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HENRY FORD HEALTH

Henry Ford Health Publication List – June 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 114 unique citations listed this month, including 108 articles and 6 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

Administration
Suleyman G, **Fadel R**, **Patel K**, **Shadid AM**, **Stuart HBC**, **Kattula M**, **Janis A**, **Maki M**, **Chao S**, **Alangaden G**, and **Brar I**. Outcomes associated with SARS-CoV-2 reinfection in individuals with natural and hybrid immunity. *J Infect Public Health* 2023; 16(8):1262-1268. PMID: 37302273. Full Text

Henry Ford Hospital, Division of Infectious Disease, 2799 West Grand BLVD, Detroit, MI 48202, USA; Wayne State University School of Medicine, 540 E. Canfield Ave., Detroit, MI 48201, USA. Electronic address: gsuleym2@hfhs.org.
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BACKGROUND: Studies comparing SARS-CoV-2 reinfection outcomes among individuals with previous infection (natural immunity) and previous infection plus vaccination (hybrid immunity) are limited. METHODS: Retrospective cohort study comparing SARS-CoV-2 reinfection among patients with hybrid immunity (cases) and natural immunity (controls) from March 2020 to February 2022. Reinfection was defined as positive PCR > 90 days after initial laboratory-confirmed SARS-CoV-2 infection. Outcomes included time to reinfection, symptom severity, COVID-19-related hospitalization, critical COVID-19 illness (need for intensive care unit, invasive mechanical ventilation, or death), length of stay (LOS). RESULTS: A total of 773 (42%) vaccinated and 1073 (58%) unvaccinated patients with reinfection were included. Most patients (62.7%) were asymptomatic. Median time to reinfection was longer with hybrid immunity (391 [311-440] vs 294 [229-406] days, $p < 0.001$). Cases were less likely to be symptomatic (34.1% vs 39.6%, $p = 0.001$) or develop critical COVID-19 (2.3% vs 4.3%, $p = 0.023$). However, there was no significant difference in rates of COVID-19-related hospitalization (2.6% vs 3.8%, $p = 0.142$) or LOS (5 [2-9] vs 5 [3-10] days, $p = 0.446$). Boosted patients had longer time to reinfection (439 [IQR 372-467] vs 324 [IQR 256-414] days, $p < 0.001$) and were less likely to be symptomatic (26.8% vs 38%, $p = 0.002$) compared to unboosted patients. Rates of hospitalization, progression to critical illness and LOS were not significantly different between the two groups. CONCLUSIONS: Natural and hybrid immunity provided protection against SARS-CoV-2 reinfection and hospitalization. However, hybrid immunity conferred stronger protection against symptomatic disease and progression to critical illness and was associated with longer time to reinfection. The stronger protection conferred by hybrid immunity against severe outcomes due to COVID-19 should be emphasized with the public to further the vaccination effort, especially in high-risk individuals.

Administration
Thariath J, Salhi RA, Kamdar N, Seiler K, Greenwood-Ericksen M, Nham W, Simpson K, **Peterson T**, and Abir M. Evaluating the pediatric mental health care continuum at an American health system. *SAGE Open Med* 2023; 11. PMID: 37362613. Full Text

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OBJECTIVE: To describe trends in the pediatric mental health care continuum and identify potential gaps in care coordination. METHODS: We used electronic medical record data from October 2016 to September 2019 to characterize the prevalence of mental health issues in the pediatric population at a large American health system. This was a single institution case study. From the electronic medical

record data, primary mental health discharge and readmission diagnoses were identified using International Classification of Diseases (ICD-9-CM, ICD-10-CM) codes. The electronic medical record was queried for mental health-specific diagnoses as defined by International Classification of Diseases classification, analysis of which was facilitated by the fact that only 176 mental health codes were billed for. Additionally, prevalence of care navigation encounters was assessed through electronic medical record query, as care navigation encounters are specifically coded. These encounter data was then segmented by care delivery setting. RESULTS: Major depressive disorder and other mood disorders comprised 49.6% and 89.4% of diagnoses in the emergency department and inpatient settings respectively compared to 9.0% of ambulatory care diagnoses and were among top reasons for readmission. Additionally, only 1% of all ambulatory care encounters had a care navigation component, whereas 86% of care navigation encounters were for mental health-associated reasons. CONCLUSIONS: Major depressive disorder and other mood disorders were more common diagnoses in the emergency department and inpatient settings, which could signal gaps in care coordination. Bridging potential gaps in care coordination could reduce emergency department and inpatient utilization through increasing ambulatory care navigation resources, improving training, and restructuring financial incentives to facilitate ambulatory care diagnosis and management of major depressive disorder and mood disorders. Furthermore, health systems can use our descriptive analytic approach to serve as a reasonable measure of the current state of pediatric mental health care in their own patient population.

Anesthesiology
Banerjee G, **Mitchell JD**, Brzezinski M, **DePorre A**, and Ballard HA. Burnout in Academic Physicians. *Perm J* 2023; 27(2):142-149. PMID: 37309180. Full Text

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The prevalence of burnout is much higher in physicians than in other occupations. Academic physicians serve important functions, training future physicians and advancing medical research in addition to doing clinical work. However, they are particularly vulnerable to burnout for reasons including low compensation for teaching, pressure to publish despite a lack of time and declining research funds, and a redistribution of clinical workload due to restrictions on trainee work hours. Junior faculty, women, and marginalized groups are the most affected. Beyond poor physician health and worse patient outcomes, burnout is strongly associated with reduced work effort and an intent to leave the profession. Moreover, physicians are leaving the workforce in record numbers, further increasing the stress on remaining physicians. Combined with a worsening of quality of patient care, this increased rate of physician burnout threatens the viability of health care organizations. This review discusses the causes and consequences of faculty burnout, as well as interventions undertaken for its mitigation.

Anesthesiology
DePorre A, **Banerjee G**, **Mitchell JD**, Brzezinski M, and Ballard HA. Burnout in Medicine: Are We Asking the Right Questions? *Perm J* 2023; 27(2):123-129. PMID: 37278061. Full Text

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After reviewing a substantial amount of published data on academic physician burnout, we were left pondering the question, "Are we on the right track with combating burnout?" This point-counterpoint manuscript details two opposing viewpoints: 1) the current approach to fighting burnout is working, and 2)

resources should be diverted and focus placed on other areas because current interventions are failing physicians. In addressing these points, we discuss four poignant questions that we discovered researching this multifaceted issue: 1) Why do current burnout interventions have limited effects on prevalence over time? 2) Who benefits from the current health care structure (is burnout a profitable and desirable consequence of our work environment)? 3) What organizational conceptual frameworks are most beneficial to improve burnout? 4) How do we take responsibility and seize the ground for our own well-being? Though these differing viewpoints provoked an engaging and lively conversation among our writing team, we all agree on one point. Burnout is an immense problem that affects physicians, patients, and society; therefore, it demands our attention and resources.

Anesthesiology
Khanna AK, Kelava M, **Ahuja S**, Makarova N, Liang C, Tanner D, and Insler SR. A nomogram to predict postoperative pulmonary complications after cardiothoracic surgery. *J Thorac Cardiovasc Surg* 2023; 165(6):2134-2146. PMID: 34689983. Full Text

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OBJECTIVE: The objective was to develop a novel scoring system that would be predictive of postoperative pulmonary complications in critically ill patients after cardiac and major vascular surgery. METHODS: A total of 17,433 postoperative patients after coronary artery bypass graft, valve, or thoracic aorta repair surgery admitted to the cardiovascular intensive care units at Cleveland Clinic Main Campus from 2009 to 2015. The primary outcome was the composite of postoperative pulmonary complications, including pneumonia, prolonged postoperative mechanical ventilation (>48 hours), or reintubation occurring during the hospital stay. Elastic net logistic regression was used on the training subset to build a prediction model that included perioperative predictors. Five-fold cross-validation was used to select an appropriate subset of the predictors. The predictive efficacy was assessed with calibration and discrimination statistics. Post hoc, of 13,353 adult patients, we tested the clinical usefulness of our risk prediction model on 12,956 patients who underwent surgery from 2015 to 2019. RESULTS: Postoperative pulmonary complications were observed in 1669 patients (9.6%). A prediction model that included baseline and demographic risk factors along with perioperative predictors had a C-statistic of 0.87 (95% confidence interval, 0.86-0.88), with a corrected Brier score of 0.06. Our prediction model maintains satisfactory discrimination (C-statistics of 0.87) and calibration (Brier score of 0.07) abilities when evaluated on an independent dataset of 12,843 recent adult patients who underwent cardiovascular surgery. CONCLUSIONS: A novel prediction nomogram accurately predicted postoperative pulmonary complications after major cardiac and vascular surgery. Intensivists may use these predictors to allow for proactive and preventative interventions in this patient population.

Anesthesiology
Younger JD, Faryami A, Prasad M, Viar D, Menkara A, **Tang A**, and Harris CA. Direct Comparison of Peak Bulk Flow Rate of Programmable Intermittent Epidural Bolus and Manual Epidural Bolus Using a Closed-End Multiorifice Catheter: An Experimental Study. *Anesth Analg* 2023; 136(6):1198-1205. PMID: 36730916. Full Text

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BACKGROUND: The programmable intermittent epidural bolus (PIEB) has been popularized as the optimal delivery technique for labor analgesia. Suggested advantages of this method are less local anesthetic consumption, improved maternal satisfaction, potentially shorter duration of labor, and decreased workload requirements for the anesthesia providers. However, a manual bolus is still routinely used for breakthrough pain when the PIEB is underperforming. METHODS: We conducted a laboratory-based study to quantify the flow through a multiorifice epidural catheter using the PIEB setting on an epidural pump compared to the manual epidural bolus. Four syringe volumes, 3, 5, 10, and 20 mL, were selected for this experiment. The flow in a manual bolus was also studied with and without the presence of an epidural catheter filter. A generalized estimating equation analysis was done to compare data between the groups. RESULTS: Regardless of the syringe size, there was a several-fold increase in flow when a manual bolus was used compared to a pump-administered dose, with the highest difference in the peak flow rate observed in 3-mL boluses with up to a 12-fold difference, while the difference was, at most, 7-fold in 5-mL and 10-mL boluses. Manual boluses without a filter achieve a mean peak flow rate higher than manual boluses with a filter. CONCLUSIONS: Our study found that manual boluses produced a higher flow rate compared to the CADD-Solis epidural pump (Smiths Medical). This study also found that the placement of a particulate filter reduces the flow rates generated while bolusing. Bulk flow rate is directly correlated with induced pressure and solution spread. Because higher bolus pressure has been shown to provide a more efficient distribution of local anesthetic and more efficient pain relief, these results may have impactful clinical significance and will pave the way for future studies.

Behavioral Health Services/Psychiatry/Neuropsychology
Felton JW, Kleinman MB, Doran K, Satinsky EN, Tralka H, Dean D, Brown CJS, Anvari MS, Bradley VD, and Magidson JF. Peer Activate: A Feasibility Trial of a Peer-Delivered Intervention to Decrease Disparities in Substance Use, Depression, and Linkage to Substance Use Treatment. *J Psychosoc Nurs Ment Health Serv* 2023; 1-9. Epub ahead of print. PMID: 37256749. Request Article

Although effective evidence-based interventions (EBIs) exist, racial/ethnic minority individuals with lower income are less likely to have access to these interventions and may experience greater stigma in the health care system, resulting in disproportionate rates of morbidity and mortality. Peer recovery specialists (PRSs) may be uniquely suited to address barriers faced by those from impoverished areas; however, peers have not traditionally been trained in implementing EBIs. The current open-label trial (N = 8) was performed to evaluate implementation and preliminary effectiveness of an adapted EBI supporting recovery, linkage to treatment, and reduced depression. Results suggest the intervention was feasible, acceptable, and appropriate for linking individuals from a community setting to substance use treatment and could be delivered with fidelity by a peer interventionist. Participants who completed the intervention demonstrated clinically reliable decreases in substance use and depressive symptoms. Findings provide initial support for PRS dissemination of EBIs to increase linkage to care and support recovery in traditionally underserved populations. [Journal of Psychosocial Nursing and Mental Health Services, xx(xx), xx-xx.].

Behavioral Health Services/Psychiatry/Neuropsychology
Huang Y, **Chen D**, **Levin AM**, **Ahmedani BK**, **Frank C**, Li M, Wang Q, **Gui H**, and Sham PC. Cross-phenotype relationship between opioid use disorder and suicide attempts: new evidence from polygenic association and Mendelian randomization analyses. *Mol Psychiatry* 2023; Epub ahead of print. PMID: 37340172. Request Article

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Clinical epidemiological studies have found high co-occurrence between suicide attempts (SA) and opioid use disorder (OUD). However, the patterns of correlation and causation between them are still not clear due to psychiatric confounding. To investigate their cross-phenotype relationship, we utilized raw phenotypes and genotypes from >150,000 UK Biobank samples, and genome-wide association summary statistics from >600,000 individuals with European ancestry. Pairwise association and a potential bidirectional relationship between OUD and SA were evaluated with and without controlling for major psychiatric disease status (e.g., schizophrenia, major depressive disorder, and alcohol use disorder). Multiple statistical and genetics tools were used to perform epidemiological association, genetic correlation, polygenic risk score prediction, and Mendelian randomizations (MR) analyses. Strong associations between OUD and SA were observed at both the phenotypic level (overall samples [OR = 2.94, P = 1.59 ×10(-14)]; non-psychiatric subgroup [OR = 2.15, P = 1.07 ×10(-3)]) and the genetic level (genetic correlation rg = 0.38 and 0.5 with or without conditioning on psychiatric traits, respectively). Consistently, increasing polygenic susceptibility to SA is associated with increasing risk of OUD (OR = 1.08, false discovery rate [FDR] =1.71 ×10(-3)), and similarly, increasing polygenic susceptibility to OUD is associated with increasing risk of SA (OR = 1.09, FDR = 1.73 ×10(-6)). However, these polygenic associations were much attenuated after controlling for comorbid psychiatric diseases. A combination of MR analyses suggested a possible causal association from genetic liability for SA to OUD risk (2-sample univariable MR: OR = 1.14, P = 0.001; multivariable MR: OR = 1.08, P = 0.001). This study provided new genetic evidence to explain the observed OUD-SA comorbidity. Future prevention strategies for each phenotype needs to take into consideration of screening for the other one.

Behavioral Health Services/Psychiatry/Neuropsychology

Loree AM, **Hecht LM**, **Yeh HH**, **Gavrilova L**, Furman K, **Westphal J**, Simon GE, Lynch FL, Beck A, Owen-Smith A, Rossom R, Daida YG, Lu CY, Boggs JM, **Frank C**, Waring S, and **Ahmedani BK**. Factors associated with suicide mortality among reproductive age women: a case-control study. *J Reprod Infant Psychol* 2023; 1-12. Epub ahead of print. PMID: 37310021. Request Article

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OBJECTIVE: Examine demographic, psychosocial, pregnancy-related, and healthcare utilisation factors associated with suicide mortality among reproductive age women. METHODS: Data from nine health care systems in the Mental Health Research Network were included. A case-control study design was used in which 290 reproductive age women who died by suicide (cases) from 2000 to 2015 were matched with 2,900 reproductive age women from the same healthcare system who did not die by suicide (controls). Conditional logistic regression was used to analyse associations between patient characteristics and suicide. RESULTS: Women of reproductive age who died by suicide were more likely to have mental health (aOR = 7.08, 95% CI: 5.17, 9.71) or substance use disorders (aOR = 3.16, 95% CI: 2.19, 4.56) and to have visited the emergency department in the year prior to index date (aOR = 3.47, 95% CI: 2.50, 4.80). Non-Hispanic White women (aOR = 0.70, 95% CI: 0.51, 0.97) and perinatal (pregnant or postpartum) women were less likely to have died by suicide (aOR = 0.27, 95% CI: 0.13, 0.58). CONCLUSIONS: Reproductive age women with mental health and/or substance use disorders, prior emergency department encounters, or who are of racial or ethnic minority status were at increased risk of suicide mortality and may benefit from routine screening and monitoring. Future research should further examine the relationship between pregnancy-related factors and suicide mortality.

Behavioral Health Services/Psychiatry/Neuropsychology

Obri MS, **Youssef RM**, **Alluri S**, **Vemulapalli K**, **Ichkhanian Y**, **Todter EN**, **Jesse MT**, and **Salgia R**. Disparities in Referrals to End-of-Life Care in Eligible Hepatocellular Carcinoma Patients. *Dig Dis Sci* 2023; Epub ahead of print. PMID: 37289417. Full Text

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BACKGROUND: Hepatocellular Carcinoma (HCC) is a malignancy with increasing incidence and morbidity. For patients with a poor prognosis, engagement with advanced care planning and end-of life (EOL) services (I.e., palliative care, hospice) can address physical, financial, and social complications of a terminal diagnosis. Minimal data exist on the demographics of the patients being referred to and enrolling in EOL services for HCC. AIMS: We aim to report the relationship between demographics and EOL service referral. METHODS: Retrospective review of a prospectively maintained high-volume liver center registry of patients diagnosed with HCC from 2004 to 2022. EOL services eligible patients were defined as BCLC stage C or D, evidence of metastases, and/or transplant ineligible. RESULTS: Black patients were more likely to be referred than white patients (OR 1.47 (1.03, 2.11)). Once referred, patients were significantly more likely to be enrolled if they had insurance coverage, though no other factors in models were significant. There were no significant differences in survival among those referred who did or did not enroll, after controlling for other factors. CONCLUSION: Black patients were more likely to be referred compared to white patients and patients who were insured were more likely to be enrolled. Whether this is indicative of black patients being appropriately referred at a higher rate, being offered EOL care instead of aggressive treatment, or other unknown factors warrants further study.

Cardiology/Cardiovascular Research

Allana SS, Kostantinis S, Simsek B, Karacsonyi J, Rempakos A, **Alaswad K**, Krestyaninov O, Khelimskiid 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, Rafeh NA, Goktekin O, ElGuindy AM, Sandoval Y, Burke MN, Rangan BV, and Brilakis ES. Distal Target Vessel Quality and Outcomes of Chronic Total Occlusion Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2023; 16(12):1490-1500. Full Text

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Background: Distal vessel quality is a key parameter in the global chronic total occlusion (CTO) crossing algorithm. Objectives: The study sought to evaluate the association of distal vessel quality with the outcomes of CTO percutaneous coronary intervention. Methods: We examined the clinical and angiographic characteristics and procedural outcomes of 10,028 CTO percutaneous coronary interventions performed at 39 U.S. and non-U.S. centers between 2012 and 2022. A poor-quality distal vessel was defined as <2 mm diameter or with significant diffuse atherosclerotic disease. In-hospital major adverse cardiac events (MACE) included death, myocardial infarction, urgent repeat target vessel revascularization, tamponade requiring pericardiocentesis or surgery, and stroke. Results: A total of 33% of all CTO lesions had poor-quality distal vessel. When compared with good-quality distal vessels, CTO lesions with a poor-quality distal vessel had higher J-CTO (Japanese chronic total occlusion) scores (2.7 ± 1.1 vs 2.2 ± 1.3; P < 0.01), lower technical (79.9% vs 86.9%; P < 0.01) and procedural (78.0% vs 86.8%; P < 0.01) success, and higher incidence of MACE (2.5% vs 1.7%; P < 0.01) and perforation (6.4% vs 3.7%; P < 0.01). A poor-quality distal vessel was independently associated with technical failure and MACE. Poor-quality distal vessels were associated with higher use of the retrograde approach (25.2% vs 14.9%; P < 0.01) and higher air kerma radiation dose (2.4 [IQR: 1.3-4.0] Gy vs 2.0 [IQR: 1.1-3.5] Gy; P < 0.01). Conclusions: A poor-quality distal vessel in CTO lesions is associated with higher lesion complexity, higher need for retrograde crossing, lower technical and procedural success, higher incidence of MACE and coronary perforation, and higher radiation dose.

