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HENRY FORD HEALTH

Henry Ford Health Publication List – February 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 106 unique citations listed this month, including 74 articles and 32 conference abstracts.

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

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Articles

Conference Abstracts

Articles

Anesthesiology

Lhila A, and **Alghanem F**. Along party Lines: Examining the gubernatorial party difference in COVID-19 mortality rates in U.S. Counties. *Prev Med Rep* 2023; 32:102142. PMID: 36816769. Full Text

College of Business Administration, Central Michigan University, Mount Pleasant, MI 48859, USA. Department of Anesthesiology, Pain Management, & Perioperative Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA.

Drawing upon the literatures on risk factors for COVID-19 and the roles of political party and political partisanship in COVID-19 policies and outcomes, this study quantifies the extent to which differences in Republican- and Democrat-governed counties' observable characteristics explain the Republican - Democrat gap in COVID-19 mortality rate in the United States. We analyze the county COVID-19 mortality rate between February 1 and December 31, 2020 and employ the Blinder-Oaxaca decomposition method. We estimate the extent to which differences in county characteristics - demographic, socioeconomic, employment, health status, healthcare access, area geography, and Republican vote share, explain the difference in COVID-19 mortality rates in counties governed by Republican vs Democrat governors. Among 3,114 counties, Republican-governed counties had significantly higher COVID-19 mortality than did Democrat-governed counties (127 ± 86 vs 97 ± 80 per 100,000 population, $p < 0.001$). Results are sensitive to which weights are used: of the total gap of 30.3 deaths per 100,000 population, 12.8 to 20.5 deaths, or 42.2-67.7 %, are explained by differences in observable characteristics of Republican- and Democratic-governed counties. Difference in support for President Trump between Republican- and Democrat-governed counties explains 25 % of the additional deaths in Republican counties. Policies aimed at improving population health and lowering racial disparity in COVID-19 outcomes may also be correlated with reducing the partisan gap in COVID-19 mortality.

Behavioral Health Services/Psychiatry/Neuropsychology

Harnett NG, Fani N, Carter S, Sanchez LD, Rowland GE, Davie WM, **Guzman C**, Lebois LAM, Ely TD, van Rooij SJH, Seligowski AV, Winters S, Grasser LR, Musey PI, Jr., Seamon MJ, House SL, Beaudoin FL, An X, Zeng D, Neylan TC, Clifford GD, Linnstaedt SD, Germine LT, Bollen KA, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Hendry PL, Sheikh S, Jones CW, Punches BE, Swor RA, Hudak LA, Pascual JL, Harris E, Chang AM, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, Bruce SE, Miller MW, Pietrzak RH, Joormann J, Barch DM, Pizzagalli DA, Harte SE, Elliott JM, Kessler RC, Koenen KC, McLean SA, Jovanovic T, Stevens JS, and Ressler KJ. Structural inequities contribute to racial/ethnic differences in neurophysiological tone, but not threat reactivity, after trauma exposure. *Mol Psychiatry* 2023; Epub ahead of print. PMID: 36725899. Full Text

Considerable racial/ethnic disparities persist in exposure to life stressors and socioeconomic resources that can directly affect threat neurocircuitry, particularly the amygdala, that partially mediates susceptibility to adverse posttraumatic outcomes. Limited work to date, however, has investigated potential racial/ethnic variability in amygdala reactivity or connectivity that may in turn be related to outcomes such as post-traumatic stress disorder (PTSD). Participants from the AURORA study (n = 283), a multisite longitudinal study of trauma outcomes, completed functional magnetic resonance imaging and psychophysiology within approximately two-weeks of trauma exposure. Seed-based amygdala connectivity and amygdala reactivity during passive viewing of fearful and neutral faces were assessed during fMRI. Physiological activity was assessed during Pavlovian threat conditioning. Participants also reported the severity of posttraumatic symptoms 3 and 6 months after trauma. Black individuals showed lower baseline skin conductance levels and startle compared to White individuals, but no differences were observed in physiological reactions to threat. Further, Hispanic and Black participants showed greater amygdala connectivity to regions including the dorsolateral prefrontal cortex (PFC), dorsal anterior cingulate cortex, insula, and cerebellum compared to White participants. No differences were observed in amygdala reactivity to threat. Amygdala connectivity was associated with 3-month PTSD symptoms, but the associations differed by racial/ethnic group and were partly driven by group differences in structural inequities. The present findings suggest variability in tonic neurophysiological arousal in the early

aftermath of trauma between racial/ethnic groups, driven by structural inequality, impacts neural processes that mediate susceptibility to later PTSD symptoms.

Cardiology/Cardiovascular Research

Abdelrahim E, **Birchak J**, **Khan A**, and **Maskoun W**. Iatrogenic cardiomyopathy in patients with manifest right supero-paraseptal accessory pathways. *Pacing Clin Electrophysiol* 2023; Epub ahead of print. PMID: 36851895. Full Text

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INTRODUCTION: We describe 2 patients with right supero-paraseptal accessory pathway (SPAP) who developed left ventricular dysfunction associated with increased degree of ventricular pre-excitation and frequent orthodromic reciprocating tachycardia (ORT) due to worsening AV node conduction. METHODS AND RESULTS: Case 1: 48-year-old female with a history of normally functioning mechanical mitral valve, CABG, and ventricular pre-excitation that worsened after her open heart surgery. She presented with frequent palpitations with documented supraventricular tachycardia (SVT) and found to have a new left ventricular dysfunction with decrease in left ventricular ejection fraction (LVEF) from 55% to 46% with dyssynchrony. Electrophysiological study confirmed a right SPAP and ORT. The pathway was successfully ablated from the antegrade approach after careful mapping. After ablation and six month follow up echocardiogram showed improvement of EF to 54% and the LV dyssynchrony resolved. Case 2: 51-year-old male with a history of frequent SVT with recent unsuccessful ablations that resulted in worsening ventricular pre-excitation, more frequent SVT and new left ventricular dysfunction (LVEF from 60% to 40%). He was started on amiodarone which resulted in significant sinus bradycardia, intermittent ventricular pre-excitation and first degree AV block with significant increase in ORT events. His Electrophysiology study confirmed SPAP which was successfully ablated from the antegrade approach after careful mapping. After one month, follow-up echocardiogram showed an improved ejection fraction to 60%. CONCLUSION: Left ventricular dysfunction due to dyssynchrony and symptomatic frequent ORT of right SPAP can develop in the setting of new iatrogenic diminished AV node conduction. Successful ablation will result in LV function recovery to baseline.

Cardiology/Cardiovascular Research

Grafton G, **Tita C**, Heuring JJ, Fain ES, Shah P, **Cowger JA**, **Alqarqaz M**, and **Basir MB**. Continuous-Flow Intra-Aortic Percutaneous Mechanical Circulatory Support in Heart Failure With Worsening Renal Function. *Circ Heart Fail* 2023; Epub ahead of print. PMID: 36802728. Request Article

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Cardiology/Cardiovascular Research

Kostantinis S, Simsek B, Karacsonyi J, Rempakos A, **Alaswad K**, **Megaly M**, Krestyaninov O, Khelimskii D, Karmpaliotis D, Jaffer FA, Khatri JJ, Poommipanit P, Patel MP, Mahmud E, Koutouzis M, Tsiafoutis I, Gorgulu S, Elbarouni B, Nicholson W, Jaber W, Rinfret S, Abi Rafeh N, Goktekin O, ElGuindy AM, Allana SS, Rangan BV, Sandoval Y, Burke MN, and Brilakis ES. Impact of proximal cap ambiguity on the procedural techniques and outcomes of chronic total occlusion percutaneous coronary intervention: Insights from the PROGRESS-CTO Registry. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 36740235. Full Text

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BACKGROUND: Proximal cap ambiguity is a key parameter in the global chronic total occlusion (CTO) percutaneous coronary intervention (PCI) crossing algorithm. METHODS: We examined the baseline characteristics and procedural outcomes of 9718 CTO PCIs performed in 9498 patients at 41 US and non-US centers between 2012 and 2022. RESULTS: Proximal cap ambiguity was present in 35% of CTO lesions. Patients whose lesions had proximal cap ambiguity were more likely to have had prior coronary artery bypass graft surgery (37% vs. 24%; $p < 0.001$). Lesions with proximal cap ambiguity were more complex with higher J-CTO score (3.1 ± 1.0 vs. 2.0 ± 1.2; $p < 0.001$) and lower technical (79% vs. 90%; $p < 0.001$) and procedural (77% vs. 89%; $p < 0.001$) success rates compared with nonambiguous CTO lesions. The incidence of major adverse cardiovascular events (MACE) was higher in cases with proximal cap ambiguity (2.5% vs. 1.7%; $p < 0.001$). The retrograde approach was more commonly used among cases with ambiguous proximal cap (50% vs. 21%; $p < 0.001$) and was more likely to be the final successful crossing strategy (29% vs. 13%; $p < 0.001$). The antegrade dissection and re-entry (ADR) "move-the-cap" techniques were also more common among cases with proximal cap ambiguity. CONCLUSIONS: Proximal cap ambiguity in CTO lesions is associated with higher utilization of the retrograde approach and ADR, lower technical and procedural success rates, and higher incidence of in-hospital MACE.

Cardiology/Cardiovascular Research
Lee JC, Geske JB, Narang A, Khalique OK, Choi AD, Sun YP, Cavalcante JL, Pinto DS, Gafoor SA, Jagasia DH, DiCarli MF, Villines TC, Little SH, Hahn RT, and **Wang DD**. Structural Heart Imaging Survey Highlights: Training, Challenges, and Practice Patterns in Interventional Imaging. *JACC Cardiovasc Imaging* 2023; 16(2):255-258. PMID: 36648041. Full Text

Cardiology/Cardiovascular Research
Megaly M, **Gandolfo C**, **Zakhour S**, Jiang M, Burgess K, Chetcuti S, Ragosta M, Adler E, Coletti A, **O'Neill B**, **Alaswad K**, and **Basir MB**. Utilization of TandemHeart in cardiogenic shock: Insights from the THEME registry. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 36748804. Full Text

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BACKGROUND: TandemHeart has been demonstrated to improve hemodynamic and metabolic complications in cardiogenic shock (CS). Contemporary outcomes have not been reported. OBJECTIVES: To evaluate the outcomes of the TandemHeart (LivaNova) in contemporary real-world use. METHODS: We analyzed baseline characteristics, hemodynamic changes, and outcomes of all patients treated with TandemHeart who were enrolled in the THEME registry, a multicenter, prospective, observational study. RESULTS: Between May 2015 and June 2019, 50 patients underwent implantation of the TandemHeart device. 22% of patients had TandemHeart implanted within 12 h, 32% within 24 h, and 52% within 48 h of CS diagnosis. Cardiac index (CI) was significantly improved 24 h after

implantation (median change 1.0, interquartile range (IQR) (0.5-1.4 L/min/m(2)). In survivors, there was a significant improvement in CI (1.0, IQR (0.5-2.25 L/min/m(2)) and lactate clearance -2.3 (-5.0 to -0.7 mmol/L). The 30-day and 180-day survival were 74% (95% confidence interval: 60%-85%) and 66% (95% confidence interval: 51%-79%), respectively. Survival was similarly high in those in whom TandemHeart has been used as a bridge to surgery (85% 180-day survival). CONCLUSION: In a contemporary cohort of patients presenting in CS, the use of TandemHeart is associated with a 74% 30-day survival and a 66% 180-day survival.

Cardiology/Cardiovascular Research

Rempakos A, Simsek B, Kostantinis S, Karacsonyi J, Choi JW, Poommipanit P, Khatri JJ, Jaber W, Rinfret S, Nicholson W, Gorgulu S, Jaffer FA, Chandwaney R, Koutouzis M, Tsiafoutis I, **Alaswad K**, Krestyaninov O, Khelimskii D, Karmpaliotis D, Uretsky BF, Patel MP, Mahmud E, Potluri S, Rangan BV, Mastrodemos OC, Allana S, Sandoval Y, Burke NM, and Brilakis ES. Impact of lesion length on the outcomes of chronic total occlusion percutaneous coronary intervention: Insights from the PROGRESS-CTO registry. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 36740236. Full Text

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BACKGROUND: The impact of occlusion length 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 10,335 CTO PCIs at 42 US and non-US centers between 2012 and 2022. The cohort was divided into two groups based on lesion length (≥20 mm vs. <20 mm). RESULTS: Long lesions were present in 7208 (70%) patients. Comorbidities were more common in patients with long CTOs. Compared with short lesions, long lesions had higher J-CTO score (2.8 ± 1.1 vs. 1.3 ± 1; $p < 0.001$) and retrograde wiring was more often the initial (15.5% vs. 4.0%; $p < 0.001$) and successful (22.8% vs. 8.2%; $p < 0.001$) crossing strategy. Long lesions were more likely to require longer procedure (123 vs. 91 min; $p < 0.001$) and fluoroscopy (47.1 vs. 32.2 min; $p < 0.001$) time, larger contrast volume (218 vs. 200 mL; $p < 0.001$) and higher air kerma radiation dose (2.4 vs. 1.7 Gy; $p < 0.001$). After adjusting for potential confounders, long lesions were associated with lower technical success (odds ratio [OR]: 0.91 per 10 mm increase; 95% confidence interval [CI]: 0.88, 0.94) and higher major adverse cardiovascular events (MACE) (OR: 1.08 per 10 mm increase; 95% CI: 1.02, 1.15). CONCLUSIONS: CTO PCI of long occlusions is independently associated with lower rates of technical success and higher rates of in-hospital MACE.

Cardiology/Cardiovascular Research

Saleem M, Sadat B, **Van Harn M**, and **Ananthasubramaniam K**. Towards a Diagnosis of Cardiac Amyloidosis: Single Center Experience with (99m) Technetium Pyrophosphate Planar Imaging and Opportunities for Standardization of Diagnostic Workflow. *Medicina (Kaunas)* 2023; 59(2). PMID: 36837580. Full Text

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Background and Objectives: Cardiac amyloidosis is a disorder caused by amyloid fibril deposition in the extracellular space of the heart. Almost all forms of clinical cardiac amyloidosis are transthyretin amyloidosis (ATTR) or light chain amyloidosis. (99m) technetium pyrophosphate ((99m)Tc PYP scan) has changed the landscape of the non-biopsy diagnosis of ATTR cardiac amyloidosis (ATTR-CA) by providing remarkably high diagnostic accuracy. We examined our experience with PYP scans in patients undergoing workup for ATTR-CA and evaluated the diagnostic workflow in patients with intermediate PYP scan results. Materials and Methods: Retrospective chart review study in which we analyzed data of 84 patients who underwent c-99m pyrophosphate (PYP) SPECT scan for the diagnosis of ATTR-CA from 2017 till 2021 at our institution. We identified three groups: Low uptake (PYPL uptake ratio < 1.2 + visual grade 1/0), n = 30, Intermediate uptake (PYPI uptake ratio 1.2-1.49, visual grade 2/3), n = 25 and High uptake (PYPH uptake ratio ≥ 1.5 + visual grade 2/3), n = 29. We reviewed patients' demographics, medical histories, echo parameters and diagnostic testing including light chain analysis, cardiac magnetic resonance results, and biopsies. Results: Mean patients' age was 73, male-to=female ratio 3:1, 59% of patients were African American. Cardiovascular comorbidities, cardiac biomarkers (BNP and Troponin) and amyloid-related neuropathy were similar in all groups. A statistically significant difference in septal thickness/posterior wall thickness and final diagnosis were found between the groups. The distribution of overall diagnostic testing ratios for the PYPI group included serum protein electrophoresis 92%, urine protein electrophoresis 65%, free light chain 80%, CMR 32%, tissue biopsy done in 20% and BM biopsy in 16%, which are similar to the ratios of other groups. Overall, 25% (n = 5, 4 TTR-CA and 1 AL Amyloid) of patients in the PYPI group had a final diagnosis of CA established with additional testing (p = 0.001 vs. other groups). Conclusions: The (99m)PYP scan is an accurate noninvasive test for cardiac ATTR-CA. Importantly, 25% of the PYPI group had a final diagnosis of ATTR-CA reiterating that diagnosis needs to be pursued in PYPI cases based on clinical suspicion. Routine evaluation and exclusion of light chain disease and establishing a consistent workflow for amyloid diagnosis and continued education for technologists and readers of PYP scans is key to a successful amyloidosis workup.

Cardiology/Cardiovascular Research

Sedhom R, Dang AT, Elwagdy A, **Megaly M**, Elgendy IY, Zahr F, Gafoor S, Mamas M, and Elbadawi A. Outcomes with plug-based versus suture-based vascular closure device after transfemoral transcatheter aortic valve replacement: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 36802100. Full Text

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Swedish Heart and Vascular Institute, Seattle, Washington, USA.
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BACKGROUND: Studies comparing plug-based (i.e., MANTA) with suture-based (i.e., ProStar XL and ProGlide) vascular closure devices (VCDs) for large-bore access closure after transcatheter aortic valve replacement (TAVR) have yielded mixed results. AIMS: To examine the comparative safety and efficacy of both types of VCDs among TAVR recipients. METHODS: An electronic database search was performed through March 2022 for studies comparing access-site related vascular complications with

plug-based versus suture-based VCDs for large-bore access site closure after transfemoral (TF) TAVR. RESULTS: Ten studies (2 randomized controlled trials [RCTs] and 8 observational studies) with 3113 patients (MANTA = 1358, ProGlide/ProStar XL = 1755) were included. There was no difference between plug-based and suture-based VCD in the incidence of access-site major vascular complications (3.1% vs. 3.3%, odds ratio [OR]: 0.89; 95% confidence interval [CI]: 0.52-1.53). The incidence of VCD failure was lower in plug-based VCD (5.2% vs. 7.1%, OR: 0.64; 95% CI: 0.44-0.91). There was a trend toward a higher incidence of unplanned vascular intervention in plug-based VCD (8.2% vs. 5.9%, OR: 1.35; 95% CI: 0.97-1.89). Length of stay was shorter with MANTA. Subgroup analyses suggested significant interaction based on study designs such that there was higher incidence of access-site vascular complications and bleeding events with plug-based versus suture-based VCD among RCTs. CONCLUSION: In patients undergoing TF-TAVR, large-bore access site closure with plug-based VCD was associated with a similar safety profile as suture-based VCD. However, subgroup analysis showed that plug-based VCD was associated with higher incidence of vascular and bleeding complications in RCTs.

Cardiology/Cardiovascular Research

Sedhom R, Elbadawi A, **Megaly M**, Athar A, Bharadwaj AS, Prasad V, Cameron SJ, Weinberg I, Mamas MA, Messerli AW, Jaber W, and Elgendy IY. Outcomes with catheter-directed thrombolysis versus catheter-directed embolectomy among patients with high-risk pulmonary embolism: A nationwide analysis. *Eur Heart J Acute Cardiovasc Care* 2023; Epub ahead of print. PMID: 36738291. Full Text

Division of Cardiology, Loma Linda University Medical Center, Loma Linda, CA, USA.
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OBJECTIVE: To examine the clinical outcomes with catheter-directed thrombolysis (CDT) vs. catheter-directed embolectomy (CDE) for high-risk pulmonary embolism (PE). BACKGROUND: Comparative data on the short-term outcomes for CDE vs. CDT among patients with high-risk PE are scarce. METHODS: The Nationwide Readmissions Database was utilized to identify hospitalizations with high-risk PE undergoing CDE or CDT from 2016 to 2019. The main outcome of interest was all-cause in-hospital mortality. Propensity score matching was used to compare the outcomes in both groups. RESULTS: Among 3,216 high-risk PE hospitalizations undergoing catheter-directed interventions, 868 (27%) received CDE, 1,864 (58%) received CDT and 484 (15%) received both procedures. In the unadjusted analysis, the rate of all-cause in-hospital mortality was not between both CDE and CDT (39.6% vs. 34.2%, P = 0.07). After propensity score matching, CDE was not associated with higher mortality (adjusted odds ratio [OR] 1.28, 95% confidence interval [CI] 0.95, 1.72, P = 0.10), intracranial hemorrhage (ICH) (adjusted OR 1.57, 95% CI 0.75, 3.29, P = 0.23) or non-ICH bleeding (adjusted OR 1.17, 95% CI 0.85, 1.62, P = 0.33). There were no differences in the length of stay, cost and 30-day unplanned readmissions between both groups. CONCLUSIONS: In this contemporary observational analysis of patients admitted with high-risk PE undergoing CDT or CDE, the rates of in-hospital mortality, ICH and non-ICH bleeding events were not different.

Cardiology/Cardiovascular Research

Simsek B, Carlino M, Ojeda S, Pan M, Rinfret S, Vemmou E, Kostantinis S, Nikolakopoulos I, Karacsonyi J, Quadros AS, Dens JA, Abi Rafeh N, Agostoni P, **Alaswad K**, Avran A, Belli KC, Choi JW, Elguindy A, Jaffer FA, Doshi D, Karmpaliotis D, Khatri JJ, Khelimskii D, Knaapen P, La Manna A, Krestyaninov O, Lamelas P, Padilla L, de Oliveira PP, Spratt JC, Tanabe M, Walsh S, Goktekin O, Gorgulu S, Mastrodemos OC, Allana S, Rangan BV, Kearney KE, Lombardi WL, Grantham JA, Hirai T, Brilakis ES, and Azzalini L. Validation of the OPEN-CLEAN Chronic Total Occlusion Percutaneous Coronary Intervention Perforation Score in a Multicenter Registry. *Am J Cardiol* 2023; 188:30-35. PMID: 36462272. Full Text

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Coronary artery perforation is one of the most common and feared complications of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). We evaluated the utility of the recently presented OPEN-CLEAN (Coronary artery bypass graft, Length of occlusion, Ejection fraction, Age, calcificatioN) perforation score in an independent multicenter CTO PCI dataset. Of the 2,270 patients who underwent CTO PCI at 7 centers, 150 (6.6%) suffered coronary artery perforation. Patients with perforations were older (69 ± 10 vs 65 ± 10, p <0.001), more likely to be women (89% vs 82%, p = 0.010), more likely to have history of previous coronary artery bypass graft (38% vs 20%, p <0.001), and unfavorable angiographic characteristics such as blunt stump (64% vs 42%, p <0.001), proximal cap ambiguity (51% vs 33%, p <0.001), and moderate-severe calcification (57% vs 43%, p = 0.001). Technical success was lower in patients with perforations (69% vs 85%, p <0.001). The area under the receiver operating characteristic curve of the OPEN-CLEAN perforation risk model was 0.74 (95%

confidence interval 0.68 to 0.79), with good calibration (Hosmer-Lemeshow p = 0.72). We found that the CTO PCI perforation risk increased with higher OPEN-CLEAN scores: 3.5% (score 0 to 1), 3.1% (score 2), 5.3% (score 3), 7.1% (score 4), 11.5% (score 5), 19.8% (score 6 to 7). In conclusion, given its good performance and ease of preprocedural calculation, the OPEN-CLEAN perforation score appears to be useful for quantifying the perforation risk for patients who underwent CTO PCI.

Cardiology/Cardiovascular Research

Trachtenberg B, and **Cowger J**. HFSA Expert Consensus Statement on the Medical Management of Patients on Durable Mechanical Circulatory Support. *J Card Fail* 2023; Epub ahead of print. PMID: 36828256. Full Text

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The medical management of patients supported with durable continuous flow left ventricular assist device (LVAD) support encompasses pharmacologic therapies administered in the preoperative, intraoperative, postoperative and chronic LVAD support stages. As patients live longer on LVAD support, the risks of LVAD-related complications and progression of cardiovascular and other diseases increase. Using existing data from cohort studies, registries, randomized trials and expert opinion, this Heart Failure Society of America Consensus Document on the Medical Management of Patients on Durable Mechanical Circulatory Support offers best practices on the management of patients on durable MCS, focusing on pharmacological therapies administered to patients on continuous flow LVADs. While quality data in the LVAD population are few, the utilization of guideline directed heart failure medical therapies (GDMT) and the importance of blood pressure management, right ventricular preload and afterload optimization, and antiplatelet and anticoagulation regimens are discussed. Recommended pharmacologic regimens used to mitigate or treat common complications encountered during LVAD support, including arrhythmias, vasoplegia, mucocutaneous bleeding, and infectious complications are addressed. Finally, this document touches on important potential pharmacological interactions from anti-depressants, herbal and nutritional supplements of relevance to providers of patients on LVAD support.

Center for Health Policy and Health Services Research

Lim S, **Schultz L**, Zakko P, **Macki M**, **Hamilton T**, **Pawloski J**, **Fadel H**, **Mansour T**, **Yeh HH**, Preston G, **Nerenz D**, **Schwalb JM**, **Abdulhak M**, Park P, Aleem I, Easton R, Khalil J, Perez-Cruet M, Park D, and **Chang V**. The Potential Negative Effects of Smoking on Cervical and Lumbar Surgery beyond Pseudoarthrosis: A Michigan Spine Surgery Improvement Collaborative (MSSIC) Study. *World Neurosurg* 2023; Epub ahead of print. PMID: 36791883. Full Text

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OBJECTIVE: The study was designed to review the Michigan Spine Surgery Improvement Collaborative (MSSIC) registry to investigate the long-term associations between current smoking status and outcomes after elective cervical and lumbar spine surgery. METHODS: Utilizing MSSIC we captured all cases from 01/01/17-11/21/20 with outcomes data available. 19,251 lumbar cases and 7,936 cervical cases were included. Multivariate regression analyses were performed to assess the relationship of smoking with the clinical outcomes. RESULTS: Current smoking status was associated with lower urinary retention and satisfaction for lumbar surgery patients and was also associated with less likelihood of achieving minimal clinically important difference (MCID) in Patient-Reported Outcomes Measurement Information System (PROMIS), back pain, leg pain, and EQ5D at 90 days and 1 year after surgery. Current smokers were also less likely to return to work at 90 days and 1 year after surgery. For cervical patients, current smokers were less likely to have urinary retention and dysphagia postoperatively. They were less likely to be satisfied with the surgery outcome at 1 year. Current smoking was associated with lower likelihood of achieving MCID in PROMIS, neck pain, arm pain, and EQ5D at various time points. There was no difference in return-to-work status. CONCLUSION: Our analysis suggests that smoking is negatively associated with functional improvement, patient satisfaction, and return-to-work after elective spine surgery.

Center for Health Policy and Health Services Research

Schulkey CE, Litwin TR, Ellsworth G, Sansbury H, **Ahmedani BK**, Choi KW, Cronin R, Kloth Y, Ashbeck AW, Sutherland S, Mapes B, Begale M, Bhat G, King P, Marginean K, Wolfe KA, Kouame A, Raquel C, Ratsimbazafy F, Bornemeier Z, Neumeier K, Baskir R, Gebo KA, Denny J, Smoller JW, and Garriock HA. Design and Implementation of the All of Us Research Program COVID-19 Participant Experience (COPE) Survey. *Am J Epidemiol* 2023; Epub ahead of print. PMID: 36799620. Full Text

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Kelly Gebo performed this work in her role as the Chief Medical and Scientific Officer of the All of Us Research Program.

In response to the rapidly evolving COVID-19 pandemic, the All of Us Research Program longitudinal cohort study developed the COVID-19 Participant Experience (COPE) survey to better understand the pandemic experiences and health impacts of COVID-19 on diverse populations within the United States. Six survey versions were deployed between May 2020 and March 2021 covering mental health, loneliness, activity, substance use, and discrimination, as well as COVID-19 symptoms, testing, treatment, and vaccination. A total of 104,910 All of Us Research Program participants, of whom over 73% were from communities traditionally underrepresented in biomedical research, completed 275,201 surveys; 9,693 completed all six surveys. Response rates varied widely among demographic groups and

were lower among participants from certain racial and ethnic minority populations, participants with low income or educational attainment, and participants with a Spanish language preference. Survey modifications improved participant response rates between the first and last surveys (13.9% to 16.1%, $p < 0.001$). This paper describes a dataset with longitudinal COVID-19 survey data in a large, diverse population that will enable researchers to address important questions related to the pandemic, a dataset which is of additional scientific value when combined with the program's other data sources.

Center for Health Policy and Health Services Research
Wastler HM, **Llamocca E**, Moe AM, Steelsmith DL, Brock G, Bridge JA, Campo JV, and Fontanella CA. Impact of Treatment Initiation and Engagement on Deliberate Self-Harm Among Individuals With First-Episode Psychosis. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 36852553. Request Article

Departments of Psychiatry and Behavioral Health (Wastler, Llamocca, Moe, Fontanella), Psychology (Moe), Biomedical Informatics (Brock), and Pediatrics (Bridge), Ohio State University, Columbus; Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit (Llamocca); Center for Suicide Prevention and Research, Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, Ohio (Steelsmith, Bridge, Fontanella); Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore (Campo).

OBJECTIVE: Individuals with psychosis are at increased risk for suicide, with the greatest risk being present during the first few months after diagnosis. The authors aimed to examine whether treatment initiation within 14 days of diagnosis and treatment engagement within 90 days of initiation reduce the risk for deliberate self-harm (DSH) among individuals with first-episode psychosis (FEP). METHODS: A retrospective longitudinal cohort design was adopted by using Ohio Medicaid claims for 6,349 adolescents and young adults ages 15-24 years with FEP. Logistic regression was used to examine factors associated with treatment initiation and engagement. Cox proportional hazard models were used to estimate the impact of treatment initiation and engagement on DSH. Propensity score weighting was used to control for sociodemographic and clinical covariates. RESULTS: Approximately 70% of the sample initiated treatment, 55% of whom engaged in treatment. Treatment initiation and engagement were associated with both demographic and clinical variables. Treatment initiation significantly reduced the hazard of DSH (average treatment effect in the entire population: hazard ratio [HR]=0.62, 95% CI=0.47-0.81; average treatment effect among those treated: HR=0.64, 95% CI=0.52-0.80). In contrast, treatment engagement was not significantly associated with DSH. CONCLUSIONS: These results suggest that the initial treatment contact is essential for reducing DSH among adolescents and young adults with FEP. Additionally, the finding that treatment engagement did not reduce DSH suggests that standard clinical care may not be sufficient for reducing DSH in this population. These findings highlight the need for suicide-specific interventions for individuals with FEP.

