.2-3036.3) cGy, 2094.8 (1306.2-3036.3) cGy and 444.4 (313.2-650.5), respectively. Fifty-nine (28%) patients had a worsening of ED after treatment: 25 (12%) started a new ED medication, 6 (3%) had a prescription change and 28 (13%) stopped ED medication. On univariate analyses pretreatment use of ED medication predicted for worsening ED: odds ratio (OR) yes vs no: 10.2 (5.0 – 20.8; p<0.001). A trend towards mean dose to penile bulb [OR ≤2343.9 vs >2343.9: 1.7 (0.9-3.2; p = 0.08)] predicting for worsening ED was observed. Mean doses to penile crux [OR <1725.8 vs > 1725.8: 2.6 (1.3-5.2; p = 0.005)] and penile shaft [OR ≤344.9 vs >344.9: 5.2 (2.2-12.2; p<0.001)] predicted for worsening ED. Use of androgen deprivation therapy, and age at time of radiotherapy were not predictive of worsening ED. On multivariate analysis, only mean dose to penile shaft [OR ≤344.9 vs >344.9: 6.3 (1.9-20.3; p = 0.002)] and pretreatment use of ED medication [OR yes vs no: 11.1 (5.3-23.2; p<0.001)] predicted for worsening ED. A neural network analysis suggested that penile shaft mean dose and pre-treatment ED medication use are the most important factors in predicting worsening ED. Conclusion: In this limited analysis, pre-treatment use of ED medication and mean dose to penile shaft predicted for worsening ED after treatment with modestly hypofractionated radiotherapy for prostate cancer.

Radiation Oncology

Bhatnagar AR, **Ghanem AI**, **Li P**, and **Elshaikh MA**. The Prognostic Impact of Substantial Lymphovascular Space Invasion in Women with FIGO Stage I Uterine Endometrioid Carcinoma with Pathologically Negative Nodal Evaluation. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S132. Full Text

A.R. Bhatnagar, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Substantiallymphovascular space invasion (LVSI) is an important predictor of lymph node involvement in women with endometrial carcinoma. However, its prognostic significance in women with stage I who had pathologic negative nodal evaluation (PNNE) was not fully evaluated. We aimed to evaluate the prognostic significance of substantial LVSI on recurrence-free (RFS), disease-specific (DSS) and overall survival (OS) in women with FIGO stage I uterine endometrioid adenocarcinoma (EC). Materials/Methods: Our uterine cancer database was queried for women with stage I EC who had a hysterectomy and PNNE at our institution between 1/1990 and 11/2022. Postoperatively, patients were managed with observation or adjuvant radiation therapy (RT) with pelvic external beam RT or vaginal cuff brachytherapy (VB). Women with synchronous malignancies and those who received adjuvant chemotherapy were excluded. Pathologic specimens were retrieved and LVSI was quantified by Gynecology pathologists (none, focal or substantial). Patients' demographics, surgical and pathologic variables were analyzed. Predictors of RFS, DSS and OS using univariate (UVA) and multivariate analysis (MVA) were studied. Results: One thousand fifty-two patients were identified with a median age of 63 years and median follow-up of 9.7 years. Median number of examined lymph node (LN) were 9 (range 4-18). 907 patients (86.2%) had no LVSI, 87 (8.3%) had focal and 58 (5.5%) had substantial LVSI. In patients with focal LVSI, 32.2% received pelvic RT and 39.1% received VB. In patients with substantial LVSI, 20.7% received pelvic RT and 58.6% received VB.Recurrence was diagnosed in 86 patients (8.2%). While any LVSI was associated with tumor recurrence, there was no significant difference for the site of initial recurrence between patients with focal vs. substantial LVSI. 5-year RFS was 93.3% (95% CI 91.5-95.1), 76.8% (67.2-87.7) and 79.1% (67.6-95.3) for no, focal and substantial LVSI. The 5-year DSS was 97.6% (96.5-98.7), 83.5% (75-93.1), and 90% (81.8-99.9); and 5-year OS was 90.7% (88.7-92.8), 72.8% (62.9-84.2) and 86% (76.2-97.2), respectively. Independent predictors of worse 5-year RFS and DSS include any LVSI, age > 60 years, higher tumor grade. Independent predictors of worse 5- year OS include any LVSI, age > 60, high comorbidity burden, and higher tumor grade. Conclusion: Our large data suggest similar recurrence-free, disease specific and OS for women with stage I uterine endometrioid carcinoma who had pathologically negative nodal evaluation and substantial or focal LVSI. There was no significant difference for the site of initial recurrence between

patients with focal or substantial LVSI. Multi-institutional pooled analyses may be needed to validate our results.

Radiation Oncology
Bruner DW, Karrison TG, Pollack A, Michalski JM, Balogh A, Rodrigues G, Horwitz EM, Faria S, Camarata AS, Lee RJ, Lukka H, Zelefsky MJ, Seiferheld W, Sandler HM, and **Movsas B**. Quality of Life Results of Addition of Androgen Deprivation Therapy and Pelvic Lymph Node Treatment to Prostate Bed Salvage Radiotherapy: NRG Oncology/RTOG 0534 SPPORT. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S24. Full Text

D.W. Bruner, Emory University, Atlanta, GA, United States

Purpose/Objective(s): Report the quality of life (QOL) analysis of the SPPORT trial of men with a detectable prostate specific antigen (PSA) after prostatectomy for prostate cancer randomized to (Arm 1) salvage prostate bed radiotherapy (PBRT), (Arm 2) 4-6 months of short-term androgen deprivation therapy (STADT) + PBRT, and (Arm 3) pelvic lymph node radiotherapy (PLNRT) + STADT + PBRT. Primary analysis established a benefit of adding PLNRT and STADT to PBRT. There was higher short term but no statistically significant difference in long term adverse events with the exception of blood or bone marrow events. Materials/Methods: QOL endpoints were assessed at baseline, 6 weeks after RT start, 1 and 5 years, including Expanded Prostate Cancer Index Composite (EPIC) (bowel, urinary, sexual, and hormonal domains), Hopkins Symptom Checklist (HSCL-25) (depressive symptoms), and the EuroQol (EQ-5D) (health state weights used in quality adjusted life years (QALYs). In addition to statistical significance, differences in scores were assessed using 0.5 standard deviation (SD) as the criterion for clinical importance. Difference among arms was assessed using pairwise t-tests, Fisher's exact test, and mixed effects regression modeling. To control for multiplicity, the p-value required for statistical significance is $p<0.025$. Results: Six hundred forty-four patients consented to QOL, about 210 on each arm. Baseline characteristics were not significantly different among arms: 81% were white and 54% <65 years. For EPIC, bowel domain scores decreased at 6 weeks post-RT then increased by years 1 and 5, although not to baseline levels. One clinically significant difference in bowel scores was Arm 3 vs. Arm 1 at 6 weeks. For the urinary domain, scores decreased at 6 weeks post-RT and remained below baseline at 1 and 5 years, but there were no significant differences among arms. For the sexual domain, there were statistically significant differences between arms at 6 weeks and 1 year with patients receiving STADT exhibiting poorer sexual QOL scores. By year 5 the differences were no longer significant. A similar pattern was seen for the hormonal domain. For HSCL-25, differences at 6 weeks were statistically but not clinically significant, and there were no significant differences at the later time points. Comparisons of QALYs for overall survival over an 8-year horizon showed no significant group differences, with a mean of about 7.8 in each arm. Regarding freedom from progression, QALY means were 5.7, 6.5, and 7.4 years for Arms 1, 2, and 3, respectively, with a significant difference between Arms 3 and 1 ($p = <.001$) favoring the more intensive treatment. Conclusion: While QOL generally declined among all arms at 6 weeks post RT, there were no clinically significant differences in QOL among arms at 5 years. QALYs for freedom from progression favored STADT + PLNRT + PBRT for salvage treatment of prostate cancer.