Cardiology/Cardiovascular Research
Aurora L, **Bhasin S**, and **Vummidi DR**. Thinking outside the brain: a rare cause of headaches and confusion. *Heart* 2023; 109(13):1006-1044. PMID: 37316171. Full Text

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Cardiology/Cardiovascular Research
Celestin C, Cires-Drouet RS, and **Osinbowale O**. Diversity, Equity, and Inclusion Task Force initiatives within the Society for Vascular Medicine: Current status and future challenges. *Vasc Med* 2023; 28(3):185-187. PMID: 37293739. Full Text

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Cardiology/Cardiovascular Research
Devgun J, De Potter T, Fabbricatore D, and **Wang DD**. Pre-cath Laboratory Planning for Left Atrial Appendage Occlusion - Optional or Essential? *Card Electrophysiol Clin* 2023; 15(2):141-150. PMID: 37076226. Full Text

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In the wake of rapid advancement in cardiovascular procedural technologies, physician-led preprocedural planning utilizing multi-modality imaging training is increasingly recognized as invaluable for procedural accuracy. Left atrial appendage occlusion (LAAO) is one such procedure in which complications such as device leak, cardiac injury, and device embolization can be decreased substantially with incorporation of physician driven imaging and digital tools. We discuss the benefits of cardiac CT and 3D printing in

preprocedural planning for the Heart Team, as well as novel applications by physicians of intraprocedural 3D angiography and dynamic fusion imaging. Furthermore, incorporation of computational modeling and artificial intelligence (AI) may yield promise. For optimal patient-centric procedural success, we advocate for standardized preprocedural imaging planning by physicians within the Heart Team as an essential part of LAAO.

Cardiology/Cardiovascular Research

Fadel RA, Scott A, **Parsons A**, **Murskyj I**, **Nasiri N**, **Abu Sayf A**, and **Ouellette D**. Tocilizumab Associated With Survival in Patients Hospitalized for COVID-19 Acute Respiratory Distress Syndrome and Low Urine Output. *J Intensive Care Med* 2023; Epub ahead of print. PMID: 37306148. Full Text

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BACKGROUND: Acute respiratory distress syndrome (ARDS) with oliguria is associated with increased mortality. Interleukin-6 (IL-6) plays an integral role in the pathophysiology of both disease processes. Patients who experience severe COVID-19 have demonstrated higher IL-6 levels compared to baseline, and use of tocilizumab has demonstrated efficacy in such cohorts. We set out to investigate the relationship between tocilizumab use, COVID-19 ARDS, low urine output, and mortality. METHODS: Retrospective cohort review of adult patients aged ≥ 18 years with COVID-19 and moderate or severe ARDS, admitted to the intensive care unit (ICU) of a tertiary referral center in metropolitan Detroit. Patients were analyzed based on presence of oliguria (defined as ≤ 0.7 mL/kg/h) on the day of intubation and exposure to tocilizumab while inpatient. The primary outcome was inpatient mortality. RESULTS: One hundred and twenty-eight patients were analyzed, 103 (80%) with low urine output, of whom 30 (29%) received tocilizumab. In patients with low urine output, risk factors associated with mortality on univariate analysis included Black race (P = .028), lower static compliance (P = .015), and tocilizumab administration (P = .002). Tocilizumab (odds ratio 0.245, 95% confidence interval 0.079-0.764, P = .015) was the only risk factor independently associated with survival on multivariate logistic regression analysis. CONCLUSION: In this retrospective cohort review of patients hospitalized with COVID-19 and moderate or severe ARDS, tocilizumab administration was independently associated with survival in patients with low urine output ≤ 0.7 mL/kg/h on the day of intubation. Prospective studies are needed to investigate the impact of urine output on efficacy of interleukin-targeted therapies in the management of ARDS.

Cardiology/Cardiovascular Research

Fukuhara S, **Tanaka D**, Brescia AA, Wai Sang SL, Grossman PM, Sukul D, Chetcuti SJ, He C, **Eng MH**, Patel HJ, and Deeb GM. Aortic valve reintervention in patients with failing transcatheter aortic bioprostheses: A statewide experience. *J Thorac Cardiovasc Surg* 2023; 165(6):2011-2020.e2015. PMID: 34538638. Full Text

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BACKGROUND: Despite the rapid adoption of transcatheter aortic valve replacement since its approval, the frequency and outcomes of aortic valve reintervention after transcatheter aortic valve replacement are poorly understood. METHODS: Valve reinterventions, either surgical transcatheter aortic valve explantation or repeat transcatheter aortic valve replacement, between 2012 and 2019 were queried using the Society of Thoracic Surgeons Database and the Transcatheter Valve Therapy Registry through the Michigan Statewide quality collaborative. The reintervention frequency and clinical outcomes including observed-to-expected mortality ratio using Society of Thoracic Surgeons Predicted Risk of Mortality were reviewed. RESULTS: Among 9694 transcatheter aortic valve replacement recipients, a total of 87 patients (0.90%) received a reintervention, consisting of 34 transcatheter aortic valve explants and 53 repeat transcatheter aortic valve replacement procedures. The transcatheter aortic valve explant group demonstrated a higher Society of Thoracic Surgeons Predicted Risk of Mortality. Reintervention cases increased from 0 in 2012 and 2013 to 26 in 2019. The proportion of transcatheter aortic valve explants among all reinterventions increased and was 65% in 2019. Self-expandable devices had a higher reintervention rate than balloon-expandable devices secondary to a higher transcatheter aortic valve explant frequency (0.58% [23/3957] vs 0.19% [11/5737]; P = .001), whereas repeat transcatheter aortic valve replacement rates were similar (0.61% [24/3957] vs 0.51% [29/5737]; P = .51). Among patients with transcatheter aortic valve explants, contraindications to repeat transcatheter aortic valve replacement included unfavorable anatomy (75%), need for other cardiac surgery (29%), other structural issues by transcatheter aortic valve device (18%), and endocarditis (12%). For transcatheter aortic valve explant and repeat transcatheter aortic valve replacement, the 30-day mortality was 15% and 2% (P = .032) and the observed-to-expected mortality ratio was 1.8 and 0.3 (P = .018), respectively. CONCLUSIONS: Aortic valve reintervention remains rare but is increasing. The clinical impact of surgical device explantation was substantial, and the proportion of transcatheter aortic valve explants was significantly higher in patients with a self-expandable device.

Cardiology/Cardiovascular Research

Keteyian SJ, **Steenson K**, **Grimshaw C**, **Mandel N**, **Koester-Qualters W**, **Berry R**, **Kerrigan DJ**, **Ehrman JK**, **Peterson EL**, and **Brawner CA**. Among Patients Taking Beta-Adrenergic Blockade Therapy, Use Measured (Not Predicted) Maximal Heart Rate to Calculate a Target Heart Rate for Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev* 2023; Epub ahead of print. PMID: 37311037. Full Text

Division of Cardiovascular Medicine, Henry Ford Health, Detroit, Michigan (Drs Keteyian, Kerrigan, Ehrman, and Brawner, Mss Steenson, Grimshaw, and Koester-Qualters, and Messrs Mandel and Berry); and Department of Public Health Sciences, Henry Ford Health, Detroit, Michigan (Dr Peterson).

PURPOSE: Among patients in cardiac rehabilitation (CR) on beta-adrenergic blockade (βB) therapy, this study describes the frequency for which target heart rate (THR) values computed using a predicted maximal heart rate (HRmax), correspond to a THR computed using a measured HRmax in the guideline-based heart rate reserve (HRreserve) method. METHODS: Before CR, patients completed a cardiopulmonary exercise test to measure HRmax, with the data used to determine THR via the HRreserve method. Additionally, predicted HRmax was computed for all patients using the 220 - age equation and two disease-specific equations, with the predicted values used to calculate THR via the straight percent and HRreserve methods. The THR was also computed using resting heart rate (HR) +20 and +30 bpm. RESULTS: Mean predicted HRmax using the 220 - age equation (161 ± 11 bpm) and the disease-specific equations (123 ± 9 bpm) differed (P < .001) from measured HRmax (133 ± 21 bpm). Also, THR computed using predicted HRmax resulted in values that were infrequently within the guideline-based HRreserve range calculated using measured HRmax. Specifically, 0 to ≤61% of patients would have had an exercise training HR that fell within the guideline-based range of 50-80% of measured HRreserve. Use of standing resting HR +20 or +30 bpm would have resulted in 100% and 48%, respectively, of patients exercising below 50% of HRreserve. CONCLUSIONS: A THR computed using either predicted HRmax or resting HR +20 or +30 bpm seldom results in a prescribed exercise intensity that is consistent with guideline recommendations for patients in CR.

Cardiology/Cardiovascular Research

Sabbah HN, Taylor C, and Vernon HJ. Temporal evolution of the heart failure phenotype in Barth syndrome and treatment with elamipretide. *Future Cardiol* 2023; Epub ahead of print. PMID: 37325898. Full Text

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Barth syndrome (BTHS) is a rare genetic disorder caused by pathogenic variants in TAFAZZIN leading to reduced remodeled cardiolipin (CL), a phospholipid essential to mitochondrial function and structure. Cardiomyopathy presents in most patients with BTHS, typically appearing as dilated cardiomyopathy (DCM) in infancy and evolving to hypertrophic cardiomyopathy (HCM) resembling heart failure (HF) with preserved ejection fraction (HFpEF) in some patients ≥12 years. Elamipretide localizes to the inner mitochondrial membrane where it associates with CL, improving mitochondrial function, structure and bioenergetics, including ATP synthesis. Numerous preclinical and clinical studies in BTHS and other forms of HF have demonstrated that elamipretide improves left ventricular relaxation by ameliorating mitochondrial dysfunction, making it well suited for therapeutic use in adolescent and adult patients with BTHS.

Cardiology/Cardiovascular Research

Simsek B, Rempakos A, Kostantinis S, Karacsonyi J, Gorgulu S, **Alaswad K**, Choi JW, Jaffer FA, Doshi D, Poommipanit P, Aygul N, Krestyaninov O, Khelimskii D, Uretsky B, Davies R, Goktekin O, ElGuindy A, Jefferson BK, Patel TN, Patel M, Sheikh A, Karmpaliotis D, Potluri S, Al-Azizi K, Mastrodemos OC, Rangan BV, Allana SS, Sandoval Y, Burke MN, and Brilakis ES. Periprocedural Mortality in Chronic Total Occlusion Percutaneous Coronary Intervention: Insights From the PROGRESS-CTO Registry. *Circ Cardiovasc Interv* 2023; 16(6):e012977. PMID: 37259859. Full Text

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BACKGROUND: Death is a rare but devastating complication of chronic total occlusion (CTO) percutaneous coronary intervention. METHODS: We examined the clinical characteristics and procedural outcomes of patients who died periprocedurally in the Prospective Global Registry for the Study of CTO

Interventions (PROGRESS-CTO). RESULTS: Of the 12 928 patients who underwent CTO percutaneous coronary intervention between 2012 and 2022, 52 (0.4%) died during the index hospitalization. Patients who died were more likely to have a history of heart failure (43% versus 28%; P=0.023). The J-CTO ([Multicenter CTO Registry of Japan]; 2.8±1.1 versus 2.4±1.3; P=0.019), PROGRESS-CTO mortality (2.6±0.9 versus 1.6±1.1; P<0.001), and PROGRESS-CTO pericardiocentesis (2.9±1.1 versus 1.9±1.3; P<0.001) scores were higher in patients who died. In these patients, the use of left ventricular assist devices was also higher (41% versus 3.5%; P<0.001), and retrograde crossing was more often the first crossing strategy (33% versus 13%; P<0.001). The cause of death was cardiac in 43 patients (83%) and noncardiac in 9 patients (17%). Complications leading to cardiac death were: tamponade in 30 patients (58%), acute myocardial infarction in 9 (17.3%), and cardiac arrest/shock in 4 (7.7%). Noncardiac causes of death were: stroke in 3 (5.8%), renal failure in 2 (3.8%), respiratory distress in 2 (3.8%), and hemorrhagic shock in 2 (3.8%). CONCLUSIONS: Approximately 0.4% of patients who underwent CTO percutaneous coronary intervention died during the index hospitalization. The main cause of death was tamponade in 58%. PROGRESS-CTO complication scores might help in risk stratification and procedural planning in patients undergoing CTO percutaneous coronary intervention. REGISTRATION: URL: https://www. CLINICALTRIALS: gov; Unique Identifier: NCT02061436.

Cardiology/Cardiovascular Research

Simsek B, Rempakos A, Kostantinis S, Karacsonyi J, Rangan BV, Mastrodemos OC, Kirtane AJ, Bortnick AE, Jneid H, Azzalini L, Milkas A, **Alaswad K**, Linzer M, Egred M, Allana SS, Rao SV, Sandoval Y, and Brilakis ES. International Psychological Well-Being Survey of Interventional Cardiologists. *JACC Cardiovasc Interv* 2023; 16(11):1401-1407. PMID: 37316149. Full Text

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Cardiology/Cardiovascular Research

Wang DD, **O'Neill BP**, **Villablanca P**, **Khan A**, **Greenberg J**, **Song T**, **Lee J**, **Frisoli T**, **Gonzalez PE**, **Pantelic M**, and **O'Neill WW**. Permutations in pacer wire implantation in patients evaluated for transcatheter tricuspid valve interventions. *Echocardiography* 2023; Epub ahead of print. PMID: 37319117. Full Text

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Pacer wire induced tricuspid regurgitation is not well-understood. The mechanisms behind pacer wired induced tricuspid regurgitation have not been clearly defined. This clinical vignette sets to identify different technical mechanisms behind cardiac lead induced tricuspid regurgitation to help optimize cardiac lead implantation strategies for future device implantation.

Cardiology/Cardiovascular Research

Ya'Qoub L, **Basir MB**, Soni K, Zimmet J, Yang J, Shunk K, Elgendy IY, and Mahtta D. Intracoronary Imaging and Physiology to Guide PCI: Are We Ready for a Class I Guideline Recommendation? *Curr Cardiol Rep* 2023; 25(7):725-734. PMID: 37261666. Full Text

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PURPOSE OF REVIEW: Over the last decade, there has been a plethora of evidence to support the utilization of intravascular coronary imaging and physiological assessment to guide percutaneous coronary interventions (PCI). While there is a class I recommendation for the use of coronary physiology to guide PCI, the use of intravascular coronary imaging remains a class IIa recommendation. Herein, we aimed to review the recent scientific evidence from major trials highlighting the consideration for a future class I guideline recommendation for the use of intracoronary imaging. RECENT FINDINGS: The benefits of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) to guide and optimize PCI have been demonstrated in several large trials. These trials have demonstrated that IVUS reduces major adverse cardiovascular events. Similarly, intracoronary physiology has been demonstrated to be an important tool to guide revascularization decision-making and been associated with a lower incidence of death, non-fatal myocardial infarction, and repeat revascularization compared with angiography alone. With existing clinical outcomes data on the benefit of intracoronary physiology and imaging-guided PCI as well as forthcoming data from ongoing trials regarding the use of these modalities, the interventional cardiology community is bound to transition from routine PCI to precision-, image-, and physiology-guided PCI.

Center for Health Policy and Health Services Research

Boyd AD, Gonzalez-Guarda R, Lawrence K, Patil CL, Ezenwa MO, O'Brien EC, Paek H, **Braciszewski JM**, Adeyemi O, Cuthel AM, Darby JE, Zigler CK, Ho PM, Faurot KR, Staman KL, Leigh JW, Dailey DL, Cheville A, Del Fiol G, Knisely MR, Grudzen CR, Marsolo K, Richesson RL, and Schlaeger JM. Potential bias and lack of generalizability in electronic health record data: reflections on health equity from the National Institutes of Health Pragmatic Trials Collaboratory. *J Am Med Inform Assoc* 2023; Epub ahead of print. PMID: 37364017. Full Text

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Embedded pragmatic clinical trials (ePCTs) play a vital role in addressing current population health problems, and their use of electronic health record (EHR) systems promises efficiencies that will increase the speed and volume of relevant and generalizable research. However, as the number of ePCTs using EHR-derived data grows, so does the risk that research will become more vulnerable to biases due to differences in data capture and access to care for different subsets of the population, thereby propagating inequities in health and the healthcare system. We identify 3 challenges-incomplete and variable capture of data on social determinants of health, lack of representation of vulnerable populations that do not access or receive treatment, and data loss due to variable use of technology-that exacerbate bias when working with EHR data and offer recommendations and examples of ways to actively mitigate bias.

Center for Health Policy and Health Services Research
Hamilton T, **Bartlett S**, **Deshpande N**, **Hadi M**, **Reese JC**, **Mansour TR**, **Telemi E**, **Springer K**, **Schultz L**, **Nerenz DR**, **Abdulhak M**, Soo T, **Schwalb J**, Khalil JG, Aleem I, Easton R, Perez-Cruet M, Park P, and **Chang V**. Association of prolonged symptom duration with poor outcomes in lumbar spine surgery: a Michigan Spine Surgery Improvement Collaborative study. *J Neurosurg Spine* 2023; 1-10. Epub ahead of print. PMID: 37347591. Full Text

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OBJECTIVE: There is a scarcity of large multicenter data on how preoperative lumbar symptom duration relates to postoperative patient-reported outcomes (PROs). The objective of this study was to determine the effect of preoperative and baseline symptom duration on PROs at 90 days, 1 year, and 2 years after lumbar spine surgery. METHODS: The Michigan Spine Surgery Improvement Collaborative registry was queried for all lumbar spine operations between January 1, 2017, to December 31, 2021, with a follow-up of 2 years. Patients were stratified into three subgroups based on symptom duration: < 3 months, 3 months to < 1 year, and ≥ 1 year. The primary outcomes were reaching the minimal clinically important difference (MCID) for the PROs (i.e., leg pain, Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF), EQ-5D, North American Spine Society satisfaction, and return to work). The EQ-5D score was also analyzed as a continuous variable to calculate quality-adjusted life years. Multivariable Poisson generalized estimating equation models were used to report adjusted risk ratios, with the < 3-month cohort used as the reference. RESULTS: There were 37,223 patients (4670 with < 3-month duration, 9356 with 3-month to < 1-year duration, and 23,197 with ≥ 1-year duration) available for analysis. Compared with patients with a symptom duration of < 1 year, patients with a symptom duration of ≥ 1 year were significantly less likely to achieve an MCID in PROMIS PF, EQ-5D, back pain relief, and leg pain relief at 90 days, 1 year, and 2 years postoperatively. Similar trends were observed for patient satisfaction and return to work. With the EQ-5D score as a continuous variable, a symptom duration of ≥ 1 year was associated with 0.04, 0.05, and 0.03 ($p < 0.001$) decreases in EQ-5D score at 90 days, 1 year, and 2 years after surgery, respectively. CONCLUSIONS: A symptom duration of ≥ 1 year was associated with poorer outcomes on several outcome metrics. This suggests that timely referral and surgery for degenerative lumbar pathology may optimize patient outcome.