Center for Health Policy and Health Services Research
Wong RJ, **Rupp L**, **Lu M**, Yang Z, Daida YG, Schmidt M, Boscarino JA, **Gordon SC**, and Chitnis AS. Prevalence of Hepatitis B Virus (HBV) and Latent Tuberculosis Co-Infection and Risk of Drug-Induced Liver Injury Across Two Large HBV Cohorts in the United States. *J Viral Hepat* 2023; Epub ahead of print. PMID: 36843435. Full Text

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The epidemiology of latent tuberculosis and hepatitis B virus (HBV-LTBI) co-infection among U.S. populations is not well studied. We aim to evaluate LTBI testing patterns and LTBI prevalence among two large U.S. cohorts of adults with chronic HBV (CHB). Adults with CHB in the Chronic Hepatitis Cohort Study (CHeCS) and Veterans Affairs national cohort were included in the analyses. Prevalence of HBV-LTBI co-infection was defined as the number of HBV patients with LTBI divided by the number of HBV patients in a cohort. Multivariable logistic regression evaluated odds of HBV-LTBI co-infection among CHB patients who underwent TB testing. Among 6,019 CHB patients in the CHeCS cohort (44% female, 47% Asian), 9.1% were tested for TB, among whom 7.7% had HBV-LTBI co-infection. Among HBV-LTBI co-infected patient, only 16.7% (n=7) received LTBI treatment, among whom 28.6% (n=2) developed DILI. Among 12,928 CHB patients in the VA cohort (94% male, 42% African American, 39% non-Hispanic white), 14.7% were tested for TB, among whom 14.5% had HBV-LTBI. Among HBV-LTBI co-infected patient, 18.6% (n=51) received LTBI treatment, among whom 3.9% (n=3) developed DILI. Presence of cirrhosis, race/ethnicity, and country of birth were observed to be associated with odds of HBV-LTBI co-infection among CHB patients who received TB testing. In summary, among two large distinct U.S. cohorts of adults with CHB, testing for LTBI was infrequent despite relatively high prevalence of HBV-LTBI co-infection. Moreover, low rates of LTBI treatment were observed among those with HBV-LTBI co-infection.

Dermatology

Bui H, Bechara FG, George R, Goldberg S, **Hamzavi I**, Kirby JS, Saylor D, and Sayed CJ. Surgical Procedural Definitions for Hidradenitis Suppurativa Developed by Expert Delphi Consensus. *JAMA Dermatol* 2023; Epub ahead of print. PMID: 36811866. Full Text

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IMPORTANCE: Various surgical approaches for hidradenitis suppurativa (HS) have been described in the literature, but the nomenclature is inconsistent. Excisions have been described as wide, local, radical, and regional with variable descriptions of margins. Deroofing procedures have been described with various approaches though descriptions of the approach are generally more uniform. No international consensus has been formed to globally standardize terminology for HS surgical procedures. Lack of such agreement may contribute to misunderstanding or misclassification in HS procedural research studies and impair clear communication among clinicians or between clinicians and patients. OBJECTIVE: To create a set of standard definitions for HS surgical procedures. DESIGN, SETTING, AND PARTICIPANTS: This consensus agreement study was conducted from January to May 2021 using the modified Delphi consensus method to reach agreement among a group of international HS experts regarding standardized definitions for an initial set of HS surgical terms, including "incision and drainage," "deroofing/unroofing," "excision," "lesional excision," and "regional excision," ultimately expanded to 10 terms. Provisional definitions were drafted based on existing literature and discussion among an expert 8-member steering committee. Online surveys were disseminated to members of the HS Foundation, direct contacts of the expert panel, and the HSPlace listserv to reach physicians with considerable experience with HS surgery. Consensus was defined as greater than 70% agreement to accept a definition. RESULTS: In the first and second modified Delphi round, 50 and 33 experts participated, respectively. Ten surgical procedural terms and definitions reached consensus with greater than 80% agreement. Overall, the term "local" excision was abandoned and replaced with the descriptors "lesional" or "regional" excision. Of note, "regional" replaced the terms "wide" and "radical" excision. Furthermore, modifiers such as "partial" vs "complete" should also be included when describing surgical procedures. A combination of these terms helped formulate the final glossary of HS surgical procedural definitions. CONCLUSION AND RELEVANCE: An international group of HS experts agreed on a set of definitions describing surgical procedures frequently used by clinicians and in the literature. The standardization and application of such

definitions are vital to allow for accurate communication, reporting consistency, and uniform data collection and study design in the future.

Dermatology
Gold LS, Papp K, Pariser D, Bhatia N, Sofen H, Albrecht L, Gooderham M, Duffin KC, Chen M, Paris M, Cheng S, Picard H, Wang Y, and Green L. Efficacy and safety of apremilast in patients with mild-to-moderate psoriasis up to 32 weeks: Results from the extension phase of the randomized, phase 3 ADVANCE trial. *J Am Acad Dermatol* 2023; 88(2):430-433. Full Text

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Dermatology
Krutmann J, Piquero-Casals J, Morgado-Carrasco D, Granger C, Trullàs C, Passeron T, and **Lim HW**. Photoprotection for people with skin of colour: needs and strategies. *Br J Dermatol* 2023; 188(2):168-175. PMID: 36763874. Full Text

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Skin of colour or pigmented skin has unique characteristics: it has a higher eumelanin-to-pheomelanin ratio, more mature melanosomes, an increased amount of melanin distributed in the upper layers of the epidermis, and more efficient DNA repair compared with lighter skin. However, individuals with skin of colour are at a significant risk of skin damage caused by ultraviolet radiation, including the development of photodermatoses and photoageing changes such as uneven skin tone, and are predisposed to pigmentary disorders. In fact, one of the most common conditions leading to dermatology consultations by patients with skin of colour is photoexacerbated pigmentary disorders. Unfortunately, individuals with skin of colour may be less prone to engage in photoprotective measures, including the use of sunscreens. Physicians are also less likely to prescribe sunscreens for them. There is thus a clear need for better education on photodamage and for more efficient and suitable photoprotection in populations with skin of colour. However, this need has thus far only partially been met, and the development of sunscreen products designed to provide optimal photoprotection for people with skin of colour remains a challenge. Targeted sunscreens for individuals with skin of colour require optimal cosmetic appeal (leaving no white residue and not disrupting skin tone). They should include broad-spectrum [ultraviolet (UV)B/UVA] protection with high sun protection factor, as well as protection against long-wave UVA (UVA1) and visible light, as these wavelengths are capable of inducing or augmenting pigmentary disorders. They may also contain depigmenting agents for patients with pigmentary disorders.

Dermatology
Lyons AB, **Ozog DM**, **Lim HW**, **Viola K**, **Tang A**, and **Jones LR**. Commentary on: Re: "The Detroit Keloid Scale: A Validated Tool for Rating Keloids" by Lyons et al. *Facial Plast Surg Aesthet Med* 2023; Epub ahead of print. PMID: 36749139. Full Text

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Dermatology

Wuennenberg J, **Kolli SS**, **Powers M**, and **Ozog D**. Surgeon's Knot With 3 Throws to Facilitate Wound Closure: A Video Walkthrough. *Dermatol Surg* 2023; Epub ahead of print. PMID: 36799887. Full Text

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Diagnostic Radiology

Soliman SB. A 75-year-old woman with left hand pain. *Skeletal Radiol* 2023; 52(2):277-278. PMID: 36028566. Full Text

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Emergency Medicine

Ayyash M, **Ayyash M**, Saad F, Alaouie M, and Blackwood RA. A comparison of the experiences, challenges and coping strategies for parents of children with autism residing in the United States and The Arab World. *J Natl Med Assoc* 2023; Epub ahead of print. PMID: 36828706. Full Text

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Most research on autism has targeted White Americans. Although challenges and coping mechanisms are present for all parents, some aspects are influenced by culture. This study aims to compare the experiences, challenges and coping strategies for parents of children with autism residing in the US and Arab countries. A survey, available in both English and Arabic, was posted electronically on social media support groups for parents of children with autism in Arab countries and the US. The survey covered experiences, challenges and coping strategies for raising a child with autism spectrum disorder. 165 surveys were collected from 15 Arab countries and 235 surveys were collected from 32 US states. On a scale from 1 to 5, with 5 being highest satisfaction, US parents reported a higher satisfaction for the overall diagnostic process with median score of 3.0 compared to 2.5 for parents in Arab countries. Parents in both countries reported information seeking/self-education about autism and acceptance and/or religion as the 2 most valuable coping strategies. Lower satisfaction with all aspects of the diagnosis process was found among parents in Arab countries compared to those residing in the US. Lack of community support for Arab parents was also a more significant challenge compared to US parents. With such poor community support for Arab parents, it is pivotal to expand upon initiatives that minimize the stigma and shame associated with an autism diagnosis to ultimately reduce challenges and allow for better parental experiences.

Emergency Medicine

Harnett NG, Fani N, Carter S, Sanchez LD, Rowland GE, Davie WM, **Guzman C**, Lebois LAM, Ely TD, van Rooij SJH, Seligowski AV, Winters S, Grasser LR, Musey PI, Jr., Seamon MJ, House SL, Beaudoin FL, An X, Zeng D, Neylan TC, Clifford GD, Linnstaedt SD, Germine LT, Bollen KA, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Hendry PL, Sheikh S, Jones CW, Punches BE, Swor RA, Hudak LA, Pascual JL, Harris E, Chang AM, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, Bruce SE, Miller MW, Pietrzak RH, Joormann J, Barch DM, Pizzagalli DA, Harte SE, Elliott JM, Kessler RC, Koenen KC, McLean SA, Jovanovic T, Stevens JS, and Ressler KJ. Structural inequities contribute to racial/ethnic differences in neurophysiological tone, but not threat reactivity, after trauma exposure. *Mol Psychiatry* 2023; Epub ahead of print. PMID: 36725899. Full Text

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Considerable racial/ethnic disparities persist in exposure to life stressors and socioeconomic resources that can directly affect threat neurocircuitry, particularly the amygdala, that partially mediates susceptibility to adverse posttraumatic outcomes. Limited work to date, however, has investigated potential racial/ethnic variability in amygdala reactivity or connectivity that may in turn be related to outcomes such as post-traumatic stress disorder (PTSD). Participants from the AURORA study (n = 283), a multisite longitudinal study of trauma outcomes, completed functional magnetic resonance imaging and psychophysiology within approximately two-weeks of trauma exposure. Seed-based amygdala connectivity and amygdala reactivity during passive viewing of fearful and neutral faces were assessed during fMRI. Physiological activity was assessed during Pavlovian threat conditioning. Participants also reported the severity of posttraumatic symptoms 3 and 6 months after trauma. Black individuals showed lower baseline skin conductance levels and startle compared to White individuals, but no differences were observed in physiological reactions to threat. Further, Hispanic and Black participants showed greater amygdala connectivity to regions including the dorsolateral prefrontal cortex (PFC), dorsal anterior cingulate cortex, insula, and cerebellum compared to White participants. No differences were observed in amygdala reactivity to threat. Amygdala connectivity was associated with 3-month PTSD symptoms, but the associations differed by racial/ethnic group and were partly driven by group differences in structural inequities. The present findings suggest variability in tonic neurophysiological arousal in the early aftermath of trauma between racial/ethnic groups, driven by structural inequality, impacts neural processes that mediate susceptibility to later PTSD symptoms.

Emergency Medicine

Mathew S, Harrison N, **Ajimal S**, Silvagi R, Reece R, **Klausner H**, Levy P, Dunne R, and O'Neil B. Treatment and Outcome Variation in Out-of-hospital Cardiac Arrest Among Four Urban Hospitals in Detroit. *Resuscitation* 2023;109731. Epub ahead of print. PMID: 36775019. Full Text

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AIMS: To determine whether out-of-hospital cardiac arrest (OHCA) post-resuscitation management and outcomes differ between four Detroit hospitals. INTRODUCTION: Significant variation exists in treatment/outcomes from OHCA. Disparities between hospitals serving a similar population is not well known. METHODS: Retrospective OHCA data was collected from the Detroit-Cardiac Arrest Registry (DCAR) between January 2014 to December 2019. Four hospitals were compared on two treatments (angiography, do not resuscitate (DNR)) and two outcomes (cerebral performance category (CPC) ≤ 2, in-hospital death). Models for death and CPC were tested with and without coronary angiography and DNR status. RESULTS: 999 patients at hospitals A - D differed ($p<0.05$) before multivariable adjustment by age, race, witnessed arrest, dispatch-emergency department (ED) time, TTM, coronary angiography, DNR order, and in-hospital death. Rates of death and CPC ≤ 2 were worse in Hospital A (82.8%, 10%, respectively) compared to others (69.1%, 14.1%). After multivariable adjustment, Hospital A performed angiography less compared to B (OR=0.17) and was more likely to initiate new DNR status than B (OR=2.9), C (OR=16.1), or D (OR=3.6). CPC ≤ 2 were worse in Hospital A compared to B (OR=0.27) and D (OR=0.35). After sensitivity analysis, CPC ≤ 2 odds did not differ for A versus B (OR=0.58, adjusted for angiography) or D (OR=0.65, adjusted for DNR). Odds of death, despite angiography and DNR differences, were worse in Hospital A compared to B (OR=1.87) and D (OR=1.81). CONCLUSION: Differing rates of DNR and coronary angiography was associated with observed disparities in favorable neurologic outcome, but not death, between four Detroit hospitals.

Emergency Medicine

Morris DC, **Zhang ZG**, **Jaehne AK**, **Zhang J**, and **Rivers EP**. CLINICAL, MOLECULAR, AND EXOSOMAL MECHANISMS OF CARDIAC AND BRAIN DYSFUNCTION IN SEPSIS. *Shock* 2023; 59(2):173-179. PMID: 36731014. Full Text

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Sepsis is a complex disease resulting from a dysregulated inflammatory response to an infection. Initiation of sepsis occurs from a localized infection that disseminates to the bloodstream placing all organ systems at risk. Septic shock is classically observed to manifest itself as systemic hypotension with hyporesponsiveness to vasopressor agents. Myocardial dysfunction occurs resulting in an inability to perfuse major organ systems throughout the body. Most importantly, the brain is hypoperfused creating an ischemic and inflammatory state resulting in the clinical observation of acute mental status changes and cognitive dysfunction commonly known as sepsis-associated encephalopathy. This short review describes the inflammatory molecular mechanisms of myocardial dysfunction, discusses the evidence of the dual roles of the microglia resulting in blood-brain barrier disruption, and suggests that septic-derived exosomes, endosome-derived lipid bilayer spheroids released from living cells, influence cardiac and neurological cellular function.

Endocrinology and Metabolism

Bhan A, **Athimulam S**, Kumari P, Pal R, Bhadada SK, **Cook BC**, **Qiu S**, and **Rao SD**. Large parathyroid adenomas: Potential mechanisms to reconcile adenoma size and disease phenotype. *Front Endocrinol (Lausanne)* 2023;14:1009516. PMID: 36817587. Full Text

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Parathyroid adenomas weighing more than 3.5 g are reported variously as "atypical", "large" or "giant" parathyroid adenomas. All such adenomas are rare variants accounting for no more than 1.5% of all parathyroid adenomas. Large parathyroid adenomas are often associated with more severe form of the disease, including osteitis fibrosa cystica (OFC) and share many biochemical, histological, and molecular features of both benign and malignant parathyroid neoplasms, and are considered a distinct clinical entity. However, the pathogenesis of oversized parathyroid adenomas and the often-associated skeletal phenotype remains unclear. We present 5 cases of primary hyperparathyroidism (PHPT) with OFC, an uncommon manifestation of contemporary PHPT, associated with larger parathyroid adenomas, seen in the Bone and Mineral Disorders Clinic of the Henry Ford Health in the last 30 years to illustrate the critical role of vitamin D nutrition in the pathogenesis of both the OFC and adenoma size. The estimated prevalence of OFC was very low 0.2%, 5 of the >3000 surgically confirmed cases of PHPT seen during this time. The mean ± SD values were: age: 36.8 ± 22.1 years (4 of the 5 <36years), serum calcium 11.6 ± 1.1 mg/dl, alkaline phosphatase 799 ± 487 IU/L, PTH 1440 ± 477 pg/ml, 25-hydroxyvitamin D 13.0 ± 8.9 ng/ml, 1,25-dihyroxyvitamin D 26.5 ± 13.7 pg/ml, urine calcium 562 ± 274 mg/day, and parathyroid adenoma weight 4.53 ± 2.2 g. Parathyroidectomy led to the resolution of both the biochemical indices and OFC in each patient without recurrence over >10 years of follow-up. Because OFC is a very rare in the West, but very common areas of endemic vitamin D deficiency, we also examined the relationship between vitamin D nutrition, as assessed by serum 25-hydroxyvitamin D level, and parathyroid adenoma weight as well as prevalence of OFC in two large secularly diverse cohorts of patients with PHPT (Detroit, USA and Chandigarh, India). Based on this relationship and the relative prevalence of OFC in these two large cohorts, we propose that vitamin D nutrition (and perhaps calcium nutrition) best explains both the adenoma size and prevalence of OFC.

Gastroenterology

Currier EE, **Ichkanian Y**, **Dabaja M**, Segovia MC, Patel Y, **Nagai S**, Sudan DL, and **Jafri SM**. Cytomegalovirus Infection Management in Multivisceral and Intestinal Transplant: A Dual Institution Study. *Transplant Proc* 2023; Epub ahead of print. PMID: 36792485. Full Text

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Intestinal transplant and multivisceral transplant were originally in pediatric populations and are relatively new procedures in adults. Despite increasing success rates in the immediate post-transplant period, infectious complications and acute and chronic rejection remain significant causes of morbidity and mortality. Previous research has shown cytomegalovirus (CMV) is the main cause of infection in this population. Due to the limited patient population, incidence of CMV viremia ranges widely and there is lack of universal protocol for treatment. This dual institution retrospective chart review between Henry Ford Hospital and Duke University analyzed adult intestinal and multivisceral transplant recipients between 2009 and 2019. Of the 32 patients identified and included in the study, 15 had CMV infection (46.9%). Of those with CMV infection, 5 (33.3%) had donor positive (D+)/recipient positive (R+) status; 5

had D-/R+; 4 had D+/R-; and one had D-/R-. There was no significant difference between mortality in those who had reported infection and not (80% vs 76.5%). The data from this study show significant rates of CMV viremia in patients undergoing intestinal transplant/multivisceral transplant with almost half of our study population having documented infection within 1 year of transplant, stressing the importance for universal protocol into CMV viremia treatment.

Gastroenterology
Selim R, and Ahn J. Pruritus in Chronic Liver Disease. *Clin Liver Dis* 2023; 27(1):47-55. PMID: 36400466. Full Text

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Pruritus can be associated with chronic liver disease, particularly cholestatic liver disease. Although the pathophysiology is uncertain, there are a few proposed mechanisms and much is still being discovered. Workup involves an assessment to rule out a dermatologic, neurologic, psychogenic, or other underlying systemic disorder. First-line therapy is cholestyramine, which is generally well tolerated and effective. In those who fail cholestyramine, alternative drugs including rifampicin and μ-opioid receptor antagonists can be considered. If medical therapy is ineffective and pruritus is significant, alternative experimental therapies such as albumin dialysis, photopheresis, plasmapheresis, and biliary diversion can be considered.

Gastroenterology
Wong RJ, **Rupp L**, **Lu M**, Yang Z, Daida YG, Schmidt M, Boscarino JA, **Gordon SC**, and Chitnis AS. Prevalence of Hepatitis B Virus (HBV) and Latent Tuberculosis Co-Infection and Risk of Drug-Induced Liver Injury Across Two Large HBV Cohorts in the United States. *J Viral Hepat* 2023; Epub ahead of print. PMID: 36843435. Full Text

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The epidemiology of latent tuberculosis and hepatitis B virus (HBV-LTBI) co-infection among U.S. populations is not well studied. We aim to evaluate LTBI testing patterns and LTBI prevalence among two large U.S. cohorts of adults with chronic HBV (CHB). Adults with CHB in the Chronic Hepatitis Cohort Study (CHeCS) and Veterans Affairs national cohort were included in the analyses. Prevalence of HBV-LTBI co-infection was defined as the number of HBV patients with LTBI divided by the number of HBV patients in a cohort. Multivariable logistic regression evaluated odds of HBV-LTBI co-infection among CHB patients who underwent TB testing. Among 6,019 CHB patients in the CHeCS cohort (44% female, 47% Asian), 9.1% were tested for TB, among whom 7.7% had HBV-LTBI co-infection. Among HBV-LTBI co-infected patient, only 16.7% (n=7) received LTBI treatment, among whom 28.6% (n=2) developed DILI. Among 12,928 CHB patients in the VA cohort (94% male, 42% African American, 39% non-Hispanic white), 14.7% were tested for TB, among whom 14.5% had HBV-LTBI. Among HBV-LTBI co-infected patient, 18.6% (n=51) received LTBI treatment, among whom 3.9% (n=3) developed DILI. Presence of cirrhosis, race/ethnicity, and country of birth were observed to be associated with odds of HBV-LTBI co-infection among CHB patients who received TB testing. In summary, among two large distinct U.S. cohorts of adults with CHB, testing for LTBI was infrequent despite relatively high prevalence of HBV-

LTBI co-infection. Moreover, low rates of LTBI treatment were observed among those with HBV-LTBI co-infection.

Hematology-Oncology
Abu Rous F, and Riano I. Challenges Faced by J-1 International Medical Graduates (IMGs) During COVID-19 Pandemic. *Cancer Invest* 2023; 1-4. Epub ahead of print. PMID: 36745487. Request Article

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In March 2020, WHO declared COVID-19 a global pandemic which led to many countries closing their borders to contain the spread of the virus, stay-at-home mandates were announced and governmental entities started working on minimal capacity. Delays in visa processing and renewal is one aspect that was hugely impacted by the pandemic and led to interruption in the training of many international medical graduates (IMGs). In this manuscript, we share our stories and perspective on the challenges faced by IMGs holding J-1 visa during COVID-19 pandemic.

Hematology-Oncology
Brahmer JR, Drake CG, **Wollner I**, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL, Gilson MM, Wang C, Selby M, Taube JM, Anders R, Chen L, Korman AJ, Pardoll DM, Lowy I, and Topalian SL. Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. *J Clin Oncol* 2023; 41(4):715-723. PMID: 36706735. Full Text

From the Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Henry Ford Health Systems, Detroit, MI; Carolina BioOncology Institute, Huntersville, NC; Washington University School of Medicine Siteman Cancer Center, St Louis, MO; and Medarex, Bloomsbury, NJ, and Milpitas, CA.

PURPOSE: Programmed death-1 (PD-1), an inhibitory receptor expressed on activated T cells, may suppress antitumor immunity. This phase I study sought to determine the safety and tolerability of anti-PD-1 blockade in patients with treatment-refractory solid tumors and to preliminarily assess antitumor activity, pharmacodynamics, and immunologic correlates. PATIENTS AND METHODS: Thirty-nine patients with advanced metastatic melanoma, colorectal cancer (CRC), castrate-resistant prostate cancer, non-small-cell lung cancer (NSCLC), or renal cell carcinoma (RCC) received a single intravenous infusion of anti-PD-1 (MDX-1106) in dose-escalating six-patient cohorts at 0.3, 1, 3, or 10 mg/kg, followed by a 15-patient expansion cohort at 10 mg/kg. Patients with evidence of clinical benefit at 3 months were eligible for repeated therapy. RESULTS: Anti-PD-1 was well tolerated: one serious adverse event, inflammatory colitis, was observed in a patient with melanoma who received five doses at 1 mg/kg. One durable complete response (CRC) and two partial responses (PRs; melanoma, RCC) were seen. Two additional patients (melanoma, NSCLC) had significant lesional tumor regressions not meeting PR criteria. The serum half-life of anti-PD-1 was 12 to 20 days. However, pharmacodynamics indicated a sustained mean occupancy of > 70% of PD-1 molecules on circulating T cells ≥ 2 months following infusion, regardless of dose. In nine patients examined, tumor cell surface B7-H1 expression appeared to correlate with the likelihood of response to treatment. CONCLUSION: Blocking the PD-1 immune checkpoint with intermittent antibody dosing is well tolerated and associated with evidence of antitumor activity. Exploration of alternative dosing regimens and combinatorial therapies with vaccines, targeted therapies, and/or other checkpoint inhibitors is warranted.

Hematology-Oncology

Choueiri TK, Labaki C, Bakouny Z, Hsu CY, Schmidt AL, de Lima Lopes G, Jr., **Hwang C**, **Singh SRK**, Jani C, Weissmann LB, Griffiths EA, Halabi S, Wu U, Berg S, O'Connor TE, Wise-Draper TM, Panagiotou OA, Klein EJ, Joshi M, Yared F, Dutra MS, Gatson NTN, Blau S, Singh H, Nanchal R, McKay RR, Nonato TK, Quinn R, Rubinstein SM, Puc M, Mavromatis BH, Vikas P, Faller B, Zaren HA, Del Prete S, Russell K, Reuben DY, Accordino MK, Singh H, Friese CR, Mishra S, Rivera DR, Shyr Y, Farmakiotis D, and Warner JL. Breakthrough SARS-CoV-2 infections among patients with cancer following two and three doses of COVID-19 mRNA vaccines: a retrospective observational study from the COVID-19 and Cancer Consortium. *Lancet Reg Health Am* 2023; 19:100445. PMID: 36818595. Full Text

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BACKGROUND: Breakthrough SARS-CoV-2 infections following vaccination against COVID-19 are of international concern. Patients with cancer have been observed to have worse outcomes associated with COVID-19 during the pandemic. We sought to evaluate the clinical characteristics and outcomes of patients with cancer who developed breakthrough SARS-CoV-2 infections after 2 or 3 doses of mRNA vaccines. METHODS: We evaluated the clinical characteristics of patients with cancer who developed breakthrough infections using data from the multi-institutional COVID-19 and Cancer Consortium (CCC19; NCT04354701). Analysis was restricted to patients with laboratory-confirmed SARS-CoV-2 diagnosed in 2021 or 2022, to allow for a contemporary unvaccinated control population; potential differences were evaluated using a multivariable logistic regression model after inverse probability of treatment weighting to adjust for potential baseline confounding variables. Adjusted odds ratios (aOR)

and 95% confidence intervals (CI) are reported. The primary endpoint was 30-day mortality, with key secondary endpoints of hospitalization and ICU and/or mechanical ventilation (ICU/MV). FINDINGS: The analysis included 2486 patients, of which 564 and 385 had received 2 or 3 doses of an mRNA vaccine prior to infection, respectively. Hematologic malignancies and recent receipt of systemic anti-neoplastic therapy were more frequent among vaccinated patients. Vaccination was associated with improved outcomes: in the primary analysis, 2 doses (aOR: 0.62, 95% CI: 0.44-0.88) and 3 doses (aOR: 0.20, 95% CI: 0.11-0.36) were associated with decreased 30-day mortality. There were similar findings for the key secondary endpoints of ICU/MV (aOR: 0.60, 95% CI: 0.45-0.82 and 0.37, 95% CI: 0.24-0.58) and hospitalization (aOR: 0.60, 95% CI: 0.48-0.75 and 0.35, 95% CI: 0.26-0.46) for 2 and 3 doses, respectively. Importantly, Black patients had higher rates of hospitalization (aOR: 1.47, 95% CI: 1.12-1.92), and Hispanic patients presented with higher rates of ICU/MV (aOR: 1.61, 95% CI: 1.06-2.44). INTERPRETATION: Vaccination against COVID-19, especially with additional doses, is a fundamental strategy in the prevention of adverse outcomes including death, among patients with cancer. FUNDING: This study was partly supported by grants from the National Cancer Institute grant number P30 CA068485 to C-YH, YS, SM, JLW; T32-CA236621 and P30-CA046592 to C.R.F; CTSA 2UL1TR001425-05A1 to TMW-D; ACS/FHI Real-World Data Impact Award, P50 MD017341-01, R21 CA242044-01A1, Susan G. Komen Leadership Grant Hunt to MKA. REDCap is developed and supported by Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH).

Hematology-Oncology

Deshpande A, Munoz J, Kelemen K, **Dabak V**, Hanbali A, and Kurzrock R. Images in Immunotherapy and Precision Oncology: Angiosarcoma of the Spleen and Liver. *J Immunother Precis Oncol* 2023; 6(1):56-58. PMID: 36751660. Full Text

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Primary splenic or hepatic angiosarcomas are ultra-rare and aggressive malignancies associated with poor prognosis. The mainstay treatments are surgical resection and chemotherapy. We report a case of angiosarcoma in a 50-year-old woman who presented with bruising, fatigue, ecchymosis, and hepatosplenomegaly. She was treated with the multi-kinase inhibitor sunitinib for 4 weeks before developing a splenic hemorrhage and succumbing. Recent studies have demonstrated the clinical benefit of immunotherapies in angiosarcomas. Additionally, sequencing techniques have showcased the diverse molecular aberrations involved in angiosarcomas, which offer opportunities for precision-matched targeted therapies such as inhibitors of the VEGF/VEGFR axis and PI3K/Akt/mTor pathway.

Hematology-Oncology

Garassino MC, **Gadgeel S**, Speranza G, Felip E, Esteban E, Dómine M, Hochmair MJ, Powell SF, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Kurata T, Gray JE, Schwarzenberger P, Jensen E, Pietanza MC, and Rodríguez-Abreu D. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. *J Clin Oncol* 2023; Epub ahead of print. PMID: 36809080. Full Text

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Clinical trials frequently include multiple end points that mature at different times. The initial report, typically on the based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.We present 5-year outcomes from the phase 3 KEYNOTE-189 study (ClinicalTrials.gov identifier: NCT02578680). Eligible patients with previously untreated metastatic nonsquamous non-small-cell lung cancer without EGFR/ALK alterations were randomly assigned 2:1 to pembrolizumab 200 mg or placebo once every 3 weeks for up to 35 cycles with pemetrexed and investigator's choice of carboplatin/cisplatin for four cycles, followed by maintenance pemetrexed until disease progression or unacceptable toxicity. Primary end points were overall survival (OS) and progression-free survival (PFS). Among 616 randomly assigned patients (n = 410, pembrolizumab plus pemetrexed-platinum; n = 206, placebo plus pemetrexed-platinum), median time from random assignment to data cutoff (March 8, 2022) was 64.6 (range, 60.1-72.4) months. Hazard ratio (95% CI) for OS was 0.60 (0.50 to 0.72) and PFS was 0.50 (0.42 to 0.60) for pembrolizumab plus platinum-pemetrexed versus placebo plus platinum-pemetrexed. 5-year OS rates were 19.4% versus 11.3%. Toxicity was manageable. Among 57 patients who completed 35 cycles of pembrolizumab, objective response rate was 86.0% and 3-year OS rate after completing 35 cycles (approximately 5 years after random assignment) was 71.9%. Pembrolizumab plus pemetrexed-platinum maintained OS and PFS benefits versus placebo plus pemetrexed-platinum, regardless of programmed cell death ligand-1 expression. These data continue to support pembrolizumab plus pemetrexed-platinum as a standard of care in previously untreated metastatic non-small-cell lung cancer without EGFR/ALK alterations.