Radiation Oncology
Chapman D, **Parikh PJ**, **Dolan JL**, **Cunningham JM**, **Czarnecki E**, **Elshaikh MA**, **Dragovic J**, **Movsas B**, and **Feldman AM**. Does Stereotactic Online Adaptive MRgRT to the Prostate Preclude the Need for Rectal Spacer. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e370. Full Text

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Purpose/Objective(s): Historical prospective trials have shown that hydrogel rectal spacers can be very effective at decreasing rectal wall dose, and in turn rectal toxicity, in patients undergoing curative intent fractionated courses of radiotherapy for prostate cancer. However, in the modern era of stereotactic online adaptive MR guided radiation (MRgRT), it's not yet determined if rectal spacers improve the potential daily need for plan adaptation. Materials/Methods: A prospective database of MRgRT patients were queried for intact prostate cancer patients who received stereotactic online adaptive MR guided

radiation. Patients were reviewed for the presence of a hydrogel rectal spacer present on the planning images. The number of adaptive fractions as well as the organs at risk out of tolerance were noted for each patient. Comparisons between number of fractions adapted as well as the number of fractions adapted for rectal constraints, were noted. For each case within this patient group that required plan adaptation, pre-specified dose constraints were finally met prior to treatment delivery. Results: A total of 27 patients were treated with stereotactic online adaptive MRgRT from 2020 to 2022. 8 patients had a hydrogel rectal spacer placed prior to treatment. Out of the 95 fractions delivered to non-hydrogel patients, 78 were adapted, with 52 for urethra, 31 for bladder, 5 for bladder neck, and 35 for rectum. Of the 40 fractions delivered to patients with a hydrogel spacer, 20 were adapted. The corresponding reasons for adaptation in this group were 14 times for the urethra, 19 times for the bladder, 8 times for the bladder neck, and 8 times for the rectum. It was common for multiple at-risk organs to require adaptation for a single fraction within both cohorts. Although the percentage of patients requiring adaptation for rectal constraints was greater in the non-hydrogel patients (36.8% vs. 20%), this was not found to be statistically significant; p value greater than 0.1. Conclusion: The presence of a rectal spacer did not significantly reduce the need for online plan adaptation of the rectum for stereotactic online adaptive MRgRT. Furthermore, patients with a rectal spacer continued to often require adaptation to meet other prescription constraints. Further work is necessary to better select patients who would benefit from hydrogel spacers in the setting of online adaptive MRgRT. Additionally, longer follow-up of this patient population coupled with a larger patient cohort overall remains needed to increase the power of this analysis and to further explore the clinical outcomes of this patient group.

Radiation Oncology

Cousins MM, Dykstra MP, Griffith K, Mietzel M, Kendrick D, Trumpower E, **Dusseau D**, Dominello MM, Boike TP, Hayman JA, **Walker EM**, Jolly S, Mierzwa ML, Jagsi R, Vicini FA, and Pierce LJ. Cannabis Use Patterns among Patients with Early-Stage Breast Cancer in a Large Multicenter Cohort from a State with Legalized Adult Non-Medical Cannabis. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e95. Full Text

M.M. Cousins, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Purpose/Objective(s): Cannabis use among patients with cancer is an area of great interest given its widespread acceptance despite the lack of supporting clinical data. The absence of data limits the understanding of potential clinical benefits of cannabis and the ability of providers to deliver evidence-based recommendations for patient care. We explored cannabis use patterns in patients with early-stage breast cancer in a large multicenter cohort in a state with legalized adult non-medical cannabis. Materials/Methods: Initial questions about cannabis use history and frequency were introduced in Michigan Radiation Oncology Quality Consortium (MROQC) breast cancer patient surveys on 2/1/2020 for female patients receiving radiation after lumpectomy for non-metastatic breast cancer. Expanded questions were introduced on 6/28/2022 to assess mode of administration, active ingredient, and reason for use. Summary statistics were generated. A multivariable model using logistic regression identified patient characteristics associated with cannabis use. Results: Among 3948 eligible patients, 2738 (69.35%) completed survey questions, and 2462/2738 (89.9%) completed the initial question on cannabis use. Among those, 364/2462 (14.8%) noted cannabis use in the last 30 days, 588 (23.9%) noted remote use (>30 days ago), 1462 (59.4%) reported never having used cannabis, 44 (1.8%) preferred not to answer cannabis use questions, and 4 (0.4%) did not provide use history. Younger age [age <50 vs 60-70, OR 2.5 (95% CI 1.65, 3.79) p<0.001)], Hispanic ethnicity [OR 2.20 (95% CI 1.06, 4.56) p = 0.03], history of smoking [OR 2.56 (95% CI 1.88, 3.48) p<0.001], current smoking [OR 4.70 (95% CI 3.22, 6.86) p<0.001)], and prior chemotherapy [OR 1.40 (95% CI 1.00, 1.96) p = 0.05] predicted recent cannabis use in a multivariable model. Of the 364 patients endorsing cannabis use in the last 30 days, 89 (24.5%), 72 (19.8%), 29 (8.0%), 66 (18.1%), 30 (8.2%), and 78 (21.4%) reported using cannabis 1-2 days, 3-5 days, 6-9 days, 10-19 days, 20-29 days, and all 30 days, respectively. The most common modes of administration among 76 individuals who responded to the expanded questionnaire to date were oral (39.4%), smoking (30.3%), and topical (10.5%). The products used contained tetrahydrocannabinol (THC; 26.3%), cannabidiol (CBD; 19.7%), balanced levels of THC and CBD (19.7%), or active ingredients that were unknown to the patient (34.2%). Patients frequently endorsed cannabis use for insomnia, anxiety, and pain. Conclusion: Many patients with early-stage breast cancer are using cannabis. Younger age, Hispanic ethnicity, smoking, and chemotherapy history are predictors of cannabis use. Patients are often

unaware of the active ingredients in the products that they use, suggesting an important role for patient education and a need to equip providers to advise patients in their care.