Center for Health Policy and Health Services Research

Huang Y, **Chen D**, **Levin AM**, **Ahmedani BK**, **Frank C**, Li M, Wang Q, **Gui H**, and Sham PC. Cross-phenotype relationship between opioid use disorder and suicide attempts: new evidence from polygenic association and Mendelian randomization analyses. *Mol Psychiatry* 2023; Epub ahead of print. PMID: 37340172. Request Article

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Clinical epidemiological studies have found high co-occurrence between suicide attempts (SA) and opioid use disorder (OUD). However, the patterns of correlation and causation between them are still not clear due to psychiatric confounding. To investigate their cross-phenotype relationship, we utilized raw phenotypes and genotypes from >150,000 UK Biobank samples, and genome-wide association summary statistics from >600,000 individuals with European ancestry. Pairwise association and a potential bidirectional relationship between OUD and SA were evaluated with and without controlling for major psychiatric disease status (e.g., schizophrenia, major depressive disorder, and alcohol use disorder). Multiple statistical and genetics tools were used to perform epidemiological association, genetic correlation, polygenic risk score prediction, and Mendelian randomizations (MR) analyses. Strong associations between OUD and SA were observed at both the phenotypic level (overall samples [OR = 2.94, P = 1.59 ×10(-14)]; non-psychiatric subgroup [OR = 2.15, P = 1.07 ×10(-3)]) and the genetic level (genetic correlation rg = 0.38 and 0.5 with or without conditioning on psychiatric traits, respectively). Consistently, increasing polygenic susceptibility to SA is associated with increasing risk of OUD (OR = 1.08, false discovery rate [FDR] =1.71 ×10(-3)), and similarly, increasing polygenic susceptibility to OUD is associated with increasing risk of SA (OR = 1.09, FDR = 1.73 ×10(-6)). However, these polygenic associations were much attenuated after controlling for comorbid psychiatric diseases. A combination of MR analyses suggested a possible causal association from genetic liability for SA to OUD risk (2-sample univariable MR: OR = 1.14, P = 0.001; multivariable MR: OR = 1.08, P = 0.001). This study provided new genetic evidence to explain the observed OUD-SA comorbidity. Future prevention strategies for each phenotype needs to take into consideration of screening for the other one.

Center for Health Policy and Health Services Research

Loree AM, **Hecht LM**, **Yeh HH**, **Gavrilova L**, Furman K, **Westphal J**, Simon GE, Lynch FL, Beck A, Owen-Smith A, Rossom R, Daida YG, Lu CY, Boggs JM, **Frank C**, Waring S, and **Ahmedani BK**. Factors associated with suicide mortality among reproductive age women: a case-control study. *J Reprod Infant Psychol* 2023; 1-12. Epub ahead of print. PMID: 37310021. Request Article

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Center for Research and Evaluation, Kaiser Permanente Georgia, Atlanta, GA, USA.
Research and Evaluation Division, HealthPartners Institute, Minneapolis, MN, USA.
Kaiser Permanente Hawaii Center for Integrated Health Care Research, Honolulu, HI, USA.
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OBJECTIVE: Examine demographic, psychosocial, pregnancy-related, and healthcare utilisation factors associated with suicide mortality among reproductive age women. METHODS: Data from nine health care systems in the Mental Health Research Network were included. A case-control study design was used in which 290 reproductive age women who died by suicide (cases) from 2000 to 2015 were matched with 2,900 reproductive age women from the same healthcare system who did not die by suicide (controls). Conditional logistic regression was used to analyse associations between patient characteristics and suicide. RESULTS: Women of reproductive age who died by suicide were more likely to have mental health (aOR = 7.08, 95% CI: 5.17, 9.71) or substance use disorders (aOR = 3.16, 95% CI: 2.19, 4.56) and to have visited the emergency department in the year prior to index date (aOR = 3.47, 95% CI: 2.50, 4.80). Non-Hispanic White women (aOR = 0.70, 95% CI: 0.51, 0.97) and perinatal (pregnant or postpartum) women were less likely to have died by suicide (aOR = 0.27, 95% CI: 0.13, 0.58). CONCLUSIONS: Reproductive age women with mental health and/or substance use disorders, prior emergency department encounters, or who are of racial or ethnic minority status were at increased risk of suicide mortality and may benefit from routine screening and monitoring. Future research should further examine the relationship between pregnancy-related factors and suicide mortality.

Center for Health Policy and Health Services Research

Shires DA, Kcomt L, Kattari L, **Liroff M**, and **Lee R**. Emergency Clinicians' Comfort Levels in Caring for Transgender Patients. *Transgend Health* 2023; 8(3):246-253. PMID: 37342475. Request Article

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OBJECTIVE: Transgender individuals report negative experiences in emergency department settings, but little is known about emergency clinicians' barriers to treating transgender patients. The purpose of this study was to explore emergency clinicians' experiences with transgender patients to better understand their comfort with caring for this population. METHODS: We conducted a cross-sectional survey of emergency clinicians in an integrated health system in the Midwest. To assess the relationship between each independent variable and the outcome variables (i.e., comfort level generally and comfort level asking transgender patients about their body parts specifically), Mann-Whitney U test or Kruskal-Wallis analysis of variance was conducted for categorical independent variables and Pearson correlations were conducted for continuous independent variables. RESULTS: Most participants (90.1%) were comfortable caring for transgender patients, whereas two-thirds (67.9%) were comfortable asking transgender patients about body parts. Although none of the independent variables was associated with increased clinician comfort level caring for transgender patients in general, White clinicians and those who were unsure how to ask patients about their gender identity or transgender-specific care they had received were less comfortable asking about body parts. CONCLUSION: Having skills to communicate with transgender patients was associated with emergency clinicians' comfort levels. In addition to offering traditional classroom-based didactics about transgender health care, providing opportunities for clinical rotations that allow clinicians-in-training to treat, and perhaps more importantly, learn from transgender patients will likely be higher yield in bolstering clinician confidence in serving this patient population.

Center for Health Policy and Health Services Research

Vance AJ, Benjamin A, Hsu J, and Berry JG. Care Coordination Programs for Infants With Complex Conditions: A Systematic Review. *Pediatrics* 2023; Epub ahead of print. PMID: 37288503. Full Text

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CONTEXT: Care coordination programs are becoming more widely available for children with complex conditions, yet we lack an understanding of programs available to infants and their benefits. OBJECTIVE: To summarize characteristics and outcomes associated with care coordination programs for infants with complex conditions. DATA SOURCES: Electronic search of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and Web of Science databases for articles published from 2010 to 2021. STUDY SELECTION: Inclusion criteria consisted of (1) peer-reviewed manuscripts about a care coordination program, (2) infants (birth to 1 year) with complex medical conditions, (3) and reported at least 1 infant, parent, or healthcare utilization outcome. DATA EXTRACTION: Data were extracted on program characteristics and outcomes (eg, infant, parent, and healthcare utilization and cost). Results were summarized by program characteristics and outcomes. RESULTS: The search returned 3189 studies. Twelve unique care coordination programs were identified from 17 studies in the final sample. Seven programs were hospital-based and 5 were outpatient-based. Most programs reported improvements with satisfaction with care, increased interactions with healthcare teams, reductions in infant mortality, and in health service use. A few programs reported increased costs related to staffing. LIMITATIONS: Few care coordination programs were identified specifically for infants and thus studies that did not report age categories (ie, infants) may not have been identified. CONCLUSIONS: Care coordination programs demonstrate cost reductions for health systems, families, and insurers and improvement in quality of care. Efforts to increase the uptake and sustain these beneficial programs need further exploration.

Center for Individualized and Genomic Medicine Research

Oni-Orisan A, Tuteja S, Hoffecker G, Smith DM, Castrichini M, Crews KR, Murphy WA, Nguyen NHK, Huang Y, Lteif C, Friede KA, Tantisira K, Aminkeng F, Voora D, Cavallari LH, Whirl-Carrillo M, Duarte JD, and **Luzum JA**. An Introductory Tutorial on Cardiovascular Pharmacogenetics for Healthcare Providers. *Clin Pharmacol Ther* 2023; Epub ahead of print. PMID: 37303270. Full Text

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Pharmacogenetics can improve clinical outcomes by reducing adverse drug effects and enhancing therapeutic efficacy for commonly used drugs that treat a wide range of cardiovascular diseases. One of the major barriers to the clinical implementation of cardiovascular pharmacogenetics is limited education on this field for current healthcare providers and students. The abundance of pharmacogenetic literature underscores its promise, but it can also be challenging to learn such a wealth of information. Moreover, current clinical recommendations for cardiovascular pharmacogenetics can be confusing because they are outdated, incomplete, or inconsistent. A myriad of misconceptions about the promise and feasibility of cardiovascular pharmacogenetics among healthcare providers also has halted clinical implementation. Therefore, the main goal of this tutorial is to provide introductory education on the use of cardiovascular pharmacogenetics in clinical practice. The target audience is any healthcare provider (or student) with patients that use or have indications for cardiovascular drugs. This tutorial is organized into the following 6 steps: (1) understand basic concepts in pharmacogenetics; (2) gain foundational knowledge of cardiovascular pharmacogenetics; (3) learn the different organizations that release cardiovascular pharmacogenetic guidelines and recommendations; (4) know the current cardiovascular drugs/drug classes to focus on clinically and the supporting evidence; (5) discuss an example patient case of cardiovascular pharmacogenetics; and (6) develop an appreciation for emerging areas in cardiovascular pharmacogenetics. Ultimately, improved education among healthcare providers on cardiovascular pharmacogenetics will lead to a greater understanding for its potential in improving outcomes for a leading cause of morbidity and mortality.

Dermatology

Boothby-Shoemaker W, Comeau N, and Daveluy S. The Dermatologist's Guide to Beards: A Review of Structure, Function, Care, and Pathology. *Clin Exp Dermatol* 2023; Epub ahead of print. PMID: 37310915. Full Text

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Facial hair is a commonly desired feature for many individuals. Despite a breadth of dermatology literature covering strategies for removing facial hair, there are no known articles summarizing strategies for facial hair growth or reviewing common facial hair pathologies. Here, we assess Google Trends to describe significant increases in terms related to facial hair growth and maintenance over the last decade, suggesting an increased public interest on this topic. Next, we review ethnic differences in facial hair growth that may affect facial hair distribution, growth, and predisposition to certain facial hair pathologies. Lastly, we review studies on agents used for facial hair growth and review common facial hair pathologies.

Dermatology

Ceresnie MS, Patel J, Tvedten EJ, **Kohli I**, and **Mohammad TF**. Blue light and the skin on social media: An analysis of posts on exposure and photoprotection strategies. *Photodermatol Photoimmunol Photomed* 2023; Epub ahead of print. PMID: 37386800. Full Text

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Dermatology
De DR, Rick JW, Shih T, Hsiao JL, **Hamzavi I**, and Shi VY. COVID-19 Infection in Hidradenitis Suppurativa Patients: A Retrospective Study. *Skin Appendage Disord* 2023; 9(3):203-206. PMID: 37325275. Full Text

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INTRODUCTION: Hidradenitis suppurativa (HS) is associated with comorbidities that are risk factors for severe COVID-19 infection. We evaluated demographics and COVID-19 outcomes in HS patients. METHODS: HS patients with COVID-19 (HS+/COVID+) and a randomized age-, race-, and sex-matched control population of patients without HS with COVID-19 (HS-/COVID+) were selected through a retrospective chart review. Data were collected on demographics, medications, comorbidities, vaccination status, and COVID-19 treatment/outcomes. Fisher's exact test was used to analyze the relationship between risk factors and COVID-19 outcomes. A p value of <0.05 was considered statistically significant. RESULTS: There were 58 HS+/COVID+ patients, primarily African American (83%, n = 48) and female (88%, n = 51). Compared to HS+/COVID+ patients, HS-/COVID+ patients were significantly more likely to have cardiovascular disease (51% vs. 24%; p = 0.0029) and be pregnant (23% vs. 4%; p = 0.0093). HS+/COVID+ and HS-/COVID+ patients did not vary significantly in vaccination rate at time of COVID-19 diagnosis (6% vs. 5%; p = 0.78). HS-/COVID+ patients were significantly more likely to have COVID-19 complications (35% vs. 7%; p = 0.001) and receive COVID-19 treatment (37% vs. 7%; p = 0.0001) when compared to HS+/COVID+ patients. CONCLUSION: Our findings support the growing evidence that having HS itself may not be a risk factor for severe COVID-19 outcomes.

Dermatology
Del Rosso J, **Stein Gold L**, Squittieri N, and Thiboutot D. Is There a Clinically Relevant Risk of Hyperkalemia with Topical Clascoterone Treatment? *J Clin Aesthet Dermatol* 2023; 16(6):20-24. PMID: 37361363. Request Article

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Clascoterone cream 1% is an androgen receptor inhibitor approved for the treatment of acne vulgaris in patients aged 12 years or older with clinical studies completed in subjects aged nine years or older. Blood potassium levels above the upper limit of normal (i.e., hyperkalemia) were reported in both clascoterone-treated and vehicle-treated patients; reported rates of hyperkalemia were approximately five percent and four percent, respectively. None of the cases of hyperkalemia were reported as adverse events and none led to study discontinuation or adverse clinical sequelae. An exposure-response analysis showed no correlation between plasma concentrations of clascoterone or its metabolite cortexolone and cases of hyperkalemia. Based on the laboratory safety profile of clascoterone demonstrated in the Phase I and Phase II studies, baseline or subsequent laboratory monitoring was not required in the Phase III studies or recommended in the FDA-approved prescribing information. The frequency of shifts to elevated potassium levels was highest in patients younger than 12 years of age treated with clascoterone, for whom clascoterone 1% is not FDA approved.

Dermatology
Del Rosso J, Sugarman J, Green L, Lain T, Levy-Hacham O, Mizrahi R, and **Stein Gold L**. Efficacy and Safety of Microencapsulated Benzoyl Peroxide and Microencapsulated Tretinoin for the Treatment of Acne Vulgaris: Results from Two Phase 3 Double-Blind, Randomized, Vehicle-Controlled Studies. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 37356627. Full Text

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BACKGROUND: Benzoyl peroxide and tretinoin are commonly prescribed acne treatments. Historically, they have been difficult to combine in a single formulation due to chemical instability, and both medications are potentially irritating. Microencapsulation helps overcome these challenges. OBJECTIVE: Examine efficacy, safety, and tolerability of encapsulated BPO/encapsulated tretinoin (E-BPO/T) cream, 3%/0.1%. METHODS: Subjects ≥9 years old with moderate to severe acne were enrolled in 2 multicenter, double-blind, vehicle-controlled, parallel trials and randomized (2:1) to 12 weeks of once-daily E-BPO/T (n=571) or vehicle cream (n=287). RESULTS: E-BPO/T was significantly superior to vehicle in both studies, with more subjects achieving IGA success with E-BPO/T (38.5%/25.4%) versus vehicle (11.5%/14.7%; P<.001/P= .017). The change from baseline in inflammatory lesion count for E-BPO/T was -21.6 versus -14.8 for vehicle (P<.001) in study 1 and -16.2 versus -14.1 (P=.018) in study 2. The changes from baseline in noninflammatory lesions for E-BPO/T were -29.7 versus -19.8 for vehicle (P<.001) and -24.2 and -17.4 (P<.001) in studies 1 and 2, respectively. E-BPO/T was well tolerated in both studies. LIMITATIONS: Long-term data are not available. CONCLUSION: E-BPO/T provided statistically significant and clinically relevant improvements in IGA and inflammatory and noninflammatory lesion counts and was well tolerated in subjects with moderate to severe acne.

Dermatology

Dimitrion P, **Loveless I**, **Zhou L**, **Mi QS**, and **Adrianto I**. The Hidradenitis Suppurativa 'Omics Database (HS-OmicsDB). *J Invest Dermatol* 2023; Epub ahead of print. PMID: 37271451. Full Text

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Dermatology

Mease PJ, Hatemi G, Paris M, Cheng S, Maes P, Zhang W, Shi R, Flower A, Picard H, and **Stein Gold L**. Apremilast Long-Term Safety Up to 5 Years from 15 Pooled Randomized, Placebo-Controlled Studies of Psoriasis, Psoriatic Arthritis, and Behçet's Syndrome. *Am J Clin Dermatol* 2023; 1-12. Epub ahead of print. PMID: 37316690. Full Text

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BACKGROUND: Since US FDA approval in 2014, apremilast has consistently demonstrated a favorable benefit-risk profile in 706,585 patients (557,379 patient-years of exposure) worldwide across approved indications of plaque psoriasis, psoriatic arthritis, and Behçet's syndrome; however, long-term exposure across these indications has not been reported. OBJECTIVE: The aim of this study was to conduct a pooled analysis of apremilast data from 15 clinical studies with open-label extension phases, focusing on long-term safety. METHODS: We analyzed longer-term safety and tolerability of apremilast 30 mg twice daily across three indications for up to 5 years, focusing on adverse events of special interest, including thrombotic events, malignancies, major adverse cardiac events (MACE), serious infections, and depression. Data were pooled across 15 randomized, placebo-controlled studies and divided into placebo-controlled or all-apremilast-exposure groups. Treatment-emergent adverse events (TEAEs) were assessed. RESULTS: Overall, 4183 patients were exposed to apremilast (6788 patient-years). Most TEAEs were mild to moderate in the placebo-controlled period (96.6%) and throughout all apremilast exposure (91.6%). TEAE rates of special interest were similar between treatment groups in the placebo-controlled period and remained low throughout all apremilast exposure. Exposure-adjusted incidence rates per 100 patient-years during all apremilast exposure were MACE, 0.30; thrombotic events, 0.10; malignancies, 1.0; serious infections, 1.10; serious opportunistic infections, 0.21; and depression, 1.78. Safety findings were consistent across indications and regions. No new safety signals were identified. CONCLUSIONS: The incidence of serious TEAEs and TEAEs of special interest was low despite long-term exposure, further establishing apremilast as a safe oral option for long-term use across indications with a favorable benefit-risk profile. CLINICAL TRIAL REGISTRATION: NCT00773734, NCT01194219, NCT01232283, NCT01690299, NCT01988103, NCT02425826, NCT03123471, NCT03721172, NCT01172938, NCT01212757, NCT01212770, NCT01307423, NCT01925768, NCT00866359, NCT02307513.

Dermatology

Shetty N, Schalka S, **Lim HW**, and **Mohammad TF**. The effects of UV filters on health and the environment. *Photochem Photobiol Sci* 2023; Epub ahead of print. PMID: 37344707. Request Article

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Sunscreens are an important means of protection against sunburns, dyspigmentation, photoaging, and photocarcinogenesis. Sunscreens come in a variety of formulations that can protect against ultraviolet B (UVB) radiation, both UVB and ultraviolet A (UVA) radiation (broad-spectrum sunscreens), and UVB, UVA, and visible light (tinted broad-spectrum sunscreens). In the USA, there is currently a paucity of FDA-approved broad-spectrum filters on the market. Studies have identified the presence of multiple UV filters in water sources globally. Many laboratory studies have implicated the potential impact of UV filters on coral reef bleaching, the food chain, and human health. However, many of these studies are performed at concentrations that are much higher than those present in the natural environment. With increasing discussion surrounding the role of organic and inorganic UV filters as potential environmental

pollutants over the past decade, approval of additional broad-spectrum filters would be an important means of alleviating the use of more controversial filters. The aim of this article is to review the effects of UV filters on health and the environment and explore potential adjunctive agents for photoprotection.