Hematology-Oncology

He K, Berz D, **Gadgeel SM**, Iams WT, Bruno DS, Blakely CM, Spira AI, Patel MR, Waterhouse DM, Richards DA, Pham A, Jotte R, Hong DS, Garon EB, Traynor A, Olson P, Latven L, Yan X, Shazer R, and Leal TA. MRTX-500 Phase 2 Trial: Sitravatinib With Nivolumab in Patients With Non-Squamous Non-Small Cell Lung Cancer Progressing On/After Checkpoint Inhibitor Therapy or Chemotherapy. *J Thorac Oncol* 2023; Epub ahead of print. PMID: 36842467. Request Article

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INTRODUCTION: Sitravatinib, a receptor tyrosine kinase inhibitor targeting TAM receptors and VEGFR2, can shift the tumor microenvironment towards an immunostimulatory state. Combining sitravatinib with checkpoint inhibitors (CPI) may augment antitumor activity. METHODS: The phase 2 MRTX-500 study evaluated sitravatinib (120 mg daily) with nivolumab (every 2/4 weeks) in patients with advanced non-squamous non-small cell lung cancer (NSCLC) who progressed on/after prior CPI (CPI-experienced) or chemotherapy (CPI-naïve). CPI-experienced patients had prior clinical benefit (PCB; complete/partial response or stable disease for ≥12 weeks then disease progression) or no PCB (NPCB) from CPI. Primary endpoint was objective response rate (ORR); secondary objectives included safety and secondary efficacy endpoints. RESULTS: Overall, 124 CPI-experienced (NPCB, n = 35; PCB, n = 89) and 32 CPI-naïve patients were treated. Investigator-assessed ORR was 11.4% in patients with NPCB, 16.9% with PCB, and 25.0% in CPI-naïve. Median progression-free survival was 3.7, 5.6, and 7.1 months with NPCB, PCB, and CPI-naïve, respectively; median overall survival was 7.9 and 13.6 months with NPCB and PCB, respectively (not reached in CPI-naïve patients; median follow-up 20.4 months). Overall, (N = 156), any grade treatment-related adverse events (TRAEs) occurred in 93.6%; grade 3/4 in 58.3%. One grade 5 TRAE occurred in a CPI-naïve patient. TRAEs led to treatment discontinuation in 14.1% and dose reduction/interruption in 42.9%. Biomarker analyses supported an immunostimulatory mechanism of action. CONCLUSIONS: Sitravatinib with nivolumab had a manageable safety profile. Although ORR was not met, this combination demonstrated antitumor activity and encouraging survival in CPI-experienced patients with non-squamous NSCLC.

Hematology-Oncology

Menjivar RE, Nwosu ZC, Du W, Donahue KL, Hong HS, Espinoza C, Brown K, Velez-Delgado A, Yan W, Lima F, Bischoff A, Kadiyala P, Salas-Escabillas D, **Crawford HC**, Bednar F, Carpenter E, Zhang Y, Halbrook CJ, Lyssiotis CA, and Pasca di Magliano M. Arginase 1 is a key driver of immune suppression in pancreatic cancer. *Elife* 2023; 12. PMID: 36727849. Full Text

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An extensive fibroinflammatory stroma rich in macrophages is a hallmark of pancreatic cancer. In this disease, it is well appreciated that macrophages are immunosuppressive and contribute to the poor response to immunotherapy; however, the mechanisms of immune suppression are complex and not fully understood. Immunosuppressive macrophages are classically defined by expression of the enzyme Arginase 1 (Arg1), which we demonstrated is potently expressed in pancreatic tumor associated macrophages from both human patients and mouse models. While routinely used as a polarization marker, Arg1 also catabolizes arginine, an amino acid required for T cell activation and proliferation. To investigate this metabolic function, we used a genetic and a pharmacologic approach to target Arg1 in pancreatic cancer. Genetic inactivation of Arg1 in macrophages, using a dual recombinase genetically engineered mouse model of pancreatic cancer, delayed formation of invasive disease, while increasing CD8(+) T cell infiltration. Additionally, Arg1 deletion induced compensatory mechanisms, including Arg1 overexpression in epithelial cells, namely Tuft cells, and Arg2 overexpression in a subset of macrophages. To overcome these compensatory mechanisms, we used a pharmacological approach to inhibit arginase. Treatment of established tumors with the arginase inhibitor CB-1158 exhibited further increased CD8(+) T cell infiltration, beyond that seen with the macrophage-specific knockout, and sensitized the tumors to anti-PD1 immune checkpoint blockade. Our data demonstrate that Arg1 drives immune suppression in pancreatic cancer by depleting Arginine and inhibiting T cell activation.

Hematology-Oncology

Murthy GSG, Kim S, Estrada-Merly N, Abid MB, Aljurf M, Assal A, Badar T, Badawy SM, Ballen K, Beitinjaneh A, Cerny J, Chhabra S, DeFilipp Z, Dholaria B, Perez MAD, **Farhan S**, Freytes CO, Gale RP, Ganguly S, Gupta V, Grunwald MR, Hamad N, Hildebrandt GC, Inamoto Y, Jain T, Jamy O, Juckett M, Kalaycio M, Krem MM, Lazarus HM, Litzow M, Munker R, Murthy HS, Nathan S, Nishihori T, Ortí G, Patel SS, Van der Poel M, Rizzieri DA, Savani BN, Seo S, Solh M, Verdonck LF, Wirk B, Yared JA, Nakamura R, Oran B, Scott B, and Saber W. Association between the choice of the conditioning regimen and outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis. *Haematologica* 2023; Epub ahead of print. PMID: 36779595. Full Text

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Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment for myelofibrosis. However, the optimal conditioning regimen either with reduced intensity conditioning (RIC) or myeloablative conditioning (MAC) is not well known. Using the Center for International Blood and Marrow Transplant Research database, we identified adults aged ≥18 years with myelofibrosis undergoing allo-HCT between 2008-2019 and analyzed the outcomes separately in the RIC and MAC cohorts based on the conditioning regimens used. Among 872 eligible patients, 493 underwent allo-HCT using RIC (Fludarabine/busulfan=166, Fludarabine/melphalan=327) and 379 using MAC (Fludarabine/busulfan=247, Busulfan/cyclophosphamide=132). In multivariable analysis with RIC, Fludarabine/melphalan was associated with inferior overall survival (HR 1.80, 95% CI 1.15-2.81, p=0.009), higher early non-relapse mortality (HR 1.81, 95% CI 1.12-2.91, p=0.01) and higher acute graft versus host disease (GVHD) (grade II-IV- HR 1.45, 95% CI 1.03-2.03, p=0.03; grade III-IV HR 2.21, 95%CI 1.28-3.83, p=0.004) compared to Fludarabine/busulfan. In the MAC setting, Busulfan/cyclophosphamide was associated with a higher acute GVHD (grade II-IV HR 2.33, 95% CI

1.67-3.25, p<0.001; grade III-IV HR 2.31, 95% CI 1.52-3.52, p<0.001) and inferior GVHD-free relapse-free survival (GRFS) (HR 1.94, 95% CI 1.49-2.53, p<0.001) as compared to Fludarabine/busulfan. Hence, our study suggests that Fludarabine/busulfan is associated with better outcomes in RIC (better overall survival, lower early non-relapse mortality, lower acute GVHD) and MAC (lower acute GVHD and better GRFS) in myelofibrosis.

Hypertension and Vascular Research
Ares GR. Ubiquitination of NKCC2 by the Cullin-RING E3 Ubiquitin Ligase Family in the Rat Thick Ascending Limb of the Loop of Henle. *Am J Physiol Renal Physiol* 2023; Epub ahead of print. PMID: 36727946. Full Text

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The Na/K/2Cl cotransporter (NKCC2) in the thick ascending limb of the loop of Henle (TAL) mediates NaCl reabsorption. Cyclic guanosine monophosphate (cGMP), the second messenger of nitric oxide and atrial natriuretic peptide, inhibits NKCC2 activity by stimulating NKCC2 ubiquitination and decreasing surface NKCC2 levels. Among the E3-ubiquitin ligase families, the Cullin-RING E3 ubiquitin ligase (CRL) family is the largest. Cullins are molecular scaffold proteins that recruit multiple subunits to form the CRL complex. We hypothesize that a CRL complex mediates the cGMP-dependent increase in NKCC2 ubiquitination in TALs. Cullin-1, -2, -3, -4A, and -5 express at the protein level, while the other members of the cullin family were expressed at the mRNA level in rats TAL. CRL complex activity is regulated by the neuronal precursor cell-expressed developmentally downregulated protein 8 (Nedd8) to cullins, process called neddylation. Inhibition of cullin neddylation blunted the cGMP-dependent increase in ubiquitinated NKCC2, while increasing the expression of cullin-1 by threefold, but this effect was not seen on other cullins. CRL complex activity is also regulated by cullin-associated Nedd8-dissociated 1 (CAND1). CAND1 binds to cullins and promotes the exchange of substrate-recognition proteins to target different proteins for ubiquitination. CAND1 inhibition exacerbated the cGMP-dependent increase in NKCC2 ubiquitination and decreased surface NKCC2 expression. Finally, cGMP increased neddylation of cullins. We conclude that the cGMP-dependent increase in NKCC2 ubiquitination is mediated by a CRL complex. To the best of our knowledge, this is the first evidence that a CRL complex mediates NKCC2 ubiquitination in native TALs.

Hypertension and Vascular Research
Zanuzzi MG, Garzon ME, Cornavaca MT, Bernabeu F, Albertini RA, Ellena G, and **Romero CA**. Social determinants of blood pressure control in a middle-income country in Latin America. *J Biosoc Sci* 2023; 1-13. Epub ahead of print. PMID: 36794341. Full Text

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Blood pressure (BP) control is a key intervention to decrease cardiovascular diseases (CVD), the main cause of death in low and middle-income countries (MIC). Scarce data on the determinants of BP control in Latin America are available. Our objective is to explore the role of gender, age, education, and income as social determinants of BP control in Argentina, a MIC with a universal health care system. We evaluated 1184 persons in two hospitals. Blood pressure was measured using automatic oscillometric devices. We selected those patients treated for hypertension. The average BP of less than 140/90 mmHg was considered a controlled BP. We found 638 hypertensive individuals, of whom 477 (75%) were receiving antihypertensive drugs, and of those, 248 (52%) had controlled BP. The prevalence of low education was more frequent in uncontrolled patients (25.3% vs. 16.1%; P < .01). We did not find association between household income, gender, and BP control. Older patients had less BP control (44% of those older than 75 years vs. 60.9% of those younger than 40; test for trend P < .05). Multivariate

regression indicates low education (OR 1.71 95% CI [1.05, 2.79]; P = .03) and older age (OR 1.01; 95% IC [1.00, 1.03]) as independent predictors of the lack of BP control. We conclude that rates of BP control are low in Argentina. In a MIC with a universal health care system low education and old age but not household income are independent predictors of the lack of BP control.

Infectious Diseases

Reyes J, Komarow L, Chen L, Ge L, Hanson BM, Cober E, **Herc E**, Alenazi T, Kaye KS, Garcia-Diaz J, Li L, Kanj SS, Liu Z, Oñate JM, Salata RA, Marimuthu K, Gao H, Zong Z, Valderrama-Beltrán SL, Yu Y, Tambyah P, Weston G, Salcedo S, Abbo LM, Xie Q, Ordoñez K, Wang M, Stryjewski ME, Munita JM, Paterson DL, Evans S, Hill C, Baum K, Bonomo RA, Kreiswirth BN, Villegas MV, Patel R, Arias CA, Chambers HF, Fowler VG, Jr., Doi Y, van Duin D, and Satlin MJ. Global epidemiology and clinical outcomes of carbapenem-resistant Pseudomonas aeruginosa and associated carbapenemases (POP): a prospective cohort study. *Lancet Microbe* 2023; Epub ahead of print. PMID: 36774938. Full Text

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BACKGROUND: Carbapenem-resistant Pseudomonas aeruginosa (CRPA) is a global threat, but the distribution and clinical significance of carbapenemases are unclear. The aim of this study was to define characteristics and outcomes of CRPA infections and the global frequency and clinical impact of carbapenemases harboured by CRPA. METHODS: We conducted an observational, prospective cohort study of CRPA isolated from bloodstream, respiratory, urine, or wound cultures of patients at 44 hospitals (10 countries) between Dec 1, 2018, and Nov 30, 2019. Clinical data were abstracted from health records and CRPA isolates were whole-genome sequenced. The primary outcome was 30-day mortality from the day the index culture was collected. We compared outcomes of patients with CRPA infections by infection type and across geographic regions and performed an inverse probability weighted analysis to assess the association between carbapenemase production and 30-day mortality. FINDINGS: We enrolled 972 patients (USA n=527, China n=171, south and central America n=127, Middle East n=91, Australia and Singapore n=56), of whom 581 (60%) had CRPA infections. 30-day mortality differed by infection type (bloodstream 21 [30%] of 69, respiratory 69 [19%] of 358, wound nine [14%] of 66, urine six [7%] of 88; p=0·0012) and geographical region (Middle East 15 [29%] of 52, south and central America 20 [27%] of 73, USA 60 [19%] of 308, Australia and Singapore three [11%] of 28, China seven [6%] of 120; p=0·0002). Prevalence of carbapenemase genes among CRPA isolates also varied by region (south and central America 88 [69%] of 127, Australia and Singapore 32 [57%] of 56, China 54 [32%] of 171, Middle East 27 [30%] of 91, USA ten [2%] of 527; p<0·0001). KPC-2 (n=103 [49%]) and VIM-2 (n=75 [36%]) were the most common carbapenemases in 211 carbapenemase-producing isolates. After excluding USA patients, because few US isolates had carbapenemases, patients with carbapenemase-producing CRPA infections had higher 30-day mortality than those with non-carbapenemase-producing CRPA infections in both unadjusted (26 [22%] of 120 vs 19 [12%] of 153; difference 9%, 95% CI 3-16) and adjusted (difference 7%, 95% CI 1-14) analyses. INTERPRETATION: The emergence of different carbapenemases among CRPA isolates in different geographical regions and the increased mortality associated with carbapenemase-producing CRPA infections highlight the therapeutic challenges posed by these organisms. FUNDING: National Institutes of Health.

Infectious Diseases

Sims MD, Khanna S, Feuerstadt P, Louie TJ, Kelly CR, Huang ES, Hohmann EL, Wang EEL, Oneto C, Cohen SH, Berenson CS, Korman L, Lee C, Lashner B, Kraft CS, **Ramesh M**, Silverman M, Pardi DS, De A, Memisoglu A, Lombardi DA, Hasson BR, McGovern BH, and von Moltke L. Safety and Tolerability of SER-109 as an Investigational Microbiome Therapeutic in Adults With Recurrent Clostridioides difficile Infection: A Phase 3, Open-Label, Single-Arm Trial. *JAMA Netw Open* 2023; 6(2):e2255758. PMID: 36780159. Full Text

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IMPORTANCE: A safe and effective treatment for recurrent Clostridioides difficile infection (CDI) is urgently needed. Antibiotics kill toxin-producing bacteria but do not repair the disrupted microbiome, which promotes spore germination and infection recurrence. OBJECTIVES: To evaluate the safety and rate of CDI recurrence after administration of investigational microbiome therapeutic SER-109 through 24 weeks. DESIGN, SETTING, AND PARTICIPANTS: This phase 3, single-arm, open-label trial (ECOSPOR IV) was conducted at 72 US and Canadian outpatient sites from October 2017 to April 2022. Adults aged 18 years or older with recurrent CDI were enrolled in 2 cohorts: (1) rollover patients from the ECOSPOR III trial who had CDI recurrence diagnosed by toxin enzyme immunoassay (EIA) and (2) patients with at least 1 CDI recurrence (diagnosed by polymerase chain reaction [PCR] or toxin EIA), inclusive of their acute infection at study entry. INTERVENTIONS: SER-109 given orally as 4 capsules daily for 3 days following symptom resolution after antibiotic treatment for CDI. MAIN OUTCOMES AND MEASURES: The main outcomes were safety, measured as the rate of treatment-emergent adverse events (TEAEs) in all patients receiving any amount of SER-109, and cumulative rates of recurrent CDI (toxin-positive diarrhea requiring treatment) through week 24 in the intent-to-treat population. RESULTS: Of 351 patients screened, 263 were enrolled (180 [68.4%] female; mean [SD] age, 64.0 [15.7] years); 29 were in cohort 1 and 234 in cohort 2. Seventy-seven patients (29.3%) were enrolled with their first CDI recurrence. Overall, 141 patients (53.6%) had TEAEs, which were mostly mild to moderate and gastrointestinal. There were 8 deaths (3.0%) and 33 patients (12.5%) with serious TEAEs; none were considered treatment related by the investigators. Overall, 23 patients (8.7%; 95% CI, 5.6%-12.8%) had recurrent CDI at week 8 (4 of 29 [13.8%; 95% CI, 3.9%-31.7%] in cohort 1 and 19 of 234 [8.1%; 95% CI, 5.0%-12.4%] in cohort 2), and recurrent CDI rates remained low through 24 weeks (36 patients [13.7%; 95% CI, 9.8%-18.4%]). At week 8, recurrent CDI rates in patients with a first recurrence were similarly low (5 of 77 [6.5%; 95% CI, 2.1%-

14.5%]) as in patients with 2 or more recurrences (18 of 186 [9.7%; 95% CI, 5.8%-14.9%]). Analyses by select baseline characteristics showed consistently low recurrent CDI rates in patients younger than 65 years vs 65 years or older (5 of 126 [4.0%; 95% CI, 1.3%-9.0%] vs 18 of 137 [13.1%; 95% CI, 8.0%-20.0%]) and patients enrolled based on positive PCR results (3 of 69 [4.3%; 95% CI, 0.9%-12.2%]) vs those with positive toxin EIA results (20 of 192 [10.4%; 95% CI, 6.5%-15.6%]). CONCLUSIONS AND RELEVANCE: In this trial, oral SER-109 was well tolerated in a patient population with recurrent CDI and prevalent comorbidities. The rate of recurrent CDI was low regardless of the number of prior recurrences, demographics, or diagnostic approach, supporting the beneficial impact of SER-109 for patients with CDI. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT03183141.

Infectious Diseases

Stefan AJ, **Herc ES**, **Gudipati S**, **Brar I**, **Vitale A**, and Tariq Z. Atypical presentation of progressive disseminated histoplasmosis in a patient recently diagnosed with AIDS. *Int J Infect Dis* 2023; 127:45-47. PMID: 36462572. Full Text

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Opportunistic infections, including progressive disseminated histoplasmosis (PDH), may have variable and surprising presentations in patients with AIDS. This can be either a primary infection or reactivation of a latent infection. Latent infections may occur due to being unmasked by the immune reconstitution inflammatory syndrome after the initiation of combined antiretroviral therapy. PDH can be difficult to diagnose in patients with AIDS due to its variable presentation and many overlapping symptoms with other opportunistic infections. Serum and urine antigen testing are highly sensitive and typically used as the initial diagnostic test to workup suspected PDH. However, negative antigen and antibody tests do not rule out Histoplasmosis capsulatum infection and suspicion should remain high for PDH in the right clinical context. A definitive diagnosis may require biopsy-proven narrow-based budding yeast. We present an interesting patient with AIDS who presented with worsening cognitive decline and was ultimately diagnosed with PDH based on biopsy histopathology in the setting of negative antigen and antibody testing.

Internal Medicine

Currier EE, **Ichkanian Y**, **Dabaja M**, Segovia MC, Patel Y, **Nagai S**, Sudan DL, and **Jafri SM**. Cytomegalovirus Infection Management in Multivisceral and Intestinal Transplant: A Dual Institution Study. *Transplant Proc* 2023; Epub ahead of print. PMID: 36792485. Full Text

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Intestinal transplant and multivisceral transplant were originally in pediatric populations and are relatively new procedures in adults. Despite increasing success rates in the immediate post-transplant period, infectious complications and acute and chronic rejection remain significant causes of morbidity and mortality. Previous research has shown cytomegalovirus (CMV) is the main cause of infection in this population. Due to the limited patient population, incidence of CMV viremia ranges widely and there is lack of universal protocol for treatment. This dual institution retrospective chart review between Henry Ford Hospital and Duke University analyzed adult intestinal and multivisceral transplant recipients between 2009 and 2019. Of the 32 patients identified and included in the study, 15 had CMV infection (46.9%). Of those with CMV infection, 5 (33.3%) had donor positive (D+)/recipient positive (R+) status; 5 had D-/R+; 4 had D+/R-; and one had D-/R-. There was no significant difference between mortality in those who had reported infection and not (80% vs 76.5%). The data from this study show significant rates

of CMV viremia in patients undergoing intestinal transplant/multivisceral transplant with almost half of our study population having documented infection within 1 year of transplant, stressing the importance for universal protocol into CMV viremia treatment.

Internal Medicine

Jadallah K, Khatatbeh M, Mazahreh T, **Sweidan A**, Ghareeb R, Tawalbeh A, Masaadeh A, Alzubi B, and Khader Y. Colorectal cancer screening barriers and facilitators among Jordanians: A cross-sectional study. *Prev Med Rep* 2023; 32:102149. PMID: 36852311. Full Text

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The factors affecting the adherence of Jordanians to colorectal cancer (CRC) screening remain underexplored. We examined the inhibitory and facilitating factors that influence the uptake of CRC screening among Jordanians. We conducted questionnaire interviews between April 2020 and June 2021 with 861 Jordanians aged 50-75. We analyzed the differences between proportions using the chi-square test. Binary logistic regression was conducted to determine factors associated with awareness of CRC and its screening. Of all participants, 41.7 % were aware of the necessity of screening for CRC, and 27.2 % were aware of at least one of the tests for CRC screening. However, only 17.2 % of participants underwent screening. In the multivariate analysis, participants with higher income (p-value < 0.001, odds ratio[OR] = 1.9, 95 % confidence interval [CI]: 1.4-2.7), higher level of education (p-value < 0.001, OR = 2.6, 95 % CI: 1.8-3.7), family history of colon cancer (p-value < 0.001, OR = 2.8, 95 % CI = 1.7-4.5), and those who had been screened for other cancers (p-value = 0.003, OR = 1.7, 95 % CI: 1.2-2.5) were more aware of the necessity of screening. Concerning barriers to screening, 'feeling well,' lack of physician endorsement, and difficult access to health care were the most commonly reported inhibitory factors (53.9 %, 52.3 %, and 31.9 %, respectively). The most commonly stated incentivizing factor was physician endorsement (82.3 %). Screening rates for CRC in eligible Jordanians remain low, albeit more than one-third of participants are aware of the necessity of screening. Enhanced awareness of barriers and incentivizing factors should help to prioritize national strategies to improve screening rates.

Internal Medicine

Mir A, Badi Y, **Bugazia S**, Nourelden AZ, Fathallah AH, Ragab KM, Alsillak M, Elsayed SM, Hagrass AI, Bawek S, Kalot M, and Brumberger ZL. Efficacy and safety of cardioprotective drugs in chemotherapy-induced cardiotoxicity: an updated systematic review & network meta-analysis. *Cardiooncology* 2023; 9(1):10. PMID: 36804940. Full Text

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BACKGROUND: Cancer patients receiving chemotherapy have an increased risk of cardiovascular complications. This limits the widespread use of lifesaving therapies, often necessitating alternate lower efficacy regimens, or precluding chemotherapy entirely. Prior studies have suggested that using common cardioprotective agents may attenuate chemotherapy-induced cardiotoxicity. However, small sample sizes and conflicting outcomes have limited the clinical significance of these results. HYPOTHESIS: A comprehensive network meta-analysis using updated and high-quality data can provide more conclusive information to assess which drug or drug class has the most significant effect in the management of chemotherapy-induced cardiotoxicity. METHODS: We performed a literature search for randomized controlled trials (RCTs) investigating the effects of cardioprotective agents in patients with chemotherapy-induced cardiotoxicity. We used established analytical tools (netmeta package in RStudio) and data extraction formats to analyze the outcome data. To obviate systematic bias in the selection and interpretation of RCTs, we employed the validated Cochrane risk-of-bias tools. Agents included were statins, aldosterone receptor antagonists (MRAs), ACEIs, ARBs, and beta-blockers. Outcomes examined were improvement in clinical and laboratory parameters of cardiac function including a decreased reduction in left ventricular ejection fraction (LVEF), clinical HF, troponin-I, and B-natriuretic peptide levels. RESULTS: Our study included 33 RCTs including a total of 3,285 patients. Compared to control groups, spironolactone therapy was associated with the greatest LVEF improvement (Mean difference (MD) = 12.80, [7.90; 17.70]), followed by enalapril (MD = 7.62, [5.31; 9.94]), nebivolol (MD = 7.30, [2.39; 12.21]), and statins (MD = 6.72, [3.58; 9.85]). Spironolactone was also associated with a significant reduction in troponin elevation (MD = - 0.01, [- 0.02; - 0.01]). Enalapril demonstrated the greatest BNP reduction (MD = - 49.00, [- 68.89; - 29.11]), which was followed by spironolactone (MD = - 16.00, [- 23.9; - 8.10]). Additionally, patients on enalapril had the lowest risk of developing clinical HF compared to the control population (RR = 0.05, [0.00; 0.75]). CONCLUSION: Our analysis reaffirmed that statins, MRAs, ACEIs, and beta-blockers can significantly attenuate chemotherapy-induced cardiotoxicity, while ARBs showed no significant effects. Spironolactone showed the most robust improvement of LVEF, which best supports its use among this population. Our analysis warrants future clinical studies examining the cardioprotective effects of cardiac remodeling therapy in cancer patients treated with chemotherapeutic agents.

Neurology

Dardiotis E, Skouras P, Varvarelis OP, Aloizou AM, Hernández AF, Liampas I, Rikos D, Dastamani M, Golokhvast KS, Bogdanos DP, Tsatsakis A, Siokas V, **Mitsias PD**, and Hadjigeorgiou GM. Pesticides and tremor: An overview of association, mechanisms and confounders. *Environ Res* 2023; 115442. Epub ahead of print. PMID: 36758916. Full Text

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Pesticides are a heterogeneous class of chemicals mainly used for the protection of crops from pests. Because of their very widespread use, acute or/and chronic exposure to these chemicals can lead to a plethora of sequelae inflicting diseases, many of which involve the nervous system. Tremor has been associated with pesticide exposure in human and animal studies. This review is aimed at assessing the studies currently available on the association between the various types of pesticides/insecticides and tremor, while also accounting for potential confounding factors. To our knowledge, this is the first coherent review on the subject. After appraising the available evidence, we call for more intensive research on this topic, as well as intonate the need of implementing future preventive measures to protect the exposed populations and to reduce potential disabilities and social drawbacks.

Neurology
LeWitt PA, **Li J**, **Wu KH**, and **Lu M**. Diagnostic metabolomic profiling of Parkinson's disease biospecimens. *Neurobiol Dis* 2023; 177:105962. PMID: 36563791. Full Text

Departments of Neurology, Henry Ford Hospital, West Bloomfield, MI, USA; Wayne State University School of Medicine, West Bloomfield, MI, USA. Electronic address: plewitt1@hfhs.org.
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BACKGROUND: Reliable and sensitive biomarkers are needed for enhancing and predicting Parkinson's disease (PD) diagnosis. OBJECTIVE: To investigate comprehensive metabolomic profiling of biochemicals in CSF and serum for determining diagnostic biomarkers of PD. METHODS: Fifty subjects, symptomatic with PD for ≥5 years, were matched to 50 healthy controls (HCs). We used ultrahigh-performance liquid chromatography linked to tandem mass spectrometry (UHPLC-MS/MS) for measuring relative concentrations of ≤1.5 kDalton biochemicals. A reference library created from authentic standards facilitated chemical identifications. Analytes underwent univariate analysis for PD association, with false discovery rate-adjusted p-value (≤0.05) determinations. Multivariate analysis (for identifying a panel of biochemicals discriminating PD from HCs) used several biostatistical methods, including logistic LASSO regression. RESULTS: Comparing PD and HCs, strong differentiation was achieved from CSF but not serum specimens. With univariate analysis, 21 CSF compounds exhibited significant differential concentrations. Logistic LASSO regression led to selection of 23 biochemicals (11 shared with those determined by the univariate analysis). The selected compounds, as a group, distinguished PD from HCs, with Area-Under-the-Receiver-Operating-Characteristic (ROC) curve of 0.897. With optimal cutoff, logistic LASSO achieved 100% sensitivity and 96% specificity (and positive and negative predictive values of 96% and 100%). Ten-fold cross-validation gave 84% sensitivity and 82% specificity (and 82% positive and 84% negative predictive values). From the logistic LASSO-chosen regression model, 2 polyamine metabolites (N-acetylcadaverine and N-acetylputrescine) were chosen and had the highest fold-changes in comparing PD to HCs. Another chosen biochemical, acisoga (N-(3-acetamidopropyl)pyrrolidine-2-one), also is a polyamine metabolism derivative. CONCLUSIONS: UHPLC-MS/MS assays provided a metabolomic signature highly predictive of PD. These findings provide further evidence for involvement of polyamine pathways in the neurodegeneration of PD.

Neurology
Morris DC, **Zhang ZG**, **Jaehne AK**, **Zhang J**, and **Rivers EP**. CLINICAL, MOLECULAR, AND EXOSOMAL MECHANISMS OF CARDIAC AND BRAIN DYSFUNCTION IN SEPSIS. *Shock* 2023; 59(2):173-179. PMID: 36731014. Full Text

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Sepsis is a complex disease resulting from a dysregulated inflammatory response to an infection. Initiation of sepsis occurs from a localized infection that disseminates to the bloodstream placing all organ systems at risk. Septic shock is classically observed to manifest itself as systemic hypotension with hyporesponsiveness to vasopressor agents. Myocardial dysfunction occurs resulting in an inability to perfuse major organ systems throughout the body. Most importantly, the brain is hypoperfused creating an ischemic and inflammatory state resulting in the clinical observation of acute mental status changes and cognitive dysfunction commonly known as sepsis-associated encephalopathy. This short review

describes the inflammatory molecular mechanisms of myocardial dysfunction, discusses the evidence of the dual roles of the microglia resulting in blood-brain barrier disruption, and suggests that septic-derived exosomes, endosome-derived lipid bilayer spheroids released from living cells, influence cardiac and neurological cellular function.