Radiation Oncology

Czarnecki E, **Dolan JL**, **Cunningham JM**, **Chapman D**, **Elshaikh MA**, **Dragovic J**, **Parikh PJ**, **Movsas B**, and **Feldman AM**. Does a Dominant Intraprostatic Lesion Boost Require Daily Adaptation when Treated with Stereotactic Online Adaptive MR-Guided Therapy? *Int J Radiat Oncol Biol Phys* 2023; 117(2):e374-e375. Full Text

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

Purpose/Objective(s): Multiple trials have demonstrated a dose-response relationship for radiation therapy in the treatment of localized prostate cancer. Recent data has also demonstrated a benefit with whole gland stereotactic radiation therapy (SBRT) in conjunction with a simultaneous integrated boost to the dominant intraprostatic lesion (DIL). SBRT with a DIL boost can often increase dose to nearby organs at risk such as the rectum and online adaptive MR guided radiation therapy (MGgRT) may offer a dosimetric and toxicity benefit. Materials/Methods: A prospective database of MRgRT patients was queried for intact prostate cancer patients who received SBRT with a SIB to the DIL. The guideline for adaptation for coverage was to ensure the PTV-prostate coverage at 95% of prescribed dose was greater than 92% or by discretion of the treating physician. Adaptions for organs at risk were made to meet prescription constraints. The number of fractions requiring adaptation to meet organs at risk constraints and/or adequate coverage were reviewed. Results: A total of 26 patients were treated with SBRT with a DIL boost using stereotactic online adaptive MRgRT from 2020 to 2022. 10 of 26 patients were treated for re-irradiation of intact prostate. Out of the 130 fractions delivered, 107 fractions required adaptation (82.3%). 59 fractions were adapted for urethra (45.2%), 48 fractions were adapted for bladder (36.9%), 36 fractions were adapted for rectum (27.7%), 23 fractions were adapted for bladder neck (17.7%), and 19 fractions were adapted for coverage (14.6%). For 53 fractions (40.8 %), adaptation was required for more than one organ at risk. Conclusion: A total of 82.3% of fractions required adaptation for patients treated with SBRT with a DIL boost using stereotactic online adaptive MRgRT. Adaptation occurred most frequently for urethral (45.2%), bladder (36.9%), and rectal constraints (27.7%). Further studies are needed to elucidate if daily adaptive online MRgRT translates to reduced patient toxicity and improved quality of life.

Radiation Oncology

Dykstra MP, Regan SN, Yin H, McLaughlin PW, Boike TP, Bhatt AK, **Walker EM**, Zaki M, Kendrick D, Mislmani M, Paluch S, Litzenberg DW, Mietzel M, Narayana V, Smith A, Jackson WC, Heimburger DK, Schipper M, and Dess RT. Androgen Deprivation Therapy Use among Intermediate Risk Prostate Cancer Patients Undergoing Radiation Therapy across a Statewide Radiation Oncology Quality Consortium. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e380-e381. Full Text

M.P. Dykstra, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Purpose/Objective(s): For men with intermediate (INT) risk prostate cancer, the addition of androgen deprivation therapy (ADT) reduces risk of PSA failure, distant metastasis, and cancer-related mortality. Moreover, the relative reduction in cancer-related adverse outcomes with ADT use appears consistent across all INT risk subgroups. The absolute benefit of ADT, however, varies by baseline risk. In contemporary practice, it is unknown which clinical factors are most strongly associated with intended ADT use. Therefore, we sought to identify such factors within the diverse practices of the Michigan Radiation Oncology Quality Consortium (MROQC). Materials/Methods: Patients with localized prostate cancer undergoing definitive radiation therapy were enrolled from 6/9/20 to 11/4/22 (n = 599). Standardized patient, physician, and physicist forms were used to collect baseline and follow-up information. Intended ADT use, defined by the treating physician, was prospectively collected and is the primary outcome of this analysis. Univariable (UVA) and multivariable analyses (MVA) associations with patient (age, race, comorbidities), tumor (T stage, Gleason, percent cores positive, and PSA), and practice-related (academic vs private) factors were performed. In addition, advanced modality testing (PET, MRI, and genomic classifiers) was available as of March 2021, and subgroup analysis were

performed where appropriate. Results: A total 351 patients across 26 centers were enrolled with INT risk disease. ADT use was intended for 46% of men (n = 162/351) which differed by men with NCCN favorable INT (21%, n = 22/105) vs unfavorable INT risk disease (57%, n = 140/246), p<0.001. Sixty two percent (n = 100/162) had an intended ADT duration of 4-6 months and 21% (n = 34/162) had ≥12 months. Older age was associated with ADT use (70 vs 67, p < 0.01); there were no significant differences by race or comorbidities number. MVA showed Gleason 4+3 (OR 4.61 [2.91 – 7.42]) and > = 50% positive cores (2.56 [1.52 – 4.37]) were significantly associated with ADT use. No significant differences were noted based on practice setting. Pelvic MRI was obtained for 71% of men (n = 197/279), genomic classifiers in 47% (n = 130/279), and PET in 2% (n = 6/282). In the subset with MRI (n = 197), adverse features (ECE, SVI, or equivocal LNs) were associated with intended ADT use (OR 3.0 [1.4 - 7.1]) after adjustment for NCCN favorable/unfavorable INT risk classification. Conclusion: Within a state-wide consortium, intended ADT use for intermediate prostate cancer is most strongly associated with Gleason score, ≥50% positive cores, NCCN unfavorable intermediate risk classification, and adverse features on MRI. Nearly half of men had genomic classifier testing underscoring the importance ongoing trials such as NRG/GU 010.