Dermatology
Siddiqui RF, and **Ozog DM**. Stylists saving lives: A program to educate hairstylists in the early detection of skin cancers. *JAAD Int* 2023; 11:145-146. PMID: 37128268. Full Text

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Dermatology
Wang J, **Adrianto I**, **Subedi K**, **Liu T**, **Wu X**, **Yi Q**, **Loveless I**, **Yin C**, **Datta I**, Sant'Angelo DB, Kronenberg M, **Zhou L**, and **Mi QS**. Integrative scATAC-seq and scRNA-seq analyses map thymic iNKT cell development and identify Cbfβ for its commitment. *Cell Discov* 2023; 9(1):61. PMID: 37336875. Full Text

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Unlike conventional αβT cells, invariant natural killer T (iNKT) cells complete their terminal differentiation to functional iNKT1/2/17 cells in the thymus. However, underlying molecular programs that guide iNKT subset differentiation remain unclear. Here, we profiled the transcriptomes of over 17,000 iNKT cells and the chromatin accessibility states of over 39,000 iNKT cells across four thymic iNKT developmental stages using single-cell RNA sequencing (scRNA-seq) and single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) to define their developmental trajectories. Our study discovered novel features for iNKT precursors and different iNKT subsets and indicated that iNKT2 and iNKT17 lineage commitment may occur as early as stage 0 (ST0) by two distinct programs, while iNKT1 commitments may occur post ST0. Both iNKT1 and iNKT2 cells exhibit extensive phenotypic and functional heterogeneity, while iNKT17 cells are relatively homogenous. Furthermore, we identified that a novel transcription factor, Cbfβ, was highly expressed in iNKT progenitor commitment checkpoint, which showed a similar expression trajectory with other known transcription factors for iNKT cells development, Zbtb16 and Egr2, and could direct iNKT cells fate and drive their effector phenotype differentiation. Conditional deletion of Cbfβ blocked early iNKT cell development and led to severe impairment of iNKT1/2/17 cell differentiation. Overall, our findings uncovered distinct iNKT developmental programs as

well as their cellular heterogeneity, and identified a novel transcription factor Cbfβ as a key regulator for early iNKT cell commitment.

Diagnostic Radiology
Aurora L, **Bhasin S**, and **Vummidi DR**. Thinking outside the brain: a rare cause of headaches and confusion. *Heart* 2023; 109(13):1006-1044. PMID: 37316171. Full Text

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Diagnostic Radiology
Dai Z, Jambor I, Taimen P, **Pantelic M**, **Elshaikh M**, **Dabaja A**, **Rogers C**, Ettala O, Boström PJ, Aronen HJ, Merisaari H, and Wen N. Prostate cancer detection and segmentation on MRI using non-local mask R-CNN with histopathological ground truth. *Med Phys* 2023; Epub ahead of print. PMID: 37358061. Full Text

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BACKGROUND: Automatic detection and segmentation of intraprostatic lesions (ILs) on preoperative multiparametric-magnetic resonance images (mp-MRI) can improve clinical workflow efficiency and enhance the diagnostic accuracy of prostate cancer and is an essential step in dominant intraprostatic lesion boost. PURPOSE: The goal is to improve the detection and segmentation accuracy of 3D ILs in MRI by a proposed a deep learning (DL)-based algorithm with histopathological ground truth. METHODS: This retrospective study included 262 patients with in vivo prostate biparametric MRI (bp-MRI) scans and were divided into three cohorts based on their data analysis and annotation. Histopathological ground truth was established by using histopathology images as delineation reference standard on cohort 1, which consisted of 64 patients and was randomly split into 20 training, 12 validation, and 32 testing patients. Cohort 2 consisted of 158 patients with bp-MRI based lesion delineation, and was randomly split into 104 training, 15 validation, and 39 testing patients. Cohort 3 consisted of 40 unannotated patients, used in semi-supervised learning. We proposed a non-local Mask R-CNN and boosted its performance by applying different training techniques. The performance of non-local Mask R-CNN was compared with baseline Mask R-CNN, 3D U-Net and an experienced radiologist's delineation and was evaluated by detection rate, dice similarity coefficient (DSC), sensitivity, and Hausdorff Distance (HD). RESULTS: The independent testing set consists of 32 patients with histopathological ground truth. With the training technique maximizing detection rate, the non-local Mask R-CNN achieved 80.5% and 94.7% detection rate; 0.548 and 0.604 DSC; 5.72 and 6.36 95 HD (mm); 0.613 and 0.580 sensitivity for ILs of all Gleason Grade groups (GGGs) and clinically significant ILs (GGG > 2), which outperformed baseline Mask R-CNN and 3D U-Net. For clinically significant ILs, the model segmentation accuracy was significantly higher than that of the experienced radiologist involved in the study, who achieved 0.512 DSC ($p = 0.04$), 8.21 ($p = 0.041$) 95 HD (mm), and 0.398 ($p = 0.001$) sensitivity. CONCLUSION: The proposed DL model achieved state-of-art performance and has the potential to help improve radiotherapy treatment planning and noninvasive prostate cancer diagnosis.

Diagnostic Radiology

Eghbali N, **Siegal D**, **Klochko C**, and Ghassemi MM. Automation of Protocoling Advanced MSK Examinations Using Natural Language Processing Techniques. *AMIA Jt Summits Transl Sci Proc* 2023; 2023:118-127. PMID: 37350898. Request Article

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Imaging examination selection and protocoling are vital parts of the radiology workflow, ensuring that the most suitable exam is done for the clinical question while minimizing the patient's radiation exposure. In this study, we aimed to develop an automated model for the revision of radiology examination requests using natural language processing techniques to improve the efficiency of pre-imaging radiology workflow. We extracted Musculoskeletal (MSK) magnetic resonance imaging (MRI) exam order from the radiology information system at Henry Ford Hospital in Detroit, Michigan. The pretrained transformer, "DistilBERT" was adjusted to create a vector representation of the free text within the orders while maintaining the meaning of the words. Then, a logistic regression-based classifier was trained to identify orders that required additional review. The model achieved 83% accuracy and had an area under the curve of 0.87.

Diagnostic Radiology

McCall KC, Liu M, Cheng SC, Abbott A, Dubey S, Young D, Johnston M, Van den Abbeele AD, Overmoyer B, and Jacene H. Report on the PET/CT Image-Based Radiation Dosimetry of [(18)F]FDHT in Women, a Validated Imaging Agent with New Applications for Evaluation of Androgen Receptor Status in Women with Metastatic Breast Cancer. *J Nucl Med Technol* 2023; Epub ahead of print. PMID: 37316304. Request Article

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In a prospective clinical trial, [(18)F]fluoro-5α-dihydrotestosterone ([(18)F]FDHT), the radiolabeled analog of the androgen dihydrotestosterone, was used as a PET/CT imaging agent for in vivo assessment of metastatic androgen receptor-positive breast cancer in postmenopausal women. To our knowledge, this article presents the first report of PET/CT image-based radiation dosimetry of [(18)F]FDHT in women. Methods: [(18)F]FDHT PET/CT imaging was performed on a cohort of 11 women at baseline before the start of therapy and at 2 additional time points during selective androgen receptor modulator (SARM) therapy for androgen receptor-positive breast cancer. Volumes of interest (VOIs) were placed over the whole body and within source organs seen on the PET/CT images, and the time-integrated activity coefficients of [(18)F]FDHT were derived. The time-integrated activity coefficients for the urinary bladder were calculated using the dynamic urinary bladder model in OLINDA/EXM software, with biologic half-life for urinary excretion derived from VOI measurements of the whole body in postvoid PET/CT images. The time-integrated activity coefficients for all other organs were calculated from VOI measurements in the organs and the physical half-life of (18)F. Organ dose and effective dose calculations were then performed using MIRDcalc, version 1.1. Results: At baseline before SARM therapy, the effective dose for [(18)F]FDHT in women was calculated as 0.020 ± 0.0005 mSv/MBq, and the urinary bladder was the organ at risk, with an average absorbed dose of 0.074 ± 0.011 mGy/MBq. Statistically significant decreases in liver SUV or uptake of [(18)F]FDHT were found at the 2 additional time points on SARM therapy (linear mixed model, $P < 0.05$). Likewise, absorbed dose to the liver also decreased by a small but statistically significant amount at the 2 additional time points (linear mixed model, $P < 0.05$). Neighboring abdominal organs of the gallbladder wall, stomach, pancreas, and adrenals also showed statistically significant decreases in absorbed dose (linear mixed model, $P < 0.05$). The urinary bladder

wall remained the organ at risk at all time points. Absorbed dose to the urinary bladder wall did not show statistically significant changes from baseline at any of the time points (linear mixed model, $P \geq 0.05$). Effective dose also did not show statistically significant changes from baseline (linear mixed model, $P \geq 0.05$). Conclusion: Effective dose for [(18)F]FDHT in women before SARM therapy was calculated as 0.020 ± 0.0005 mSv/MBq. The urinary bladder wall was the organ at risk, with an absorbed dose of 0.074 ± 0.011 mGy/MBq.

Diagnostic Radiology
Wang DD, **O'Neill BP**, **Villablanca P**, **Khan A**, **Greenberg J**, **Song T**, **Lee J**, **Frisoli T**, **Gonzalez PE**, **Pantelic M**, and **O'Neill WW**. Permutations in pacer wire implantation in patients evaluated for transcatheter tricuspid valve interventions. *Echocardiography* 2023; Epub ahead of print. PMID: 37319117. Full Text

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Pacer wire induced tricuspid regurgitation is not well-understood. The mechanisms behind pacer wired induced tricuspid regurgitation have not been clearly defined. This clinical vignette sets to identify different technical mechanisms behind cardiac lead induced tricuspid regurgitation to help optimize cardiac lead implantation strategies for future device implantation.

Emergency Medicine
Goyal N, **Vohra T**, and **Hurst GM**. The Jackson 5 System for Creating Rank Order Lists: Easy as A-B-C, 1-2-3. *J Grad Med Educ* 2023; 15(3):394-395. PMID: 37363658. Full Text

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Emergency Medicine
Hewitt M, **Ma P**, **Coyle E**, **Leidlein S**, Jennings K, **Wanis N**, and **Miller J**. Natural language processing improves estimates of the epidemiology of cannabinoid hyperemesis syndrome. *Am J Emerg Med* 2023; Epub ahead of print. PMID: 37349236. Full Text

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Emergency Medicine
Hinojosa CA, Liew A, An X, Stevens JS, Basu A, van Rooij SJH, House SL, Beaudoin FL, Zeng D, Neylan TC, Clifford GD, Jovanovic T, Linnstaedt SD, Germine LT, Rauch SL, Haran JP, Storrow AB, **Lewandowski C**, Musey PI, Hendry PL, Sheikh S, Jones CW, Punches BE, Kurz MC, Swor RA, Hudak LA, Pascual JL, Seamon MJ, Datner EM, Chang AM, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, Sergot P, Sanchez LD, Bruce SE, Miller MW, Pietrzak RH, Joormann J, Pizzagalli DA, Sheridan JF, Harte SE, Elliott JM, Kessler RC, Koenen KC, McLean SA, Ressler KJ, and Fani N. Associations of alcohol and cannabis use with change in posttraumatic stress disorder and depression symptoms over time in recently trauma-exposed individuals. *Psychol Med* 2023; 1-12. Epub ahead of print. PMID: 37309917. Full Text

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BACKGROUND: Several hypotheses may explain the association between substance use, posttraumatic stress disorder (PTSD), and depression. However, few studies have utilized a large multisite dataset to understand this complex relationship. Our study assessed the relationship between alcohol and cannabis use trajectories and PTSD and depression symptoms across 3 months in recently trauma-exposed civilians. METHODS: In total, 1618 (1037 female) participants provided self-report data on past 30-day alcohol and cannabis use and PTSD and depression symptoms during their emergency department (baseline) visit. We reassessed participant's substance use and clinical symptoms 2, 8, and 12 weeks posttrauma. Latent class mixture modeling determined alcohol and cannabis use trajectories in the sample. Changes in PTSD and depression symptoms were assessed across alcohol and cannabis use trajectories via a mixed-model repeated-measures analysis of variance. RESULTS: Three trajectory classes (low, high, increasing use) provided the best model fit for alcohol and cannabis use. The low alcohol use class exhibited lower PTSD symptoms at baseline than the high use class; the low cannabis use class exhibited lower PTSD and depression symptoms at baseline than the high and increasing use classes; these symptoms greatly increased at week 8 and declined at week 12. Participants who already use alcohol and cannabis exhibited greater PTSD and depression symptoms at baseline that increased at week 8 with a decrease in symptoms at week 12. CONCLUSIONS: Our findings suggest that alcohol and cannabis use trajectories are associated with the intensity of posttrauma psychopathology. These findings could potentially inform the timing of therapeutic strategies.

Emergency Medicine

Patel K, **Singh V**, and **Bissonette A**. A Combination of Beta-Blockade and Calcium Channel Blockade Leading to Bradycardia, Renal Failure, Atrioventricular Blockade, Shock, and Hyperkalemia (BRASH) Syndrome: A Case Report. *Cureus* 2023; 15(6):e40176. PMID: 37337555. Full Text

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The BRASH syndrome is a recently recognized syndrome and the acronym stands for bradycardia, renal failure, atrioventricular (AV) blockade, shock, and hyperkalemia. We discuss a case of a 56-year-old female with a history of heart failure who presented in a critical state following recent adjustments to her carvedilol dosage while she was simultaneously on verapamil. This combination of AV nodal-blocking agents induced bradycardia in the patient, leading to shock and renal hypoperfusion complicated by hyperkalemia that required the use of a temporary transvenous pacemaker before she made a full recovery. The case report highlights the fact that this combination of medications alone may have had a synergistic effect that led to BRASH in our patient.

Emergency Medicine

Popp LM, Ashburn NP, Snavely AC, Allen BR, Christenson RH, Madsen T, Mumma BE, **Nowak R**, Stopyra JP, Wilkerson RG, and Mahler SA. Race differences in cardiac testing rates for patients with chest pain in a multisite cohort. *Acad Emerg Med* 2023; Epub ahead of print. PMID: 37306075. Full Text

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BACKGROUND: Identifying and eliminating racial health care disparities is a public health priority. However, data evaluating race differences in emergency department (ED) chest pain care are limited. METHODS: We conducted a secondary analysis of the High-Sensitivity Cardiac Troponin T to Optimize Chest Pain Risk Stratification (STOP-CP) cohort, which prospectively enrolled adults with symptoms suggestive of acute coronary syndrome without ST-elevation from eight EDs in the United States from 2017 to 2018. Race was self-reported by patients and abstracted from health records. Rates of 30-day noninvasive testing (NIT), cardiac catheterization, revascularization, and adjudicated cardiac death or myocardial infarction (MI) were determined. Logistic regression was used to evaluate the association between race and 30-day outcomes with and without adjustment for potential confounders. RESULTS: Among 1454 participants, 42.3% (615/1454) were non-White. At 30 days NIT occurred in 31.4% (457/1454), cardiac catheterization in 13.5% (197/1454), revascularization in 6.0% (87/1454), and cardiac death or MI in 13.1% (190/1454). Among Whites versus non-Whites, NIT occurred in 33.8% (284/839) versus 28.1% (173/615; odds ratio [OR] 0.76, 95% confidence interval [CI] 0.61-0.96) and catheterization in 15.9% (133/839) versus 10.4% (64/615; OR 0.62, 95% CI 0.45-0.84). After covariates were adjusted for, non-White race remained associated with decreased 30-day NIT (adjusted OR [aOR] 0.71, 95% CI 0.56-0.90) and cardiac catheterization (aOR 0.62, 95% CI 0.43-0.88). Revascularization occurred in 6.9% (58/839) of Whites versus 4.7% (29/615) of non-Whites (OR 0.67, 95% CI 0.42-1.04). Cardiac death or MI at 30 days occurred in 14.2% of Whites (119/839) versus 11.5% (71/615) of non-Whites (OR 0.79 95% CI 0.57-1.08). After adjustment there was still no association between race and 30-day revascularization (aOR 0.74, 95% CI 0.45-1.20) or cardiac death or MI (aOR 0.74, 95% CI 0.50-1.09). CONCLUSIONS: In this U.S. cohort, non-White patients were less likely to receive NIT and cardiac catheterization compared to Whites but had similar rates of revascularization and cardiac death or MI.

Emergency Medicine

Shires DA, Kcomt L, Kattari L, **Liroff M**, and **Lee R**. Emergency Clinicians' Comfort Levels in Caring for Transgender Patients. *Transgend Health* 2023; 8(3):246-253. PMID: 37342475. Request Article

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OBJECTIVE: Transgender individuals report negative experiences in emergency department settings, but little is known about emergency clinicians' barriers to treating transgender patients. The purpose of this study was to explore emergency clinicians' experiences with transgender patients to better understand their comfort with caring for this population. METHODS: We conducted a cross-sectional survey of emergency clinicians in an integrated health system in the Midwest. To assess the relationship between each independent variable and the outcome variables (i.e., comfort level generally and comfort level asking transgender patients about their body parts specifically), Mann-Whitney U test or Kruskal-Wallis analysis of variance was conducted for categorical independent variables and Pearson correlations were conducted for continuous independent variables. RESULTS: Most participants (90.1%) were comfortable caring for transgender patients, whereas two-thirds (67.9%) were comfortable asking transgender patients about body parts. Although none of the independent variables was associated with increased clinician comfort level caring for transgender patients in general, White clinicians and those who were unsure how to ask patients about their gender identity or transgender-specific care they had received were less comfortable asking about body parts. CONCLUSION: Having skills to communicate with transgender patients was associated with emergency clinicians' comfort levels. In addition to offering traditional classroom-based didactics about transgender health care, providing opportunities for clinical rotations that allow clinicians-in-training to treat, and perhaps more importantly, learn from transgender patients will likely be higher yield in bolstering clinician confidence in serving this patient population.

Family Medicine

Shires DA, Kcomt L, Kattari L, **Liroff M**, and **Lee R**. Emergency Clinicians' Comfort Levels in Caring for Transgender Patients. *Transgend Health* 2023; 8(3):246-253. PMID: 37342475. Request Article

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School of Social Work, Wayne State University, Detroit, Michigan, USA.
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OBJECTIVE: Transgender individuals report negative experiences in emergency department settings, but little is known about emergency clinicians' barriers to treating transgender patients. The purpose of this study was to explore emergency clinicians' experiences with transgender patients to better understand their comfort with caring for this population. METHODS: We conducted a cross-sectional survey of emergency clinicians in an integrated health system in the Midwest. To assess the relationship between each independent variable and the outcome variables (i.e., comfort level generally and comfort level asking transgender patients about their body parts specifically), Mann-Whitney U test or Kruskal-Wallis analysis of variance was conducted for categorical independent variables and Pearson correlations were conducted for continuous independent variables. RESULTS: Most participants (90.1%) were comfortable caring for transgender patients, whereas two-thirds (67.9%) were comfortable asking transgender patients about body parts. Although none of the independent variables was associated with increased clinician comfort level caring for transgender patients in general, White clinicians and those who were unsure how to ask patients about their gender identity or transgender-specific care they had received were less comfortable asking about body parts. CONCLUSION: Having skills to communicate with transgender patients was associated with emergency clinicians' comfort levels. In addition to offering traditional classroom-based didactics about transgender health care, providing opportunities for clinical rotations that allow clinicians-in-training to treat, and perhaps more importantly, learn from transgender patients will likely be higher yield in bolstering clinician confidence in serving this patient population.