Neurology
Salam MA, Al-Amin MY, Pawar JS, **Akhter N**, and Lucy IB. Conventional methods and future trends in antimicrobial susceptibility testing. *Saudi J Biol Sci* 2023; 30(3):103582. PMID: 36852413. Full Text

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Antimicrobial susceptibility testing is an essential task for selecting appropriate antimicrobial agents to treat infectious diseases. Constant evolution has been observed in methods used in the diagnostic microbiology laboratories. Disc diffusion or broth microdilution are classical and conventional phenotypic methods with long turnaround time and labour-intensive but still widely practiced as gold-standard. Scientists are striving to develop innovative, novel and faster methods of antimicrobial susceptibility testing to be applicable for routine microbiological laboratory practice and research. To meet the requirements, there is an increasing trend towards automation, genotypic and micro/nano technology-based innovations. Automation in detection systems and integration of computers for online data analysis and data sharing are giant leaps towards versatile nature of automated methods currently in use. Genotypic methods detect a specific genetic marker associated with resistant phenotypes using molecular amplification techniques and genome sequencing. Microfluidics and microdroplets are recent addition in the continuous advancement of methods that show great promises with regards to safety and speed and have the prospect to identify and monitor resistance mechanisms. Although genotypic and microfluidics methods have many exciting features, however, their applications into routine clinical laboratory practice warrant extensive validation. The main impetus behind the evolution of methods in antimicrobial susceptibility testing is to shorten the overall turnaround time in obtaining the results and to enhance the ease of sample processing. This comprehensive narrative review summarises major conventional phenotypic methods and automated systems currently in use, and highlights principles of some of the emerging genotypic and micro/nanotechnology-based methods in antimicrobial susceptibility testing.

Neurosurgery
Hadi M, Deshpande N, **Hamilton T**, and **Chang V**. Commentary: Prone Transpsoas Lateral Lumbar Interbody Fusion for Degenerative Lumbar Spine Disease: Case Series With an Operative Video Using Fluoroscopy-Based Instrument Tracking Guidance. *Oper Neurosurg (Hagerstown)* 2023; Epub ahead of print. PMID: 36746003. Full Text

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Neurosurgery
Lim S, **Schultz L**, Zakko P, **Macki M**, **Hamilton T**, **Pawloski J**, **Fadel H**, **Mansour T**, **Yeh HH**, Preston G, **Nerenz D**, **Schwalb JM**, **Abdulhak M**, Park P, Aleem I, Easton R, Khalil J, Perez-Cruet M, Park D, and **Chang V**. The Potential Negative Effects of Smoking on Cervical and Lumbar Surgery beyond Pseudoarthrosis: A Michigan Spine Surgery Improvement Collaborative (MSSIC) Study. *World Neurosurg* 2023; Epub ahead of print. PMID: 36791883. Full Text

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OBJECTIVE: The study was designed to review the Michigan Spine Surgery Improvement Collaborative (MSSIC) registry to investigate the long-term associations between current smoking status and outcomes after elective cervical and lumbar spine surgery. METHODS: Utilizing MSSIC we captured all cases from 01/01/17-11/21/20 with outcomes data available. 19,251 lumbar cases and 7,936 cervical cases were included. Multivariate regression analyses were performed to assess the relationship of smoking with the clinical outcomes. RESULTS: Current smoking status was associated with lower urinary retention and satisfaction for lumbar surgery patients and was also associated with less likelihood of achieving minimal clinically important difference (MCID) in Patient-Reported Outcomes Measurement Information System (PROMIS), back pain, leg pain, and EQ5D at 90 days and 1 year after surgery. Current smokers were also less likely to return to work at 90 days and 1 year after surgery. For cervical patients, current smokers were less likely to have urinary retention and dysphagia postoperatively. They were less likely to be satisfied with the surgery outcome at 1 year. Current smoking was associated with lower likelihood of achieving MCID in PROMIS, neck pain, arm pain, and EQ5D at various time points. There was no difference in return-to-work status. CONCLUSION: Our analysis suggests that smoking is negatively associated with functional improvement, patient satisfaction, and return-to-work after elective spine surgery.

Neurosurgery
Zervos TM, Jago SS, Erwood MS, **Basheer A**, **Lee IY**, Lubin FD, **Schultz L**, and **Walters BC**. A Multicenter Allelic Analysis of Diffuse Idiopathic Skeletal Hyperostosis: Nature Versus Nurture? *Neurosurgery* 2023; Epub ahead of print. PMID: 36802217. Full Text

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BACKGROUND: Diffuse idiopathic skeletal hyperostosis (DISH) is an incompletely defined disease process with no known unifying pathophysiological mechanism. OBJECTIVE: To our knowledge, no genetic studies have been performed in a North American population. To summarize genetic findings from previous studies and to comprehensively test for these associations in a novel and diverse, multi-institutional population. METHODS: Cross-sectional, single nucleotide polymorphism (SNP) analysis was performed in 55 of 121 enrolled patients with DISH. Baseline demographic data were available on 100

patients. Based on allele selection from previous studies and related disease conditions, sequencing was performed on COL11A2, COL6A6, fibroblast growth factor 2 gene, LEMD3, TGFB1, and TLR1 genes and compared with global haplotype rates. RESULTS: Consistent with previous studies, older age (mean 71 years), male sex predominance (80%), a high frequency of type 2 diabetes (54%), and renal disease (17%) were observed. Unique findings included high rates of tobacco use (11% currently smoking, 55% former smoker), a higher predominance of cervical DISH (70%) relative to other locations (30%), and an especially high rate of type 2 diabetes in patients with DISH and ossification of the posterior longitudinal ligament (100%) relative to DISH alone (100% vs 47%, P < .001). Compared with global allele rates, we found higher rates of SNPs in 5 of 9 tested genes (P < .05). CONCLUSION: We identified 5 SNPs in patients with DISH that occurred more frequently than a global reference. We also identified novel environmental associations. We hypothesize that DISH represents a heterogeneous condition with both multiple genetic and environmental influences.

Obstetrics, Gynecology and Women's Health Services

Ayyash M, **Ayyash M**, Saad F, Alaouie M, and Blackwood RA. A comparison of the experiences, challenges and coping strategies for parents of children with autism residing in the United States and The Arab World. *J Natl Med Assoc* 2023; Epub ahead of print. PMID: 36828706. Full Text

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Most research on autism has targeted White Americans. Although challenges and coping mechanisms are present for all parents, some aspects are influenced by culture. This study aims to compare the experiences, challenges and coping strategies for parents of children with autism residing in the US and Arab countries. A survey, available in both English and Arabic, was posted electronically on social media support groups for parents of children with autism in Arab countries and the US. The survey covered experiences, challenges and coping strategies for raising a child with autism spectrum disorder. 165 surveys were collected from 15 Arab countries and 235 surveys were collected from 32 US states. On a scale from 1 to 5, with 5 being highest satisfaction, US parents reported a higher satisfaction for the overall diagnostic process with median score of 3.0 compared to 2.5 for parents in Arab countries. Parents in both countries reported information seeking/self-education about autism and acceptance and/or religion as the 2 most valuable coping strategies. Lower satisfaction with all aspects of the diagnosis process was found among parents in Arab countries compared to those residing in the US. Lack of community support for Arab parents was also a more significant challenge compared to US parents. With such poor community support for Arab parents, it is pivotal to expand upon initiatives that minimize the stigma and shame associated with an autism diagnosis to ultimately reduce challenges and allow for better parental experiences.

Obstetrics, Gynecology and Women's Health Services

Herzog TJ, Pignata S, Ghamande SA, Rubio MJ, Fujiwara K, Vulsteke C, Armstrong DK, Sehouli J, Coleman RL, Gabra H, Scambia G, Monk BJ, Arranz JA, Ushijima K, **Hanna R**, Zamagni C, Wenham RM, González-Martín A, Slomovitz B, Jia Y, Ramsay L, Tewari KS, Weil SC, and Vergote IB. Randomized phase II trial of farletuzumab plus chemotherapy versus placebo plus chemotherapy in low CA-125 platinum-sensitive ovarian cancer. *Gynecol Oncol* 2023; 170:300-308. PMID: 36758420. Full Text

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OBJECTIVE: The primary purpose of this study was to determine if farletuzumab, an antifolate receptor-α monoclonal antibody, improved progression-free survival (PFS) versus placebo when added to standard chemotherapy regimens in patients with platinum-sensitive recurrent ovarian cancer (OC) in first relapse (platinum-free interval: 6-36 months) with low cancer antigen 125 (CA-125) levels. METHODS: Eligibility included CA-125 ≤ 3 x upper limit of normal (ULN, 105 U/mL), high-grade serous, platinum-sensitive recurrent OC, previous treatment with debulking surgery, and first-line platinum-based chemotherapy with 1st recurrence between 6 and 36 months since frontline platinum-based treatment. Patients received investigator's choice of either carboplatin (CARBO)/paclitaxel (PTX) every 3 weeks or CARBO/pegylated liposomal doxorubicin (PLD) every 4 weeks x6 cycles in combination with either farletuzumab [5 mg/kg weekly] or placebo randomized in a 2:1 ratio. Maintenance treatment with farletuzumab (5 mg/kg weekly) or placebo was given until disease progression or intolerance. RESULTS: 214 patients were randomly assigned to farletuzumab+chemotherapy (142 patients) versus placebo+chemotherapy (72 patients). The primary efficacy endpoint, PFS, was not significantly different between treatment groups (1-sided α = 0.10; p-value = 0.25; hazard ratio [HR] = 0.89, 80% confidence interval [CI]: 0.71, 1.11), a median of 11.7 months (95% CI: 10.2, 13.6) versus 10.8 months (95% CI: 9.5, 13.2) for farletuzumab+chemotherapy and placebo+chemotherapy, respectively. No new safety concerns were identified with the combination of farletuzumab+chemotherapy. CONCLUSIONS: Adding farletuzumab to standard chemotherapy does not improve PFS in patients with OC who were platinum-sensitive in first relapse with low CA-125 levels. Folate receptor-α expression was not measured in this study. (Clinical Trial Registry NCT02289950).

Ophthalmology and Eye Care Services

Kasetty VM, **Aye J**, **Patel N**, Tripathi N, **Hessburg T**, **Kumar N**, **Desai UR**, and **Hamad AE**. Outcomes and complications of primary rhegmatogenous retinal detachment repair with pars plana vitrectomy in young adults. *Int J Retina Vitreous* 2023; 9(1):11. PMID: 36814290. Full Text

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BACKGROUND: Scleral buckling has been the standard for rhegmatogenous retinal detachment repair in young patients given the typical lack of posterior vitreous detachment, phakic status, and lower risk of proliferative vitreoretinopathy. In older patients, pars plana vitrectomy alone is typically used for rhegmatogenous retinal detachment repair. We report the outcomes and complications of pars plana vitrectomy for rhegmatogenous retinal detachment in young eyes. METHODS: Retrospective, single-center cohort study. Medical records of patients between 15 to 45 years of age undergoing primary pars plana vitrectomy for rhegmatogenous retinal detachment repair between 2010 and 2020 were carefully reviewed. All analyses were performed using the Kruskal-Wallis tests for numeric covariates between age groups. RESULTS: Eyes were stratified by age: 15-24 (group 1, n = 10), 25-34 (group 2, n = 14), and 35-45 (group 3, n = 38). The average number of surgeries were 1.9, 1.4, and 1.1 in groups 1, 2, and 3, respectively ($p = 0.004$). Single surgery success rates were 50%, 64%, and 92% in groups 1, 2 and 3, respectively ($p = 0.005$). Final reattachment rates were 80%, 93%, 100% in groups 1, 2, and 3, respectively ($p = 0.568$). Proliferative vitreoretinopathy developed in 50%, 7%, and 8% of eyes in groups 1, 2, and 3, respectively ($p < 0.001$). CONCLUSION: While the final reattachment rates were excellent in all groups, the higher rates of proliferative vitreoretinopathy and lower single surgery success rate in younger patients may suggest that primary pars plana vitrectomy may not be the optimal repair method in these age groups.

Ophthalmology and Eye Care Services

Newman-Casey PA, Resnicow K, Winter S, Niziol LM, **Darnley-Fisch D**, **Imami N**, McHaney-Conner P, Musch DC, Mitchell J, and Heisler M. The Support, Educate, Empower personalized glaucoma coaching trial design. *Clin Trials* 2023; Epub ahead of print. PMID: 36855233. Full Text

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BACKGROUND: Glaucoma is a chronic disease that affects 3 million Americans. Glaucoma is most often asymptomatic until very late in its course when treatment is more difficult and extensive peripheral vision loss has already occurred. Taking daily medications can mitigate this vision loss, but at least half of people with glaucoma do not take their prescribed medications regularly. The purpose of this study is to improve glaucoma medication adherence among those with medically treated glaucoma and poor self-reported adherence using the Support, Educate, Empower personalized coaching program. METHODS/DESIGN: This study is a two-site randomized controlled trial enrolling 230 participants with poor self-reported glaucoma medication adherence. The trial has two arms, an intervention arm and a control arm. Participants in the intervention arm receive personalized glaucoma education and motivational interviewing-based coaching over 6 months from a trained non-physician interventionist for three in-person sessions with between visit phone calls for check-ins where current adherence level is reported to participants. Participants also can elect to have visual, audio, text or automated phone call medication dose reminders. Participants in the control arm continue usual care with their physician and receive non-personalized glaucoma educational materials via mail in parallel to the three in-person coaching sessions to control for glaucoma knowledge content. All participants receive a medication adherence monitor. The primary outcome is the proportion of prescribed doses taken on schedule during the 6-month period. The secondary outcome is glaucoma related distress. The exploratory outcome is intraocular pressure. DISCUSSION: The personalized education and motivational-interviewing-based intervention that we are testing is comprehensive in that it addresses the wide range of barriers to adherence that people with glaucoma encounter. Leveraging a custom-built web-based application to generate the personalized content and the motivational-interviewing-based prompts to guide the coaching sessions will make this program both replicable and scalable and can be integrated into clinical care

utilizing trained non-physician providers. Although this type of self-management support is not currently reimbursed for glaucoma as it is for diabetes, this trial could help shape future policy change should the intervention be found effective.

Orthopedics/Bone and Joint Center

Bishai SK, Ball GRS, **King C**, **Ierardi K**, Bodine M, Ayad M, and Warren J. Arthroscopic Latarjet Learning Curve: Operating Time Decreases After 25 Cases. *Arthrosc Sports Med Rehabil* 2023; 5(1):e179-e184. PMID: 36866290. Full Text

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PURPOSE: To demonstrate the learning curve associated with the arthroscopic Latarjet procedure and create a timetable to proficiency. METHODS: Using retrospective data of a single surgeon, consecutive patients who had an arthroscopic Latarjet procedure performed between December 2015 and May 2021 were initially reviewed for inclusion in the study. Patients were excluded if medical data were insufficient for accurate surgical time record, their surgery was transitioned to open or minimally invasive, or if their surgery was performed in conjunction with a second procedure for a separate issue. All surgeries were performed on an outpatient basis and sports participation was the most common reason for initial glenohumeral dislocation. RESULTS: Fifty-five patients were identified. Of these, 51 met the inclusion criteria. Analysis of operative times for all 51 procedures demonstrated that proficiency with the arthroscopic Latarjet procedure was obtained after 25 cases. This number was determined by 2 methods using statistical analysis ($P < .05$). The average operative time over the course of the first 25 cases was 105.68 minutes and beyond 25 cases was 82.41 minutes. Male gender was seen in 86.3 percent of the patients. The average age of the patients was 28.6 years old. CONCLUSIONS: With continued transition towards bony augmentation procedures for addressing glenoid bone deficiency there is an increasing demand for the arthroscopic bony glenoid reconstruction procedures including the Latarjet procedure. It is a challenging procedure with a substantial initial learning curve. For a skilled arthroscopist there is a significant decrease in overall surgical time after the first 25 cases. CLINICAL RELEVANCE: The arthroscopic Latarjet procedure has advantages over the open Latarjet approach; however, it is controversial because it is technically challenging. It is important for surgeons to understand when they can expect to be proficient with the arthroscopic approach.

Orthopedics/Bone and Joint Center

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

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

and the potential for iatrogenic sural nerve injury. The purpose of this Technical Note is to describe a technique using high-resolution ultrasound guidance intraoperatively during minimally invasive repair of the Achilles tendon. This technique minimizes the drawbacks of poor visualization associated with percutaneous repair, while providing the benefit of a minimally invasive approach.

Orthopedics/Bone and Joint Center

Gardinier JD, **Chougule A**, **Mendez D**, Daly-Seiler C, and **Zhang C**. Periosteal Bone Formation Varies with Age in Periostin Null Mice. *Calcif Tissue Int* 2023; Epub ahead of print. PMID: 36729140. Full Text

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Periostin, also known as osteoblast-specific factor 2, is a matricellular protein predominantly expressed at the periosteum of bone. During growth and development, periostin contributes to periosteal expansion by facilitating osteoblast differentiation and mineralization. Later in life, periosteal expansion provides an adaptive strategy to increase tissue strength without requiring substantial increase in bone mass. However, the function of periostin past skeletal maturity and during advanced aging is relatively unknown. The objective of this study was to examine the function of periostin in maintaining bone mass and tissue strength across different ages. In periostin null mice (Postn-/-), periosteal bone formation was significantly reduced in young (3 months) and adult mice (9 months). The lack of bone formation resulted in reduced bone mass and ultimate strength. Conversely, periosteal bone formation increased at advanced ages in 18-month-old Postn-/- mice. The increase in periosteal mineralization at advanced ages coincides with increased expression of vitronectin and osteopontin. Periosteal progenitors from Postn-/- mice displayed an increased capacity to mineralize when cultured on vitronectin, but not type-1 collagen. Altogether, these findings demonstrate the unique role of periostin in regulating periosteal bone formation at different ages and the potential for vitronectin to compensate in the absence of periostin.

Orthopedics/Bone and Joint Center

Murphy PB, Kasotakis G, Haut ER, Miller A, Harvey E, Hasenboehler E, Higgins T, **Hoegler J**, Mir H, Cantrell S, Obremskey WT, Wally M, Attum B, Seymour R, Patel N, Ricci W, Freeman JJ, Haines KL, Yorkgitis BK, and Padilla-Jones BB. Efficacy and safety of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of acute pain after orthopedic trauma: a practice management guideline from the Eastern Association for the Surgery of Trauma and the Orthopedic Trauma Association. *Trauma Surg Acute Care Open* 2023; 8(1):e001056. PMID: 36844371. Full Text

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OBJECTIVES: Fracture is a common injury after a traumatic event. The efficacy and safety of non-steroidal anti-inflammatory drugs (NSAIDs) to treat acute pain related to fractures is not well established. METHODS: Clinically relevant questions were determined regarding NSAID use in the setting of trauma-induced fractures with clearly defined patient populations, interventions, comparisons and appropriately selected outcomes (PICO). These questions centered around efficacy (pain control, reduction in opioid use) and safety (non-union, kidney injury). A systematic review including literature search and meta-analysis was performed, and the quality of evidence was graded per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The working group reached consensus on the final evidence-based recommendations. RESULTS: A total of 19 studies were identified for analysis. Not all outcomes identified as critically important were reported in all studies, and the outcome of pain control was too heterogenous to perform a meta-analysis. Nine studies reported on non-union (three randomized control trials), six of which reported no association with NSAIDs. The overall incidence of non-union in patients receiving NSAIDs compared with patients not receiving NSAIDs was 2.99% and 2.19% (p=0.04), respectively. Of studies reporting on pain control and reduction of opioids, the use of NSAIDs reduced pain and the need for opioids after traumatic fracture. One study reported on the outcome of acute kidney injury and found no association with NSAID use. CONCLUSIONS: In patients with traumatic fractures, NSAIDs appear to reduce post-trauma pain, reduce the need for opioids and have a small effect on non-union. We conditionally recommend the use of NSAIDs in patients suffering from traumatic fractures as the benefit appears to outweigh the small potential risks.

Otolaryngology – Head and Neck Surgery

Lyons AB, **Ozog DM**, **Lim HW**, **Viola K**, **Tang A**, and **Jones LR**. Commentary on: Re: "The Detroit Keloid Scale: A Validated Tool for Rating Keloids" by Lyons et al. *Facial Plast Surg Aesthet Med* 2023; Epub ahead of print. PMID: 36749139. Full Text

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Otolaryngology – Head and Neck Surgery

Mansour Y, and Kulesza R. Noradrenergic axons hitch hiking along the human abducens nerve. *Anat Cell Biol* 2023; Epub ahead of print. PMID: 36726235. Full Text

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The abducens nerve (AN; cranial nerve VI) exits the brainstem at the inferior pontine sulcus, pierces the dura of the posterior cranial fossa, passes through the cavernous sinus in close contact to the internal carotid artery (ICA) and traverses the superior orbital fissure to reach the orbit to innervate the lateral rectus muscle. At its exit from the brainstem, the AN includes only axons from lower motor neurons in the abducens nucleus. However, as the AN crosses the ICA it receives a number of branches from the internal carotid sympathetic plexus. The arrangement, neurochemical profile and function of these sympathetic axons running along the AN remain unresolved. Herein, we use gross dissection and microscopic study of hematoxylin and eosin-stained sections and sections with tyrosine hydroxylase immunolabeling. Our results suggest the AN receives multiple bundles of unmyelinated axons that use norepinephrine as a neurotransmitter consistent with postganglionic sympathetic axons.

Pathology and Laboratory Medicine

Arena CJ, **Kenney RM**, Kendall RE, **Tibbetts RJ**, and **Veve MP**. Respiratory culture nudge improves antibiotic prescribing for Moraxella catarrhalis and Haemophilus influenzae lower respiratory tract infections. *Antimicrob Steward Healthc Epidemiol* 2023; 3(1):e23. PMID: 36777952. Full Text

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We compared optimal antibiotic prescribing before and after implementing an interpretive β-lactamase microbiology comment for Haemophilus influenzae and Moraxella catarrhalis in lower respiratory-tract infections. The postintervention group was associated with 5-fold increased odds of optimal de-escalation (adjusted odds ratio, 5.03; 95% confidence interval, 2.57-9.87).

Pathology and Laboratory Medicine

Benbrook DM, Deng W, Gold MA, Rai R, Conrad R, van der Wel H, **Husain S**, Moore K, Spirtos N, Jackson AL, Zakhour M, Mathews CA, and West CM. Association of Sialyl Tn antigen with cervical cancer lymph node status: An NRG oncology/GOG study. *Gynecol Oncol* 2023; 171:67-75. PMID: 36827840. Full Text

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OBJECTIVE: Detection of lymph node metastases in cervical cancer patients is important for guiding treatment decisions, however accuracies of current detection methods are limited. We evaluated associations of abnormal glycosylation, represented by Tn and STn antigens on mucin (MUC) proteins, in

primary tumor specimens with lymph node metastasis or recurrence of cervical cancer patients. METHODS: Surgical specimens were prospectively collected from 139 patients with locally-advanced cervical cancer undergoing lymphadenectomy enrolled in a nation-wide clinical trial (NCT00460356). Of these patients, 133 had primary cervix tumor, 67 had pelvic lymph node (PLN) and 28 had para-aortic lymph node (PALN) specimens. Fixed tissue serial sections were immunohistochemically stained for Tn, STn, MUC1 or MUC4. Neuraminidase was used to validate Tn versus STn antibody specificity. Stain scores were compared with clinical characteristics. RESULTS: Primary tumor STn expression above the median was associated with negative PLN status (p-value: 0.0387; odds ratio 0.439, 95% CI: 0.206 to 0.935). PLN had higher STn compared to primary tumor, while primary tumor had higher MUC1 compared to PALN, and MUC4 compared to PALN or PLN ($p = 0.017$, $p = 0.011$, $p = 0.016$ and $p < 0.001$, respectively). Tn and STn expression correlated in primary tumor, PALN, and PLN, Tn and MUC1 expression correlated in primary tumors only (Spearman correlation coefficient [r] = 0.301, $r = 0.686$, $r = 0.603$ and $r = 0.249$, respectively). CONCLUSIONS: STn antigen expression in primary cervical tumors is a candidate biomarker for guiding treatment decisions and for mechanistic involvement in PLN metastases.

Pathology and Laboratory Medicine

Bhan A, **Athimulam S**, Kumari P, Pal R, Bhadada SK, **Cook BC**, **Qiu S**, and **Rao SD**. Large parathyroid adenomas: Potential mechanisms to reconcile adenoma size and disease phenotype. *Front Endocrinol (Lausanne)* 2023; 14:1009516. PMID: 36817587. Full Text

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Parathyroid adenomas weighing more than 3.5 g are reported variously as "atypical", "large" or "giant" parathyroid adenomas. All such adenomas are rare variants accounting for no more than 1.5% of all parathyroid adenomas. Large parathyroid adenomas are often associated with more severe form of the disease, including osteitis fibrosa cystica (OFC) and share many biochemical, histological, and molecular features of both benign and malignant parathyroid neoplasms, and are considered a distinct clinical entity. However, the pathogenesis of oversized parathyroid adenomas and the often-associated skeletal phenotype remains unclear. We present 5 cases of primary hyperparathyroidism (PHPT) with OFC, an uncommon manifestation of contemporary PHPT, associated with larger parathyroid adenomas, seen in the Bone and Mineral Disorders Clinic of the Henry Ford Health in the last 30 years to illustrate the critical role of vitamin D nutrition in the pathogenesis of both the OFC and adenoma size. The estimated prevalence of OFC was very low 0.2%, 5 of the >3000 surgically confirmed cases of PHPT seen during this time. The mean ± SD values were: age: 36.8 ± 22.1 years (4 of the 5 <36years), serum calcium 11.6 ± 1.1 mg/dl, alkaline phosphatase 799 ± 487 IU/L, PTH 1440 ± 477 pg/ml, 25-hydroxyvitamin D 13.0 ± 8.9 ng/ml, 1,25-dihyroxyvitamin D 26.5 ± 13.7 pg/ml, urine calcium 562 ± 274 mg/day, and parathyroid adenoma weight 4.53 ± 2.2 g. Parathyroidectomy led to the resolution of both the biochemical indices and OFC in each patient without recurrence over >10 years of follow-up. Because OFC is a very rare in the West, but very common areas of endemic vitamin D deficiency, we also examined the relationship between vitamin D nutrition, as assessed by serum 25-hydroxyvitamin D level, and parathyroid adenoma weight as well as prevalence of OFC in two large secularly diverse cohorts of patients with PHPT (Detroit, USA and Chandigarh, India). Based on this relationship and the relative prevalence of OFC in these two large cohorts, we propose that vitamin D nutrition (and perhaps calcium nutrition) best explains both the adenoma size and prevalence of OFC.

Pathology and Laboratory Medicine
Stefan AJ, **Herc ES**, **Gudipati S**, **Brar I**, **Vitale A**, and Tariq Z. Atypical presentation of progressive disseminated histoplasmosis in a patient recently diagnosed with AIDS. *Int J Infect Dis* 2023; 127:45-47. PMID: 36462572. Full Text

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Opportunistic infections, including progressive disseminated histoplasmosis (PDH), may have variable and surprising presentations in patients with AIDS. This can be either a primary infection or reactivation of a latent infection. Latent infections may occur due to being unmasked by the immune reconstitution inflammatory syndrome after the initiation of combined antiretroviral therapy. PDH can be difficult to diagnose in patients with AIDS due to its variable presentation and many overlapping symptoms with other opportunistic infections. Serum and urine antigen testing are highly sensitive and typically used as the initial diagnostic test to workup suspected PDH. However, negative antigen and antibody tests do not rule out Histoplasmosis capsulatum infection and suspicion should remain high for PDH in the right clinical context. A definitive diagnosis may require biopsy-proven narrow-based budding yeast. We present an interesting patient with AIDS who presented with worsening cognitive decline and was ultimately diagnosed with PDH based on biopsy histopathology in the setting of negative antigen and antibody testing.

Pharmacy
Arena CJ, **Kenney RM**, Kendall RE, **Tibbetts RJ**, and **Veve MP**. Respiratory culture nudge improves antibiotic prescribing for Moraxella catarrhalis and Haemophilus influenzae lower respiratory tract infections. *Antimicrob Steward Healthc Epidemiol* 2023; 3(1):e23. PMID: 36777952. Full Text

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We compared optimal antibiotic prescribing before and after implementing an interpretive β-lactamase microbiology comment for Haemophilus influenzae and Moraxella catarrhalis in lower respiratory-tract infections. The postintervention group was associated with 5-fold increased odds of optimal de-escalation (adjusted odds ratio, 5.03; 95% confidence interval, 2.57-9.87).

Pharmacy
Cheng JWM, Colucci V, **Kalus JS**, and Spinler SA. Sodium-Glucose Cotransporter 2 Inhibitors Among Heart Failure With Mildly Reduced and Preserved Ejection Fraction. *Ann Pharmacother* 2023; Epub ahead of print. PMID: 36800904. Full Text

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OBJECTIVE: Results from large placebo-controlled randomized trials in patients with heart failure with mid-range ejection fraction (HFmrEF) and HF with preserved EF (HFpEF) have become available recently. This article discusses results of these clinical trials. DATA SOURCES: Peer-reviewed articles

were identified from MEDLINE (1966 to December 31, 2022) using search terms dapagliflozin, empagliflozin, SGLT-2Is, HFmrEF, and HFpEF. STUDY SELECTION AND DATA EXTRACTION: Eight completed, pertinent clinical trials were included. DATA SYNTHESIS: EMPEROR-Preserved, and DELIVER demonstrated that empagliflozin and dapagliflozin reduce CV death and heart failure hospitalization (HHF) in patients with HFmrEF and HFpEF, with/without diabetes when added to a standard heart failure (HF) regimen. The benefit is primarily due to reduction in HHF. Additional data from post hoc analyses of trials of dapagliflozin, ertugliflozin, and sotagliflozin suggest that these benefits may be a class effect. Benefits appear greatest in patients with left ventricular ejection fraction 41% up to about 65%. RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE: While many pharmacologic treatments have been proven to reduce mortality and improve cardiovascular (CV) outcomes in people with HFmrEF and HF with reduced EF (HFrEF), there are few therapy which improve CV outcome in people with HFpEF. SGLT-2I become one of the first class of pharmacologic agent that can be used to reduce HHF and CV mortality. CONCLUSION: Studies showed that empagliflozin and dapagliflozin reduce the combined risk of CV death or HHF in patients with HFmrEF and HFpEF when added to a standard HF regimen. Given that benefit has now been demonstrated across the spectrum of HF, SGLT-2Is should be considered one of the standard HF pharmacotherapy.