Radiation Oncology

Ghanem AI, **Gilbert M**, **Keller C**, **Gardner G**, **Mayerhoff R**, and **Siddiqui F**. Definitive and Salvage Radiotherapy Compared to Other Modalities for Laryngeal Carcinoma in Situ. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e583. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): We sought to analyze survival endpoints for laryngeal carcinoma in situ (CIS) undergoing definitive radiotherapy (RT) compared to other modalities. Materials/Methods: Usingour prospectively maintained head and neck cancer database, we identified laryngeal CIS patients treated between 6/2001 and 12/2021. We excluded low-grade dysplasia, CIS with any synchronous invasive squamous cell carcinoma (SCC) within 3 months of the initial CIS biopsy and cases with inadequate follow up. Patients were offered either definitive RT, CO2/KTP laser ablation, photodynamic therapy (PDT) or any sort of therapeutic excision. After first line treatment, follow-up includes visits every 3-6 months with laryngoscopy and biopsies as appropriate. For recurrent CIS beyond 6 months of first line treatment, we reported salvage therapies received and long-term outcomes were reported. Using Kaplan-Meier curves and log-rank test we investigated recurrence free (RFS), progression to invasive SCC free (IFS) and overall (OS) survival across treatment groups. Patients managed with salvage RT were compared to first line RT recipients. Results: Atotal of 85 CIS cases were included: median age 65 years (IQR: 55-74), 73 males (85%) and 70 white (82.4%). 86% had a history of smoking with median pack year of 38 (IQR: 20-55) and 66% had a history of alcohol use. CIS was glottic in most of the cases (90.6%: 66% unilateral, 21% bilateral & 13% involved commissure); with only 9.4% in the supraglottic region. RT was used in 49.4% (n = 42) after biopsy (55%) or surgery (45%) with median dose of 63 Gy/28 fractions, mainly by 3D conformal RT (76%). The remaining 50.6% (n = 43) got therapeutic excision alone (commonly microflap excision) (46.5%), CO2/KTP laser (32.6%) or PDT (20.9%). Demographics and clinicopathological details were non-different between RT and non-RT patients except for Charlson comorbidity index: median 2 (IQR 1-3) in non-RT vs 1 (IQR 0-2) in 1ry RT; p = 0.007. After a median follow-up of 4.8 years (IQR 3.5), 51.8% had recurrent disease, 21.2% progressed to invasive SCC and 9.4% had laryngectomies mainly for invasive SCC after RT. First line RT had improved 2-(83% vs 39%) and 5-(74% vs 22%) year RFS vs non-RT therapies (p<0.001). Nevertheless, 2- and 5-year IFS (89% vs 98% and 80% vs 79%) and OS (92% vs 93% and 81% vs 77%) were non-significant among both (p>0.05 for all). Among non-RT cases with CIS recurrences, 12/35 (34%) had salvage RT. Following RT, salvage RT patients had similar 2- and 5-year RFS (81% vs 83% and 81% vs 74%) and IFS (81% vs 89% and 81% vs 80%) compared to first line RT (p>0.05 for all). All cases with CIS recurrences were salvaged successfully with 100% living with no CIS at latest follow-up. Conclusion: Laryngeal CIS can be treated with a wide range of modalities including 1ry RT which has better recurrence free survival. Nevertheless, non-RT recurrent CIS can be salvaged successfully with many options including RT with equivalent long-term results.

Radiation Oncology

Lassman AB, Polley MC, Iwamoto FM, Sloan AE, Wang TJC, Aldape KD, Wefel JS, Gondi V, Gutierrez AN, Manasawala M, Gilbert MR, Sulman EP, Wolchok JD, Greene RM, Neil EC, Lukas RV, Goldlust SA, Snuderl M, Dignam JJ, Won M, **Movsas B**, and Mehta MP. NRG ONCOLOGY STUDY BN007: RANDOMIZED PHASE II/III TRIAL OF IPILIMIUMAB (IPI) PLUS NIVOLUMAB (NIVO) VS. TEMOZOLOMIDE (TMZ) IN MGMT-UNMETHYLATED (UMGMT) NEWLY DIAGNOSED GLIOBLASTOMA (NGBM). *Neuro-Oncology* 2023; 25:ii2. Full Text

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BACKGROUND: New therapies are especially needed for uMGMT nGBM. NRG Oncology BN002 (phase I) demonstrated safety and preliminary efficacy of Ipi+Nivo for nGBM, leading to BN007 as phase II/III. METHODS: Adults with uMGMT nGBM (WHO 2016) and KPS ≥ 70 were randomized to RT and concurrent and adjuvant Ipi+Nivo or TMZ, stratified by glioma-recursive partitioning analysis class (RPA), intent to use tumortreating fields (NCT04396860). Phase II primary endpoint was progressionfree survival (PFS), powered 95% to detect a hazard ratio (HR) ≤0.58 with 1-sided 0.15 significance after 100 events. If p<0.15, then phase III would accrue with overall survival (OS) as primary endpoint. Corticosteroids were disallowed at Ipi+Nivo start. Histology, biomarkers, and PFS were assessed centrally. RESULTS: Among 374 patients screened, 159 were randomized in phase II (79 Ipi+Nivo, 80 TMZ). Demographics (age median 60 years, range 28-79; male 66%, white 88%, not Hispanic/Latino 89%), KPS (90- 100 61%), extent of resection (gross total 65% per local PI), and RPA (III 10%, IV 73%, V 17%) were well-balanced between arms. After 100 PFS events, the pre-planned phase II analysis demonstrated no improvement for Ipi+Nivo vs. TMZ [median 7.7 (95% CI: 6.5, 8.5) vs. 8.5 (95% CI: 7.1, 10.4) months; HR 1.47 (95% CI: 0.98-2.2); 1-sided p=0.96]. OS is immature (>50% alive, 13.7 months median follow-up) but without observed difference between arms [median ~13 months each; HR 0.95 (95% CI: 0.61-1.49); 1-sided p=0.36]. On the Ipi+Nivo arm, treatment-related grade 3, 4, and 5 events were reported in 26 (33.3%), 4 (5.1%), and 2 (2.6%; colitis and autoimmune disorder, n=1 each) patients. CONCLUSION: Ipi+Nivo did not improve PFS for uMGMT nGBM. Accrual permanently closed after phase II. No new safety signals were identified. Molecular analyses and survival follow-up are ongoing.

Radiation Oncology

Regan SN, Dykstra MP, Yin H, McLaughlin PW, Boike TP, Bhatt AK, **Walker EM**, Zaki M, Kendrick D, Mislmani M, Paluch S, Litzenberg DW, Mietzel M, Narayana V, Smith A, Jackson WC, Heimburger DK, Schipper M, and Dess RT. ADT Use and Nodal Irradiation in Men Receiving Post-Prostatectomy Salvage Radiotherapy within a Statewide Radiation Oncology Quality Consortium. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e430-e431. Full Text