Gastroenterology

Gordon SC, Kaushik A, Chastek B, Anderson A, and Yehoshua A. Characteristics associated with receipt of treatment among patients diagnosed with chronic hepatitis C virus. *J Viral Hepat* 2023; Epub ahead of print. PMID: 37377165. Full Text

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Although current guidelines recommend that nearly all patients with chronic hepatitis C virus (HCV) infection receive treatment, a substantial proportion remain untreated. We conducted an administrative claims analysis to provide real-world data on treatment patterns and characteristics of treated versus untreated patients among individuals with HCV in the United States. Adults with an HCV diagnosis from 01 July 2016 through 30 September 2020 and continuous health plan enrolment for 12 months before and ≥1 month after the diagnosis date were identified in the Optum Research Database. Descriptive and multivariable analyses were conducted to evaluate the association between patient characteristics and the rate of treatment. Of 24,374 patients identified with HCV, only 30% initiated treatment during follow-up. Factors associated with increased rate of treatment included younger age versus age 75+ (hazard ratio [HR] 1.50-1.83 depending on age group), commercial versus Medicare insurance (HR 1.32), and diagnosis by a specialist versus a primary care physician (HR 2.56 and 2.62 for gastroenterology and infectious disease or hepatology, respectively) ($p < .01$ for all). Several baseline comorbidities were associated with decreased rate of treatment, including psychiatric disorders (HR 0.87), drug use disorders (HR 0.85) and cirrhosis (HR 0.42) ($p < .01$ for all). These findings highlight existing HCV treatment inequities, particularly among older patients and those with psychiatric disorders, substance use disorders or chronic comorbidities. Targeted efforts to increase treatment uptake in these populations could mitigate a considerable future burden of HCV-related morbidity, mortality and healthcare costs.

Hematology-Oncology

Drilon A, Sharma MR, Johnson ML, Yap TA, **Gadgeel S**, Nepert D, Feng G, Reddy MB, Harney AS, Elsayed M, Cook AW, Wong CE, Hinklin RJ, Jiang Y, Brown EN, Neitzel NA, Laird ER, Wu WI, Singh A, Wei P, Ching KA, Gaudino JJ, Lee PA, Hartley DP, and Rothenberg SM. SHP2 Inhibition Sensitizes Diverse Oncogene-Addicted Solid Tumors to Re-treatment with Targeted Therapy. *Cancer Discov* 2023; Epub ahead of print. PMID: 37269335. Full Text

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Rationally targeted therapies have transformed cancer treatment, but many patients develop resistance through bypass signaling pathway activation. PF-07284892 (ARRY-558) is an allosteric SHP2 inhibitor designed to overcome bypass-signaling-mediated resistance when combined with inhibitors of various oncogenic drivers. Activity in this setting was confirmed in diverse tumor models. Patients with ALK fusion-positive lung cancer, BRAFV600E-mutant colorectal cancer, KRASG12D-mutant ovarian cancer, and ROS1 fusion-positive pancreatic cancer who previously developed targeted therapy resistance were treated with PF-07284892 on the first dose level of a first-in-human clinical trial. After progression on PF-07284892 monotherapy, a novel study design allowed the addition of oncogene-directed targeted therapy that had previously failed. Combination therapy led to rapid tumor and circulating tumor DNA (ctDNA) responses and extended the duration of overall clinical benefit. SIGNIFICANCE: PF-07284892-targeted therapy combinations overcame bypass-signaling-mediated resistance in a clinical setting in which neither component was active on its own. This provides proof of concept of the utility of SHP2 inhibitors in overcoming resistance to diverse targeted therapies and provides a paradigm for accelerated testing of novel drug combinations early in clinical development. See related commentary by Hernando-Calvo and Garralda.

Hematology-Oncology

Ducreux M, Abou-Alfa GK, Bekaii-Saab T, Berlin J, Cervantes A, de Baere T, Eng C, Galle P, Gill S, Gruenberger T, Haustermans K, Lamarca A, Laurent-Puig P, Llovet JM, Lordick F, Macarulla T, Mukherji D, Muro K, Obermannova R, O'Connor JM, O'Reilly EM, Osterlund P, **Philip P**, Prager G, Ruiz-Garcia E, Sangro B, Seufferlein T, Tabernero J, Verslype C, Wasan H, and Van Cutsem E. The management of hepatocellular carcinoma. Current expert opinion and recommendations derived from the 24th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2022. *ESMO Open* 2023; 8(3):101567. PMID: 37263081. Full Text

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This article summarises expert discussion on the management of patients with hepatocellular carcinoma (HCC), which took place during the 24th World Gastrointestinal Cancer Congress (WGICC) in Barcelona, July 2022. A multidisciplinary approach is mandatory to ensure an optimal diagnosis and staging of HCC, planning of curative and therapeutic options, including surgical, embolisation, ablative strategies, or

systemic therapy. Furthermore, in many patients with HCC, underlying liver cirrhosis represents a challenge and influences the therapeutic options.

Hematology-Oncology

Moey MYY, Hennessy C, French B, Warner JL, Tucker MD, Hausrath DJ, Shah DP, DeCara JM, Bakouny Z, Labaki C, Choueiri TK, Dent S, Akhter N, Ismail-Khan R, Tachiki L, Slosky D, Polonsky TS, Awosika JA, Crago A, Wise-Draper T, **Balanchivadze N**, **Hwang C**, Fecher LA, Gomez CG, Hayes-Lattin B, Glover MJ, Shah SA, Gopalakrishnan D, Griffiths EA, Kwon DH, Koshkin VS, Mahmood S, Bashir B, Nonato T, Razavi P, McKay RR, Nagaraj G, Oligino E, Puc M, Tregubenko P, Wulff-Burchfield EM, Xie Z, Halfdanarson TR, Farmakiotis D, Klein EJ, Robilotti EV, Riely GJ, Durand JB, Hayek SS, Kondapalli L, Berg S, O'Connor TE, Bilen MA, Castellano C, Accordino MK, Sibel B, Weissmann LB, Jani C, Flora DB, Rudski L, Dutra MS, Nathaniel B, Ruíz-García E, Vilar-Compte D, Gupta S, Morgans A, and Nohria A. COVID-19 severity and cardiovascular outcomes in SARS-CoV-2-infected patients with cancer and cardiovascular disease. *Transl Oncol* 2023; 34:101709. PMID: 37302348. Full Text

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BACKGROUND: Data regarding outcomes among patients with cancer and co-morbid cardiovascular disease (CVD)/cardiovascular risk factors (CVRF) after SARS-CoV-2 infection are limited. OBJECTIVES: To compare Coronavirus disease 2019 (COVID-19) related complications among cancer patients with and without co-morbid CVD/CVRF. METHODS: Retrospective cohort study of patients with cancer and laboratory-confirmed SARS-CoV-2, reported to the COVID-19 and Cancer Consortium (CCC19) registry from 03/17/2020 to 12/31/2021. CVD/CVRF was defined as established CVD or no established CVD, male ≥ 55 or female ≥ 60 years, and one additional CVRF. The primary endpoint was an ordinal COVID-19 severity outcome including need for hospitalization, supplemental oxygen, intensive care unit (ICU), mechanical ventilation, ICU or mechanical ventilation plus vasopressors, and death. Secondary endpoints included incident adverse CV events. Ordinal logistic regression models estimated associations of CVD/CVRF with COVID-19 severity. Effect modification by recent cancer therapy was evaluated. RESULTS: Among 10,876 SARS-CoV-2 infected patients with cancer (median age 65 [IQR 54-74] years, 53% female, 52% White), 6253 patients (57%) had co-morbid CVD/CVRF. Co-morbid CVD/CVRF was associated with higher COVID-19 severity (adjusted OR: 1.25 [95% CI 1.11-1.40]). Adverse CV events were significantly higher in patients with CVD/CVRF (all p<0.001). CVD/CVRF was associated with worse COVID-19 severity in patients who had not received recent cancer therapy, but not in those undergoing active cancer therapy (OR 1.51 [95% CI 1.31-1.74] vs. OR 1.04 [95% CI 0.90-1.20], p(interaction) <0.001). CONCLUSIONS: Co-morbid CVD/CVRF is associated with higher COVID-19 severity among patients with cancer, particularly those not receiving active cancer therapy. While infrequent, COVID-19 related CV complications were higher in patients with comorbid CVD/CVRF. (COVID-19 and Cancer Consortium Registry [CCC19]; NCT04354701).

Hematology-Oncology

Negrao MV, Spira AI, Heist RS, Jänne PA, Pacheco JM, Weiss J, **Gadgeel SM**, Velastegui K, Yang W, Der-Torossian H, Christensen JG, and Sabari JK. Intracranial Efficacy of Adagrasib in Patients From the KRYSTAL-1 Trial With KRAS(G12C)-Mutated Non-Small-Cell Lung Cancer Who Have Untreated CNS Metastases. *J Clin Oncol* 2023; Epub ahead of print. PMID: 37327468. Full Text

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Clinical trials frequently include multiple end points that mature at different times. The initial report, typically 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.Patients with Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutated non-small-cell lung cancer (NSCLC) and untreated CNS metastases have a worse prognosis than similar patients without KRAS mutations. Adagrasib has previously demonstrated CNS penetration preclinically and cerebral spinal fluid penetration clinically. We evaluated adagrasib in patients with KRAS(G12C)-mutated NSCLC and untreated CNS metastases from the KRYSTAL-1 trial (ClinicalTrials.gov identifier: NCT03785249; phase Ib cohort), in which adagrasib 600 mg was administered orally, twice daily. Study outcomes included the safety and clinical activity (intracranial [IC] and systemic) by blinded independent central review. Twenty-five patients with KRAS(G12C)-mutated NSCLC and untreated CNS metastases were enrolled and evaluated (median follow-up, 13.7 months); 19 patients were radiographically evaluable for IC activity. Safety was consistent with previous reports of adagrasib, with grade 3 treatment-related adverse events (TRAEs) in 10 patients (40%) and one grade 4 (4%) and no grade 5 TRAEs. The most common CNS-specific TRAEs included dysgeusia (24%) and dizziness (20%). Adagrasib demonstrated an IC objective response rate of 42%, disease control rate of 90%, progression-free survival of 5.4 months, and median overall survival of 11.4 months. Adagrasib is the first KRAS(G12C) inhibitor to prospectively demonstrate IC activity in patients with KRAS(G12C)-mutated NSCLC and untreated CNS metastases, supporting further investigation in this population.

Hematology-Oncology
Wani K, **Patel K**, and **Dabak V**. Hepatotoxicity After CDK 4/6 Inhibitor Initiation in the Treatment of Hormone-Positive Metastatic Breast Cancer. *Cureus* 2023; 15(6):e40871. PMID: 37363122. Full Text

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Cancer cells proliferate using various mechanisms. One mechanism of preventing tumor cell growth is blockade of the cyclin-dependent kinase (CDK) 4/6 axis. Multiple CDK 4/6 inhibitors - ribociclib, palbociclib, and abemaciclib - have significantly improved progression-free survival rates. However, they can cause hepatotoxicity. We present a case of a 67-year-old female who was diagnosed with stage 1C invasive ductal carcinoma. She was treated with letrozole and ribociclib due to recurrence as metastatic disease, but within 10 days, she developed transaminitis. She then started palbociclib but experienced elevated transaminases within two weeks, needing discontinuation of palbociclib. Subsequent positron-emission tomography/computed tomography imaging showed disease progression, and she was started on fulvestrant. We considered adding abemaciclib, but the patient declined and has had stable disease for more than a year on fulvestrant. CDK 4/6 inhibitors are used to treat metastatic breast cancer and are generally well tolerated. The most common side effect is neutropenia; however, our patient developed transaminitis. The novelty of our case is the development of hepatotoxicity even after the introduction of another CDK 4/6 inhibitor, indicating at least some degree of class effect. In summary, CDK 4/6 inhibitors have significantly improved outcomes in hormone-positive metastatic breast cancers. However, a small percentage suffer from hepatic injury enough to warrant discontinuation of the drug, and we must continue to assess the risk versus benefit profile when offering them to our patients.

Hospital Medicine
Feldeisen T, Alexandris-Souphis C, Haymart B, Kong X, Kline-Rogers E, Handoo F, **Kaatz S**, Ali M, Kozlowski J, **Shah V**, **Krol G**, Froehlich JB, and Barnes GD. Anticoagulation Changes Following Major and Clinically Relevant Nonmajor Bleeding Events in Non-valvular Atrial Fibrillation Patients. *J Pharm Pract* 2023; 36(3):542-547. PMID: 34962835. Full Text

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Background: Bleeding events are common complications of oral anticoagulant drugs, including both warfarin and the direct oral anticoagulants (DOACs). Some patients have their anticoagulant changed or discontinued after experiencing a bleeding event, while others continue the same treatment. Differences in anticoagulation management between warfarin- and DOAC-treated patients following a bleeding event are unknown. Methods: Patients with non-valvular atrial fibrillation from six anticoagulation clinics taking warfarin or DOAC therapy who experienced an International Society of Thrombosis and Haemostasis (ISTH)-defined major or clinically relevant non-major (CRNM) bleeding event were identified between 2016 and 2020. The primary outcome was management of the anticoagulant following bleeding (discontinuation, change in drug class, and restarting of same drug class). DOAC- and warfarin-treated patients were propensity matched based on the individual elements of the CHA2DS2-VASc and HAS-BLED scores as well as the severity of the bleeding event. Results: Of the 509 patients on warfarin therapy and 246 on DOAC therapy who experienced a major or CRNM bleeding event, the majority of patients continued anticoagulation therapy. The majority of warfarin (231, 62.6%) and DOAC patients (201, 81.7%) restarted their previous anticoagulation. Conclusion: Following a bleeding event, most patients restarted anticoagulation therapy, most often with the same type of anticoagulant that they previously had been taking.

Infectious Diseases

Hong H, Friedland A, Hu M, Anstrom KJ, Halabi S, **McKinnon JE**, Amaravadi R, Rojas-Serrano J, Abella BS, Portillo-Vázquez AM, Woods CW, Hernandez AF, Boulware DR, Naggie S, and Rajasingham R. Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomised clinical trials. *BMJ Open* 2023; 13(6):e065305. PMID: 37328184. Full Text

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OBJECTIVE: We studied the safety and efficacy of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 in healthcare workers (HCWs), using a meta-analysis of randomised controlled trials (RCTs). DATA SOURCES: PubMed and EMBASE databases were searched to identify randomised trials studying HCQ. STUDY SELECTION: Ten RCTs were identified (n=5079 participants). DATA EXTRACTION AND SYNTHESIS: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in this systematic review and meta-analysis between HCQ and placebo using a Bayesian random-effects model. A pre-hoc statistical analysis plan was written. MAIN OUTCOMES: The primary efficacy outcome was PCR-confirmed SARS-CoV-2 infection and the primary safety outcome was incidence of adverse events. The secondary outcome included clinically suspected SARS-CoV-2 infection. RESULTS: Compared with placebo, HCWs randomised to HCQ had no significant difference in PCR-confirmed SARS-CoV-2 infection (OR 0.92, 95% credible interval (CI): 0.58, 1.37) or clinically suspected SARS-CoV-2 infection (OR 0.78, 95% CI: 0.57, 1.10), but significant difference in adverse events (OR 1.35, 95% CI: 1.03, 1.73). CONCLUSIONS AND RELEVANCE: Our meta-analysis of 10 RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs found that

compared with placebo, HCQ does not significantly reduce the risk of confirmed or clinically suspected SARS-CoV-2 infection, while HCQ significantly increases adverse events. PROSPERO REGISTRATION NUMBER: CRD42021285093.

Infectious Diseases
Jarrah J, **Alsaadi A**, **Putman EM**, and **Williams J**. Polymicrobial bacteremia in a heart transplant recipient: More than what meets the eye. *Am J Transplant* 2023; 23(6):854-856. Full Text

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Infectious Diseases
Suleyman G, **Fadel R**, **Patel K**, **Shadid AM**, **Stuart HBC**, **Kattula M**, **Janis A**, **Maki M**, **Chao S**, **Alangaden G**, and **Brar I**. Outcomes associated with SARS-CoV-2 reinfection in individuals with natural and hybrid immunity. *J Infect Public Health* 2023; 16(8):1262-1268. PMID: 37302273. Full Text

Henry Ford Hospital, Division of Infectious Disease, 2799 West Grand BLVD, Detroit, MI 48202, USA; Wayne State University School of Medicine, 540 E. Canfield Ave., Detroit, MI 48201, USA. Electronic address: gsuleym2@hfhs.org.
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BACKGROUND: Studies comparing SARS-CoV-2 reinfection outcomes among individuals with previous infection (natural immunity) and previous infection plus vaccination (hybrid immunity) are limited. METHODS: Retrospective cohort study comparing SARS-CoV-2 reinfection among patients with hybrid immunity (cases) and natural immunity (controls) from March 2020 to February 2022. Reinfection was defined as positive PCR > 90 days after initial laboratory-confirmed SARS-CoV-2 infection. Outcomes included time to reinfection, symptom severity, COVID-19-related hospitalization, critical COVID-19 illness (need for intensive care unit, invasive mechanical ventilation, or death), length of stay (LOS). RESULTS: A total of 773 (42%) vaccinated and 1073 (58%) unvaccinated patients with reinfection were included. Most patients (62.7%) were asymptomatic. Median time to reinfection was longer with hybrid immunity (391 [311-440] vs 294 [229-406] days, $p < 0.001$). Cases were less likely to be symptomatic (34.1% vs 39.6%, $p = 0.001$) or develop critical COVID-19 (2.3% vs 4.3%, $p = 0.023$). However, there was no significant difference in rates of COVID-19-related hospitalization (2.6% vs 3.8%, $p = 0.142$) or LOS (5 [2-9] vs 5 [3-10] days, $p = 0.446$). Boosted patients had longer time to reinfection (439 [IQR 372-467] vs 324 [IQR 256-414] days, $p < 0.001$) and were less likely to be symptomatic (26.8% vs 38%, $p = 0.002$) compared to unboosted patients. Rates of hospitalization, progression to critical illness and LOS were not significantly different between the two groups. CONCLUSIONS: Natural and hybrid immunity provided protection against SARS-CoV-2 reinfection and hospitalization. However, hybrid immunity conferred stronger protection against symptomatic disease and progression to critical illness and was associated with longer time to reinfection. The stronger protection conferred by hybrid immunity against severe outcomes due to COVID-19 should be emphasized with the public to further the vaccination effort, especially in high-risk individuals.