Public Health Sciences

Kitajima T, Rajendran L, **Lisznyai E**, **Lu M**, **Shamaa T**, **Ivanics T**, **Yoshida A**, Claasen M, **Abouljoud MS**, Sapisochin G, and **Nagai S**. Lymphopenia at the time of transplant is associated with short-term mortality after deceased donor liver transplantation. *Am J Transplant* 2023; 23(2):248-256. PMID: 36804132. Full Text

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Absolute lymphocyte count (ALC) is considered a surrogate marker for nutritional status and immunocompetence. We investigated the association between ALC and post-liver transplant outcomes in patients who received a deceased donor liver transplant (DDLT). Patients were categorized by ALC at liver transplant: low (<500/μL), mid (500-1000/μL), and high ALC (>1000/μL). Our main analysis used retrospective data (2013-2018) for DDLT recipients from Henry Ford Hospital (United States); the results were further validated using data from the Toronto General Hospital (Canada). Among 449 DDLT recipients, the low ALC group demonstrated higher 180-day mortality than mid and high ALC groups (83.1% vs 95.8% and 97.4%, respectively; low vs mid: P = .001; low vs high: P < .001). A larger proportion of patients with low ALC died of sepsis compared with the combined mid/high groups (9.1% vs 0.8%; P < .001). In multivariable analysis, pretransplant ALC was associated with 180-day mortality (hazard ratio, 0.20; P = .004). Patients with low ALC had higher rates of bacteremia (22.7% vs 8.1%; P < .001) and cytomegaloviremia (15.2% vs 6.8%; P = .03) than patients with mid/high ALC. Low ALC pretransplant through postoperative day 30 was associated with 180-day mortality among patients who received rabbit antithymocyte globulin induction (P = .001). Pretransplant lymphopenia is associated with short-term mortality and a higher incidence of posttransplant infections in DDLT patients.

Public Health Sciences

LeWitt PA, **Li J**, **Wu KH**, and **Lu M**. Diagnostic metabolomic profiling of Parkinson's disease biospecimens. *Neurobiol Dis* 2023; 177:105962. PMID: 36563791. Full Text

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BACKGROUND: Reliable and sensitive biomarkers are needed for enhancing and predicting Parkinson's disease (PD) diagnosis. OBJECTIVE: To investigate comprehensive metabolomic profiling of biochemicals in CSF and serum for determining diagnostic biomarkers of PD. METHODS: Fifty subjects, symptomatic with PD for ≥5 years, were matched to 50 healthy controls (HCs). We used ultrahigh-performance liquid chromatography linked to tandem mass spectrometry (UHPLC-MS/MS) for measuring relative concentrations of ≤1.5 kDalton biochemicals. A reference library created from authentic standards facilitated chemical identifications. Analytes underwent univariate analysis for PD association, with false discovery rate-adjusted p-value (≤0.05) determinations. Multivariate analysis (for identifying a panel of biochemicals discriminating PD from HCs) used several biostatistical methods, including logistic LASSO regression. RESULTS: Comparing PD and HCs, strong differentiation was achieved from CSF but not serum specimens. With univariate analysis, 21 CSF compounds exhibited significant differential concentrations. Logistic LASSO regression led to selection of 23 biochemicals (11 shared with those determined by the univariate analysis). The selected compounds, as a group, distinguished PD from HCs, with Area-Under-the-Receiver-Operating-Characteristic (ROC) curve of 0.897. With optimal cutoff, logistic LASSO achieved 100% sensitivity and 96% specificity (and positive and negative predictive values of 96% and 100%). Ten-fold cross-validation gave 84% sensitivity and 82% specificity (and 82% positive and 84% negative predictive values). From the logistic LASSO-chosen regression model, 2 polyamine metabolites (N-acetylcadaverine and N-acetylputrescine) were chosen and had the highest fold-changes in comparing PD to HCs. Another chosen biochemical, acisoga (N-(3-acetamidopropyl)pyrrolidine-2-one), also is a polyamine metabolism derivative. CONCLUSIONS: UHPLC-MS/MS assays provided a metabolomic signature highly predictive of PD. These findings provide further evidence for involvement of polyamine pathways in the neurodegeneration of PD.

Public Health Sciences

Lim S, **Schultz L**, Zakko P, **Macki M**, **Hamilton T**, **Pawloski J**, **Fadel H**, **Mansour T**, **Yeh HH**, Preston G, **Nerenz D**, **Schwalb JM**, **Abdulhak M**, Park P, Aleem I, Easton R, Khalil J, Perez-Cruet M, Park D, and **Chang V**. The Potential Negative Effects of Smoking on Cervical and Lumbar Surgery beyond Pseudoarthrosis: A Michigan Spine Surgery Improvement Collaborative (MSSIC) Study. *World Neurosurg* 2023; Epub ahead of print. PMID: 36791883. Full Text

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OBJECTIVE: The study was designed to review the Michigan Spine Surgery Improvement Collaborative (MSSIC) registry to investigate the long-term associations between current smoking status and outcomes after elective cervical and lumbar spine surgery. METHODS: Utilizing MSSIC we captured all cases from 01/01/17-11/21/20 with outcomes data available. 19,251 lumbar cases and 7,936 cervical cases were included. Multivariate regression analyses were performed to assess the relationship of smoking with the clinical outcomes. RESULTS: Current smoking status was associated with lower urinary retention and satisfaction for lumbar surgery patients and was also associated with less likelihood of achieving minimal clinically important difference (MCID) in Patient-Reported Outcomes Measurement Information System (PROMIS), back pain, leg pain, and EQ5D at 90 days and 1 year after surgery. Current smokers were also less likely to return to work at 90 days and 1 year after surgery. For cervical patients, current smokers were less likely to have urinary retention and dysphagia postoperatively. They were less likely to be satisfied with the surgery outcome at 1 year. Current smoking was associated with lower likelihood of achieving MCID in PROMIS, neck pain, arm pain, and EQ5D at various time points. There was no difference in return-to-work status. CONCLUSION: Our analysis suggests that smoking is negatively associated with functional improvement, patient satisfaction, and return-to-work after elective spine surgery.

Public Health Sciences

Lyons AB, **Ozog DM**, **Lim HW**, **Viola K**, **Tang A**, and **Jones LR**. Commentary on: Re: "The Detroit Keloid Scale: A Validated Tool for Rating Keloids" by Lyons et al. *Facial Plast Surg Aesthet Med* 2023; Epub ahead of print. PMID: 36749139. Full Text

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Public Health Sciences

Ramkumar SP, Simpson MC, **Adjei Boakye E**, Bukatko AR, Antisdel JL, Massa ST, and Osazuwa-Peters N. High-risk human papillomavirus 16/18 associated with improved survival in sinonasal squamous cell carcinoma. *Cancer* 2023; Epub ahead of print. PMID: 36808090. Full Text

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BACKGROUND: There has been conflicting evidence on the independent prognostic role of human papillomavirus (HPV) status in sinonasal cancer. The objective of this study was to assess whether the survival of patients with sinonasal cancer differs based on various HPV statuses, including HPV-negative, positive for the high-risk HPV-16 and HPV-18 (HPV16/18) subtypes, and positive for other high-risk and low-risk HPV subtypes. METHODS: In this retrospective cohort study, data from the National Cancer Database were extracted from the years 2010-2017 for patients who had primary sinonasal cancer (N = 12,009). The outcome of interest was overall survival based on HPV tumor status. RESULTS: Study included an analytic cohort of 1070 patients with sinonasal cancer who had confirmed HPV tumor status (732 [68.4%] HPV-negative; 280 [26.2%] HPV16/18-positive; 40 [3.7%] positive for other high-risk HPV;

and 18 [1.7%] positive for low-risk HPV). HPV-negative patients had the lowest all-cause survival probability at 5 years postdiagnosis (0.50). After controlling for covariates, HPV16/18-positive patients had a 37% lower mortality hazard than HPV-negative patients (adjusted hazard ratio, 0.63; 95% confidence interval [CI], 0.48-0.82). Patients aged 64-72 years (crude prevalence ratio, 0.66; 95% CI, 0.51-0.86) and 73 years and older (crude prevalence ratio, 0.43; 95% CI, 0.31-0.59) presented with lower rates of HPV16/18-positive sinonasal cancer than those aged 40-54 years. In addition, Hispanic patients had a 2.36 times higher prevalence of non-HPV16/18 sinonasal cancer than non-Hispanic White patients. CONCLUSIONS: These data suggest that, for patients with sinonasal cancer, HPV16/18-positive disease may confer a significant survival advantage compared with HPV-negative disease. Other high-risk and low-risk HPV subtypes have survival rates similar to the rates for HPV-negative disease. HPV status might be an important independent prognostic factor in sinonasal cancer that could be used in patient selection and clinical decisions.

Public Health Sciences

Saleem M, Sadat B, **Van Harn M**, and **Ananthasubramaniam K**. Towards a Diagnosis of Cardiac Amyloidosis: Single Center Experience with (99m) Technetium Pyrophosphate Planar Imaging and Opportunities for Standardization of Diagnostic Workflow. *Medicina (Kaunas)* 2023; 59(2). PMID: 36837580. Full Text

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Background and Objectives: Cardiac amyloidosis is a disorder caused by amyloid fibril deposition in the extracellular space of the heart. Almost all forms of clinical cardiac amyloidosis are transthyretin amyloidosis (ATTR) or light chain amyloidosis. (99m) technetium pyrophosphate ((99m)Tc PYP scan) has changed the landscape of the non-biopsy diagnosis of ATTR cardiac amyloidosis (ATTR-CA) by providing remarkably high diagnostic accuracy. We examined our experience with PYP scans in patients undergoing workup for ATTR-CA and evaluated the diagnostic workflow in patients with intermediate PYP scan results. Materials and Methods: Retrospective chart review study in which we analyzed data of 84 patients who underwent c-99m pyrophosphate (PYP) SPECT scan for the diagnosis of ATTR-CA from 2017 till 2021 at our institution. We identified three groups: Low uptake (PYPL uptake ratio < 1.2 + visual grade 1/0), n = 30, Intermediate uptake (PYPI uptake ratio 1.2-1.49, visual grade 2/3), n = 25 and High uptake (PYPH uptake ratio ≥ 1.5 + visual grade 2/3), n = 29. We reviewed patients' demographics, medical histories, echo parameters and diagnostic testing including light chain analysis, cardiac magnetic resonance results, and biopsies. Results: Mean patients' age was 73, male-to=female ratio 3:1, 59% of patients were African American. Cardiovascular comorbidities, cardiac biomarkers (BNP and Troponin) and amyloid-related neuropathy were similar in all groups. A statistically significant difference in septal thickness/posterior wall thickness and final diagnosis were found between the groups. The distribution of overall diagnostic testing ratios for the PYPI group included serum protein electrophoresis 92%, urine protein electrophoresis 65%, free light chain 80%, CMR 32%, tissue biopsy done in 20% and BM biopsy in 16%, which are similar to the ratios of other groups. Overall, 25% (n = 5, 4 TTR-CA and 1 AL Amyloid) of patients in the PYPI group had a final diagnosis of CA established with additional testing (p = 0.001 vs. other groups). Conclusions: The (99m)PYP scan is an accurate noninvasive test for cardiac ATTR-CA. Importantly, 25% of the PYPI group had a final diagnosis of ATTR-CA reiterating that diagnosis needs to be pursued in PYPI cases based on clinical suspicion. Routine evaluation and exclusion of light chain disease and establishing a consistent workflow for amyloid diagnosis and continued education for technologists and readers of PYP scans is key to a successful amyloidosis workup.

Public Health Sciences

Straughen JK, **Clement J**, **Schultz L**, **Alexander G**, **Hill-Ashford Y**, and **Wisdom K**. Community health workers as change agents in improving equity in birth outcomes in Detroit. *PLoS One* 2023; 18(2):e0281450. PMID: 36787290. Full Text

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We examined whether pairing pregnant women with community health workers improved pregnancy outcomes among 254 Black women with singleton pregnancies participating in the Women-Inspired Neighborhood (WIN) Network: Detroit using a case-control design. A subset (N = 63) of women were recontacted and asked about program satisfaction, opportunities, and health behaviors. Michigan Vital Statistics records were used to ascertain controls (N = 12,030) and pregnancy and infant health outcomes. Logistic and linear regression were used to examine the association between WIN Network participation and pregnancy and infant health outcomes. The WIN Network participants were less likely than controls to be admitted to the neonatal intensive care unit (odds ratio = 0.55, 95% CI 0.33-0.93) and had a longer gestational length (mean difference = 0.42, 95% CI 0.02-0.81). Community health workers also shaped participants' view of opportunities to thrive. This study demonstrates that community health workers can improve pregnancy outcomes for Black women.

Public Health Sciences

Wong RJ, **Rupp L**, **Lu M**, Yang Z, Daida YG, Schmidt M, Boscarino JA, **Gordon SC**, and Chitnis AS. Prevalence of Hepatitis B Virus (HBV) and Latent Tuberculosis Co-Infection and Risk of Drug-Induced Liver Injury Across Two Large HBV Cohorts in the United States. *J Viral Hepat* 2023; Epub ahead of print. PMID: 36843435. Full Text

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The epidemiology of latent tuberculosis and hepatitis B virus (HBV-LTBI) co-infection among U.S. populations is not well studied. We aim to evaluate LTBI testing patterns and LTBI prevalence among two large U.S. cohorts of adults with chronic HBV (CHB). Adults with CHB in the Chronic Hepatitis Cohort Study (CHeCS) and Veterans Affairs national cohort were included in the analyses. Prevalence of HBV-LTBI co-infection was defined as the number of HBV patients with LTBI divided by the number of HBV patients in a cohort. Multivariable logistic regression evaluated odds of HBV-LTBI co-infection among CHB patients who underwent TB testing. Among 6,019 CHB patients in the CHeCS cohort (44% female, 47% Asian), 9.1% were tested for TB, among whom 7.7% had HBV-LTBI co-infection. Among HBV-LTBI co-infected patient, only 16.7% (n=7) received LTBI treatment, among whom 28.6% (n=2) developed DILI. Among 12,928 CHB patients in the VA cohort (94% male, 42% African American, 39% non-Hispanic white), 14.7% were tested for TB, among whom 14.5% had HBV-LTBI. Among HBV-LTBI co-infected patient, 18.6% (n=51) received LTBI treatment, among whom 3.9% (n=3) developed DILI. Presence of cirrhosis, race/ethnicity, and country of birth were observed to be associated with odds of HBV-LTBI co-infection among CHB patients who received TB testing. In summary, among two large distinct U.S. cohorts of adults with CHB, testing for LTBI was infrequent despite relatively high prevalence of HBV-LTBI co-infection. Moreover, low rates of LTBI treatment were observed among those with HBV-LTBI co-infection.

Radiation Oncology

Herr DJ, Yin H, Allen SG, Bergsma D, Dragovic AF, Dess RT, Matuszak M, Grubb M, Dominello M, **Movsas B**, Kestin LL, Hayman JA, Paximadis P, Schipper M, and Jolly S. Cardiac and pulmonary dosimetric parameters in lung cancer patients undergoing post-operative radiation therapy across a state-wide consortium. *Pract Radiat Oncol* 2023; Epub ahead of print. PMID: 36754278. Full Text

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PURPOSE/OBJECTIVES: The recently published Lung ART trial reported increased rates of cardiac and pulmonary toxicity in the post-operative radiation therapy (PORT) arm. It remains unknown whether the dosimetric parameters reported in Lung ART are representative of contemporary real-world practice, which remains relevant for patients undergoing post-operative RT for positive surgical margins. The purpose of this study is to examine heart and lung dose exposure in patients receiving post-operative radiation therapy for non-small cell lung cancer (NSCLC) across a statewide consortium. MATERIALS/METHODS: From 2012 to 2022, demographic and dosimetric data were prospectively collected for 377 patients at 27 academic and community centers within [redacted] undergoing PORT for non-metastatic NSCLC. Dosimetric parameters for target coverage and Organ at Risk (OAR) exposure were calculated using data from dose volume histograms, and rates of 3D-CRT and IMRT utilization were assessed. RESULTS: Fifty-one percent of patients in this cohort had N2 disease at the time of surgery, 25% had a positive margin. Sixty-six percent of patients were treated with IMRT compared to 32% with 3D-CRT. Planning target volume (PTV) was significantly smaller in patients treated with 3D-CRT (149.2 cc vs. 265.4 cc, $p<0.0001$). Median mean heart dose for all patients was 8.7 Gy (IQR 3.5, 15.3), median heart V5 was 35.2% (IQR 18.5, 60.2) and median heart V35 was 9% (IQR 3.2, 17.7). Median mean lung dose (MLD) was 11.4 Gy (IQR 8.1, 14.3), median lung V20 was 19.6% (IQR 12.7, 25.4). These dosimetric parameters did not significantly differ by treatment modality (IMRT vs. 3D-CRT) or in patients with positive vs. negative surgical margins. CONCLUSIONS: With increased rates of IMRT use, cardiac and lung dosimetric parameters in this state-wide consortium are slightly lower than those reported in Lung ART. These data provide useful benchmarks for treatment planning in patients undergoing post-operative RT for positive surgical margins.

Radiation Oncology

Medhora M, Morauski Y, Williams J, Wilson JF, Jacobs ER, **Brown SL**, Doctrow S, Sharma M, and Fish BL. John E. Moulder (1945-2022) The Father of Mitigation of Late Responding Normal Tissue to Ionizing Radiation. *Radiat Res* 2023; 199(2):211-215. PMID: 36745153. Request Article

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Sleep Medicine

Reffi AN, **Drake CL**, **Kalmbach DA**, Jovanovic T, Norrholm SD, **Roth T**, Casement MD, and **Cheng P**. Pre-pandemic sleep reactivity prospectively predicts distress during the COVID-19 pandemic: The protective effect of insomnia treatment. *J Sleep Res* 2023; 32(1):e13709. PMID: 36053867. Full Text

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The COVID-19 pandemic is a rare stressor that has precipitated an accompanying mental health crisis. Prospective studies traversing the pandemic's onset can elucidate how pre-existing disease vulnerabilities augured risk for later stress-related morbidity. We examined how pre-pandemic sleep reactivity predicted maladaptive stress reactions and depressive symptoms in response to, and during, the pandemic. This study is a secondary analysis of a randomised controlled trial from 2016 to 2017 comparing digital cognitive behavioural therapy for insomnia (dCBT-I) against sleep education (N = 208). Thus, we also assessed whether dCBT-I moderated the association between pre-pandemic sleep reactivity and pandemic-related distress. Pre-pandemic sleep reactivity was measured at baseline using the Ford Insomnia Response to Stress Test. In April 2020, participants were recontacted to report pandemic-related distress (stress reactions and depression). Controlling for the treatment condition and the degree of COVID-19 impact, higher pre-pandemic sleep reactivity predicted more stress reactions ($\beta = 0.13$, ± 0.07 SE, $p = 0.045$) and depression ($\beta = 0.22$, ± 0.07 SE, $p = 0.001$) during the pandemic. Further, the odds of reporting clinically significant stress reactions and depression during the pandemic were over twice as high in those with high pre-pandemic sleep reactivity. Notably, receiving dCBT-I in 2016-2017 mitigated the relationship between pre-pandemic sleep reactivity and later stress reactions (but not depression). Pre-pandemic sleep reactivity predicted psychological distress 3-4 years later during the COVID-19 pandemic, and dCBT-I attenuated its association with stress reactions, specifically. Sleep reactivity may inform prevention and treatment efforts by identifying individuals at risk of impairment following stressful events.

Surgery

Choi WJ, **Ivanics T**, Gravely A, Gallinger S, Sapisochin G, and O'Kane GM. Optimizing Circulating Tumour DNA Use in the Perioperative Setting for Intrahepatic Cholangiocarcinoma: Diagnosis, Screening, Minimal Residual Disease Detection and Treatment Response Monitoring. *Ann Surg Oncol* 2023; Epub ahead of print. PMID: 36808320. Full Text

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In this review, we present the current evidence and future perspectives on the use of circulating tumour DNA (ctDNA) in the diagnosis, management and understanding the prognosis of patients with intrahepatic cholangiocarcinoma (iCCA) undergoing surgery. Liquid biopsies or ctDNA maybe utilized to:

(1) determine the molecular profile of the tumour and therefore guide the selection of molecular targeted therapy in the neoadjuvant setting, (2) form a surveillance tool for the detection of minimal residual disease or cancer recurrence after surgery, and (3) diagnose and screen for early iCCA detection in high-risk populations. The potential for ctDNA can be tumour-informed or -uninformed depending on the goals of its use. Future studies will require ctDNA extraction technique validations, with standardizations of both the platforms and the timing of ctDNA collections.

Surgery
Choi WJ, **Ivanics T**, Gravely A, Gallinger S, Sapisochin G, and O'Kane GM. ASO Visual Abstract: Optimizing Circulating Tumor DNA Use in the Perioperative Setting for Intrahepatic Cholangiocarcinoma-Diagnosis, Screening, Minimal Residual Disease Detection, and Treatment Response Monitoring. *Ann Surg Oncol* 2023; Epub ahead of print. PMID: 36847955. Full Text

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Surgery
Choi WJ, Perez FM, Gravely A, **Ivanics T**, Claasen M, Abraham L, Abreu P, Visser R, Gallinger S, Hansen BE, and Sapisochin G. Preoperative neutrophil-to-lymphocyte ratio is prognostic for early recurrence after curative intrahepatic cholangiocarcinoma resection. *Ann Hepatobiliary Pancreat Surg* 2023; Epub ahead of print. PMID: 36804209. Full Text

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BACKGROUNDS/AIMS: Within two years of surgery, 70% of resected intrahepatic cholangiocarcinoma (iCCA) recur. Better biomarkers are needed to identify those at risk of "early recurrence" (ER). In this study, we defined ER and investigated whether preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic-inflammatory index were prognostic of both overall relapse and ER after curative hepatectomy for iCCA. METHODS: A retrospective cohort of patients who underwent curative-intent hepatectomy for iCCA between 2005 and 2017 were created. The cut-off timepoint for the ER of iCCA was estimated using a piecewise linear regression model. Univariable analyses of recurrence were conducted for the overall, early, and late recurrence periods. For the early and late recurrence periods, multivariable Cox regression with time-varying regression coefficient analysis was used. RESULTS: A total of 113 patients were included in this study. ER was defined as recurrence within 12 months of a curative resection. Among the included patients, 38.1% experienced ER. In the univariable model, a higher preoperative NLR (> 4.3) was significantly associated with an increased risk of recurrence overall and in the first 12 months after curative surgery. In the multivariable model, a higher NLR was associated with a higher recurrence rate overall and in the ER period (≤ 12 months), but not in

the late recurrence period. CONCLUSIONS: Preoperative NLR was prognostic of both overall recurrence and ER after curative iCCA resection. NLR is easily obtained before and after surgery and should be integrated into ER prediction tools to guide preoperative treatments and intensify postoperative follow-up.

Surgery
Currier EE, **Ichkanian Y**, **Dabaja M**, Segovia MC, Patel Y, **Nagai S**, Sudan DL, and **Jafri SM**. Cytomegalovirus Infection Management in Multivisceral and Intestinal Transplant: A Dual Institution Study. *Transplant Proc* 2023; Epub ahead of print. PMID: 36792485. Full Text

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Intestinal transplant and multivisceral transplant were originally in pediatric populations and are relatively new procedures in adults. Despite increasing success rates in the immediate post-transplant period, infectious complications and acute and chronic rejection remain significant causes of morbidity and mortality. Previous research has shown cytomegalovirus (CMV) is the main cause of infection in this population. Due to the limited patient population, incidence of CMV viremia ranges widely and there is lack of universal protocol for treatment. This dual institution retrospective chart review between Henry Ford Hospital and Duke University analyzed adult intestinal and multivisceral transplant recipients between 2009 and 2019. Of the 32 patients identified and included in the study, 15 had CMV infection (46.9%). Of those with CMV infection, 5 (33.3%) had donor positive (D+)/recipient positive (R+) status; 5 had D-/R+; 4 had D+/R-; and one had D-/R-. There was no significant difference between mortality in those who had reported infection and not (80% vs 76.5%). The data from this study show significant rates of CMV viremia in patients undergoing intestinal transplant/multivisceral transplant with almost half of our study population having documented infection within 1 year of transplant, stressing the importance for universal protocol into CMV viremia treatment.

Surgery
Ivanics T, Claasen M, Patel MS, Giorgakis E, Khorsandi SE, Srinivasan P, Prachalias A, Menon K, Jassem W, Cortes M, Sayed BA, Mathur AK, Walker K, Taylor R, Heaton N, Mehta N, Segev DL, Massie AB, van der Meulen JHP, Sapisochin G, and Wallace D. Outcomes after liver transplantation using deceased after circulatory death donors: A comparison of outcomes in the UK and the US. *Liver Int* 2023; Epub ahead of print. PMID: 36737866. Full Text

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BACKGROUND AND AIMS: Identifying international differences in utilization and outcomes of liver transplantation (LT) after donation after circulatory death (DCD) donation provides a unique opportunity for benchmarking and population-level insight. METHODS: Adult (≥18 years) LT data between 2008 and 2018 from the UK and US were used to assess mortality and graft failure after DCD LT. We used time-dependent Cox-regression methods to estimate hazard ratios (HR) for risk-adjusted short-term (0-90 days) and longer-term (90 days-5 years) outcomes. RESULTS: One-thousand five-hundred-and-sixty LT receipts from the UK and 3426 from the US were included. Over the study period, the use of DCD livers increased from 15.7% to 23.9% in the UK compared to 5.1% to 7.6% in the US. In the UK, DCD donors were older (UK:51 vs. US:33 years) with longer cold ischaemia time (UK: 437 vs. US: 333 min). Recipients in the US had higher Model for End-stage Liver Disease (MELD) scores, higher body mass index, higher proportions of ascites, encephalopathy, diabetes and previous abdominal surgeries. No difference in the risk-adjusted short-term mortality or graft failure was observed between the countries. In the longer-term (90 days-5 years), the UK had lower mortality and graft failure (adj.mortality HR:UK: 0.63 (95% CI: 0.49-0.80); graft failure HR: UK: 0.72, 95% CI: 0.58-0.91). The cumulative incidence of retransplantation was higher in the UK (5 years: UK: 11.9% vs. 4.6%; p < .001). CONCLUSIONS: For those receiving a DCD LT, longer-term post-transplant outcomes in the UK are superior to the US, however, significant differences in recipient illness, graft quality and access to retransplantation were seen between the two countries.

Surgery
Kitajima T, Rajendran L, **Lisznyai E**, **Lu M**, **Shamaa T**, **Ivanics T**, **Yoshida A**, Claasen M, **Abouljoud MS**, Sapisochin G, and **Nagai S**. Lymphopenia at the time of transplant is associated with short-term mortality after deceased donor liver transplantation. *Am J Transplant* 2023; 23(2):248-256. PMID: 36804132. Full Text

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Absolute lymphocyte count (ALC) is considered a surrogate marker for nutritional status and immunocompetence. We investigated the association between ALC and post-liver transplant outcomes in patients who received a deceased donor liver transplant (DDLT). Patients were categorized by ALC at liver transplant: low (<500/μL), mid (500-1000/μL), and high ALC (>1000/μL). Our main analysis used retrospective data (2013-2018) for DDLT recipients from Henry Ford Hospital (United States); the results were further validated using data from the Toronto General Hospital (Canada). Among 449 DDLT recipients, the low ALC group demonstrated higher 180-day mortality than mid and high ALC groups (83.1% vs 95.8% and 97.4%, respectively; low vs mid: P = .001; low vs high: P < .001). A larger proportion of patients with low ALC died of sepsis compared with the combined mid/high groups (9.1% vs 0.8%; P < .001). In multivariable analysis, pretransplant ALC was associated with 180-day mortality (hazard ratio, 0.20; P = .004). Patients with low ALC had higher rates of bacteremia (22.7% vs 8.1%; P <

.001) and cytomegaloviremia (15.2% vs 6.8%; P = .03) than patients with mid/high ALC. Low ALC pretransplant through postoperative day 30 was associated with 180-day mortality among patients who received rabbit antithymocyte globulin induction (P = .001). Pretransplant lymphopenia is associated with short-term mortality and a higher incidence of posttransplant infections in DDLT patients.

Surgery
Okeke B, Hillmon C, Jones J, Obanigba G, Obi A, Nkansah M, Odiase N, Khanipov K, and **Okereke IC**. The relationship of social determinants and distress in newly diagnosed cancer patients. *Sci Rep* 2023; 13(1):2153. PMID: 36750604. Full Text

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Patients with a new cancer diagnosis can experience distress when diagnosed. There are disparities in treatment of cancer patients based on social determinants, but minimal research exists on the relationship of those social determinants and distress after a new cancer diagnosis. Our goals were to determine the social determinants associated with distress after a new cancer diagnosis and determine the relationship of distress with outcome. Patients with a new cancer diagnosis at one institution from January 2019 to December 2020 were analyzed. Patients were given the National Comprehensive Cancer Network (NCCN) distress thermometer during their first visit. Demographics, tumor characteristics, clinical variables and survival were recorded. Patients were also asked to share specific factors that led to distress, including: (1) financial, (2) transportation, (3) childcare and (4) religious. A total of 916 patients returned distress thermometers. Mean age was 59.1 years. Females comprised 71.3 (653/916) percent of the cohort. On Dunn's multiple comparison, the following factors were associated with increased distress level: female ($p < 0.01$), ages 27 to 45 ($p < 0.01$), uninsured ($p < 0.01$) and unemployed ($p < 0.01$). Patients with higher distress scores also experienced worse overall survival ($p < 0.05$). Females, young patients, uninsured patients and unemployed patients experience more distress after a new cancer diagnosis. Increased distress is independently associated with worse overall survival. Social determinants can be used to predict which patients may require focused interventions to reduce distress after a new cancer diagnosis.