S.N. Regan, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Purpose/Objective(s): For men with biochemical recurrence after radical prostatectomy, salvage radiotherapy (SRT) is a standard of care. Outcomes are improved when SRT is delivered at lower PSA levels, and there has been increased emphasis on more timely treatment. With early SRT, however, there remains uncertainty as to the optimal use and duration of androgen deprivation therapy (ADT) and pelvic lymph node radiation (PLNRT). Moreover, PET imaging and genomic classifiers have emerged as tools to guide treatment decisions, but their uptake in routine practice is unknown. To address these questions, we analyzed a contemporary cohort treated with SRT within the Michigan Radiation Oncology Quality Consortium (MROQC). We hypothesized that ADT and PLNRT practices would reflect recent trial results in this setting. Materials/Methods: Eligible patients receiving SRT at an MROQC center were enrolled from 06/09/20 to 11/04/22. Data was prospectively collected via patient-, physician-, and physicist-completed forms. Patients were matched to the Michigan Urological Surgery Improvement Collaborative (MUSIC) database for additional treatment- and patient-related data. Univariable (UVA) and multivariable analyses (MVA) were performed to test associations between patient/tumor factors and ADT or PLNRT use. Results: A total of 191 patients across 26 centers were enrolled in the MROQC database. Of these, 116 were matched to the MUSIC database. Median time from RP to SRT was 17 months (IQR 8 – 33 months). The median post-RP PSA prior to SRT was 0.25 (IQR 0.16 – 0.60). Early SRT was defined as

pre-SRT PSA ≤0.5, and 27% (n = 31/116) had a pre-SRT PSA >0.5. Twenty-eight were pT3b/T4, 97% were pN0/NX, and 51% had positive surgical margins. Fractionation was conventional (>28 fractions) in 58% and moderate hypofractionation (20-28 fractions) in 38%. Table 1 describes the patients receiving ADT and/or PLNRT. Median ADT duration was 6 mo (IQR 6 – 7 mo). MVA revealed pre-SRT PSA >0.5 (OR 5.05 [1.89 – 15.33]) and pT3b/T4 disease (OR 4.23 [1.40 – 14.56]) were significantly associated with ADT use (p <0.05), but not grade group (GG) or margin status. PLNRT was significantly associated with pre-SRT PSA >0.5 (OR 3.04 [1.21 – 8.42], p <0.05) but not pT stage, margin status, or GG. PET imaging was performed in 37% of men (52% negative, 21% prostate bed alone uptake, and 26% lymph node positivity) and genomic classifiers were performed in 24%. Conclusion: Nearly 75% of biochemically recurrent prostate cancer patients within MROQC received early SRT, and about half received ADT. A pre-SRT PSA >0.5 was strongly associated with ADT and PLNRT. With prostate bed SRT alone, very few received ADT. Given the considerable heterogeneity in treatment, additional studies may help identify patients who most benefit from ADT + PLNRT, and who may be spared potential added toxicity.

Radiation Oncology

Runge CL, Lyness J, Gillison M, Adelstein DJ, Harari PM, Ringash JG, Geiger JL, Krempl GA, Blakaj D, Bates J, Galloway TJ, Jones CU, Gensheimer M, Dunlap NE, Phan J, Caudell J, Pennington D, Torres-Saavedra P, Yom SS, Le QT, and **Movsas B**. Hearing Outcomes in Cisplatin or Cetuximab Combined with Radiation for Patients with HPV-Associated Oropharyngeal Cancer in NRG/RTOG 1016. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S122-S123. Full Text

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Purpose/Objective(s): NRG/RTOG 1016 was a noninferiority phase 3 trial comparing the efficacy of radiation with either cisplatin (RT+Cisp) or cetuximab (RT+Cetux) for patients with HPV+ oropharyngeal cancer (OPC). Perceived hearing handicap was included as a patient-reported outcome (PRO) secondary endpoint. The primary hypothesis was that perceived hearing handicap would be greater for patients receiving RT+Cisp compared to RT+Cetux. Materials/Methods: Perceived hearing handicap was measured at baseline, end of treatment, 3, 6, and 12-months post-treatment using the Hearing Handicap Inventory for Adults Screening Version (HHIA-S), a 10-item self-assessment questionnaire designed to measure patients' reactions to their hearing loss. Total HHIA-S scores range from 0 to 40; higher total score indicates more severe perceived hearing handicap. Hearing handicap categories (none, mild/moderate, and severe) were also analyzed. Mixed ordinal logistic models were used to analyze the raw HHIA-S scores and handicap categories (2-sided alpha 0.05). Results: Participation in the PRO assessments was optional, with 368 patients participating in the hearing PRO. No significant differences in patient/tumor characteristics were found between PRO participants/non-participants. Pre-treatment (mean [SD]) HHIA-S scores were not different for RT+Cisp (3.23 [6.28]) and RT+Cetux (4.77 [8.14]) groups. Post-treatment HHIA-S scores increased for RT+Cisp, and remained stable at the later follow-up time points. RT+Cetux scores remained stable from baseline. Change score from pre- to post-treatment was higher for RT+Cisp (4.32, 95% CI = [2.57, 6.07]) than RT+Cetux (0.08, 95% CI = [-1.15, 1.31]; p < 0.001). For hearing handicap category, post-treatment RT+Cisp had a significantly higher percentage of mild/moderate and severe cases (32%) compared to RT+Cetux (20%). From pre- to post-treatment, worsening of hearing handicap category from normal to mild/moderate or severe was greater for RT+Cisp (24%) than for RT+Cetux (9%). The conditional odds of being in a higher self-perceived hearing handicap category in the RT+Cisp arm were 3.57 (95% CI [2.04, 6.25]) times that in the RT+Cetux arm. Averaging over patients, the marginal odds ratio was 2.46 (95% CI [1.65, 3.66]). Conclusion: Patients receiving concurrent RT+Cisp for HPV-associated OPC have significantly higher odds of worsening self-perceived hearing handicap after treatment than with RT+Cetux. This was consistent across time through one-year post-treatment. These findings inform hearing-related outcomes for patients with HPV-associated OPC.

Radiation Oncology

Zhu S, **Gilbert M**, **Ghanem AI**, **Siddiqui F**, and **Thind K**. Feasibility of Using Zero-Shot Learning in Transformer-Based Natural Language Processing Algorithm for Key Information Extraction from Head and Neck Tumor Board Notes. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e500. Full Text

S. Zhu, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Natural language processing (NLP) technology has the potential to automate information aggregation and summarization in oncology. One example is the automation of patient registry creation. In this work, we aim to show (1) the feasibility of using modern NLP algorithms to extract key information from tumor board notes, and (2) the impact of prompt engineering on the quality of the results. Materials/Methods: In this IRB-approved study, we obtained the texts of head and neck tumor board notes for 306 unique patients. Five key pieces of information used to create a patient registry were predefined: age, gender, tumor histology, tumor stage, and primary location. The NLP algorithm used was a modified Text-To-Text Transfer Transformer (T5) model that was initially trained on the Colossal Clean Crawled Corpus (C4) dataset and subsequently fine-tuned on the Stanford Question Answering Dataset (SQuAD) to perform the downstream task of extractive question answering. The NLP model and trained weights were obtained from the Hugging Face platform. During inference, the entire body of the tumor board note and a related question were fed as inputs, and the model predicted a sequence of texts in response to the question. Two sets of questions of similar semantic meanings were used. Questions in prompt set #1 included “What is the gender?”, “What is the age?”, “What is the type of carcinoma in pathological diagnosis?”, “What is the stage?”, and “Where is the carcinoma located at?”. Questions in prompt set #2 include “Is the patient male or female?”, “How old is the patient?”, “What kind of cancer?”, “What is the cancer stage?”, and “What is the tumor location?”. Each model-predicted response was compared to the ground truth extracted from the tumor board notes. A response was classified as true if it is consistent with the ground truth, otherwise, it was deemed false. The response accuracy for each question was subsequently calculated. Results: The median number of words in each tumor board note was 448 (range, 219 – 1505). The accuracy of the NLP algorithm for each question from either set is reported in Table 1. Algorithm performance is higher for extracting objective information such as age, gender, and histology. In addition, it was found that questions of similar semantic meanings but with different wording can lead to significantly different results. Conclusion: We demonstrated that a transformer-based extractive question-answering NLP algorithm can be successfully used for extracting information from head and neck tumor board notes with zero-shot learning. Furthermore, our results highlight the significance of prompt engineering for applying NLP for this task. Future work on finetuning these algorithms to oncology-specific texts can potentially enhance algorithm performance for more difficult tasks.