Internal Medicine
Bhatia K, Sabharwal B, **Gupta K**, Lopez PD, Kaur A, Bhatia HK, **Gandhi KD**, Niroula S, Correa A, Birati EY, Argulian E, Fox A, and Mahmood K. Clinical outcomes of intravenous Iron therapy in patients with heart failure and Iron deficiency: Meta-analysis and trial sequential analysis of randomized clinical trials. *J Cardiol* 2023; Epub ahead of print. PMID: 37380069. Full Text

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BACKGROUND: Iron deficiency in patients with heart failure (HF) is underdiagnosed and undertreated. The role of intravenous (IV) iron is well-established to improve quality of life measures. Emerging evidence also supports its role in preventing cardiovascular events in patients with HF. METHODOLOGY: We conducted a literature search of multiple electronic databases. Randomized controlled trials that compared IV iron to usual care among patients with HF and reported cardiovascular (CV) outcomes were included. Primary outcome was the composite of first heart failure hospitalization (HFH) or CV death. Secondary outcomes included HFH (first or recurrent), CV death, all-cause mortality, hospitalization for any cause, gastrointestinal (GI) side effects, or any infection. We performed trial sequential and cumulative meta-analyses to evaluate the effect of IV iron on the primary endpoint, and on HFH. RESULTS: Nine trials enrolling 3337 patients were included. Adding IV iron to usual care significantly reduced the risk of first HFH or CV death [risk ratio (RR) 0.84; 95 % confidence interval (CI) 0.75-0.93; I(2) = 0 %; number needed to treat (NNT) 18], which was primarily driven by a reduction in the risk of HFH of 25 %. IV iron also reduced the risk of the composite of hospitalization for any cause or death (RR 0.92; 95 % CI 0.85-0.99; I(2) = 0 %; NNT 19). There was no significant difference in the risk of CV death, all-cause mortality, adverse GI events, or any infection among patients receiving IV iron compared to usual care. The observed benefits of IV iron were directionally consistent across trials and crossed both the statistical and trial sequential boundaries of benefit. CONCLUSION: In patients with HF and iron deficiency, the addition of IV iron to usual care reduces the risk of HFH without affecting the risk of CV or all-cause mortality.

Internal Medicine

Fadel RA, Scott A, **Parsons A**, **Murskyj I**, **Nasiri N**, **Abu Sayf A**, and **Ouellette D**. Tocilizumab Associated With Survival in Patients Hospitalized for COVID-19 Acute Respiratory Distress Syndrome and Low Urine Output. *J Intensive Care Med* 2023; Epub ahead of print. PMID: 37306148. Full Text

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BACKGROUND: Acute respiratory distress syndrome (ARDS) with oliguria is associated with increased mortality. Interleukin-6 (IL-6) plays an integral role in the pathophysiology of both disease processes. Patients who experience severe COVID-19 have demonstrated higher IL-6 levels compared to baseline, and use of tocilizumab has demonstrated efficacy in such cohorts. We set out to investigate the relationship between tocilizumab use, COVID-19 ARDS, low urine output, and mortality. METHODS: Retrospective cohort review of adult patients aged ≥ 18 years with COVID-19 and moderate or severe ARDS, admitted to the intensive care unit (ICU) of a tertiary referral center in metropolitan Detroit. Patients were analyzed based on presence of oliguria (defined as ≤ 0.7 mL/kg/h) on the day of intubation and exposure to tocilizumab while inpatient. The primary outcome was inpatient mortality. RESULTS: One hundred and twenty-eight patients were analyzed, 103 (80%) with low urine output, of whom 30 (29%) received tocilizumab. In patients with low urine output, risk factors associated with mortality on univariate analysis included Black race (P = .028), lower static compliance (P = .015), and tocilizumab administration (P = .002). Tocilizumab (odds ratio 0.245, 95% confidence interval 0.079-0.764, P = .015) was the only risk factor independently associated with survival on multivariate logistic regression analysis. CONCLUSION: In this retrospective cohort review of patients hospitalized with COVID-19 and moderate or severe ARDS, tocilizumab administration was independently associated with survival in patients with

low urine output ≤ 0.7 mL/kg/h on the day of intubation. Prospective studies are needed to investigate the impact of urine output on efficacy of interleukin-targeted therapies in the management of ARDS.

Internal Medicine
Feldeisen T, Alexandris-Souphis C, Haymart B, Kong X, Kline-Rogers E, Handoo F, **Kaatz S**, Ali M, Kozlowski J, **Shah V**, **Krol G**, Froehlich JB, and Barnes GD. Anticoagulation Changes Following Major and Clinically Relevant Nonmajor Bleeding Events in Non-valvular Atrial Fibrillation Patients. *J Pharm Pract* 2023; 36(3):542-547. PMID: 34962835. Full Text

Frankel Cardiovascular Center, Michigan Medicine, Ann Arbor, MI, USA. RINGGOLD: 21614
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William Beaumont Hospital, Royal Oak, MI, USA. RINGGOLD: 21818
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Background: Bleeding events are common complications of oral anticoagulant drugs, including both warfarin and the direct oral anticoagulants (DOACs). Some patients have their anticoagulant changed or discontinued after experiencing a bleeding event, while others continue the same treatment. Differences in anticoagulation management between warfarin- and DOAC-treated patients following a bleeding event are unknown. Methods: Patients with non-valvular atrial fibrillation from six anticoagulation clinics taking warfarin or DOAC therapy who experienced an International Society of Thrombosis and Haemostasis (ISTH)-defined major or clinically relevant non-major (CRNM) bleeding event were identified between 2016 and 2020. The primary outcome was management of the anticoagulant following bleeding (discontinuation, change in drug class, and restarting of same drug class). DOAC- and warfarin-treated patients were propensity matched based on the individual elements of the CHA2DS2-VASc and HAS-BLED scores as well as the severity of the bleeding event. Results: Of the 509 patients on warfarin therapy and 246 on DOAC therapy who experienced a major or CRNM bleeding event, the majority of patients continued anticoagulation therapy. The majority of warfarin (231, 62.6%) and DOAC patients (201, 81.7%) restarted their previous anticoagulation. Conclusion: Following a bleeding event, most patients restarted anticoagulation therapy, most often with the same type of anticoagulant that they previously had been taking.

Internal Medicine
Jarrah J, **Alsaadi A**, **Putman EM**, and **Williams J**. Polymicrobial bacteremia in a heart transplant recipient: More than what meets the eye. *Am J Transplant* 2023; 23(6):854-856. Full Text

J. Jarrah, Infectious Diseases Division, Henry Ford Hospital, Detroit, MI, United States

Internal Medicine
Obri MS, **Youssef RM**, **Alluri S**, **Vemulapalli K**, **Ichkhanian Y**, **Todter EN**, **Jesse MT**, and **Salgia R**. Disparities in Referrals to End-of-Life Care in Eligible Hepatocellular Carcinoma Patients. *Dig Dis Sci* 2023; Epub ahead of print. PMID: 37289417. Full Text

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BACKGROUND: Hepatocellular Carcinoma (HCC) is a malignancy with increasing incidence and morbidity. For patients with a poor prognosis, engagement with advanced care planning and end-of life (EOL) services (I.e., palliative care, hospice) can address physical, financial, and social complications of a terminal diagnosis. Minimal data exist on the demographics of the patients being referred to and enrolling in EOL services for HCC. AIMS: We aim to report the relationship between demographics and EOL service referral. METHODS: Retrospective review of a prospectively maintained high-volume liver center registry of patients diagnosed with HCC from 2004 to 2022. EOL services eligible patients were defined

as BCLC stage C or D, evidence of metastases, and/or transplant ineligible. RESULTS: Black patients were more likely to be referred than white patients (OR 1.47 (1.03, 2.11)). Once referred, patients were significantly more likely to be enrolled if they had insurance coverage, though no other factors in models were significant. There were no significant differences in survival among those referred who did or did not enroll, after controlling for other factors. CONCLUSION: Black patients were more likely to be referred compared to white patients and patients who were insured were more likely to be enrolled. Whether this is indicative of black patients being appropriately referred at a higher rate, being offered EOL care instead of aggressive treatment, or other unknown factors warrants further study.

Internal Medicine
Patel K, **Singh V**, and **Bissonette A**. A Combination of Beta-Blockade and Calcium Channel Blockade Leading to Bradycardia, Renal Failure, Atrioventricular Blockade, Shock, and Hyperkalemia (BRASH) Syndrome: A Case Report. *Cureus* 2023; 15(6):e40176. PMID: 37337555. Full Text

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

The BRASH syndrome is a recently recognized syndrome and the acronym stands for bradycardia, renal failure, atrioventricular (AV) blockade, shock, and hyperkalemia. We discuss a case of a 56-year-old female with a history of heart failure who presented in a critical state following recent adjustments to her carvedilol dosage while she was simultaneously on verapamil. This combination of AV nodal-blocking agents induced bradycardia in the patient, leading to shock and renal hypoperfusion complicated by hyperkalemia that required the use of a temporary transvenous pacemaker before she made a full recovery. The case report highlights the fact that this combination of medications alone may have had a synergistic effect that led to BRASH in our patient.

Internal Medicine
Patel K, **Wani K**, **Daneshvar A**, and **Omar J**. Unusual Etiology of Chronic Cough and Syncope as Chiari Malformation Type 1. *Cureus* 2023; 15(6):e40598. PMID: 37337558. Full Text

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

Chronic cough is a common chief complaint in ambulatory clinics. Unlike most cases that are caused by upper airway cough syndrome, gastroesophageal reflux disease, asthma, and non-asthmatic eosinophilic bronchitis, chronic cough can also be the presenting feature of a Chiari malformation. Our case is that of a 39-year-old female who had a chronic cough associated with shortness of breath, and when severe, associated with loss of consciousness. Her cough was refractory to conventional management. Further workup including pulmonary functions tests (PFT), laryngoscopy, high-resolution CT of the chest, an upper GI series, and esophageal pH manometry study were all normal. An MRI of her brain was obtained due to her syncopal episodes and revealed findings concerning a type 1 Chiari malformation. She subsequently underwent a Chiari decompression with patchy duraplasty and tonsilloplasty with cervical vertebrae 1 and 2 (C1-C2) laminectomy with a resolution of her symptoms. Chiari malformations are sometimes inherited but are often sporadic in nature, and, thus, appropriate diagnosis is key. Our patient is unique in that she presented at an older age, suggesting that atypical etiologies of a chronic cough refractory to conventional treatments must be considered.

Internal Medicine
Sambandam S, Serbin P, Senthil T, Varatharaj S, Sakthivelnathan V, **Ramanan SP**, and Mounasamy V. Patient Characteristics, Length of Stay, Cost of Care, and Complications in Super-Obese Patients Undergoing Total Hip Arthroplasty: A National Database Study. *Clin Orthop Surg* 2023; 15(3):380-387. PMID: 37274508. Full Text

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BACKGROUND: The purpose of this study was to compare postoperative complication rates in super-obese (SO) patients with a body mass index (BMI) ≥ 50 kg/m(2) undergoing total hip arthroplasty (THA) versus non-super-obese (NSO) patients undergoing THA. METHODS: In this retrospective study using the National Inpatient Sample (NIS) database, 1,646 cases of THA in SO (BMI ≥ 50 kg/m(2)) patients were reviewed. We used International Classification of Diseases (ICD)-10 codes to assess postoperative variables including length of stay, cost of care (cost of inpatient hospitalization), and medical and surgical complications among SO patients undergoing THA compared to NSO patients before being discharged. RESULTS: A comparison of demographic variables showed there were more women in both groups and nearly 17.2% of SO patients were diabetic patients, 11.1% of SO patients were tobacco users, and 74.8% of the SO patients were whites (African American, 15.1%; Hispanic, 2.9%). The mean length of stay was 3.43 days in the SO group and 2.32 days in the NSO group, and this difference was statistically significant. The cost of care was $79,784.64 for the SO group, which was significantly higher than $66,821.75 for the NSO group. The SO group also showed higher odds of developing medical complications such as anemia (odds ratio [OR], 1.555; 95% confidence interval [CI], 1.395-1.734; p < 0.001), acute renal failure (OR, 3.375; 95% CI, 2.816-4.045; p < 0.001), pneumonia (OR, 2.319; 95% CI, 1.241-4.331; p = 0.014), and need for blood transfusion (OR, 1.596; 95% CI, 1.289-1.975; p < 0.001). The SO patients also showed a higher risk of several postoperative surgical complications such as periprosthetic fractures, infection, and wound dehiscence. CONCLUSIONS: Postoperative complication rates in SO patients were higher than those in the NSO group. Length of stay and cost of care were higher, whereas the mean age was lower for the SO group. Therefore, THA in SO patients should be undertaken only after careful consideration and preferably in a tertiary facility capable of handling all medical and surgical in-hospital complications.

Internal Medicine

Suleyman G, **Fadel R**, **Patel K**, **Shadid AM**, **Stuart HBC**, **Kattula M**, **Janis A**, **Maki M**, **Chao S**, **Alangaden G**, and **Brar I**. Outcomes associated with SARS-CoV-2 reinfection in individuals with natural and hybrid immunity. *J Infect Public Health* 2023; 16(8):1262-1268. PMID: 37302273. Full Text

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BACKGROUND: Studies comparing SARS-CoV-2 reinfection outcomes among individuals with previous infection (natural immunity) and previous infection plus vaccination (hybrid immunity) are limited. METHODS: Retrospective cohort study comparing SARS-CoV-2 reinfection among patients with hybrid immunity (cases) and natural immunity (controls) from March 2020 to February 2022. Reinfection was defined as positive PCR > 90 days after initial laboratory-confirmed SARS-CoV-2 infection. Outcomes included time to reinfection, symptom severity, COVID-19-related hospitalization, critical COVID-19 illness (need for intensive care unit, invasive mechanical ventilation, or death), length of stay (LOS). RESULTS: A total of 773 (42%) vaccinated and 1073 (58%) unvaccinated patients with reinfection were included. Most patients (62.7%) were asymptomatic. Median time to reinfection was longer with hybrid immunity (391 [311-440] vs 294 [229-406] days, p < 0.001). Cases were less likely to be symptomatic (34.1% vs 39.6%, p = 0.001) or develop critical COVID-19 (2.3% vs 4.3%, p = 0.023). However, there was no significant difference in rates of COVID-19-related hospitalization (2.6% vs 3.8%, p = 0.142) or LOS (5 [2-9] vs 5 [3-10] days, p = 0.446). Boosted patients had longer time to reinfection (439 [IQR 372-467] vs 324 [IQR 256-414] days, p < 0.001) and were less likely to be symptomatic (26.8% vs 38%, p = 0.002) compared to unboosted patients. Rates of hospitalization, progression to critical illness and LOS were not significantly different between the two groups. CONCLUSIONS: Natural and hybrid immunity provided protection against SARS-CoV-2 reinfection and hospitalization. However, hybrid immunity conferred

stronger protection against symptomatic disease and progression to critical illness and was associated with longer time to reinfection. The stronger protection conferred by hybrid immunity against severe outcomes due to COVID-19 should be emphasized with the public to further the vaccination effort, especially in high-risk individuals.

Internal Medicine

Wani K, **Patel K**, and **Dabak V**. Hepatotoxicity After CDK 4/6 Inhibitor Initiation in the Treatment of Hormone-Positive Metastatic Breast Cancer. *Cureus* 2023; 15(6):e40871. PMID: 37363122. Full Text

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Cancer cells proliferate using various mechanisms. One mechanism of preventing tumor cell growth is blockade of the cyclin-dependent kinase (CDK) 4/6 axis. Multiple CDK 4/6 inhibitors - ribociclib, palbociclib, and abemaciclib - have significantly improved progression-free survival rates. However, they can cause hepatotoxicity. We present a case of a 67-year-old female who was diagnosed with stage 1C invasive ductal carcinoma. She was treated with letrozole and ribociclib due to recurrence as metastatic disease, but within 10 days, she developed transaminitis. She then started palbociclib but experienced elevated transaminases within two weeks, needing discontinuation of palbociclib. Subsequent positron-emission tomography/computed tomography imaging showed disease progression, and she was started on fulvestrant. We considered adding abemaciclib, but the patient declined and has had stable disease for more than a year on fulvestrant. CDK 4/6 inhibitors are used to treat metastatic breast cancer and are generally well tolerated. The most common side effect is neutropenia; however, our patient developed transaminitis. The novelty of our case is the development of hepatotoxicity even after the introduction of another CDK 4/6 inhibitor, indicating at least some degree of class effect. In summary, CDK 4/6 inhibitors have significantly improved outcomes in hormone-positive metastatic breast cancers. However, a small percentage suffer from hepatic injury enough to warrant discontinuation of the drug, and we must continue to assess the risk versus benefit profile when offering them to our patients.

Nephrology

Abreo AP, Kataria D, Amrutkar C, Singh A, **Samaniego M**, and Singh N. Stroke and kidney transplantation. *Curr Opin Organ Transplant* 2023; Epub ahead of print. PMID: 37352894. Full Text

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PURPOSE OF REVIEW: This review will focus on the epidemiological data, risk factors, and management of stroke before and after kidney transplant. Stroke is highly prevalent in waitlisted patients as well as kidney transplant recipients and is associated with impaired transplant outcomes. Multiple traditional, nontraditional, and transplanted risk factors increase the risk of stroke. RECENT FINDINGS: Although the risk of stroke is reduced after kidney transplantation compared with remaining on dialysis, the morbidity and mortality from stroke after transplantation remain significant. SUMMARY: Early screening for risk factors before and after a kidney transplant and following the Kidney Disease Improving Global Outcomes (KDIGO) management guidelines could minimize the incidence of stroke and transplant outcomes.

Neurology

Huang H, Chen L, Sanberg PR, Dimitrijevic M, Shetty AK, Sharma HS, Wu P, Bryukhovetskiy A, Al-Zoubi ZM, **Chopp M**, Young W, Saberi H, Moviglia G, Sarnowska A, Sharma A, He X, Muresanu DF, Jeon SR, Feng S, Cho KS, Alvarez EO, Kuźma-Kozakiewicz M, Kuffler D, Otom A, Herrera-Marschitz M, Moniche F, Koliakos G, Ao Q, Guo X, von Wild KRH, Cheng L, Al-Zoubi A, Zhao J, Guo X, Mao G, Han F, Hu Y, Xue M, Song J, Zhang X, Chen X, Chen L, Zheng Z, Wang D, Zhang W, Qiao L, Xiang G, Liu J, Zhao RC, and Zhang Q. Beijing declaration of International Association of Neurorestoratology (2023 Xi'an version). *J Neurorestoratology* 2023; 11(2). Full Text

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Neurology
Huang H, Sanberg PR, Chen L, **Chopp M**, and Sharma HS. Explanation and elaboration: Development of Beijing declaration of International Association of Neurorestoratology. *J Neurorestoratology* 2023; 11(2). Full Text

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Neurology
Son JP, Kim EH, Shin EK, Kim DH, Sung JH, Oh MJ, Cha JM, **Chopp M**, and Bang OY. Mesenchymal Stem Cell-Extracellular Vesicle Therapy for Stroke: Scalable Production and Imaging Biomarker Studies. *Stem Cells Transl Med* 2023; Epub ahead of print. PMID: 37311045. Full Text

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A major clinical hurdle to translate MSC-derived extracellular vesicles (EVs) is the lack of a method to scale-up the production of EVs with customized therapeutic properties. In this study, we tested whether EV production by a scalable 3D-bioprocessing method is feasible and improves neuroplasticity in animal models of stroke using MRI study. MSCs were cultured in a 3D-spheroid using a micro-patterned well. The EVs were isolated with filter and tangential flow filtration and characterized using electron microscopy, nanoparticle tracking analysis, and small RNA sequencing. Compared to conventional 2D culture, the production-reproduction of EVs (the number/size of particles and EV purity) obtained from 3D platform were more consistent among different lots from the same donor and among different donors. Several microRNAs with molecular functions associated with neurogenesis were upregulated in EVs obtained from 3D platform. EVs induced both neurogenesis and neuritogenesis via microRNAs (especially, miR-27a-3p and miR-132-3p)-mediated actions. EV therapy improved functional recovery on behavioral tests and reduced infarct volume on MRI in stroke models. The dose of MSC-EVs of 1/30 cell dose had similar therapeutic effects. In addition, the EV group had better anatomical and functional connectivity on diffusion tensor imaging and resting-state functional MRI in a mouse stroke model. This study shows that clinical-scale MSC-EV therapeutics are feasible, cost-effective, and improve functional recovery following experimental stroke, with a likely contribution from enhanced neurogenesis and neuroplasticity.