Surgery
Rajendran L, Murillo Perez CF, **Ivanics T**, Claasen M, Hansen BE, Wallace D, Yoon PD, and Sapisochin G. Outcomes of liver transplantation in non-alcoholic steatohepatitis (NASH) versus non-NASH associated hepatocellular carcinoma. *HPB (Oxford)* 2023; Epub ahead of print. PMID: 36828740. Full Text

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BACKGROUND: Non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC) is a rising indication for liver transplantation. This unique population, with multiple comorbidities, has potential for worse post-transplant outcomes. We compared post-transplant survival of NASH and non-NASH HCC patients using a large cohort. METHODS: Adults transplanted for HCC between 2008 and 2018, from United Network for Organ Sharing (UNOS) and University Health Network (UHN) databases were divided into two populations: NASH and non-NASH. Recipient characteristics and post-transplant survival were compared. Subgroup analyses were performed within and beyond Milan criteria. RESULTS: 2071 of 20,672 (10.0%) patients underwent transplantation for NASH HCC, with annual proportional increase of 1.2%UHN ($p = 0.02$) and 1.3%UNOS ($p < 0.001$). The 1-,3-,5-year post-transplant survival were 90.8%, 83.9%, 76.3% NASH HCC versus 91.9%, 82.1%, 74.9% non-NASH HCC ($p = 0.94$). No survival differences were observed in populations within or beyond Milan. Competing-risk analysis demonstrated no differences in risk for cardiovascular-related death (HR1.24, 95%CI 0.87-1.55, $p = 0.16$), or HCC recurrence-related death (HR1.21, 95%CI 0.89-1.65, $p = 0.23$). NASH HCC patients had lower risk of liver-related deaths (HR0.57, 95%CI 0.34-0.98, $p = 0.04$). DISCUSSION: NASH HCC is a rising indication for liver transplantation. Despite demographic differences, no post-transplantation survival differences were observed between NASH and non-NASH HCC. This justifies equivalent organ allocation, irrespective of NASH status.

Urology

Arora S, **Bronkema C**, **Majdalany SE**, **Corsi N**, **Rakic I**, **Piontkowski A**, **Sood A**, **Davis MJ**, **Modonutti D**, Novara G, **Rogers CG**, and **Abdollah F**. Impact of preexisting opioid dependence on morbidity, length of stay, and inpatient cost of urological oncological surgery. *World J Urol* 2023; Epub ahead of print. PMID: 36754878. Full Text

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OBJECTIVES: To determine the incidence of preexisting opioid dependence in patients undergoing elective urological oncological surgery. In addition, to quantify the impact of preexisting opioid dependence on outcomes and cost of common urologic oncological procedures at a national level in the USA. METHODS: We used the National Inpatient Sample (NIS) to study 1,609,948 admissions for elective partial/radical nephrectomy, radical prostatectomy, and cystectomy procedures. Trends of preexisting opioid dependence were studied over 2003-2014. We use multivariable-adjusted analysis to compare opioid-dependent patients to those without opioid dependence (reference group) in terms of outcomes, namely major complications, length of stay (LOS), and total cost. RESULTS: The incidence of opioid dependence steadily increased from 0.6 per 1000 patients in 2003 to 2 per 1000 in 2014. Opioid-dependent patients had a significantly higher rate of major complications (18 vs 10%; $p < 0.001$) and longer LOS (4 days (IQR 2-7) vs 2 days (IQR 1-4); $p < 0.001$), when compared to the non-opioid-dependent counterparts. Opioid dependence also increased the overall cost by 48% (adjusted median cost $18,290 [IQR 12,549-27,715] vs. $12,383 [IQR 9225-17,494] in non-opioid-dependent, $p < 0.001$). Multivariable analysis confirmed the independent association of preexisting opioid dependence with major complications, length of stay in 4th quartile, and total cost in 4th quartile. CONCLUSIONS: The incidence of preexisting opioid dependence before elective urological oncology is increasing and is associated with

adverse outcomes after surgery. There is a need to further understand the challenges associated with opioid dependence before surgery and identify and optimize these patients to improve outcomes.

Urology

Kloer C, Blasdel G, **Shakir N**, Parker A, Itzel Gómez A, Zhao LC, and Bluebond-Langner R. Does Genital Self-image Correspond with Sexual Health before and after Vaginoplasty? *Plast Reconstr Surg Glob Open* 2023; 11(2):e4806. PMID: 36817276. Full Text

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Patient-reported outcomes regarding sexual health are lacking or have not been validated for transgender patients following vaginoplasty. The aim of this study is to further characterize the difference in sexual health, genital self-image, and the relationship between them for patients who were pre- and postvaginoplasty. METHODS: A community advisory board informed an anonymous online survey utilizing patient-reported outcomes. Pre- and postvaginoplasty respondents were recruited online. Survey measures included the Female Genital Self-Image Scale (FGSIS) and the Patient-Reported Outcomes Measurement Information System sexual health measures. Welch approximation t tests were performed for FGSIS and Patient-Reported Outcomes Measurement Information System questions, using Bonferroni correction. RESULTS: A total of 690 respondents prevaginoplasty (n = 525; 76%) and postvaginoplasty (n = 165; 24%) participated. The postoperative cohort, compared with the preoperative cohort, reported higher scores for orgasm (P = 0.0003), satisfaction (P = 0.001), and pleasure (P = 0.002). FGSIS total score was higher among postoperative respondents (79.4% ± 17.1%) than preoperative respondents (50.6% ± 15.1%) (P < 0.0001). Using Spearman rho, no significant correlation between FGSIS total score and any Patient-Reported Outcomes Measurement Information System subsectional measures was observed for the postoperative cohort, but a correlation (P <0.001) was observed for the preoperative cohort. CONCLUSIONS: Individuals who are contemplating vaginoplasty have worse sexual health and genital self-image than those who underwent vaginoplasty, yet genital self-image does not correlate directly with sexual health. Sexual health is multimodal for each person.

Conference Abstracts

Allergy and Immunology
Afshan T, **Kulkarni A**, Smith J, Blackshere T, Tesson E, Hartert T, Rivera-Spoljaric K, **Zoratti E**, **Joseph C**, Gangnon R, Gern J, and Singh AM. Examining virtual research recruitment and participant diversity in a multi-center birth cohort, Childhood Allergy and the NeOnatal Environment" (CANOE). *J Allergy Clin Immunol* 2023; 151(2):AB183. Full Text

Rationale: Recruitment for a NIH/ECHO-supported multi-center birth cohort, “Childhood Allergy and the NeOnatal Environment” (CANOE) stopped due to the COVID-19 pandemic. Redesign of study procedures emphasized virtual and socially distanced activities. We hypothesized that “virtual” recruitment methods (social media, websites, email) would surpass “traditional” methods (in-clinic, telephone, flyers/print materials) and increase enrollment of families from diverse backgrounds and communities. Methods: Pregnant women (n=439, target 500) were recruited from four academic medical centers in Detroit MI, Madison WI, Nashville TN, and St. Louis MO. We collected demographic and social information by questionnaires and examined race, ethnicity, age, parity, and employment status in relation to recruitment method using chi-square tests. Results: In-clinic and telephone recruitment comprised 55% of enrollment, followed by print materials (17%), and social media and email (15%). The cohort includes families self-identifying as Caucasian/White (63%), African American/Black (27%), Hispanic/Latino (3.3%), Asian (3.5%), and mixed races (1.2%). This reflects site demographics for White and Black patients, while other populations are not as well recruited into this cohort. Recruitment method success did not vary by race, ethnicity, maternal age, or employment status (p=ns for each comparison). Most (63%) multigravida mothers (9.1% of participants) were recruited in clinic, while primigravida participants were recruited more evenly via all methods. Conclusions: “Virtual” recruitment methods comprised a smaller proportion of cohort enrollment than hypothesized and study recruitment method did not vary by race/ethnicity; however, consideration of combined, varied, and novel recruitment methods may add to the development of best practices for more representative research study recruitment.

Allergy and Immunology
Biagini J, Martin L, He H, Bacharier L, Gebretsadik T, Hartert T, Jackson D, **Kim H**, Miller R, Rivera-Spoljaric K, Schauberger E, Singh AM, Visness C, **Wegienka G**, Ownby D, Gold D, Martinez F, **Johnson CC**, Wright A, Gern J, and Hershey GK. The Pediatric Asthma Risk Score: A New Gold Standard for Asthma Prediction. *J Allergy Clin Immunol* 2023; 151(2):AB320. Full Text

Rationale: Early prediction of asthma is critical to identify potential primary prevention strategies. The Pediatric Asthma Risk Score (PARS) is a continuous score to predict early-life asthma but was developed and validated in relatively homogenous populations. We compared PARS directly to the Asthma Predictive Index (API) and validated in 10 cohorts with varying race, ethnicity, sex, cohort type, missing data and birth decades, and perform a meta-analysis across all 10 cohorts. Methods: We utilized data from 5674 children participating in the Children’s Respiratory and Environmental Workgroup. We applied both PARS and the API in each cohort, as well as harmonized across all cohorts, and directly compared the ability of each tool to predict asthma development at ages 5-10. Results: The PARS area under the curve (AUC) was significantly higher than the AUC of the API in 9 cohorts (p-value range 0.01 - <0.001). The PARS AUC did not differ by cohort type (high risk or general population), decade of enrollment, race, sex, ethnicity, missing PARS factors or polysensitization definition (skin prick test vs. specific IgE). The weights of the 6 PARS factors in the meta-analysis were very similar to the original weights, validating the original PARS scoring. Conclusions: This multi-cohort study makes the PARS the most validated model of asthma prediction in children to date, not only with respect to the number of cohorts used but also with regards to capturing the diversity of asthma in the United States. Future studies may consider PARS the new gold standard in pediatric asthma risk prediction.

Allergy and Immunology

Chu S, Ayars A, **Coleman D**, and Khokhar D. Can COVID-19 vaccinations cause chronic urticaria? *J Allergy Clin Immunol* 2023; 151(2):AB137. Full Text

Rationale: Adverse reactions to COVID-19 vaccinations have garnered significant attention from both the public and medical community. Delayed onset urticaria has been described as an adverse reaction to COVID-19 vaccination, but this phenotype has not been fully characterized thus specific evaluation and treatment strategies have not been developed. Methods: We conducted a retrospective chart review of patients presenting for evaluation of urticaria (acute or chronic) to the University of Washington Allergy Clinics between 12/14/2020 and 12/14/2021. Records were reviewed for development of delayed onset, persistent urticaria occurring following receipt of a COVID-19 vaccination or a history of chronic spontaneous urticaria that worsened after COVID-19 vaccination. Demographic and clinical data including age, sex, co-morbid conditions, treatments attempted, and treatment response was obtained. Results: 22 total patients were determined to have urticaria thought to be attributed to Pfizer and Moderna COVID-19 vaccinations. Six of the 22 (27%) had pre-existing chronic spontaneous urticaria (CSU) which worsened notably after vaccination, and 16 (73%) had novel development of delayed urticaria following vaccination. Patients received a range of treatments including H1-antihistamines, H2-antihistamines, leukotriene inhibitors, oral steroids, omalizumab, cyclosporine, and acupuncture. The majority of patients had improvement or resolution while a minority had worsening urticaria despite treatments at the time of evaluation. Conclusions: COVID-19 vaccinations may result in the development of chronic urticaria in select patients and may worsen control of urticaria in some patients with previously diagnosed chronic urticaria. Additional studies are needed to characterize these patients and determine optimal management strategies.

Allergy and Immunology

Da Silva Antunes R, Frazier A, Pomés A, Calatroni A, Wood R, O'Connor G, Pongracic J, Hershey GK, Kercsmar C, Gill M, Liu A, **Zoratti E**, Kattan M, Busse P, Bacharier L, Teach S, Wheatley L, Togias A, Busse W, Jackson D, and Sette A. Down-Modulation of Cockroach (CR) Allergen-specific Th2 Cell Responses Following Subcutaneous German Cockroach Allergen Immunotherapy (SCIT). *J Allergy Clin Immunol* 2023; 151(2):AB322. Full Text

Rationale: The responses of T cells to subcutaneous allergen immunotherapy (SCIT) are not fully elucidated. We conducted a functional immunological evaluation of cockroach (CR) allergen-specific CD4+ T cell reactivity in the double-blinded, placebo-controlled, multi-center CRITICAL study. Methods: Participants (8-17 years of age) with mild to moderate, well-controlled asthma received 12 months of maintenance dosing of CR SCIT (n=20) or placebo (n=26). Peripheral blood mononuclear cells (PBMC) were isolated prior to, and after 12 months of therapy. CD4+ T cell responses at baseline and after treatment were assessed using overlapping peptide pools derived from 11 well-defined CR allergens and intracellular cytokine staining for IL-4, IFNg, and IL-10 production. T cell responses were further evaluated in terms of magnitude, cytokine polarization, and allergen immunodominance. Results: Significant down-modulation of the total magnitude of CD4+ T cell responses was observed with SCIT but not placebo, with a significant change between groups (-4.46±0.82 vs. −1.81±0.72, respectively, p = 0.020). Responses were driven by a decrease in IL-4 (-4.87±0.86 vs. −1.09±0.75, p = 0.002) with unaltered IFNg and IL-10 production, reflecting a shift towards a Th1 polarization profile (1.35±0.58 vs. −0.37±0.50, in SCIT and placebo respectively, p = 0.031). The largest effects were observed against the allergens Bla g 5 and Bla g 9, which are dominantly recognized, suggesting that dominant responses are susceptible to modulation. Conclusions: Our results demonstrate a significant down-regulation of CR-specific Th2 cell responses in urban children with asthma who received SCIT, compared with those who received placebo.

Allergy and Immunology

Eapen A, **Sitarik A**, Biagini J, Jackson D, **Joseph C**, **Kim H**, Martin L, Rivera-Spoljaric K, Schauberger E, **Wegienka G**, Gern J, and Singh AM. Longitudinal assessment of Allergic Outcomes and Atopic Dermatitis Phenotypes in The Children's Respiratory and Environmental Workgroup (CREW) Birth Cohort Consortium. *J Allergy Clin Immunol* 2023; 151(2):AB146. Full Text

Rationale: Atopic dermatitis (AD) is a heterogenous inflammatory skin disease often associated with other allergic diseases. We characterized AD phenotypes and associated allergic outcomes longitudinally across a multi-site consortium. Methods: AD expression in 11 U.S. birth cohorts from the CREW (Children's Respiratory and Environmental Workgroup) consortium was assessed in each year of life from age 0-7 years (N=7,900). Longitudinal Latent Class Analysis was performed to identify AD phenotypes. Five classes of AD were identified: Persistent AD (15.4%), Early AD with Potential Reoccurrence (2.7%), Late-Onset AD (7.0%), Transient Early AD (3.0%), and Minimal/No AD (72.0%). Serum allergen sensitization patterns and allergic clinical disease were associated with AD phenotype using multinomial logistic regression with a 3-step procedure to account for uncertainty in class membership. Results: Children with Persistent AD, Early AD with Potential Reoccurrence, and Transient Early AD were more likely to have food allergy compared to those with Minimal/No AD (OR[95% CI]=2.73[2.15, 3.45], 2.69[1.63, 4.45], 2.54[1.55, 4.16], respectively). These groups had similarly higher odds of food sensitization. Persistent AD (OR[95% CI]=1.81[1.48, 2.21]) and Early AD with Potential Reoccurrence (OR[95% CI]=3.66[1.90, 7.05]) had significantly higher odds of ever asthma relative to Minimal/No AD. At both 2-4 years and 5-7 years, persistent AD (OR[95% CI]=1.35[1.04, 1.74], 1.25[1.01, 1.53]) and Late-Onset AD (OR[95% CI]=1.68[1.13, 2.50], 2.22[1.33, 3.70]) relative to Minimal/No AD had higher odds of allergic rhinitis. Conclusions: Longitudinal AD phenotypes had varying associations with allergic sensitization, food allergy, asthma and allergic rhinitis, demonstrating the heterogeneity of allergic comorbidity risk associated with AD.

Allergy and Immunology

Gaberino C, Segnitz RM, Cox M, Bacharier L, Calatroni A, Gill M, Stokes J, Liu A, Cohen R, Makhija M, Hershey GK, O'Connor G, **Zoratti E**, Teach S, Kattan M, Becker P, Togias A, Busse W, Jackson D, and Altman M. Mepolizumab Alters Regulation of Airway Type-2 Inflammation in Urban Children with Asthma by Disrupting Eosinophil Gene Expression but Enhancing Mast Cell and Epithelial Pathways. *J Allergy Clin Immunol* 2023; 151(2):AB125. Full Text

Rationale: Mepolizumab (anti-IL5) reduces asthma exacerbations in urban children. We previously utilized nasal transcriptomics to identify inflammatory pathways (gene co-expression modules) associated with exacerbations despite this therapy. To understand mepolizumab's precise impact on these pathways, we assess gene co-expression and loss of correlation, "decoherence," using differential co-expression network analyses. Methods: 290 urban children (6-17 years) with exacerbation-prone asthma and blood eosinophils ≥150/microliter were randomized (1:1) to q4 week placebo or mepolizumab injections added to guideline-based care for 52 weeks. Nasal lavage samples were collected before and during treatment for RNA-sequencing. Differential co-expression of gene networks was evaluated to assess interactions and regulatory aspects of type-2 and eosinophilic airway inflammation. Results: Mepolizumab, but not placebo, significantly reduced the overall expression of an established type-2 inflammation gene co-expression module (fold change=0.77, p=0.002) enriched for eosinophil, mast cell, and epithelial IL-13 response genes (242 genes). Mepolizumab uncoupled co-expression of genes in this pathway. During mepolizumab, but not placebo treatment, there was significant loss of correlation among eosinophil-specific genes including RNASE2 (EDN), RNASE3 (ECP), CLC, SIGLEC8, and IL5RA contrasting a reciprocal increase in correlation among mast cell-specific genes (TPSAB1, CPA3, FCER1A), T2 cytokines (IL4, IL5, and IL13), and POSTN. Conclusions: These results suggest mepolizumab disrupts the regulatory interactions of gene co-expression among airway eosinophils, mast cells and epithelium by interrupting transcription regulation in eosinophils with enhancement in mast cell and epithelial inflammation. This paradoxical effect may contribute to an incomplete reduction of asthma exacerbations and demonstrates how differential co-expression network analyses can identify targets for more precise therapies.

Allergy and Immunology

Patel S, Altman M, Cox M, Bacharier L, Calatroni A, Gill M, Stokes J, Liu A, Cohen R, Makhija M, Hershey GK, O'Connor G, **Zoratti E**, Teach S, Kattan M, Becker P, Togias A, Busse W, and Jackson D. Epithelial-Associated Inflammatory Pathways Underlie Residual Asthma Exacerbations in Urban Children Treated with Mepolizumab Therapy. *J Allergy Clin Immunol* 2023; 151(2):AB222. Full Text

Rationale: Identification of airway inflammatory pathways in asthma has proven essential to understanding mechanisms of disease and has led to effective personalized treatment with biologic therapies. However, relatively little is known about patterns of airway inflammation at the time of respiratory illnesses and how such patterns relate to responsiveness to biologic therapies. Methods: The MUPPITS-1 (n=106) and MUPPITS-2 (n=290) studies investigated asthma exacerbations in urban children with exacerbation-prone asthma and ≥150/microliter blood eosinophils. Children in both studies received guidelines-based asthma care; in MUPPITS-2, participants were additionally randomized (1:1) to placebo or mepolizumab. Nasal lavage samples were collected during respiratory illnesses for RNA-sequencing and analyzed by modular analysis to assess genome-wide expression patterns associated with exacerbation illnesses. Results: Among 284 illnesses, exacerbations that occurred in the absence of mepolizumab therapy showed significantly higher upregulation of eosinophil associated inflammatory pathways (fold change values [FC]=1.27-1.43, p-values<0.05), including a Type-2 inflammation module composed of eosinophil, mast cell, and IL-13 response genes. In contrast, exacerbations that occurred while on mepolizumab therapy showed significantly higher upregulation of several epithelial inflammatory pathways (FC=1.36-1.64, p-values<0.05) including TGF-β/Smad3 signaling, extracellular matrix production, and epidermal growth factor receptor signaling. Conclusions: These results indicate that novel inflammatory pathways, likely originating from the airway epithelium and distinct from Type-2 or eosinophilic inflammation, drive residual exacerbations that occur in children treated with mepolizumab therapy added to guideline-based care. These findings identify likely mechanisms of persistent disease expression in these children despite significant depletion of eosinophils and can identify novel treatment targets for future studies.

Allergy and Immunology

Sitarik A, Biagini J, **Eapen A**, Jackson D, **Joseph C**, **Kim H**, Martin L, Rivera-Spoljaric K, Schauberger E, **Wegienka G**, Gern J, and Singh AM. Longitudinal Characterization of Atopic Dermatitis Phenotypes in The Children's Respiratory and Environmental Workgroup (CREW) Birth Cohort Consortium. *J Allergy Clin Immunol* 2023; 151(2):AB145. Full Text

Rationale: Previously identified longitudinal patterns of atopic dermatitis (AD) may lack generalizability and precision due to small sample size and limited time points. We identify and describe longitudinal AD phenotypes in a large consortium study. Methods: Data from 11 birth cohorts across the United States from the CREW (Children’s Respiratory and Environmental Workgroup) consortium were harmonized to determine physician diagnosis of AD in each year of life from 0-7 years of age (N=7,900). AD phenotypes were identified using Longitudinal Latent Class Analysis, and relationships with demographic variables were determined using multinomial logistic regression with a 3-step procedure to account for uncertainty in class membership. Results: We identified 5 classes of AD expression, selected based on model fit, interpretability, and clinical utility: Persistent AD (15.4%), Early AD with Potential Reoccurrence (2.7%), Late-Onset AD (7.0%), Transient Early AD (3.0%), and Minimal/No AD (72.0%). Males had significantly higher odds of Persistent AD (OR [95% CI]=1.47 [1.22, 1.75]) and Early AD with Potential Reoccurrence (OR [95% CI]=1.89 [1.19, 2.94]). Relative to White children, Black children had higher odds of Persistent AD (OR [95% CI]=2.50 [2.05, 3.05]), Early AD with Potential Reoccurrence (OR [95% CI]=3.07 [1.94, 4.85]), and Transient Early AD (OR [95% CI]=4.12 [2.62, 6.48]). Conclusions: Five AD phenotypes exist in a diverse national sample of children. Black children and males are at increased risk of early and persistent AD. These findings illustrate potential risk factors to target AD prevention.

Allergy and Immunology

Zoratti E, Wood R, O G, Pongracic J, Makhija M, Hershey GK, Sherenian M, Gill M, Gruchalla R, Chambliss J, Liu A, Kattan M, Busse P, Bacharier L, Rivera-Spoljaric K, Sheehan W, Jackson D, Gergen P, Togias A, Calatroni A, Visness C, Cho K, Sette A, Altman M, and Busse W. The Effect of Subcutaneous German Cockroach Immunotherapy (SCIT) on Nasal Allergen Challenge (NAC) and Cockroach-specific Antibody Responses Among Urban Children and Adolescents. *J Allergy Clin Immunol* 2023; 151(2):AB320. Full Text

Rationale: Cockroach allergy contributes to asthma and rhinitis morbidity among many urban children. Treatment with cockroach SCIT could be beneficial. Methods: 8-17 year-old children with mild-moderate asthma from 11 urban sites participated in a randomized double-blind placebo-controlled SCIT trial using non-standardized, glycerinated German cockroach extract. Positive cockroach skin tests, cockroach-specific IgE, and nasal challenge response with total nasal symptom scores (TNSS) ≥6 or maximal sneeze scores of 3 during a graded NAC were required for enrollment. Following dose escalation, 0.4 ml of undiluted extract was targeted for maintenance dosing (~7 mcg Bla g2/dose). The primary endpoint was change in NAC-induced mean TNSS from baseline to one year post randomization. Changes in cockroach-specific IgE (CRsIgE) and IgG4 (CRsIgG4) were also analyzed. Results: Mean TNSS did not significantly change from baseline in either group (placebo n=29, SCIT n=28). There was no significant difference in the change in mean TNSS between placebo and SCIT [−0.79±0.35 vs. −1.02±0.37, respectively, difference=0.2(−1.15, 0.70), p=0.63]. Baseline CRsIgE and CRsIgG4 didn't differ between groups. Mean CRsIgE decreased in both groups following treatment: 3.6 to 2.3 kU/L (0.64 fold change), p=0.015 and 8.3 to 4.2 kU/L (0.51 fold change), p<0.001 in placebo and SCIT respectively, but did not differ between groups [p=0.33]. Significant increases in CRsIgG4 post-treatment were observed among SCIT recipients only: 0.07 to 12.3 mg/L (176 fold change), p<0.001. Conclusions: Cockroach SCIT increased CRsIgG4 levels but did not significantly alter NAC-induced TNSS responses. The extent to which NAC in these children may reflect clinical efficacy for rhinitis or asthma is uncertain.

Cardiology/Cardiovascular Research

Abu-Much A, Maini A, Grines CL, Bharadwaj A, Moses JW, Zhang Y, Redfors B, Bellumkonda L, Li Y, Truesdell AG, Baron SJ, Lansky AJ, **Basir MB**, and **O'Neill W**. CRT-700.05 Impella Utilization in High-Risk Percutaneous Coronary Intervention Mitigates the Risks of Procedural and Clinical Adverse Events Independent of Left Ventricular Ejection Fraction: The Protect III Study. *JACC Cardiovasc Interv* 2023; 16(4):S107. Full Text

Background: Left ventricular (LV) dysfunction is associated with an increased risk of adverse events in patients undergoing percutaneous coronary intervention (PCI). However, the impact of LV ejection fraction (LVEF) on the outcomes of Impella-supported high-risk PCI (HRPCI) is unknown. Methods: Patients enrolled in the prospective, multicenter, and observational PROTECT III study from March 2017 to March 2020 who underwent Impella-supported HRPCI at the operator's discretion (non-cardiogenic shock). Patients were divided into three tertiles (T) based on baseline LVEF: T1 (the lowest), T2, and T3 (the highest). The primary outcome is the rate of 90-day major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death, myocardial infarction, stroke/transient ischemic attack, and repeated revascularization as adjudicated by an independent CEC. Results: Of 1237 patients, 940 with available baseline LVEF were analyzed. T1 included 353 patients (mean LVEF 19.6±4.7), T2 included 274 patients (mean LVEF 32.2±3.5), and T3 included 313 patients (mean LVEF 52.6±9.2). Patients in the higher tertiles were older, more likely to be females, presented more with acute coronary syndrome, and had more frequent left main disease. Also, severely calcified lesions and atherectomy utilization were more frequent in the higher tertiles. The rates of 90-day MACCE were comparable across all tertiles. Furthermore, PCI-related complications and 1-year mortality were also comparable (Table). After multivariable adjustment, 90-day MACCE was not significantly different between the LVEF tertiles (p=0.32). Conclusion: In patients with HRPCI supported by Impella, the rates of in-hospital adverse events, PCI-related complications, 90-day MACCE, and 1-year mortality were comparable among the different LVEF tertiles. [Formula presented]

Cardiology/Cardiovascular Research

Bashir H, Reardon M, Goel SS, Fam N, Jelisejevas J, Webb JG, Ye J, **Frisoli TM**, Siddiqui M, Garcia S, Answini GA, and Kereiakes DJ. CRT-700.1 Multi-Center Compassionate use Early Feasibility Evaluation of J-Valve Transcatheter Treatment for Severe Aortic Valve Regurgitation: Preliminary Results. *JACC Cardiovasc Interv* 2023; 16(4):S85-S86. Full Text

Background: Although transcatheter aortic valve replacement (TAVR) is accepted therapy for treatment of symptomatic severe aortic valve stenosis (AS), current devices are associated with increased procedural complications and sub-optimal outcomes when used to treat of aortic valve regurgitation (AR). Severe AR is the indication for 20-30% of surgical aortic valve replacements and is associated with increased morbidity and mortality. J-valve is a short frame, self-expanding TAVR device. (Figure) specifically designed for treatment of severe AR. Anchor rings facilitate commissural alignment and secure attachment to non-calcified native valves. Methods: From Sept 2019 through Oct 2022, patients with symptomatic severe AR who were not surgical candidates or excluded from the ALIGN-AR trial were enrolled into a compassionate use early feasibility study at 5 North American centers. All patients signed informed consent for protocol approved by respective institutional review boards. Results: Data from 13/28 patients (mean age 80 yrs; 38.5% male) with symptomatic (92.3% NYHA class III/IV; mean LVEF 48% [range 23-64%]) severe (92% grade III/IV) AR, atrial fibrillation (53.8%), and pacemaker/ICD (15.4%), had J-valve TAVR (15.4% alternative access). There were no deaths to 30 days and post-procedural AR grade was none/trivial in all patients. In follow-up (mean 333 days) there are 0 cardiac deaths (total mortality 30.7%; 3 malignancies, 1 sepsis). Serial echocardiograms demonstrate AR grade none/mild in 89%, and 100% at 30 days and 1 year respectively). Conclusion: Despite high risk profile, preliminary analysis of this multi-center compassionate use study suggests that J-valve is safe with durable effectiveness for the treatment of symptomatic severe AR. Full data set on all patients will be presented. [Formula presented]

Cardiology/Cardiovascular Research

Hussain B, **Basir MB**, Mahmood A, Belur A, and Alexander T. CRT-700.66 Principal Diagnosis and Independent Predictors for 30-Day Readmissions in Primary Cardiac Tumor Patients. *JACC Cardiovasc Interv* 2023; 16(4):S110. Full Text

Background: Primary cardiac tumors (PCT) are rare with an incidence of 0.3-0.7%. We aimed to study the rate, causes and independent predictors for 30-day readmissions in patients diagnosed with PCT using a national level database. Methods: We conducted a retrospective cohort analysis using the National Readmissions Database between 2016-2018. ICD-10 codes were used to identify patients with benign and malignant PCT. Patients <18 years and December admissions were excluded. Primary outcomes were the readmission rate and principal diagnosis for 30-day readmissions in patients hospitalized with primary diagnosis of PCT. Multivariate logistic regression was used for analysis. Results: 4451 patients were admitted with the primary diagnosis of PCT, out of which 4348 patients were discharged alive. Among those discharged alive, 13.8% (599 patients) were readmitted within 30 days. The most common principal diagnosis for 30-day readmissions were subsequent admission for benign PCT (17.12%), atrial fibrillation (8.1%), sepsis (5.3%), pneumonia (4.04%), hypertensive heart disease with heart failure (2.6%), supraventricular tachycardia (2.54%), non-inflammatory pericardial effusion (2.31%), and pleural effusion (2.22). For the index admissions, 65.7% were females, and mean age was 60.8 years. The in-hospital mortality rate for index admissions was 2.28% while it was 2.36% for the readmission. For the index admission, mean length of stay was 8 days while mean total charges were $163,636. For all the readmissions combined, the total length of stay was 3598 days and combined total charges were $54.7 million. The independent predictors for readmission were atrial fibrillation (OR 0.71, p=0.02), myocardial infarction (OR 2.89, p=0.006), acute liver failure/hepatic cirrhosis (OR 2.34, p=0.02), and diabetes mellitus (OR 1.75, p=0.002). Conclusion: In patients with a principal diagnosis of PCT, the 30-day readmission rate is 13.8% and the most common principal diagnosis for readmissions are PCT complications, atrial fibrillation, supraventricular tachycardia, pneumonia, sepsis, hypertensive heart disease with heart failure, pericardial effusion, and pleural effusion.