Surgery

Ivanics T, **Jafri SM**, **Muszkat Y**, **Rizzari M**, **Abouljoud M**, **Yoshida A**, and **Nagai S**. A risk factor analysis of donor-specific factors on one- and threeyear post-transplant mortality after multi visceral transplantation. *Transplantation* 2023; 107(9):210-211. Full Text

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

Background: Patients undergoing combined liver and intestine transplantation (multi visceral transplantation [MVT]) represent a particularly vulnerable patient population. These patients have specific quality requirements for suitable donors. We sought to evaluate the effects of various marginal donor qualities on posttransplant outcomes in MVT patients. Methods: The Organ Procurement and Transplantation Network/ United Network for Organ Sharing database was used to identify all adult recipients of liver and intestine listed between 01/01/2010 and 01/25/2021. Outcomes included 1- and 3-year post-transplant patient survival and mortality. Results: A total of 268 MVTs were identified. Of these, 232 were intestine-liver-pancreas, 32 were intestine-liver-kidney, and four were intestine-liver. Of the MVTs, donor age >40 was present in 36/268(13%), donor body mass index(BMI)>30 in 10/268(4%), donor diabetes 1/268(0%), any donor pressor requirement in 108/268(40%), and multiple donor pressor requirements in 11/268(4%). The 1- and 3-year survival for donor age <40 vs. ≥40 was 65.8% vs. 52.1%;p=0.13 and 50.1%vs.48.9%;p=0.53. Similarly, the 1- and 3-year survival for no donor pressor requirement vs. donor pressor requirement were 61.9%vs.67.5%;p=0.61 and 45.8% vs. 57.0%;p=0.24, respectively. The 1-year survival for various cold ischemia cutoffs were ≤6.50hr 64.4%vs.6.51-7.56hr 63.9%vs.7.57-8.79hr 69.8% vs. ≥8.80hr 57.6%;p=0.50 and 3-year survival for the various cutoffs were ≤6.50hr 50.4%vs.6.51-7.56hr 54.0%vs.7.57-8.79hr 47.0% vs. ≥8.80hr 47.9%;p=0.83(Figure 1). Conclusions: Donors with older age(>40yo), high BMI, and/or multiple pressor requirements were not often used for MVT probably due to its careful donor selection. While no statistically significant donor-

specific risk factors were noted to be associated with posttransplant mortality, older donor age(>40yo) and longer CIT(≥8.8hr) tended to worsen short-term outcome(1-year survival). Within this context, to maintain appropriate outcomes, the choice of MVT donors should be selective. There may a room to expand donor pool/donor selection criteria in MVT without adversely impacting outcomes.

Surgery

Ivanics T, Wallace D, Claasen M, **Rizzari M**, **Abouljoud M**, **Yoshida A**, **Nagai S**, and Bernal W. Era-specific improvements in age-disparate outcomes after liver transplantation for acute liver failure: a population-based analysis of the United Kingdom and Ireland. *Transplantation* 2023; 107(9):19. Full Text

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

Background: Emergency liver transplantation(LT)can be lifesaving in patients with acute liver failure(ALF),but waitlist and post-LT mortality may be high. Recipient age has been implicated as a key determinant of both, but how its effects have been impacted by recent improvements in post-LT outcomes is poorly characterized. In a large national cohort, we evaluated the impact of age on waitlist and post-LT outcomes and investigated how this has changed over time. Methods: We identified all patients listed for super urgent LT for ALF in the UK and Ireland from the NHSBT and the UK liver transplant registry between 1995-2021 and used Cox regression methods to assess the impact of age on waitlist and post-transplant mortality. Post-LT mortality hazard was assessed in early(0-3months)and late(3months-5years)follow-up epochs and across different eras of LT(1995-2009&2010-2021). Results: A total of 2,505 patients were listed for a super urgent LT for ALF, of whom 1,842 received an LT. Older patients had higher body mass index, fewer had renal, ventilatory, and inotropic support at listing, and were less likely to have paracetamol-induced liver failure. Donor characteristics were similar between age groups. There was no significant difference between the age groups in the adjusted cause-specific hazard of waitlist mortality. Stratified by the era of LT, there was no difference in the early(0-3months)post-LT mortality between recipients in the youngest and oldest groups. In the later post-transplant period(3months-5years),those in the older age groups had higher mortality, largely driven by poorer longerterm outcomes in the early era. Stratifying by age groups, the later era was associated with significantly lower overall post-LT mortality. Conclusions: For ALF patients, waitlist and short-term(0-3months) post-LT outcomes are similar across age groups. Era-specific improvements have occurred in long-term post-LT outcomes and have attenuated the disparate excess mortality hazard in older compared to the younger age groups.

Urology

Ramirez Dominguez LB, Medina IJ, Matamoros-Volante A, Fernandez SM, **Rambhatla A**, Rosas IM, and Agarwal A. EMBRYO EUPLOIDY RATES ARE NOT INCREASED BY THE REPEATED ADDITION OF ANTIOXIDANTS TO THE CULTURE MEDIA WHEN COMPARED TO INITIAL ANTIOXIDANTS SUPPLEMENTATION. *Fertil Steril* 2023; 120(4):e283-e284. Full Text