Neurosurgery
Bagher-Ebadian H, **Brown SL**, Ghassemi MM, **Nagaraja TN**, Valadie OG, Acharya PC, **Cabral G**, **Divine G**, **Knight RA**, **Lee IY**, **Xu JH**, **Movsas B**, **Chetty IJ**, and **Ewing JR**. Dynamic contrast enhanced (DCE) MRI estimation of vascular parameters using knowledge-based adaptive models. *Sci Rep* 2023; 13(1):9672. PMID: 37316579. Full Text

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We introduce and validate four adaptive models (AMs) to perform a physiologically based Nested-Model-Selection (NMS) estimation of such microvascular parameters as forward volumetric transfer constant, K(trans), plasma volume fraction, v(p), and extravascular, extracellular space, v(e), directly from Dynamic Contrast-Enhanced (DCE) MRI raw information without the need for an Arterial-Input Function (AIF). In sixty-six immune-compromised-RNU rats implanted with human U-251 cancer cells, DCE-MRI studies estimated pharmacokinetic (PK) parameters using a group-averaged radiological AIF and an extended Patlak-based NMS paradigm. One-hundred-ninety features extracted from raw DCE-MRI information were used to construct and validate (nested-cross-validation, NCV) four AMs for estimation of model-based regions and their three PK parameters. An NMS-based a priori knowledge was used to fine-tune the AMs to improve their performance. Compared to the conventional analysis, AMs produced stable maps of vascular parameters and nested-model regions less impacted by AIF-dispersion. The performance (Correlation coefficient and Adjusted R-squared for NCV test cohorts) of the AMs were: 0.914/0.834, 0.825/0.720, 0.938/0.880, and 0.890/0.792 for predictions of nested model regions, v(p), K(trans), and v(e), respectively. This study demonstrates an application of AMs that quickens and improves DCE-MRI based quantification of microvasculature properties of tumors and normal tissues relative to conventional approaches.

Neurosurgery
Bredel M, Espinosa L, Kim H, Scholtens DM, McElroy JP, Rajbhandari R, Meng W, Kollmeyer TM, **Malta TM**, Quezada MA, Harsh GR, Lobo-Jarne T, Solé L, Merati A, Nagaraja S, Nair S, White JJ, Thudi NK, Fleming JL, Webb A, Natsume A, Ogawa S, Weber RG, Bertran J, Haque SJ, Hentschel B, Miller CR, Furnari FB, Chan TA, Grosu AL, Weller M, Barnholtz-Sloan JS, Monje M, Noushmehr H, Jenkins RB, Rogers CL, MacDonald DR, Pugh SL, and Chakravarti A. Haploinsufficiency of NFKBIA reshapes the epigenome antipodal to the IDH mutation and imparts disease fate in diffuse gliomas. *Cell Rep Med* 2023; 4(6):101082. PMID: 37343523. Full Text

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Genetic alterations help predict the clinical behavior of diffuse gliomas, but some variability remains uncorrelated. Here, we demonstrate that haploinsufficient deletions of chromatin-bound tumor suppressor NFKB inhibitor alpha (NFKBIA) display distinct patterns of occurrence in relation to other genetic markers and are disproportionately present at recurrence. NFKBIA haploinsufficiency is associated with unfavorable patient outcomes, independent of genetic and clinicopathologic predictors. NFKBIA deletions reshape the DNA and histone methylome antipodal to the IDH mutation and induce a transcriptome landscape partly reminiscent of H3K27M mutant pediatric gliomas. In IDH mutant gliomas, NFKBIA deletions are common in tumors with a clinical course similar to that of IDH wild-type tumors. An externally validated nomogram model for estimating individual patient survival in IDH mutant gliomas confirms that NFKBIA deletions predict comparatively brief survival. Thus, NFKBIA haploinsufficiency aligns with distinct epigenome changes, portends a poor prognosis, and should be incorporated into models predicting the disease fate of diffuse gliomas.

Neurosurgery

Gielniewski B, Poleszak K, Roura AJ, Szadkowska P, Jacek K, Krol SK, Guzik R, Wiechecka P, Maleszewska M, Kaza B, Marchel A, Czernicki T, Koziarski A, Zielinski G, Styk A, Kawecki M, Szczylik C, Czepko R, Banach M, Kaspera W, Szopa W, Bujko M, Czapski B, Zabek M, Iżycka-Świeszewska E, Kloc W, Nauman P, Cieslewicz J, Grajkowska W, **Morosini N**, **Noushmehr H**, Wojtas B, and Kaminska B. Targeted sequencing of cancer-related genes reveals a recurrent TOP2A variant which affects DNA binding and coincides with global transcriptional changes in glioblastoma. *Int J Cancer* 2023; Epub ahead of print. PMID: 37338006. Full Text

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High-grade gliomas are aggressive, deadly primary brain tumors. Median survival of patients with glioblastoma (GBM, WHO grade 4) is 14 months and <10% of patients survive 2 years. Despite improved surgical strategies and forceful radiotherapy and chemotherapy, the prognosis of GBM patients is poor and did not improve over decades. We performed targeted next-generation sequencing with a custom panel of 664 cancer- and epigenetics-related genes, and searched for somatic and germline variants in 180 gliomas of different WHO grades. Herein, we focus on 135 GBM IDH-wild type samples. In parallel, mRNA sequencing was accomplished to detect transcriptomic abnormalities. We present the genomic alterations in high-grade gliomas and the associated transcriptomic patterns. Computational analyses and biochemical assays showed the influence of TOP2A variants on enzyme activities. In 4/135 IDH-wild type GBMs we found a novel, recurrent mutation in the TOP2A gene encoding topoisomerase 2A (allele frequency [AF] = 0.03, 4/135 samples). Biochemical assays with recombinant, wild type (WT) and variant proteins demonstrated stronger DNA binding and relaxation activity of the variant protein. GBM patients carrying the altered TOP2A had shorter overall survival (median OS 150 vs 500 days, P = .0018). In the GBMs with the TOP2A variant we found transcriptomic alterations consistent with splicing dysregulation. luA novel, recurrent TOP2A mutation, which was found exclusively in four GBMs, results in the TOP2A E948Q variant with altered DNA binding and relaxation activities. The deleterious TOP2A mutation resulting in transcription deregulation in GBMs may contribute to disease pathology.

Neurosurgery

Hamilton T, **Bartlett S**, **Deshpande N**, **Hadi M**, **Reese JC**, **Mansour TR**, **Telemi E**, **Springer K**, **Schultz L**, **Nerenz DR**, **Abdulhak M**, Soo T, **Schwalb J**, Khalil JG, Aleem I, Easton R, Perez-Cruet M, Park P, and **Chang V**. Association of prolonged symptom duration with poor outcomes in lumbar spine surgery: a Michigan Spine Surgery Improvement Collaborative study. *J Neurosurg Spine* 2023; 1-10. Epub ahead of print. PMID: 37347591. Full Text

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OBJECTIVE: There is a scarcity of large multicenter data on how preoperative lumbar symptom duration relates to postoperative patient-reported outcomes (PROs). The objective of this study was to determine the effect of preoperative and baseline symptom duration on PROs at 90 days, 1 year, and 2 years after lumbar spine surgery. METHODS: The Michigan Spine Surgery Improvement Collaborative registry was queried for all lumbar spine operations between January 1, 2017, to December 31, 2021, with a follow-up

of 2 years. Patients were stratified into three subgroups based on symptom duration: < 3 months, 3 months to < 1 year, and ≥ 1 year. The primary outcomes were reaching the minimal clinically important difference (MCID) for the PROs (i.e., leg pain, Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF), EQ-5D, North American Spine Society satisfaction, and return to work). The EQ-5D score was also analyzed as a continuous variable to calculate quality-adjusted life years. Multivariable Poisson generalized estimating equation models were used to report adjusted risk ratios, with the < 3-month cohort used as the reference. RESULTS: There were 37,223 patients (4670 with < 3-month duration, 9356 with 3-month to < 1-year duration, and 23,197 with ≥ 1-year duration) available for analysis. Compared with patients with a symptom duration of < 1 year, patients with a symptom duration of ≥ 1 year were significantly less likely to achieve an MCID in PROMIS PF, EQ-5D, back pain relief, and leg pain relief at 90 days, 1 year, and 2 years postoperatively. Similar trends were observed for patient satisfaction and return to work. With the EQ-5D score as a continuous variable, a symptom duration of ≥ 1 year was associated with 0.04, 0.05, and 0.03 ($p < 0.001$) decreases in EQ-5D score at 90 days, 1 year, and 2 years after surgery, respectively. CONCLUSIONS: A symptom duration of ≥ 1 year was associated with poorer outcomes on several outcome metrics. This suggests that timely referral and surgery for degenerative lumbar pathology may optimize patient outcome.

Neurosurgery
Kocakavuk E, Johnson KC, **Sabedot TS**, Reinhardt HC, **Noushmehr H**, and Verhaak RGW. Hemizygous CDKN2A deletion confers worse survival outcomes in IDHmut-noncodel gliomas. *Neuro Oncol* 2023; Epub ahead of print. PMID: 37329568. Full Text

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Neurosurgery
Nulty P, **Mason W**, **Peterson EL**, **Cook B**, **Rock J**, **Eide J**, and **Craig JR**. Using Ipratropium Bromide Nasal Spray Response as a Screening Tool in the Diagnostic Workup of Cerebrospinal Fluid Rhinorrhea. *Laryngoscope* 2023; Epub ahead of print. PMID: 37265206. Full Text

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OBJECTIVES: Unilateral clear thin rhinorrhea (UCTR) can be concerning for a nasal cerebrospinal fluid (CSF) leak. Beta-2 transferrin electrophoresis has been the gold standard for initial non-invasive confirmatory testing for CSF rhinorrhea, but there can be issues with fluid collection and testing errors. Ipratropium bromide nasal spray (IBNS) is highly effective at reducing rhinitis-related rhinorrhea, and should presumably not resolve CSF rhinorrhea. This study assessed whether different clinical features and IBNS response helped predict presence or absence of CSF rhinorrhea. METHODS: A prospective cohort study was conducted where all patients with UCTR had nasal fluid tested for beta-2 transferrin, and were prescribed 0.06% IBNS. Patients were diagnosed with CSF rhinorrhea or other rhinologic conditions. Clinical variables like IBNS response (rhinorrhea reduction), positional worsening, salty taste, postoperative state, female gender, and body-mass index were assessed for their ability to predict CSF rhinorrhea. Sensitivity, specificity, and predictive values and odds ratios were calculated for all clinical variables. RESULTS: Twenty patients had CSF rhinorrhea, and 53 had non-CSF etiologies. Amongst clinical variables assessed for predicting CSF absence or presence, significant associations were shown for IBNS response (OR = 844.66, p = 0.001), positional rhinorrhea worsening (OR = 8.22, p = 0.049), and body-mass index ≥30 (OR = 2.92, p = 0.048). IBNS response demonstrated 96% sensitivity and 100% specificity, and 100% positive and 91% negative predictive values for predicting CSF rhinorrhea. CONCLUSIONS: In patients with UCTR, 0.06% IBNS response is an excellent screening tool for

excluding CSF rhinorrhea, and should be considered in the diagnostic workup of CSF rhinorrhea. LEVEL OF EVIDENCE: 2 Laryngoscope, 2023.

Neurosurgery
Peart R, Melnick K, Cibula J, **Walbert T**, Gerstner ER, Rahman M, Peters KB, Mrugala M, and Ghiaseddin A. Clinical management of seizures in patients with meningiomas: Efficacy of surgical resection for seizure control and patient-tailored postoperative anti-epileptic drug management. *Neurooncol Adv* 2023; 5(Suppl 1):i58-i66. PMID: 37287578. Full Text

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Meningiomas are the most common primary intracranial tumor. They are slow growing and often incidentally found tumors that arise from the arachnoid villi. As they grow, they have a greater likelihood of becoming symptomatic with seizures being one of the most clinically significant symptoms. Seizures are more likely to present as a symptom of larger meningiomas and meningiomas that compress cortical areas particularly those in non-skull base locations. These seizures are often managed medically, utilizing the same anti-seizure medications that are used to treat other causes of epilepsy. We discuss common anti-seizure medications used including valproate, phenobarbital, carbamazepine, phenytoin, lacosamide, lamotrigine, levetiracetam and topiramate and their common adverse effects. The goal of pharmacotherapy for seizure control is to maximize seizure control while minimizing the adverse effects of the medication. The decision to provide medical management is dependent on individual seizure history and plans for surgical treatment. Patients who did not require seizure prophylaxis before surgery are commonly prescribed seizure prophylaxis postoperatively. Symptomatic meningiomas not controlled by medical management alone are commonly evaluated for surgical resection. The efficacy of surgical resection in providing seizure freedom is dependent on several features of the tumor including tumor size, the extent of the peritumoral edema, the number of tumors, sinus infiltration and the degree of resection.

Neurosurgery
Telemi E, and **Chang V**. Minimally Invasive Transforaminal Thoracic Interbody Fusion: 2-Dimensional Operative Video. *Oper Neurosurg (Hagerstown)* 2023; Epub ahead of print. PMID: 37307059. Full Text

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

Neurosurgery
Wang J, **Adrianto I**, **Subedi K**, **Liu T**, **Wu X**, **Yi Q**, **Loveless I**, **Yin C**, **Datta I**, Sant'Angelo DB, Kronenberg M, **Zhou L**, and **Mi QS**. Integrative scATAC-seq and scRNA-seq analyses map thymic iNKT cell development and identify Cbfβ for its commitment. *Cell Discov* 2023; 9(1):61. PMID: 37336875. Full Text

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Unlike conventional αβT cells, invariant natural killer T (iNKT) cells complete their terminal differentiation to functional iNKT1/2/17 cells in the thymus. However, underlying molecular programs that guide iNKT subset differentiation remain unclear. Here, we profiled the transcriptomes of over 17,000 iNKT cells and the chromatin accessibility states of over 39,000 iNKT cells across four thymic iNKT developmental stages using single-cell RNA sequencing (scRNA-seq) and single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) to define their developmental trajectories. Our study discovered novel features for iNKT precursors and different iNKT subsets and indicated that iNKT2 and iNKT17 lineage commitment may occur as early as stage 0 (ST0) by two distinct programs, while iNKT1 commitments may occur post ST0. Both iNKT1 and iNKT2 cells exhibit extensive phenotypic and functional heterogeneity, while iNKT17 cells are relatively homogenous. Furthermore, we identified that a novel transcription factor, Cbfβ, was highly expressed in iNKT progenitor commitment checkpoint, which showed a similar expression trajectory with other known transcription factors for iNKT cells development, Zbtb16 and Egr2, and could direct iNKT cells fate and drive their effector phenotype differentiation. Conditional deletion of Cbfβ blocked early iNKT cell development and led to severe impairment of iNKT1/2/17 cell differentiation. Overall, our findings uncovered distinct iNKT developmental programs as well as their cellular heterogeneity, and identified a novel transcription factor Cbfβ as a key regulator for early iNKT cell commitment.

Neurosurgery

Youngerman BE, Banu MA, Khan F, McKhann GM, Schevon CA, Jagid JR, Cajigas I, Theodotou CB, Ko A, Buckley R, Ojemann JG, Miller JW, Laxton AW, Couture DE, Popli GS, Buch VP, Halpern CH, Le S, Sharan AD, Sperling MR, Mehta AD, Englot DJ, Neimat JS, Konrad PE, Sheth SA, Neal EG, Vale FL, Holloway KL, **Air EL**, **Schwalb JM**, D'Haese PF, and Wu C. Long-term outcomes of mesial temporal laser interstitial thermal therapy for drug-resistant epilepsy and subsequent surgery for seizure recurrence: a multi-centre cohort study. *J Neurol Neurosurg Psychiatry* 2023; Epub ahead of print. PMID: 37336643. Full Text

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BACKGROUND: Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) is a minimally invasive alternative to surgical resection for drug-resistant mesial temporal lobe epilepsy (mTLE). Reported rates of seizure freedom are variable and long-term durability is largely unproven. Anterior temporal lobectomy (ATL) remains an option for patients with MRgLITT treatment failure. However, the safety and efficacy of this staged strategy is unknown. METHODS: This multicentre, retrospective cohort study included 268 patients consecutively treated with mesial temporal MRgLITT at 11 centres between 2012 and 2018. Seizure outcomes and complications of MRgLITT and any subsequent surgery are reported. Predictive value of preoperative variables for seizure outcome was assessed. RESULTS: Engel I seizure freedom was achieved in 55.8% (149/267) at 1 year, 52.5% (126/240) at 2 years and 49.3% (132/268) at the last follow-up ≥1 year (median 47 months). Engel I or II outcomes were achieved in 74.2% (198/267) at 1 year, 75.0% (180/240) at 2 years and 66.0% (177/268) at the last follow-up. Preoperative focal to bilateral tonic-clonic seizures were independently associated with seizure recurrence. Among patients with seizure recurrence, 14/21 (66.7%) became seizure-free after subsequent ATL and 5/10 (50%) after repeat MRgLITT at last follow-up≥1 year. CONCLUSIONS: MRgLITT is a viable treatment with durable outcomes for patients with drug-resistant mTLE evaluated at a comprehensive epilepsy centre. Although seizure freedom rates were lower than reported with ATL, this series represents the early experience of each centre and a heterogeneous cohort. ATL remains a safe and effective treatment for well-selected patients who fail MRgLITT.

Nursing

Wojack CA, **Marrocco AM**, Enstrom JC, and Casida J. Thromboelastography: A Novel Approach to Hemostasis in Cardiac Surgery. *AACN Adv Crit Care* 2023; 34(2):139-144. PMID: 37289626. Request Article

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Jeanne Caitlyn Enstrom is Instructor of Nursing, Vanderbilt University School of Nursing, and Nurse Practitioner, Cardiac Intensive Care Unit, Nashville, Tennessee.
Jesus Casida is Endowed Professor and Executive Director, Eleanor Mann School of Nursing, University of Arkansas, Fayetteville, Arkansas.