Cardiology/Cardiovascular Research
Hussain B, **Basir MB**, and Paul T. CRT-101.10 Outcomes of Underlying Infiltrative Cardiomyopathy in Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2023; 16(4):S8. Full Text

Background: Evidence on the prognosis of infiltrative cardiomyopathy in patients undergoing percutaneous coronary intervention (PCI) has not been well established. Our objective was to assess the prevalence of infiltrative cardiomyopathy including amyloidosis, sarcoidosis and hemochromatosis in PCI patients and its effect on mortality. Methods: National Inpatient Sample 2016-2019 was used to conduct a retrospective analysis by identifying a cohort of patients who underwent PCI with infiltrative cardiomyopathy using respective ICD-10 codes. Primary outcome was the effect of infiltrative cardiomyopathy on mortality in patients undergoing PCI. Secondary outcomes were the independent predictors of mortality. Multivariate logistic regression model was used for analysis. Results: 1.93 million patients were hospitalized for undergoing PCI, out of which 6270 patients had infiltrative cardiomyopathy (prevalence 0.33%). Subgroup analysis showed that 710 patients had underlying amyloidosis (prevalence 0.04%), 4300 patients had sarcoidosis (prevalence 0.23%) and 1280 patients had hemochromatosis (prevalence 0.07%). Mean age of patients undergoing PCI with infiltrative cardiomyopathy was 61 years, 54% were females and 53.5% were white. Patients undergoing PCI were predominantly males (67%) but patient with infiltrative cardiomyopathy who underwent PCI were predominantly females (54%). Underlying amyloidosis was associated with two fold increased odds of mortality in patients undergoing PCI (OR 2.13, 95% CI 1.08-4.23, p=0.029). While sarcoidosis (OR 1.11, 95% CI 0.73-1.7, p=0.6) and hemochromatosis (OR 0.79, 95% CI 0.32-1.92, p=0.6) were not significantly associated with mortality in patients undergoing PCI. The independent predictors of mortality in patients undergoing PCI with infiltrative cardiomyopathy are arrhythmias (OR 2.59, OR 1.14-5.9, p=0.02), cardiac arrest (OR 10.3, CI 3.8-27.6, p=0.00), pulmonary embolism (OR 5.8, CI 1.06-32.4, p=0.04), kidney disease (OR 4.5, CI 1.99-10.3, p=0.00) and liver disease OR 3.5, CI 1.34-9.1, p=0.01). Conclusion: Prevalence of infiltrative cardiomyopathy in patients undergoing PCI is 0.33%. Amyloidosis is associated with significantly increased odds of mortality in patients undergoing PCI while sarcoidosis and hemochromatosis are not significantly associated with mortality. Arrhythmias, cardiac arrest, pulmonary embolism, kidney and liver disease are independently associated with increased mortality in infiltrative cardiomyopathy patients undergoing PCI.

Cardiology/Cardiovascular Research
Hussain B, Dhulipala V, Jafry AH, and **Basir MB**. CRT-700.53 Risk of Heart Block Development in Surgical Management of Congenital Heart Disease. *JACC Cardiovasc Interv* 2023; 16(4):S99. Full Text

Background: There is a paucity of data regarding the risk for heart block during surgical repair of congenital heart disease (CHD). We sought to identify the prevalence and prognosis of heart block in patient's requiring surgical intervention for CHD. Methods: National Inpatient Sample 2016-2019 was used to conduct a retrospective analysis by identifying a cohort of patients admitted for surgical management for atrial septal defect repair/replacement (ASDR), ventricular septal defect repair/replacement (VSDR) and patent ductus arteriosus closure (PDAC) using respective ICD-10 codes. Primary outcome was the risk of developing heart blocks including atrioventricular and bundle branch/fascicular blocks which was assessed with multivariate logistic regression model. Results: 7.6% patients with ASD underwent ASDR, 10.4% patients with VSD underwent VSDR and 8.8% patients with PDA underwent PDAC. Heart blocks were observed in 12% of ASD patients undergoing ASDR, 10% of VSD patients undergoing VSDR and 8.8% of PDA patients undergoing PDAC. Mean age was 38.9 years for patients undergoing ASDR developing heart blocks, 11.48 years for patients undergoing VSDR developing heart blocks and 10.3 months for patients undergoing PDAC developing heart blocks. On analysis of patients who developed heart blocks after undergoing surgery for CHD, we found that 51.5% were males, 48.4% were females, 57.8% were white, 12.7% were African-American and 17.6% were Hispanic. ASDR was associated with increased odds of developing heart blocks in patients with ASD (OR 3.89, CI 3.6-4.2, p<0.001) and VSDR was associated with increased odds of developing heart blocks in VSD patients (OR 9.31, CI 8-10.7, p<0.001). While, PDAC was associated with even higher odds of developing heart blocks in PDA patients (OR 12.75, CI 10.4-15.6, p<0.001). ASDR was associated with decreased mortality in ASD patients (OR 0.85, CI 0.74-0.98, p=0.036), VSDR had no significant association with mortality in VSD patients (OR 0.99, p=0.9) and PDAC was associated with minimally

increased mortality (OR 1.16, CI 1.001-1.36, p=0.04). Conclusion: Heart blocks are prevalent among the patients undergoing surgical treatment for CHD. Surgical repair of CHD is strongly associated with the risk of developing heart blocks, highest risk being with PDAC followed by VSDR and ASDR.

Cardiology/Cardiovascular Research
Pahuja M, **O'Neill W**, Karas RH, Moses J, Udelson J, Faraz H, and Kapur NK. CRT-100.04 Delaying Reperfusion Plus LV Unloading Reduces Infarct Size: A Per-Protocol-Analysis of the STEMI_DTU Pilot Study. *JACC Cardiovasc Interv* 2023; 16(4):S8-S9. 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
Rymer J, Alhanti B, Kemp S, Bhatt D, Angiolillo D, Diaz M, Garratt KN, Waksman R, Kirtane A, Ang L, Bach R, Barker C, Jenkins R, **Basir M**, Sullivan A, El-Sabae H, Brothers L, Washam J, Ohman M, Jones S, and Wang T. CRT-100.12 Risk of Bleeding Among Cangrelor-Treated Patients Administered Upstream P2Y12 Inhibitor Therapy. *JACC Cardiovasc Interv* 2023; 16(4):S14. Full Text

Introduction: Little is known about the use of cangrelor in patients with MI who are treated with an oral P2Y12 inhibitor upstream prior to cardiac catheterization. Methods: CAMEO (Cangrelor in Acute MI: Effectiveness and Outcomes) is a 12-hospital observational registry studying platelet inhibition for MI patients undergoing cardiac cath. Upstream oral P2Y12 inhibition was defined as receipt of an oral P2Y12 inhibitor within 24 hours prior to hospitalization or in-hospital prior to cath. Among cangrelor-treated patients, we compared bleeding after cangrelor use through 7 days post-discharge between patients with and w/o upstream oral P2Y12 inhibitor exposure using logistic regression. We examined rates of bleeding among patients with a shorter (<1 hour) vs. longer (1-3 hours or >3 hours) duration between the last oral dose and cangrelor start. Results: Among 1,775 cangrelor-treated MI patients, 433 (24.4%) had upstream oral P2Y12 inhibitor treatment prior to cath. Of these, 165 patients (38%) started cangrelor within 1 hour, 109 (25%) between 1-3 hours, and 134 (31%) > 3 hours after the in-hospital oral P2Y12 inhibitor dose. Cangrelor-treated patients who received upstream treatment were more likely to have a history of prior PCI, MI, PAD, and diabetes and to be clopidogrel-treated (all p<0.01) compared w/o upstream treatment. There was no significant difference in risk of bleeding among cangrelor-treated patients with and w/o upstream oral P2Y12 inhibitor exposure (Table). While bleeding events were higher in patients with longer delays to cangrelor initiation, bleeding risk was not significant after adjustment (Table). Conclusions: Bleeding risk was not observed to be higher in cangrelor-treated patients after upstream oral P2Y12 inhibitor exposure compared with patients treated with cangrelor w/o upstream oral P2Y12 inhibitor exposure. [Formula presented]

Cardiology/Cardiovascular Research

Velagapudi P, Abu-Much A, Bellumkonda L, Maini A, Redfors B, Lansky AJ, Li Y, Grines CL, Batchelor WB, **O'Neill WW**, and Cohen DJ. CRT-700.34 Short-Term Outcomes Among Aortic Valve Stenosis Patients Undergoing Impella-Supported High-Risk Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2023; 16(4):S92-S93. Full Text

Background: Among patients undergoing percutaneous coronary intervention (PCI), severe aortic stenosis (AS) is associated with an increased risk of adverse outcomes. Although the use of mechanical circulatory support with Impella has been shown to improve 90-day outcomes in patients undergoing high-risk PCI (HRPCI), there is little information about the safety of this approach in pts with severe AS. We, therefore, sought to evaluate the efficacy and safety outcomes of Impella-supported HRPCI among patients with varying severity of AS. Methods: We studied patients enrolled in PROTECT III—a multicenter study of patients undergoing Impella-supported HRPCI. Patients were classified according to the severity of AS: none/trivial, mild, moderate, and severe. The primary outcome was the rate of major adverse cardiac and cerebrovascular events (MACCE) at 90 days, defined as the composite of all-cause death, MI, stroke/ TIA, and revascularization. Secondary outcomes included in-hospital PCI-related complications, stroke/TIA, and vascular complications requiring surgery. Results: Of 596 patients with echocardiographic data, 490 had no/trivial AS, and 34, 27, and 45 had mild, moderate, or severe AS, respectively. Patients with AS were older, less likely to have diabetes, more likely to have left main disease, and had higher left ventricular ejection fractions (Table). Severely calcified lesions and the use of atherectomy were more frequent among patients with moderate or severe AS. There were no differences in rates of PCI-related complications, stroke/TIA, 30-day MACCE, or 90-day MACCE according to AS severity. Rates of transfusion were higher among patients with AS—regardless of severity. Conclusion: Among patients undergoing Impella-supported HRPCI, PCI-related complications and 90-day outcomes did not differ based on AS status or severity. [Formula presented]

Hematology-Oncology

Azar I, Gandhi N, Nagasaka M, Gong J, Nazha B, Choucair K, Khushman MM, Soares HP, El-Deiry WS, **Philip PA**, Lou E, Farrell AP, Swensen J, Oberley MJ, Abraham J, Nabhan C, Goel S, Korn WM, Shields AF, and Azmi AS. Molecular characterization and clinical outcomes of pancreatic neuroendocrine tumors (pNENs) harboring PAK4-NAMPT alterations. *J Clin Oncol* 2023; 41(4):649. Full Text

I. Azar

Background: The mTOR inhibitor, Everolimus (EVE), is FDA-approved for the treatment of advanced PNENs on the basis of delay of progression. The RADIANT-3 trial showed an increase in PFS from 4.6 to 11 months compared to placebo with an ORR of only 5%. Prior studies suggest that targeting the aberrant expression of mTOR regulators p21 activated kinase 4 (PAK4) and nicotinamide adenine dinucleotide biosynthesis enzyme nicotinamide phosphoribosyltransferase (NAMPT) in PNENs sensitizes these tumors to EVE. To further qualify these observations, we queried a large real-world dataset of PNENs, characterizing the molecular and immune landscapes, as well as the clinical outcomes associated with aberrant PAK4 and NAMPT expression. Methods: 294 cases of PNENs were analyzed using Next Generation Sequencing (NextSeq) and Whole Exome and Whole Transcriptome Sequencing (NovaSeq) at Caris Life Sciences (Phoenix, AZ). For our analyses, we stratified our study cohort into four groups based on the median expression of PAK4 and NAMPT: PAK4-low/NAMPT-low, PAK4-low/ NAMPT-high, PAK4-high/NAMPT-low and PAK4-high/NAMPT-high. Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U, and p-values were adjusted for multiple comparisons (q , 0.05). Results: High prevalence of mutations in PTEN (10.71% vs 1.18%; $p < 0.05$, $q > 0.05$), a tumor suppressor of the mTOR pathway and high expression of genes activated in response to mTOR activation such as SLC2A1 (3.07-fold), PFKP (3.32-fold), SCD (2.70-fold), MVK (2.92-fold) and G6PD (2.58-fold) were observed in PAK4-high/NAMPT-high compared to the PAK4-low/NAMPTlow tumors (all q , 0.05). A congruent enrichment of PI3K/AKT/mTOR and glycolysis pathways by single-sample gene set enrichment analysis was observed in these tumors (all q , 0.05). When querying the immune landscape, we observed enrichment in inflammatory response, IL6/JAK/STAT3, IL2/STAT5 signaling pathways and immune checkpoint genes such as PDCD1 (5.14-fold), CD274 (2.84-fold), PDCD1LG2 (2.44-fold), CD80 (3.00-fold), CD86 (2.82-fold), IDO1 (1.92-fold), LAG3 (3.09-fold), HAVCR2 (2.66-fold) and CTLA4 (4.49-

fold) in the PAK4-high/NAMPT-high tumors (all q,0.05). Immune cell infiltration estimates revealed an increase in Neutrophils, NK cells and Tregs in the PAK4-high/NAMPT-high tumors ($p < 0.05$, $q > 0.05$). Conclusions: Our study demonstrates that PAK4-high/NAMPT-high PNENs are associated with distinct molecular and immune profiles. While the dual blockade of PAK4 and NAMPT has been reported to enhance the efficacy of EVE in PNENs, whether such a blockade would enhance the efficacy of immunotherapeutics warrants further investigation.

Hematology-Oncology
Kamgar M, Khan HY, Aboukameel A, Bannoura S, Chung BY, Szabo A, Li Y, Al Hallak MN, **Philip PA**, George B, Christians KK, Evans DB, Tsai S, Erickson B, Luther S, Azmi AS, and Hall WA. A phase I study of CPI-613 (devimistat) in combination with chemoradiation in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2023; 41(4):TPS760. Full Text

M. Kamgar

Background: Local tumor progression is a cause of significant mortality and morbidity in patients with unresectable pancreatic ductal adenocarcinoma (PDAC). Effective approaches to achieve durable local control are urgently needed. Metabolic reprogramming and enhanced mitochondrial function, both hallmarks of PDAC, are known contributors to chemo- and radio-resistance. CPI-613, a lipoic acid analog that selectively inhibits components of the Krebs cycle in tumors, showed promising preclinical synergy in combination with gemcitabine and radiation therapy (gem-RT). Methods: We describe a single-arm, single-center, open-label, phase I study designed to determine the maximumtolerated dose of CPI-613 when used concomitantly with gemcitabine and intensity modulated radiation therapy (IMRT) for local control of PDAC. CPI-613 will be administered once weekly by intravenous infusion over approximately 2 hours at a starting dose of 500 mg/m2 and dose-escalated/de-escalated using a Bayesian optimal interval design. Gemcitabine will be given once weekly at 400 mg/m2 dosage and IMRT as 54 Gray (Gy) in 30 fractions (1.8 Gy per fraction) with five fractions given per week. Up to 24 patients will be enrolled for the study after meeting the following main eligibility criteria, which include: pathologically confirmed PDAC; inoperable disease that by institutional pancreatic multidisciplinary tumor board or multidisciplinary review are considered to benefit from definitive local control of the primary tumor; ECOG of 0-2; and adequate organ and marrow function after completion of intended systemic chemotherapy. The secondary objectives are to determine the recommended phase II dose of CPI-613 when used with gem-RT, safety and tolerability of CPI-613-gem-RT, overall survival, local progression-free survival (PFS), overall PFS, patient-reported quality of life after treatment, and late gastrointestinal toxicities following treatment with CPI-613-gem-RT.

Hematology-Oncology
Lin Y, Kopetz S, Jacobs SA, Lucas PC, Sahin IH, Deming DA, **Philip PA**, Hong TS, Khalil YR, Loree JM, Wolmark N, Yothers G, George TJ, and Dasari A. NRG GI008: Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-US). Christopher Hanyoung Lieu. *J Clin Oncol* 2023; 41(4):TPS260. Full Text

Y. Lin

Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). However, circulating tumor DNA (ctDNA) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery in CC patients (pts), and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA-) are at a much lower risk of recurrence and may be spared the toxicities associated with AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established.We hypothesize that for pts whose CC has been resected, ctDNA status may be used to risk-stratify for making decisions about AC. Methods: In this prospective phase II/III trial, up to 1,912 pts with resected stage III A, B (all pts) and stage II, IIIC (ctDNA+ only) CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor-informed assay (Signatera™, bespoke assay), those who are ctDNA- (Cohort A)

will be randomized to immediate AC with fluoropyrimidine (FP) + oxaliplatin (Ox) for 3-6 mos per established guidelines vs. serial ctDNA monitoring. Patients who are ctDNA+ postoperatively or with serial monitoring (Cohort B) will be randomized to FP+Ox vs. more intensive AC with addition of irinotecan (I) for 6 mos. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) (phase III) in the immediate vs. delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox vs FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, as well as post-operative plus serial matched/normal blood samples, will be collected for exploratory correlative research. Active enrollment across the NCTN started in June, 2022.

Hematology-Oncology
Miesbach W, Escobar M, Boggio L, Bonanad S, Castaman G, Darguard Y, Giermasz A, Hermans C, **Kuriakose P**, Quon D, Reding M, Tran DQ, Windyga J, Bonzo D, Macie C, and Mahlangu J. EFFICACY AND SAFETY OF EPTACOG BETA (RECOMBINANT HUMAN FVIIA) ACCORDING TO AGE IN PERSONS WITH HAEMOPHILIA A/B WITH INHIBITORS UNDERGOING SURGICAL PROCEDURES. *Haemophilia* 2023; 29:102. Full Text

W. Miesbach, Department of Coagulation Disorders and the Comprehensive Care Haemophilia Centre, Goethe University Hospital, Frankfurt, Germany

Introduction: Eptacog beta (CEVENFACTA®) is a new rFVIIa approved by the EMA for the treatment of bleeding events and prevention of bleeding during surgery in persons with haemophilia A/B with inhibitors (PwHABI) aged ≥12 years (y). Methods: PERSEPT 3 was a Phase 3 (NCT02020369) trial of eptacog beta in PwHABI who required surgical procedures. Eptacog beta was administered at an initial dose of 200µg/kg or 75µg/kg for major or minor procedures respectively. This was followed by 75µg/kg for ≥5 (major procedures) or ≥2 (minor procedures) days. Haemostatic efficacy was assessed using a 4-point scale during the intra and postoperative care period (primary efficacy endpoint was determined by the investigator at the study centre 48±4h after the last dose of eptacog beta, based on the totality of the assessments performed on the patient (pt) at each timepoint). This post-hoc analysis compared the efficacy and safety of eptacog beta by age (pts aged <12 vs ≥12y). Results: Twelve pts were included (<12y: n=5, 1 major and 4 minor procedures; ≥12y: n=7, 5 major and 2 minor procedures). The primary endpoint success proportion was 100% (95% CI: 39.8-100) in pts aged <12y (4 successes, 1 missing) and 71.4% (95% CI: 29.0-96.3) in pts aged ≥12y (5 successes; 2 failures). The intraoperative success proportion was 100% (95% CI: 47.8-100) for pts aged <12y (5 successes) and 100% (95% CI: 59.0-100) for pts aged ≥12y (7 successes). The success proportion 24h post-procedure was 100% (95% CI: 47.8-100) for pts aged <12y (5 successes) and 100% (95% CI: 47.8-100) for pts aged ≥12y (5 successes; 2 missing). Two pts discontinued treatment (1 aged <12y withdrew consent; 1 aged ≥12y due to an adverse event (AE): postprocedural hematoma). One pt experienced 2 serious AEs leading to death, both were considered unrelated to the treatment. No allergic or thrombotic events occurred; no neutralising antibodies were detected. Antifibrinolytics were used concomitantly with eptacog beta in 4 patients without any safety concerns. Discussion/Conclusion: This post-hoc subgroup analysis shows that eptacog beta is effective and well-tolerated in perioperative care irrespective of patient age (<12 vs ≥12y), supporting the use of eptacog beta for bleed management (prevention and treatment) in major and minor surgical procedures in all PwHABI.

Hematology-Oncology
Overman MJ, Guthrie KA, Salem ME, Pedersen KS, Kalyan A, Colby S, Fakih M, Gholami S, Gold PJ, Chiorean EG, Hochster HS, and **Philip PA**. Randomized, phase II selection study of ramucirumab and paclitaxel versus FOLFIRI in refractory small bowel adenocarcinoma: SWOG S1922. *J Clin Oncol* 2023; 41(4):TPS784. Full Text

M.J. Overman

Background: Small bowel adenocarcinoma is a rare malignancy with limited evidence to support the choice of systemic chemotherapy beyond the frontline setting. Though second-line therapy has historically been extrapolated from colorectal cancers, recent molecular data has demonstrated small bowel adenocarcinoma to be genomically unique when compared to either colon or gastric cancer. Retrospective analyses of irinotecan- and taxane-based therapies and one prospective phase II clinical trial of nab-paclitaxel have demonstrated clinical activity in this cancer. Ramucirumab/paclitaxel represents an active combination in the management of gastric cancer. SWOG 1922 evaluates the use of FOLFIRI or ramucirumab/paclitaxel in the second- and later-line setting for small bowel adenocarcinoma. Methods: This is randomized, phase II, selection design clinical trial of FOLFIRI (5-fluorouracil, leucovorin and irinotecan) every two weeks or ramucirumab D1,15 and paclitaxel D1,8,15 every 4 weeks with the primary endpoint of progression-free survival (PFS). Secondary endpoints include response rate, overall survival, and safety. Archived paraffin tumor tissue collection and serial blood collections are included for correlative analyses. Key eligibility criteria include having mismatch repair proficient/microsatellite stable small bowel adenocarcinoma (ampullary location excluded); metastatic or locally advanced unresectable disease; prior fluoropyrimidine and/or oxaliplatin therapy; no prior treatment with irinotecan, ramucirumab, or taxanes; no recent bleeding, blood clots, or bowel perforation/fistula; and Zubrod performance status of 0/1. Measurable disease is not required. The null hypothesis is median PFS of 2.5 months. If a median PFS of at least 3.5 months is observed in one or both arms, the goal is to choose the better regimen with respect to this endpoint. The design provides a 90% probability of selecting the more active arm, assuming a hazard ratio of 1.4, if both arms meet this threshold. This trial is open and, as of September 1, 2021, 21 of 94 planned patients have been enrolled.

Hematology-Oncology

Raghav KPS, Guthrie KA, Kopetz S, Tan BR, Denlinger CS, Fakih M, Overman MJ, Dasari A, Corum LR, Hicks LG, Patel M, Esparaz BT, Kazmi SMA, Alluri N, Colby S, Gholami S, Gold PJ, Chiorean EG, Hochster HS, and **Philip PA**. A randomized phase 2 study of trastuzumab and pertuzumab (TP) compared to cetuximab and irinotecan (CETIRI) in advanced/metastatic colorectal cancer (mCRC) with HER2 amplification: SWOG S1613. *J Clin Oncol* 2023; 41(4):140. Full Text

K.P.S. Raghav

Background: HER2 (ERBB2) over-expression and amplification (HER2+) is seen in a small but distinct subset (2-3%) of mCRC and is enriched in RAS/BRAF wild type (WT) tumors. This subset is characterized by a limited response to anti-epidermal growth factor receptor monoclonal antibodybased (anti-EGFR) therapy and a promising response to dual-HER2 inhibition. Methods: In this multicenter, open label, randomized, phase 2 trial, we enrolled 54 patients with RAS/BRAF WT HER2+ mCRC who had had disease progression after 1 or 2 previous therapies. HER2 status was confirmed centrally with immunohistochemistry (IHC) and in-situ hybridization (ISH). HER2+ was defined as IHC 3+ or 2+ and ISH amplified (dual-probe HER2/CEP17 ratio > 2.0). Patients were then randomly assigned in a 1:1 ratio to receive either TP (trastuzumab [loading 8 mg/kg then 6 mg/kg] + pertuzumab [loading 840 mg then 420 mg] every 3 weeks) or CETIRI (cetuximab 500 mg/m2 + irinotecan 180 mg/m2 every 2 weeks). Crossover was allowed for patients on CETIRI arm to TP (cTP) after progression. Restaging (per RECIST v1.1) was performed at 6 and 12 weeks and then every 8 weeks until progression. The primary endpoint was progression-free survival (PFS). Key secondary endpoints were overall response rate (ORR), overall survival (OS) and safety. Results: A total of 54 (out of planned 62 due to low accrual) patients were randomized to TP (26) and CETIRI (28) between 10/2017 and 12/2021. By 8/18/2022, 20 patients had crossed over to cTP arm. One CETIRI patient was not analyzable. The results for key endpoints by protocol defined stratification factors, prior irinotecan (Piri) (yes or no) and HER2/CEP17 ratio (HCR) (>5 or ≤5), are summarized as of data cut-off of 9/6/2022. PFS did not vary significantly by treatment: medians 4.4 (95%CI: 1.9 - 7.6) months in TP group and 3.7 (95%CI: 1.6 - 6.7) months in CETIRI group (p = 0.35). Grade≥3 adverse events occurred in 23%, 46% and 40% of patients in TP, CETIRI and cTP groups. Conclusions: Dual-HER2 inhibition with TP appears to be a safe and effective treatment option for patients with RAS/BRAF WT HER2+ mCRC with a promising response rate of31%.Higher level of HER2 amplification may provide a greater degree of clinical benefit from TP compared to CETIRI. Future correlative efforts will explore biomarkers of response/resistance with this strategy. (Table Presented).

Hematology-Oncology
Reiss KA, Hong SC, Kasi A, O'Reilly EM, Maithel SK, Yao X, Hamilton SR, Boursi B, Pishvaian MJ, Klempner SJ, Domchek SM, Catalano PJ, Chiorean EG, **Philip PA**, and O'Dwyer PJ. APOLLO: A randomized phase II double-blind study of olaparib versus placebo following curative intent therapy in patients with resected pancreatic cancer and a pathogenic BRCA1, BRCA2 or PALB2 mutation-ECOG-ACRIN EA2192. *J Clin Oncol* 2023; 41(4):TPS763. Full Text

K.A. Reiss

Background: A meaningful subset of PDAC is characterized by a homologous recombination deficiency (HRD). The most well-defined patients within this group are those with pathogenic variants in BRCA1, BRCA2 and PALB2. In the metastatic setting, PARP inhibitor maintenance provides a progression-free survival benefit after a period of platinum based chemotherapy1,2, but the role of PARP inhibitors in the curative intent setting is undefined. The OlympiA study established one year of olaparib as the standard of care for patients with BRCA-related, early stage breast cancer who completed all other curative-intent treatment3. Therefore, we have designed a randomized, phase II double-blind study of one year of olaparib vs placebo in patients with pancreatic cancer and a germline or somatic variant in BRCA or PALB2 who have completed all curative intent therapy. Methods: We have enrolled and treated 23 of 152 planned patients on study NCT 04858334/EA2192. Eligibility criteria include: a pathogenic germline or somatic variant in BRCA1, BRCA2 or PALB2 as determined by local laboratory (central review required); completion of curative-intent resection and ≥ three months of multi-agent chemotherapy; no evidence of recurrent disease. At enrollment, patients must be within 12 weeks of their last anti-cancer intervention. Patients are randomized 2:1 to receive oral olaparib 300 mg twice daily or placebo for 12 28-day cycles. The primary endpoint is relapse-free survival. Overall survival is a secondary endpoint. Tumor tissue, fecal material (for microbiome analysis) and serial ctDNA samples are being collected.

Hematology-Oncology
Shroff RT, Guthrie KA, Scott AJ, Borad MJ, Goff LW, Matin K, Mahipal A, Kalyan A, Javle MM, Aghajanian C, Tan BR, Cheema PS, Patel AK, Iyer RV, Kelley RK, Thumar JR, El-Khoueiry AB, Chiorean EG, Hochster HS, and **Philip PA**. SWOG 1815 A phase III randomized trial of gemcitabine, cisplatin, and nab-paclitaxel versus gemcitabine and cisplatin in newly diagnosed, advanced biliary tract cancers. *J Clin Oncol* 2023; 41(4):LBA490. Full Text

R.T. Shroff

Background: Biliary tract cancers (BTCs) are a heterogeneous group of malignancies with a dismal prognosis. Gemcitabine-based regimens are the standard of care in advanced disease, but median overall survival (OS) is roughly 12 months. The addition of albumin-bound paclitaxel to gemcitabine and cisplatin (GAP) demonstrated promising efficacy in a 60 patient, single-arm phase II study (Shroff et al, JAMA Oncol 2019), with observed median OS of 19.2 months. Methods: SWOG 1815 is a randomized, open-label, phase III trial comparing GAP to gemcitabine/cisplatin (GC). The study included newly diagnosed advanced BTC patients (pts), randomized 2:1 to GAP vs. GC. GAP included gemcitabine at 800 mg/m2, cisplatin at 25 mg/m2 and albumin-bound paclitaxel at 100 mg/m2 on days 1 and 8 of a 21-day cycle. GC included standard dosing of gemcitabine at 1000 mg/m2 and cisplatin at 25 mg/m2 on days 1 and 8 of a 21-day cycle. Pts were treated until progression. The primary endpoint was overall survival (OS) with a target hazard ratio of 0.7 with 90% power and a 1-sided alpha of 0.025; randomization was stratified by disease site (intrahepatic cholangiocarcinoma [CCA] vs gallbladder adenocarcinoma [GBC] vs extrahepatic CCA), disease stage (locally advanced vs metastatic), and Zubrod PS 0 vs 1. Results: Of 441 eligible pts randomized, 55% were female. 67% of patients had intrahepatic CCA, 16% had GBC and 17% had extrahepatic CCA. Most pts had metastases (73%). Median OS with GAP vs. GC was 14 vs. 12.7 mo respectively (HR 0.93, 95% CI 0.74-1.19, p=0.58), ORR (confirmed and unconfirmed) 34% vs25% (p=0.11) and median PFS 8.2 vs 6.4 mo (HR 0.92, 95% CI 0.72-1.16, p=0.47), respectively. Grade 3 and 4 treatment related adverse events (TRAEs) in ≥10% of pts for GAP and GC were anemia, neutropenia, and thrombocytopenia. GAP had more ≥ grade 3 hematologic AEs compared to the GC arm (60% vs. 45%, p=0.003). Discontinuation due to toxicity was at 24% vs 19% (p=0.26) with GAP vs GC. In exploratory subset analyses, GAP vs GC improved OS in pts

with locally advanced disease (medians 19.2 vs 13.7 mo; HR 0.67, 95% CI 0.42- 1.06, p=0.09) and in GBC pts (medians 17.0 vs 9.3 mo; HR 0.74, 95% CI 0.41-1.35, p=0.33). ORR for GAP vs GC in GBC was 50% vs 24% (p=0.09) and for locally advanced disease 28 vs 21% p=0.74. Conclusions: SWOG 1815 did not result in a statistically significant improvement in median OS with GAP vs. GC. The GAP regimen had higher rates of TRAEs without a statistically significant difference in discontinuation rates. Pts with locally advanced disease and GBC may benefit from the use of GAP. Further analyses are ongoing to understand potential benefit of GAP in subsets of BTC pts. Funding: NIH/National Cancer Institute grants CA180888, CA180819, CA180820, CA180821, and CA180868; and in part by Celgene Corporation, Summit, NJ (subsidiary of Bristol Myer Squibb).