OBJECTIVE: To evaluate the euploidy rates and the mitochondrial DNA in human embryos after either repeated vs initial antioxidants supplementation to culture media. MATERIALS AND METHODS: This prospective study was conducted at CITMER, Mexico from April 2020 to November 2022. A total of 217 patients (age 37.95 ± 4.04 years old) undergoing ICSI were included. Zygotes were cultured under either 20% or 5% oxygen tension in two groups: Group 1: (n=835 zygotes) supplementation with antioxidants every 12 hours to lower the oxidation reduction potential (ORP) levels to a physiological state in culture media. Group 2: (n=1232 zygotes) supplementation with antioxidants only at the beginning of the culture (from gametes handling until fertilization check). Euploidy rates and mitochondrial DNA (mtDNA) by PGT-A were evaluated. A total of 2067 sibling zygotes were divided into two groups after fertilization check. Zygotes were cultured at 8% CO2, either 20% or 5% O2, 37°C to blastocyst stage. Trophectoderm biopsy was performed in 901 embryos. Group 1: 396 embryos were biopsied. Group 2: 505 embryos were biopsied. Biopsies were analyzed by next generation sequencing (NGS). RESULTS: There is a mild tendency of an increase of the euploidy rate when antioxidants were added to the culture media every 12 hours at 5% oxygen tension (5%: 44% vs 40.8%, p=0.55; 20% 41.3% vs 40.8%, p=0.99), however no significant differences were detected. There is no statistical evidence that there is a variation in the mitochondrial DNA among the groups for aneuploid embryos (5%: 1.64 ± 0.81 vs 1.47 ± 0.83 and 20%: 1.64 ± 0.82 vs 1.64 ± 0.87, p=0.36). However, in euploid embryos, there is a mild decrease in

mitochondrial DNA in the group cultured with repeated antioxidants addition at 20% oxygen tension compared to initial addition (5%: 1.36 ± 0.72 vs 1.27 ± 0.8 and 20%: 1.36 ± 0.73 vs 1.54 ± 0.71, p=0.053) CONCLUSIONS: Repeated antioxidants supplementation in culture media did not differ from initial supplementation on euploidy rates nor mitochondrial DNA. IMPACT STATEMENT: The adjustment of ORP levels in culture media by the addition of antioxidants at 12 hours intervals does not increase euploidy rates and mtDNA of blastocysts. In addition, it is possible that elevated levels of ORP in culture media do not modify the chromosomal status of embryos. More studies are needed to confirm these findings. SUPPORT: No financial support was required for this studio. REFERENCES: Gardner, D.K.; Kuramoto, T.; Tanaka, M.; Mitzumoto, S.; Montag, M.; Yoshida, A. Prospective Randomized Multicentre Comparison on Sibling Oocytes Comparing G-Series Media System with Antioxidants versus Standard G-Series Media System. Reprod Biomed Online 2020, 40(5), 637-644,.

Urology

Ramirez Dominguez LB, Medina IJ, Matamoros-Volante A, **Rambhatla A**, Figueroa Mendez MG, Villar L, García Pérez AD, Delgadillo D, Rosas IM, and Agarwal A. REPEATED ANTIOXIDANT SUPPLEMENTATION OF CULTURE MEDIA IMPROVES BLASTOCYST FORMATION IN HOMOLOGOUS SIBLING ZYGOTES FROM INFERTILE PATIENTS UNDER DIFFERENT O2 CONCENTRATIONS. *Fertil Steril* 2023; 120(4):e213. Full Text

STUDY QUESTION: Do the repeated vs initial antioxidants (AOXs) supplementation to culture media of homologous sibling zygotes strategies increase blastocyst utilization and expansion rates in IVF/ICSI cycles under two different O2 concentrations? OBJECTIVE: To evaluate the effect of repeated and initial AOXs supplementation of sibling zygotes in the blastocyst utilization and expansion rates in IVF/ICSI cycles under two different O2 concentrations MATERIALS AND METHODS: This prospective study was conducted at CITMER, Mexico from April 2020 to November 2022. We included a total of 293 patients younger than 37 years old (mean age 32.1 ± 3.4 years old) and normal ovarian response (more than 6 retrieved oocytes) undergoing IVF/ICSI. A total of 3603 zygotes were divided into 4 groups and cultured in the following conditions until blastocyst stage: Group 1A: 793 zygotes 20% O2 with antioxidants every 12 hours to stabilize the oxidation reduction potential (ORP) levels at physiological state during the entire culture period, Group 1B: 1286 zygotes 20% O2 with antioxidants at the beginning of the culture (from gametes handling until fertilization check), Group 2A: 695 zygotes 5% O2 with antioxidants every 12 hours, Group 2B: 829 zygotes 5% O2 with antioxidants at the beginning. Embryo development was assessed. Odds ratio and Fisher test were performed. p<0.05=significant. RESULTS: Overall, the group supplemented with AOXs every 12 hours had a significantly higher blastocyst expansion rate on days 5 (1A: 31.3% vs 1B: 28%, p=0.11; 2A: 28.8% vs 2B: 23%, p=0.01*) and 6 (1A: 5.9% vs 3.7%, p=0.02*; 2A: 5.5% vs 4.9%, p=0.65), usable blastocyst formation rate on day 5 (1A: 45.3% vs 1B: 44.2%, p=0.65; 2A: 45.2% vs 2B: 39.6%, p=0.03*), as well as usable blastocyst formation rate on day 6 (1A: 7.9% vs 1B: 4.7%, p<0.01*; 2A: 7.1% vs 6.8%, p=0.84) compared to the group with only initial AOXs supplementation. The results of the embryo culture with AOXs during the entire incubation at 20% O2 tension are similar to the culture with antioxidants only at the beginning of the culture at 5% O2 tension. CONCLUSIONS: Antioxidant supplementation every 12 hours compared to initial AOXs supplementation improved the rates of blastocyst expansion and formation of usable blastocysts on day 5 and day 6 in patients younger than 37 years old and normal ovarian response undergoing IVF/ICSI. When comparing both O2 tensions (5% vs 20%), in both antioxidant-supplemented culture strategies, usable and expanded blastocysts rates were similar. IMPACT STATEMENT: Repeated antioxidant supplementation in culture media could potentially support embryo development in both 5% and 20% O2 tension compared to only baseline antioxidants supplementation. However, more studies need to focus on pregnancy and live birth rates, as well as the safety of using this method for antioxidant supplementation. SUPPORT: No financial support was required for this studio.

Urology

Ramos R, Soputro N, Sauer Calvo R, Nguyen J, **Wilder S**, Ferguson E, Iarajuli T, Chavali JS, **Rogers C**, Ahmed M, Crivellaro S, and Kaouk J. Single-port transvesical robot-assisted simple prostatectomy a multi-institutional series from the SPARC. *Eur Urol Open Sci* 2023; 55:S254-S255. Full Text