Hospital Medicine

DeCamillo D, Haymart B, Kong X, **Kaatz S**, Ali M, and Barnes G. ADVERSE EVENTS IN LOW VERSUS NORMAL BODY WEIGHT PATIENTS PRESCRIBED APIXABAN OR RIVAROXABAN FOR ATRIAL FIBRILLATION. *Am J Hematol* 2023; 98:E26. Full Text

D. DeCamillo, University of Michigan, Ann Arbor, MI, United States

Title: Adverse Events in Low versus Normal Body Weight Patients Prescribed Apixaban or Rivaroxaban for Atrial Fibrillation. Background: Clinical trials comparing direct oral anticoagulants (DOACs) to warfarin included only a small number of patients that weighed less than 60 kilograms (kg). The safety and efficacy of DOACs in low weight adult patients with atrial fibrillation (AF) is still unclear. Published data is not only sparse but have mixed outcomes. Therapy with DOACs may increase bleeding and/or clotting risk with uncertain antithrombotic benefit in low weight patients. Objective: To assess bleeding and thrombotic event rates for patients with AF that are prescribed a DOAC and have a low body weight (less than 60 kg) versus patients that have a normal body weight (60 to 100 kg). Methods: Within the Michigan Anticoagulation Quality Improvement Initiative (MAQI2), we analyzed data for patients with AF prescribed apixaban or rivaroxaban from 2017 through 2021 who had at least 12 months of follow-up. Patients were excluded if they were prescribed dosing different from package insert instructions. Patients were divided by weight into low (less than 60 kg) and normal (60 to 100 kg) cohorts. Assessments included rates of thrombotic events, major bleeding events (International Society on Thrombosis and Haemostasis [ISTH]), and non-major bleeding events requiring an Emergency Department (ED) visit. Patient characteristics were compared using Chi-square and t-test. Bleeding event rates were adjusted for age, gender, and diabetes mellitus and thrombotic event rates were adjusted by CHA2DS2-VASc score. Poisson regression was used to estimate adjusted adverse event rates to control for potentially confounding covariates (apixaban only due to few patients prescribed rivaroxaban). Results: A total of 616 patients met the inclusion criteria: 83 (13.5%) low weight and 533 (86.5%) normal weight. Most patients were prescribed apixaban (88.5%) with the low weight cohort more often prescribed the lower dose of apixaban (55% versus 6.2%, p<0.0001). The low weight cohort had a higher mean age (78.9% versus 74.4%, p<0.0002), proportion of females (94% versus 54%, p<0.0001) and CHA2DS2-VASc score (4.4 (1.6) versus 3.9 (1.6)), but a lower proportion of patients with diabetes mellitus (9.6% versus 25.1%, p<0.0018) [Table 1]. In the unadjusted analysis of patients prescribed apixaban, non-major bleeding events requiring an ED visit (10.8 per 100 patient-years versus 7.4 per 100 patient-years, p<0.0001), occurred more often in the low versus normal weight patient cohort [Table 2]. However, adjusted analysis found no statistically significant difference in events in low and normal weight cohorts prescribed apixaban [Table 2]. Comparisons within patients prescribed rivaroxaban could not be made due to a small sample size of low weight patients. Conclusions: Among low weight patients with AF the use of apixaban was not associated with bleeding (major and non-major) or thrombotic events after adjusting for potential confounding covariates. Larger studies may offer further insight into the overall safety and efficacy of DOAC therapy in these patients. (Table Presented).

Neurosurgery

Asmaro K, Lee CK, Xu Y, Vigo V, Hirschauer TJ, Rodrigues AJ, and Fernandez-Miranda JC. Incidence of Diplopia Secondary to Cranial Neuropathies after Endoscopic Endonasal Pituitary and Transcavernous Surgery. *J Neurol Surg B Skull Base* 2023; 84. Full Text

K. Asmaro, Henry Ford Health, Detroit, MI, United States

Background: Resection of cavernoinvasive pituitary tumors has been a lonastandina topic of controversy due to the risks of surgery within the cavernous sinus. Recent advances in suraical anatomy and techniques have paved the way for endoscopic transcavernous surgery (TCS) to address patholoay in this reaion. Objective: We aim to elucidate the rates of diplopia secondary to cranial neuropathy after endoscopic endonasal skull base approaches for pituitary tumor suraery. Methods: A prospectively collected and retrospective cohort analysis of 248 consecutive suraeries for pituitary tumor via an endoscopic endonasal approach between 2018 and 2022. Results: The median aae was 49 years old: 56% women, 128 functional (52%) and 49 residual/recurrent tumors (20%). Pituitary surgery without cavernous access was performed in 132 patients, while 116 patients (47%) underwent 132 TCS (16 patients with bilateral approaches). TCS was utilized on 60% of patients with functional adenomas compared with 33% of patients with non-secretina tumors ($p < 0.01$). A total of 17 patients (7%) developed diplopia: 4 CN III, 10 CN VI, and 3 had both CN III and VI palsies. Diplopia was more common after TCS compared with routine transsellar pituitary suraery, 11% versus 1.5% (OR: 8.33, 95% CI: 1.87-37.21; $p < 0.01$). Patients with bilateral cavernous sinus surgery had an increased risk for cranial neuropathy, 45% versus 11% (OR: 4.09, 95% CI: 1.18-14.18, $p < 0.05$). Patients with residual/recurrent disease were more likely to underao at least one-sided TCS compared with first time surgery patients (76 vs. 40%, $p < 0.01$), repeat surgery did not confer an increased risk of diplopia compared with first time TCS (OR: 1.68, 95% CI: 0.57-4.98, $p = 0.34$). Isolated medial wall resection ($n = 48$) carried a 2% risk of diplopia compared with 16%, 18%, and 22% for surgery in the superior ($n = 55$), posterior ($n = 60$), and inferior ($n = 45$) compartments of the cavernous sinus, respectively; meanwhile, lateral compartment surgery ($n = 12$) had a 33% risk of diplopia. All patients with CN III palsy had surgery within the superior compartment. Cessation of diplopia and return of normal extraocular movements occurred at a rate of 18, 45, 82, and 100% at 2 weeks, 3 months, 4 months, and 6 months postoperatively, respectively. The aross total resection rate for this series is 85% with a remission rate of 88% for functional tumors. There was no incidence of carotid artery injury or stroke. Conclusion: Pituitary surgery carries a risk for ocular dysmotility and diplopia which is increased when extended into the cavernous sinus; isolated medial wall resection, however, does not exhibit a sianificantly increased risk profile compared with routine transsellar pituitary suraery. Bilateral TCS carries a heiahtened risk profile, likely due to increased packina Sampfte ouput 'to Tst' PDF'Comble onlyhannels. All patients in our series, however, made a complete recovery without M a n a a e F>ref e r e n c es lona-term sequelae, makina TCS safe and effective for the treatment of cavernoinvasive pituitary patholoay. These outcomes, alona with the hiah resection and remission rates, supports the benefit of TCS for invasive and functional adenomas.

Neurosurgery

Asmaro K, Xu Y, Vigo V, Lee CK, Moon JH, and Fernandez-Miranda JC. Endoscopic Transcavernous Surgery for Pituitary Tumors within the Lateral Cavernous Sinus: Advancing towards the Lateral Frontier. *J Neurol Surg B Skull Base* 2023; 84. Full Text

K. Asmaro, Henry Ford Health, Detroit, MI, United States

Background: Recent anatomical advances have divided the cavernous sinus into four partitions, the inferior, superior, posterior, and lateral compartments. The lateral compartment is considered the most difficult and least forgiving due to its intimate relationship with the inferolateral trunk, tentorial artery, dorsal meningeal artery, as well as cranial nerves III-VI. Objective: We aim to study the role and efficacy of endoscopic transcavernous surgery for cavernoinvasive pituitary pathology located within the lateral compartment of the cavernous sinus. Methods: A prospectively collected and retrospective cohort analysis of 248 consecutive surgeries for pituitary tumor via an endoscopic endonasal approach between 2018 and 2022. Results: We identified 12 patients, median age 41.5, 10 were women (83%), 6 (50%) functional tumors who underwent endoscopic TCS in the lateral compartment. The sensitivity of preoperative MRI to detect lateral compartment disease (Knosp: 4) was 50%. The majority (67%) of lateral compartment disease was present when all four compartments were also invaded, but 3 (25%) and 1 (8%) were alongside two and one invaded compartment, respectively. 40% of patients had gross total resection and 3 patients (50%) achieved biochemical remission. Postoperative cranial neuropathy was present in four patients (33%): two CN III, one CN VI, and one patient had both CN III and VI palsies. All patients with postoperative diplopia recovered at 2 weeks ($n = 1$), 3 months ($n = 2$), and 6 months ($n =$

1). There was no incidence of carotid injury or stroke. Conclusion: Surgery within the lateral cavernous sinus remains challenging but can be performed in the experienced hands with limited, transient morbidity pertaining to diplopia from cranial neuropathy extraocular motility dysfunction. Patient selection is key, as it can be beneficial to patients suffering from uncontrollable functional disease without the untoward side effects of radiotherapy.

Neurosurgery

Mackie H, Yassin-Kassab A, **Ray A**, **Eide JG**, **Robin AM**, **Asmaro K**, **Rock JP**, and **Craig JR**. Rapidly Injecting 10 MG of Intrathecal Fluorescein Caused No Neurologic Complications. *J Neurol Surg B Skull Base* 2023; 84. Request Article

H. Mackie, Michigan State University College of Human Medicine, East Lansing, MI, United States

Background: Intrathecal fluorescein (ITF) is often effective in localizing nasal cerebrospinal fluid (CSF) leaks along the skull base under nasal endoscopy. Previous reports of seizures and paralysis have led to administration practices aimed at minimizing the risk of these potentially catastrophic neurologic complications. Since these early reports, surgeons have often reported injecting ITF slowly over a variable number of minutes, and that it should be diluted either in saline or patients' CSF. However, no study has assessed whether ITF administration duration or dilution alters the risks of these neurologic complications. Methods: From September 2015 through August 2022, all patients undergoing ITF injection through lumbar drains for localization of possible or confirmed nasal CSF leaks were included. All patients had ITF administered by mixing 0.1 mL of 10% fluorescein (10 mg) with 3 to 5 mL of CSF, with no additional fluorescein dilution. The solutions were then injected through lumbar drains rapidly over 1 to 2 seconds. Patient demographics, CSF leak etiologies, and histories of seizures or cerebrovascular accidents were recorded. Results: Sixty-one patients were included, mean age was 56.3 ± 15.6 years, and 82% were female. Fifty patients had CSF leaks repaired successfully, and 11 patients had negative explorations. CSF leaks were due to the following etiologies: idiopathic intracranial hypertension (76%), skull base tumors (10%), accidental trauma (8%), and surgical trauma (6%). Four patients had histories of seizure disorders, and five patients had remote histories of prior cerebrovascular accidents. There were no intraoperative or postoperative episodes of seizure, paralysis, or other neurologic complications. Conclusion: Injecting 10 mg of ITF through lumbar drains rapidly and without true dilution resulted in no seizures, paralysis, or other neurologic complications in patients undergoing endoscopic exploration with or without nasal CSF leak repair.

Otolaryngology – Head and Neck Surgery

Eide JG, Kshirsagar RS, Wen C, Qatanani A, Harris J, Abello EH, Kuan EC, Palmer JN, and Adappa ND. The Impact of Preoperative Frailty on Endoscopic Cerebrospinal Fluid Leak Repair Outcomes in the Anterior Skull Base. *J Neurol Surg B Skull Base* 2023; 84. Request Article

J.G. Eide, Henry Ford Health, Detroit, MI, United States

Background: Measurements of surgical frailty estimate a patient's ability to withstand the physiologic stress of a procedure. There is limited data regarding the impact of frailty on endoscopic cerebrospinal fluid (CSF) leak repair. Methods: Patients undergoing CSF leak repair at two tertiary academic skull base programs were retrospectively reviewed. Demographic, treatment, and postoperative outcomes data were recorded. Frailty was calculated using validated indexes, including the American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index (CCI), and the Modified 5-Item Frailty Index (mFI-5). Outcomes included 30-day medical and surgical complications and readmission. Results: A total of 185 patients were included with 128 (69.2%) female patients and average age of 54 ± 14 years. The average BMI was 34.6 ± 8.5. The most common identified etiology was idiopathic intracranial hypertension (IIH) in 64 patients (34.6%). The average duration of leak was 9.31 ± 22.14 months. 125 patients (68%) underwent perioperative lumbar drain placement (primarily to measure intracranial pressures and definitively diagnose IIH). Most patients were ASA class 3 (48.6%) with mean CCI 2.14 ± 2.23 and mFI-5 0.97 ± 0.90. Three patients had postoperative CSF leaks, with an overall repair success rate of 98.4%. There was no association between increased frailty and 30-day medical outcomes (myocardial infarction, cerebrovascular accident, pneumonia, pulmonary embolism/deep vein thrombosis,

and meningitis), surgical outcomes (bleeding requiring transfusion, postoperative CSF leak), or readmission (all $p > 0.05$). Discussion: Endoscopic CSF leak repair in a frail population, including lumbar drain placement and postoperative bedrest, did not have an increased rate of complications. Previous data suggests there are increased complications in open craniotomy procedures in patients with significant comorbidities. Our preliminary data suggests that the endoscopic approach to CSF leak repair may be better tolerated in the frail population.

Otolaryngology – Head and Neck Surgery

Mackie H, Yassin-Kassab A, **Ray A**, **Eide JG**, **Robin AM**, **Asmaro K**, **Rock JP**, and **Craig JR**. Rapidly Injecting 10 MG of Intrathecal Fluorescein Caused No Neurologic Complications. *J Neurol Surg B Skull Base* 2023; 84. Request Article

H. Mackie, Michigan State University College of Human Medicine, East Lansing, MI, United States

Background: Intrathecal fluorescein (ITF) is often effective in localizing nasal cerebrospinal fluid (CSF) leaks along the skull base under nasal endoscopy. Previous reports of seizures and paralysis have led to administration practices aimed at minimizing the risk of these potentially catastrophic neurologic complications. Since these early reports, surgeons have often reported injecting ITF slowly over a variable number of minutes, and that it should be diluted either in saline or patients' CSF. However, no study has assessed whether ITF administration duration or dilution alters the risks of these neurologic complications. Methods: From September 2015 through August 2022, all patients undergoing ITF injection through lumbar drains for localization of possible or confirmed nasal CSF leaks were included. All patients had ITF administered by mixing 0.1 mL of 10% fluorescein (10 mg) with 3 to 5 mL of CSF, with no additional fluorescein dilution. The solutions were then injected through lumbar drains rapidly over 1 to 2 seconds. Patient demographics, CSF leak etiologies, and histories of seizures or cerebrovascular accidents were recorded. Results: Sixty-one patients were included, mean age was 56.3 ± 15.6 years, and 82% were female. Fifty patients had CSF leaks repaired successfully, and 11 patients had negative explorations. CSF leaks were due to the following etiologies: idiopathic intracranial hypertension (76%), skull base tumors (10%), accidental trauma (8%), and surgical trauma (6%). Four patients had histories of seizure disorders, and five patients had remote histories of prior cerebrovascular accidents. There were no intraoperative or postoperative episodes of seizure, paralysis, or other neurologic complications. Conclusion: Injecting 10 mg of ITF through lumbar drains rapidly and without true dilution resulted in no seizures, paralysis, or other neurologic complications in patients undergoing endoscopic exploration with or without nasal CSF leak repair.

Public Health Sciences

Afshan T, **Kulkarni A**, Smith J, Blackshere T, Tesson E, Hartert T, Rivera-Spoljaric K, **Zoratti E**, **Joseph C**, Gangnon R, Gern J, and Singh AM. Examining virtual research recruitment and participant diversity in a multi-center birth cohort, Childhood Allergy and the NeOnatal Environment" (CANOE). *J Allergy Clin Immunol* 2023; 151(2):AB183. Full Text

Rationale: Recruitment for a NIH/ECHO-supported multi-center birth cohort, “Childhood Allergy and the NeOnatal Environment” (CANOE) stopped due to the COVID-19 pandemic. Redesign of study procedures emphasized virtual and socially distanced activities. We hypothesized that “virtual” recruitment methods (social media, websites, email) would surpass “traditional” methods (in-clinic, telephone, flyers/print materials) and increase enrollment of families from diverse backgrounds and communities. Methods: Pregnant women (n=439, target 500) were recruited from four academic medical centers in Detroit MI, Madison WI, Nashville TN, and St. Louis MO. We collected demographic and social information by questionnaires and examined race, ethnicity, age, parity, and employment status in relation to recruitment method using chi-square tests. Results: In-clinic and telephone recruitment comprised 55% of enrollment, followed by print materials (17%), and social media and email (15%). The cohort includes families self-identifying as Caucasian/White (63%), African American/Black (27%), Hispanic/Latino (3.3%), Asian (3.5%), and mixed races (1.2%). This reflects site demographics for White and Black patients, while other populations are not as well recruited into this cohort. Recruitment method success did not vary by race, ethnicity, maternal age, or employment status (p=ns for each comparison). Most (63%) multigravida mothers (9.1% of participants) were recruited in clinic, while primigravida

participants were recruited more evenly via all methods. Conclusions: “Virtual” recruitment methods comprised a smaller proportion of cohort enrollment than hypothesized and study recruitment method did not vary by race/ethnicity; however, consideration of combined, varied, and novel recruitment methods may add to the development of best practices for more representative research study recruitment.

Public Health Sciences
Biagini J, Martin L, He H, Bacharier L, Gebretsadik T, Hartert T, Jackson D, **Kim H**, Miller R, Rivera-Spoljaric K, Schauberger E, Singh AM, Visness C, **Wegienka G**, Ownby D, Gold D, Martinez F, **Johnson CC**, Wright A, Gern J, and Hershey GK. The Pediatric Asthma Risk Score: A New Gold Standard for Asthma Prediction. *J Allergy Clin Immunol* 2023; 151(2):AB320. Full Text

Rationale: Early prediction of asthma is critical to identify potential primary prevention strategies. The Pediatric Asthma Risk Score (PARS) is a continuous score to predict early-life asthma but was developed and validated in relatively homogenous populations. We compared PARS directly to the Asthma Predictive Index (API) and validated in 10 cohorts with varying race, ethnicity, sex, cohort type, missing data and birth decades, and perform a meta-analysis across all 10 cohorts. Methods: We utilized data from 5674 children participating in the Children’s Respiratory and Environmental Workgroup. We applied both PARS and the API in each cohort, as well as harmonized across all cohorts, and directly compared the ability of each tool to predict asthma development at ages 5-10. Results: The PARS area under the curve (AUC) was significantly higher than the AUC of the API in 9 cohorts (p-value range 0.01 - <0.001). The PARS AUC did not differ by cohort type (high risk or general population), decade of enrollment, race, sex, ethnicity, missing PARS factors or polysensitization definition (skin prick test vs. specific IgE). The weights of the 6 PARS factors in the meta-analysis were very similar to the original weights, validating the original PARS scoring. Conclusions: This multi-cohort study makes the PARS the most validated model of asthma prediction in children to date, not only with respect to the number of cohorts used but also with regards to capturing the diversity of asthma in the United States. Future studies may consider PARS the new gold standard in pediatric asthma risk prediction.

Public Health Sciences
Eapen A, **Sitarik A**, Biagini J, Jackson D, **Joseph C**, **Kim H**, Martin L, Rivera-Spoljaric K, Schauberger E, **Wegienka G**, Gern J, and Singh AM. Longitudinal assessment of Allergic Outcomes and Atopic Dermatitis Phenotypes in The Children's Respiratory and Environmental Workgroup (CREW) Birth Cohort Consortium. *J Allergy Clin Immunol* 2023; 151(2):AB146. Full Text

Rationale: Atopic dermatitis (AD) is a heterogenous inflammatory skin disease often associated with other allergic diseases. We characterized AD phenotypes and associated allergic outcomes longitudinally across a multi-site consortium. Methods: AD expression in 11 U.S. birth cohorts from the CREW (Children’s Respiratory and Environmental Workgroup) consortium was assessed in each year of life from age 0-7 years (N=7,900). Longitudinal Latent Class Analysis was performed to identify AD phenotypes. Five classes of AD were identified: Persistent AD (15.4%), Early AD with Potential Reoccurrence (2.7%), Late-Onset AD (7.0%), Transient Early AD (3.0%), and Minimal/No AD (72.0%). Serum allergen sensitization patterns and allergic clinical disease were associated with AD phenotype using multinomial logistic regression with a 3-step procedure to account for uncertainty in class membership. Results: Children with Persistent AD, Early AD with Potential Reoccurrence, and Transient Early AD were more likely to have food allergy compared to those with Minimal/No AD (OR[95% CI]=2.73[2.15, 3.45], 2.69[1.63, 4.45], 2.54[1.55, 4.16], respectively). These groups had similarly higher odds of food sensitization. Persistent AD (OR[95% CI]=1.81[1.48, 2.21]) and Early AD with Potential Reoccurrence (OR[95% CI]=3.66[1.90, 7.05]) had significantly higher odds of ever asthma relative to Minimal/No AD. At both 2-4 years and 5-7 years, persistent AD (OR[95% CI]=1.35[1.04, 1.74], 1.25[1.01, 1.53]) and Late-Onset AD (OR[95% CI]=1.68[1.13, 2.50], 2.22[1.33, 3.70]) relative to Minimal/No AD had higher odds of allergic rhinitis. Conclusions: Longitudinal AD phenotypes had varying associations with allergic sensitization, food allergy, asthma and allergic rhinitis, demonstrating the heterogeneity of allergic comorbidity risk associated with AD.

Public Health Sciences

Sitarik A, Biagini J, **Eapen A**, Jackson D, **Joseph C**, **Kim H**, Martin L, Rivera-Spoljaric K, Schauberger E, **Wegienka G**, Gern J, and Singh AM. Longitudinal Characterization of Atopic Dermatitis Phenotypes in The Children's Respiratory and Environmental Workgroup (CREW) Birth Cohort Consortium. *J Allergy Clin Immunol* 2023; 151(2):AB145. Full Text

Rationale: Previously identified longitudinal patterns of atopic dermatitis (AD) may lack generalizability and precision due to small sample size and limited time points. We identify and describe longitudinal AD phenotypes in a large consortium study. Methods: Data from 11 birth cohorts across the United States from the CREW (Children's Respiratory and Environmental Workgroup) consortium were harmonized to determine physician diagnosis of AD in each year of life from 0-7 years of age (N=7,900). AD phenotypes were identified using Longitudinal Latent Class Analysis, and relationships with demographic variables were determined using multinomial logistic regression with a 3-step procedure to account for uncertainty in class membership. Results: We identified 5 classes of AD expression, selected based on model fit, interpretability, and clinical utility: Persistent AD (15.4%), Early AD with Potential Reoccurrence (2.7%), Late-Onset AD (7.0%), Transient Early AD (3.0%), and Minimal/No AD (72.0%). Males had significantly higher odds of Persistent AD (OR [95% CI]=1.47 [1.22, 1.75]) and Early AD with Potential Reoccurrence (OR [95% CI]=1.89 [1.19, 2.94]). Relative to White children, Black children had higher odds of Persistent AD (OR [95% CI]=2.50 [2.05, 3.05]), Early AD with Potential Reoccurrence (OR [95% CI]=3.07 [1.94, 4.85]), and Transient Early AD (OR [95% CI]=4.12 [2.62, 6.48]). Conclusions: Five AD phenotypes exist in a diverse national sample of children. Black children and males are at increased risk of early and persistent AD. These findings illustrate potential risk factors to target AD prevention.

Radiation Oncology

Aguilera TA, **Parikh P**, Ghaly M, Hoffe SE, Herman JM, Caster JM, Kim DW, Costello J, Malafa MP, Beg MS, Moser EC, Kennedy EP, Terry K, and Kurman M. Greco-2: A randomized, phase 2 study of stereotactic body radiation therapy (SBRT) in combination with rucosopasem (GC4711) in the treatment of locally advanced or borderline resectable nonmetastatic pancreatic cancer. *J Clin Oncol* 2023; 41(4):TPS766. Full Text

T.A. Aguilera

Background: While treatment of pancreatic cancer has advanced, survival rates remain low. Stereotactic body radiotherapy (SBRT; high dose per fraction radiation) may exhibit improved clinical outcomes in locally advanced pancreatic cancer but carries potential gastrointestinal toxicity risks. Rucosopasem (GC4711) is one of a class of investigational selective dismutase mimetics that rapidly and specifically converts superoxide to hydrogen peroxide. Studies have shown that normal cells tolerate hydrogen peroxide fluxes better than cancer cells. As radiation response modifiers, dismutase mimetics have the potential to increase tumor control of SBRT without compromising radiation safety. In a pilot phase 1/2 trial in patients with pancreatic cancer, avasopasem, a dismutase mimetic related to rucosopasem, nearly doubled median overall survival in patients receiving SBRT vs placebo plus SBRT. Improvements versus placebo were also observed in local tumor control, time to metastases, and progression-free survival. Altogether, these data support the hypothesis that rucosopasem may improve survival and the benefit-risk ratio of SBRT by improving efficacy without increasing gastrointestinal toxicity. Methods: GRECO-2 is a phase 2, multicenter, randomized, double-blind, placebo-controlled study (NCT04698915) to determine the effect of adding rucosopasem to SBRT on overall survival in patients with borderline resectable or locally advanced, unresectable nonmetastatic pancreatic cancer following initial chemotherapy with a FOLFIRINOX-based regimen or a gemcitabine doublet. Approximately 160 patients will be randomized (approximately 35 sites) to receive rucosopasem 100 mg or placebo via IV infusion over 15 minutes, prior to each SBRT fraction (5 x 10 Gy). Patients judged to be resectable will undergo surgical exploration within 8 weeks after SBRT. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, locoregional control, time to metastasis, surgical resection rate, RO resection rate, best overall response, in-field local response, and safety (acute and late toxicities). Exploratory endpoints include PRO-CTCAE and CA19-9 normalization.

Radiation Oncology
Parikh P, Asbun D, Chuong MD, Portelance L, Datta J, Bassetti MF, Weber SM, Zaki BI, Smith KD, Raldow AC, Donahue TR, Kim H, Hawkins WG, Kelly P, Low D, Lee P, Fuss M, and **Kwon DS**. Surgical outcomes after neoadjuvant ablative dose radiation among patients with borderline resectable and locally advanced pancreas cancer from the multi-institutional phase 2 Stereotactic MR-Guided Adaptive Radiation Therapy (SMART) trial. *J Clin Oncol* 2023; 41(4):718. Full Text

P. Parikh

Background: Acute grade 3+ toxicity was rare in the multi-institutional phase 2 stereotactic MR-guided on-table adaptive radiation therapy (SMART) trial (NCT03621644) for locally advanced and borderline resectable pancreatic cancer (LAPC/BRPC). Surgery may be considered after ablative SMART although the feasibility and safety of this is not well understood. Postoperative outcomes of the subset of patients in the SMART trial are examined here. Methods: Trial eligibility included BRPC or LAPC without metastases after a minimum of 3 months of induction chemotherapy. All patients received SMART prescribed to 50 Gy in 5 fractions using an integrated 0.35T MR-radiation therapy device equipped with cutting edge soft tissue tracking, automatic beam gating, and on-table adaptive replanning. Surgery was permitted after SMART, often after multi-disciplinary review. Perioperative details and postoperative outcomes, including morbidity, mortality, and overall survival (OS), were analyzed. Results: 136 patients across 13 sites were enrolled between 2019-2022. 44 patients (32.4%) had surgery after SMART (33 BRPC, 11 LAPC). Surgical procedures included pancreaticoduodenectomy (81.8%), distal pancreatectomy with splenectomy (9.1%), total pancreatectomy (6.8%), and distal pancreatectomy with celiac axis resection (2.3%). 52.3% required vascular resection/reconstruction, a majority of which were venous resections (65.2%), with a smaller proportion needing both venous/ arterial (21.7%), or arterial (13%). Surgery was performed after a mean 51.4 ± 52.8 days from SMART. Postoperative hospitalization was 10.5 ± 8.9 days. Nine patients (20.5%) had Clavien-Dindo complications of grade III or higher; 3 deaths resulted from post-pancreatectomy hemorrhage in patients who had portal vein resection. One-year OS in patients who had surgery versus no surgery after SMART was 66% vs. 43%, respectively. Conclusions: These are the first prospectively evaluated surgical outcomes after 5-fraction ablative SMART for BRPC/LAPC. The rate of surgery for BRPC compares favorably to radiated patients on the Alliance A021501 trial. Despite the use of ablative radiation dose and frequent need for vascular resection, the incidence of serious surgical complications was similar to what is reported after non-ablative radiation therapy. However, several deaths occurred after surgery and we therefore we urge caution when considering surgery after ablative radiation therapy. Further analysis of other variables such as the time between SMART and surgery, approaches to vascular resections, and discrete events such as delayed gastric emptying, operative duration, and post-operative pancreatic fistula are needed to better understand the surgical morbidity seen in these patients.

Surgery
Parikh P, Asbun D, Chuong MD, Portelance L, Datta J, Bassetti MF, Weber SM, Zaki BI, Smith KD, Raldow AC, Donahue TR, Kim H, Hawkins WG, Kelly P, Low D, Lee P, Fuss M, and **Kwon DS**. Surgical outcomes after neoadjuvant ablative dose radiation among patients with borderline resectable and locally advanced pancreas cancer from the multi-institutional phase 2 Stereotactic MR-Guided Adaptive Radiation Therapy (SMART) trial. *J Clin Oncol* 2023; 41(4):718. Full Text

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