Introduction & Objectives: Our aim is to report the results of the novel single-port (SP) transvesical (TV) robot-assisted simple prostatectomy (RASP) by presenting a multi-institutional series from the Single-Port Advanced Research Consortium (SPARC). Materials & Methods: Data from four institutions were collected prospectively and analyzed. SP TV RASP was performed in patients with severely symptomatic BPH. A 3 cm suprapubic incision was made to access the bladder directly with the SP access port. The procedure included two steps: 1) Excision of the prostatic adenoma 2) 360° reconstruction with a mucosal flap (Figure 1). Results: A total of 117 cases were analyzed. All cases were completed successfully without the need for conversion. Mean age and body mass index were 67 years and 28 kg/m2, respectively. Median Charlson comorbidity index was 3, up to 42% and 28% of the patients had a history of abdominal surgery and prostatic procedures, respectively. The median preoperative volume was 149.5 cc (IQR: 109-196). The most common indication for surgery was urinary retention (59%). Median operative time and estimated blood loss were 162 minutes and 100 ml, respectively. There were 3 intraoperative complications during the initial experience, all of them were air emboli due to high pneumovesicum pressure (>12 mmHg). Median specimen weight was 81 g (IQR: 59-123) and incidental adenocarcinoma was found in 5 cases (4.3%). The median pain score at discharge was 2/10, 92% did not require narcotics at discharge. Planned outpatient cases were discharged within 24 hours 85% of the time. Median catheter duration was 6 days. Biochemical and functional results are shown in Figure 2. Conclusions: SP TV RASP is a feasible outpatient technique for patients with severe BPH. The 360° mucosal flap reconstruction step provides hemostasis and fast recovery. [Figure presented]

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Soputro N, Chavali JS, Ferguson EL, Ramos-Carpinteyro R, Calvo RS, Nguyen J, Moschovas MC, **Wilder S**, Okhawere K, Sanchez De La Rosa R, Saini I, **Peabody J**, Badani KK, **Rogers C**, Joseph J, Nix JW, Patel V, Stifelman MD, Ahmed M, Crivellaro S, Kim M, and Kaouk JH. Complications of dsngle-port robotic radical prostatectomy: A multi-institutional report from the Single-Port Advanced Research Consortium (SPARC). *Eur Urol Open Sci* 2023; 55:S82-S83. Full Text

Introduction & Objectives: Following its introduction, recent years have seen the increasing utility of the purpose-built Single-Port (SP) robotic platform for varying approaches of robotic radical prostatectomy (RARP). Despite earlier series demonstrating favourable perioperative outcomes, there remains a paucity of evidence highlighting the morbidity of these procedures. Hence, this study sought to evaluate the perioperative complication following different approaches of SP-RARP using a multi-institutional database. Materials & Methods: A retrospective review was performed on the prospectively maintained, Institutional Review Board (IRB)-approved Single-Port Advanced Research Consortium (SPARC) database. All patients who underwent transperitoneal (TP), extraperitoneal (EP), and transvesical (TV) SP-RARP by 11 surgeons across 9 centers between 2019 and 2022 were included. The rates and reasons for the 90-day postoperative complication and readmission were analyzed for each surgical approach separately. Results: A total of 1103 patients were identified, which included 244, 712, and 147 patients who had TP, EP, and TV SP-RARP, respectively. Intraoperative complications were reported in five patients (0.4%), all of whom belonged to the TP cohort. Postoperative complications were noted in 143 patients (13%) with the majority being minor complications (Clavien-Dindo grade ≤2). The incidence of non-urological complications were significantly lower in the TV cohort (TP 8.2% vs. EP 6.3% vs. TV 3.4%, p = <0.05). The 90-day readmission rate was 3.9%. [Figure presented] Conclusions: SP-RARP provided a safe and effective addition to the repertoire of minimally-invasive surgical management for prostate cancer with a relatively low risk of 90-day postoperative complication and readmission. The varying surgical approaches were associated with different complication profiles, with markedly reduced non-urological complications following the more localized transvesical access.

Urology
Tinsley SA, Olabode S, Thomas MV, and **Dabaja AA**. ASSESSING FUNDING AND PUBLIC INTEREST INTO MALE AND FEMALE INFERTILITY: ANALYSIS OF NIH REPORTER & GOOGLE TRENDS DATABASES. *Fertil Steril* 2023; 120(4):e267-e268. Full Text

OBJECTIVE: Infertility affects male and female patients equally within the United States of America. However, previous studies have alluded to disparities in research funding allocation to specific specialties and their applicable diseases or conditions. The objective of this study is to identify trends in funding for

infertility research for Urology and Obstetrics & Gynecology departments in the United States of America. MATERIALS AND METHODS: The National Institutes of Health (NIH) NIH RePORTER, (https://reporter.nih.gov), was queried to assess trends in research funding. The advanced search function was used to assess funding for the search term 'Infertility' for both Urology departments and Obstetrics and Gynecology departments. This study assessed funding to those departments within the United States of America, between 2004 to 2022. Additionally, Google Trends, (https://trends.google.com/trends/?geo=US), was queried to assess public health interest in the search terms 'Male Infertility' and 'Female Infertility', in the United States of America, between 2004 to 2022. Statistical analysis was performed to identify statistically significant differences, using RStudio Software. RESULTS: Departments of Urology had a median grant acquisition of ($460,599), while departments of Obstetrics and Gynecology had a median grant acquisition of ($300,930). The total amount of grant acquisition from the NIH for departments of Urology was ($22,523,049), while departments of Obstetrics and Gynecology had significantly higher amount of funding ($436,643,124), p-value <0.001. Interestingly, the average relative search volume for 'Male infertility' (39.55), was significantly higher than 'Female Infertility' (30.08), p-value <0.001. Additionally, both the average annual relative search volumes for 'Male Infertility' and 'Female Infertility' decreased significantly, from 69.42 to 55.17 (p-value <0.001) and 56.42 to 26.83 (p-value <0.001), respectively between 2004 to 2022. CONCLUSIONS: Currently, there is a great disparity in research funding to male infertility research conducted in Urology departments and female infertility research conducted in Obstetrics and Gynecology departments. Furthermore, it appears a disparity exist between male infertility and female infertility interest. Advocacy amongst healthcare professionals and community stakeholders should strive to achieve equity in research funding allocation and public health interest toward male and female infertility. IMPACT STATEMENT: There are significant disparities related to research funding and public health interest toward male infertility and female infertility. Health policy advocacy ought to be encouraged to increase research funding and public health interest toward male and female infertility in efforts to promote equity. SUPPORT: No External or Internal Funding

Books and Book Chapters

Hematology-Oncology
Rybkin I, and **Gadgeel SM**. Immunotherapy of Lung Cancer. In: Kauczor HU, Parizel PM, Wilfred CG, Peh JJL, eds. *Medical Radiology*. Part F1269; 2023:371-384. Request Chapter

Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI, United States

Pulmonary and Critical Care Medicine
Simoff MJ, **Diaz-Mendoza J**, Peralta AR, **Debiane LG**, and **Cohen A**. Advances in Supportive and Palliative Care for Lung Cancer Patients. In: Kauczor HU, Parizel PM, Wilfred CG, Peh JJL, eds. *Medical Radiology*. Part F1269; 2023:809-829. Request Chapter

Interventional Pulmonology and Lung Cancer Screening, Henry Ford Hospital/Wayne State University School of Medicine, Detroit, MI, United States