Ophthalmology and Eye Care Services

Kasetty VM, **Hamati J**, Li H, **Goldman DJ**, and **Ober MD**. Analysis of AUPO-Compliant Vitreoretinal Surgery Fellowship Directors. *Ophthalmol Retina* 2023; Epub ahead of print. PMID: 37331656. Request Article

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We provide an overview of the background and achievements of vitreoretinal surgery fellowship directors. Overall, they have excellent academic records. Women fellowship directors are underrepresented proportionally to current trainees and demographic trends in the field.

Orthopedics/Bone and Joint Center

Gaio NM, **Turner EHG**, and Spiker AM. Hip Manipulation Under Anesthesia for Post-Hip Arthroscopy Pericapsular Scarring: Indications and Techniques. *Arthrosc Tech* 2023; 12(6):e983-e989. Full Text

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Hip arthroscopy has become an increasingly common procedure with expanding indications over the last several decades. With the increase in number of procedures performed a complication profile has emerged, although there is yet to be a formal classification system for complications. The most cited complications include lateral femoral cutaneous nerve neuropraxia, other sensory deficits, chondral or labral iatrogenic damage, superficial infection and deep vein thrombosis. One complication that has not yet been well documented in the literature is pericapsular scarring/adhesions resulting in decreased hip range of motion and function. If this complication is noted to persist after adequate impingement resection and a rigorous post-operative physical therapy regimen, the senior author has addressed this with a hip manipulation under anesthesia. Therefore, this techniques paper aims to describe pericapsular scarring as a post hip-arthroscopy condition which may cause pain and demonstrate our technique to address this diagnosis through hip manipulation under anesthesia.

Orthopedics/Bone and Joint Center

Makhni EC, and **Hennekes ME**. The Use of Patient-Reported Outcome Measures in Clinical Practice and Clinical Decision Making. *J Am Acad Orthop Surg* 2023; Epub ahead of print. PMID: 37364243. Full Text

From the Henry Ford Health, Detroit, MI.

Patient-reported outcome measures (PROMs) are highly effective measures of quality of care and outcomes that matter to patients regarding their physical, mental, and social health. While PROMs have played a notable role in research and registry reporting, they are also useful as clinical tools. Real-time PROM collection can be integrated into routine clinical care with immediate access to scores within the electronic health record. This can be integral when discussing treatment options and using decision aids. PROM scores can also be useful for postoperative monitoring. Various approaches to quantifying clinical efficacy have been developed, including the minimal clinically important difference, the substantial clinical benefit, and the patient acceptable symptom state (PASS). As the patient experience and patient-reported outcome measurement of health-related outcomes become increasingly emphasized in patient-centered, high value care, so too will the importance of methods to gauge clinical benefit using these instruments for improved clinical decision-making.

Orthopedics/Bone and Joint Center

Rahman TM, **Hansen L**, **Blackmond N**, **Sandhu A**, **Shaw JH**, and **Davis JJ**. Impact of Alignment and Alignment Correction on Outcomes Following Robotic Medial Unicompartmental Knee Arthroplasty. *J Arthroplasty* 2023; Epub ahead of print. PMID: 37271235. Full Text

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BACKGROUND: The purpose of this study was to retrospectively examine the relationship between preoperative and postoperative alignment in robotic unicompartmental knee arthroplasty (UKA) and postoperative patient-reported outcome measures. METHODS: A retrospective review of 374 patients who underwent robotic-assisted UKA was conducted. Patient demographics, history, and preoperative and postoperative Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS-JR) scores were obtained via chart review. Average follow-up period was 2.4 years (range: 0.4 to 4.5 years) to chart review and 9.5 months (range: 6 to 48 months) to latest KOOS-JR. Preoperative and postoperative robotically-measured knee alignment was obtained from operative reports. Incidence of conversion to total knee arthroplasty (TKA) was determined by review of a health information exchange tool. RESULTS: Multivariate regressions showed no statistically significant relationship between preoperative alignment, postoperative alignment, or degrees of alignment correction and change in KOOS-JR score or achievement of KOOS-JR minimal clinically important difference (MCID) ($P > .05$). Patients who had >8 degrees of postoperative varus alignment had on average a 20% lower achievement of KOOS-JR MCID compared to patients who had <8 degrees of postoperative varus alignment; however, this difference was not statistically significant ($P > .05$). There were 3 patients who required conversion to TKA in the follow-up period, with no significant relationship to alignment variables ($P > .05$). CONCLUSION: There was no significant difference in KOOS-JR change for those patients who had a larger or smaller degree of deformity correction, and correction did not predict MCID achievement.

Orthopedics/Bone and Joint Center

Wilson TG, **Baghel M**, **Kaur N**, **Moutzouros V**, **Davis J**, and **Ali SA**. Characterization of miR-335-5p and miR-335-3p in human osteoarthritic tissues. *Arthritis Res Ther* 2023; 25(1):105. PMID: 37328905. Full Text

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OBJECTIVE: We aimed to characterize the expression patterns, gene targets, and functional effects of miR-335-5p and miR-335-3p among seven primary human knee and hip osteoarthritic tissue types. METHODS: We collected synovial fluid, subchondral bone, articular cartilage, synovium, meniscus/labrum, infrapatellar/acetabular fat, anterior cruciate ligament/ligamentum teres, and vastus medialis oblique/quadratus femoris muscle (n = 7-20) from surgical patients with early- or late-stage osteoarthritis (OA) and quantified miR-335-5p and miR-335-3p expression by real-time PCR. Predicted gene targets were measured in knee OA infrapatellar fat following miRNA inhibitor transfection (n = 3), and prioritized gene targets were validated following miRNA inhibitor and mimic transfection (n = 6). Following pathway analyses, we performed Oil-Red-O staining to assess changes in total lipid content in infrapatellar fat. RESULTS: Showing a 227-fold increase in knee OA infrapatellar fat (the highest expressing tissue) versus meniscus (the lowest expressing tissue), miR-335-5p was more abundant than miR-335-3p (92-fold increase). MiR-335-5p showed higher expression across knee tissues versus hip tissues, and in late-stage versus early-stage knee OA fat. Exploring candidate genes, VCAM1 and MMP13 were identified as putative direct targets of miR-335-5p and miR-335-3p, respectively, showing downregulation with miRNA mimic transfection. Exploring candidate pathways, predicted miR-335-5p

gene targets were enriched in a canonical adipogenesis network (p = 2.1e - 5). Modulation of miR-335-5p in late-stage knee OA fat showed an inverse relationship to total lipid content. CONCLUSION: Our data suggest both miR-335-5p and miR-335-3p regulate gene targets in late-stage knee OA infrapatellar fat, though miR-335-5p appears to be more prominent, with tissue-, joint-, and stage-specific effects.

Otolaryngology – Head and Neck Surgery
Choi E, **Leonard KW**, **Jassal JS**, **Levin AM**, **Ramachandra V**, and **Jones LR**. Artificial Intelligence in Facial Plastic Surgery: A Review of Current Applications, Future Applications, and Ethical Considerations. *Facial Plast Surg* 2023; Epub ahead of print. PMID: 37353051. Request Article

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From virtual chat assistants to self-driving cars, artificial intelligence (AI) is often heralded as the technology that has and will continue to transform this generation. Among widely adopted applications in other industries, its potential use in medicine is being increasingly explored, where the vast amounts of data present in electronic health records and need for continuous improvements in patient care and workflow efficiency present many opportunities for AI implementation. Indeed, AI has already demonstrated capabilities for assisting in tasks such as documentation, image classification, and surgical outcome prediction. More specifically, this technology can be harnessed in facial plastic surgery, where the unique characteristics of the field lends itself well to specific applications. AI is not without its limitations, however, and the further adoption of AI in medicine and facial plastic surgery must necessarily be accompanied by discussion on the ethical implications and proper usage of AI in healthcare. In this article, we review current and potential uses of AI in facial plastic surgery, as well as its ethical ramifications.

Otolaryngology – Head and Neck Surgery
Deeb R. Ethnically Sensitive Rhinoplasty. *Facial Plast Surg* 2023; Epub ahead of print. PMID: 37279876. Request Article

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Ethnically sensitive rhinoplasty presents a unique challenge. There are a large number of variations in skin tone, skin thickness, and structural deformities, which require a high degree of thoughtfulness and planning. A thorough history and physical examination are the cornerstone to achieving a good result. An open and honest discussion is necessary to fully understand the patient's goals. The surgeon should clearly define which goals are achievable and which are not. An individualized approach with special consideration toward maintaining ethnic heritage is imperative. Conservative techniques will help achieve a natural, balanced outcome and will allow for preservation of nasal function.

Otolaryngology – Head and Neck Surgery
Mansour Y, and Kulesza R. Noradrenergic axons hitch hiking along the human abducens nerve. *Anat Cell Biol* 2023; 56(2):271-275. 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.

Otolaryngology – Head and Neck Surgery
Mason W, **Levin AM**, **Buhl K**, **Ouchi T**, **Parker B**, **Tan J**, Ashammakhi N, and **Jones L**. Translational Research Techniques for the Facial Plastic Surgeon: An Overview. *Facial Plast Surg* 2023; Epub ahead of print. PMID: 37339663. Request Article

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The field of Facial Plastic and Reconstructive Surgery (FPRS) is an incredibly diverse, multi-specialty field that seeks innovative and novel solutions for the management of physical defects on the head and neck. To aid in the advancement of medical and surgical treatments for these defects, there has been a recent emphasis on the importance of translational research. With recent technological advancements, there are now a myriad of research techniques that are widely accessible for physician and scientist use in translational research. Such techniques include integrated multiomics, advanced cell culture and microfluidic tissue models, established animal models, and emerging computer models generated using bioinformatics. The following article discusses these various research techniques and how they have and can be used for research in the context of various important diseases within the field of FPRS.

Otolaryngology – Head and Neck Surgery
Nulty P, **Mason W**, **Peterson EL**, **Cook B**, **Rock J**, **Eide J**, and **Craig JR**. Using Ipratropium Bromide Nasal Spray Response as a Screening Tool in the Diagnostic Workup of Cerebrospinal Fluid Rhinorrhea. *Laryngoscope* 2023; Epub ahead of print. PMID: 37265206. Full Text

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OBJECTIVES: Unilateral clear thin rhinorrhea (UCTR) can be concerning for a nasal cerebrospinal fluid (CSF) leak. Beta-2 transferrin electrophoresis has been the gold standard for initial non-invasive confirmatory testing for CSF rhinorrhea, but there can be issues with fluid collection and testing errors. Ipratropium bromide nasal spray (IBNS) is highly effective at reducing rhinitis-related rhinorrhea, and should presumably not resolve CSF rhinorrhea. This study assessed whether different clinical features and IBNS response helped predict presence or absence of CSF rhinorrhea. METHODS: A prospective cohort study was conducted where all patients with UCTR had nasal fluid tested for beta-2 transferrin, and were prescribed 0.06% IBNS. Patients were diagnosed with CSF rhinorrhea or other rhinologic conditions. Clinical variables like IBNS response (rhinorrhea reduction), positional worsening, salty taste, postoperative state, female gender, and body-mass index were assessed for their ability to predict CSF rhinorrhea. Sensitivity, specificity, and predictive values and odds ratios were calculated for all clinical variables. RESULTS: Twenty patients had CSF rhinorrhea, and 53 had non-CSF etiologies. Amongst clinical variables assessed for predicting CSF absence or presence, significant associations were shown for IBNS response (OR = 844.66, p = 0.001), positional rhinorrhea worsening (OR = 8.22, p = 0.049), and body-mass index ≥30 (OR = 2.92, p = 0.048). IBNS response demonstrated 96% sensitivity and 100% specificity, and 100% positive and 91% negative predictive values for predicting CSF rhinorrhea. CONCLUSIONS: In patients with UCTR, 0.06% IBNS response is an excellent screening tool for

excluding CSF rhinorrhea, and should be considered in the diagnostic workup of CSF rhinorrhea. LEVEL OF EVIDENCE: 2 Laryngoscope, 2023.

Otolaryngology – Head and Neck Surgery
Pandrangi VC, Mace JC, Abiri A, Adappa ND, Beswick DM, Chang EH, **Eide JG**, Fung N, Hong M, Johnson BJ, Kohanski MA, Kshirsagar RS, Kuan EC, Le CH, Lee JT, Nabavizadeh SA, Obermeyer IP, Palmer JN, Pinheiro-Neto CD, Smith TL, Snyderman CH, Suh JD, Wang EW, Wang MB, Choby G, and Geltzeiler M. Recurrence patterns among patients with sinonasal mucosal melanoma: A multi-institutional study. *Int Forum Allergy Rhinol* 2023; Epub ahead of print. PMID: 37265013. Full Text

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OBJECTIVE: To evaluate recurrence patterns and survival after recurrence among patients with sinonasal mucosal melanoma (SNMM). METHODS: This was a multi-institutional retrospective review from seven U.S. institutions of patients with SNMM from 1991 to 2022. Recurrence was categorized as local, regional, distant, or multifocal. Kaplan-Meier tests were used to evaluate disease-free survival (DFS), overall survival (OS), and post-recurrence survival (PRS) reported with standard errors (SE) and log-rank testing used for comparison. Cox-regression was further used, with hazard ratios (HR) and 95% confidence intervals (CI) reported. RESULTS: Among 196 patients with SNMM, there were 146 patients with recurrence (74.5%). Among all patients, 60-month DFS (SE) was 15.5% (2.9%), 60-month OS (SE) was 44.7% (3.7%), mean age ± standard deviation at diagnosis was 69.7 ± 12.5 years, and 54.6% were female. In 26 patients who underwent primary treatment of the neck, 60-month DFS did not differ from no treatment ($p > 0.05$). Isolated distant recurrence was most common (42.8%), followed by local (28.3%), multifocal (20.7%), and regional recurrence (8.3%). Among patients with regional recurrence in the neck, there was no 60-month PRS benefit for patients undergoing salvage neck dissection or radiation ($p > 0.05$). Among patients with distant recurrence, only immunotherapy was associated with improved 12-month PRS (HR = 0.32, 95% CI = 0.11-0.92, $p = 0.034$), and no treatment group was associated with improved 24- or 60-month PRS ($p > 0.05$). CONCLUSION: SNMM is associated with a high recurrence rate and poor survival. Primary treatment of the neck was not associated with reduced recurrence, and immunotherapy for treatment of distant recurrence was associated with increased 12-month PRS.

Pathology and Laboratory Medicine
Jarrah J, **Alsaadi A**, **Putman EM**, and **Williams J**. Polymicrobial bacteremia in a heart transplant recipient: More than what meets the eye. *Am J Transplant* 2023; 23(6):854-856. Full Text

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Pathology and Laboratory Medicine
Kezlarian B, **Montecalvo J**, Bodd FM, Chang JC, Riedel E, White C, Rekhtman N, and Sauter JL. Diagnosis of thoracic SMARCA4-deficient undifferentiated tumor in cytology. *Cancer Cytopathol* 2023; Epub ahead of print. PMID: 37278102. Full Text

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INTRODUCTION: Although alterations in SMARCA4-deficient occur in non-small cell lung carcinoma (SD-NSCLC), thoracic SMARCA4-deficient undifferentiated tumor (TSDUT) is recognized as a distinct entity in the 2021 World Health Organization Classification of Thoracic Tumors because of unique morphologic, immunophenotypic and molecular features, and worse survival compared with SD-NSCLC. Cytologic diagnosis of TSDUT is clinically important because of its aggressive behavior and because it is often diagnosed by fine-needle aspiration because TSDUTs are usually unresectable at presentation. Here, we identify cytologic features that can be used for recognition of TSDUT and distinction from SD-NSCLC. MATERIALS AND METHODS: Cytomorphologic features were investigated in cytology specimens from patients with TSDUT (n = 11) and compared with a control group of patients with SD-NSCLC (n = 20). RESULTS: The presence of classic rhabdoid morphology, at least focally, was entirely specific for TSDUT (n = 6, 55%) compared with SD-NSCLC (n = 0) in this study. TSDUT more frequently showed tumor necrosis (n = 11, 100% vs. n = 8, 40%; p = .001), dominant single-cell pattern on aspirate smears or touch preparation slides (n = 8 [of 9], 80% vs. n = 3, 15%; p = .010), nuclear molding (n = 5, 45% vs. n = 1, 5%; p = .013), and indistinct cell borders (n = 11, 100% vs. n = 5, 25%; P < .001) compared with SD-NSCLC, respectively. CONCLUSIONS: Cytomorphologic features occurring more frequently in TSDUT include tumor necrosis, dominant single-cell pattern, nuclear molding indistinct cell borders, and focal rhabdoid cells. Presence of these features in a cytology specimen of an undifferentiated tumor, particularly in a patient with a thoracic mass, should raise suspicion for TSDUT and prompt appropriate ancillary workup.

Pathology and Laboratory Medicine

Nulty P, **Mason W**, **Peterson EL**, **Cook B**, **Rock J**, **Eide J**, and **Craig JR**. Using Ipratropium Bromide Nasal Spray Response as a Screening Tool in the Diagnostic Workup of Cerebrospinal Fluid Rhinorrhea. *Laryngoscope* 2023; Epub ahead of print. PMID: 37265206. Full Text

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OBJECTIVES: Unilateral clear thin rhinorrhea (UCTR) can be concerning for a nasal cerebrospinal fluid (CSF) leak. Beta-2 transferrin electrophoresis has been the gold standard for initial non-invasive confirmatory testing for CSF rhinorrhea, but there can be issues with fluid collection and testing errors. Ipratropium bromide nasal spray (IBNS) is highly effective at reducing rhinitis-related rhinorrhea, and should presumably not resolve CSF rhinorrhea. This study assessed whether different clinical features and IBNS response helped predict presence or absence of CSF rhinorrhea. METHODS: A prospective cohort study was conducted where all patients with UCTR had nasal fluid tested for beta-2 transferrin, and were prescribed 0.06% IBNS. Patients were diagnosed with CSF rhinorrhea or other rhinologic conditions. Clinical variables like IBNS response (rhinorrhea reduction), positional worsening, salty taste, postoperative state, female gender, and body-mass index were assessed for their ability to predict CSF rhinorrhea. Sensitivity, specificity, and predictive values and odds ratios were calculated for all clinical variables. RESULTS: Twenty patients had CSF rhinorrhea, and 53 had non-CSF etiologies. Amongst clinical variables assessed for predicting CSF absence or presence, significant associations were shown for IBNS response (OR = 844.66, p = 0.001), positional rhinorrhea worsening (OR = 8.22, p = 0.049), and body-mass index ≥30 (OR = 2.92, p = 0.048). IBNS response demonstrated 96% sensitivity and 100% specificity, and 100% positive and 91% negative predictive values for predicting CSF rhinorrhea. CONCLUSIONS: In patients with UCTR, 0.06% IBNS response is an excellent screening tool for excluding CSF rhinorrhea, and should be considered in the diagnostic workup of CSF rhinorrhea. LEVEL OF EVIDENCE: 2 Laryngoscope, 2023.

Pathology and Laboratory Medicine
Samuel L. Preface. *Clin Lab Med* 2023; 43(2):ix-x. PMID: 37169448. Full Text

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Pathology and Laboratory Medicine
Wald AI, Pingpank JF, Ongchin M, Hall LB, Jones H, Altpeter S, Liebdzinski M, Hamed AB, Derby J, Nikiforova MN, Bell PD, Paniccia A, Zureikat AH, Gorantla VC, Rhee JC, Thomas R, Bartlett DL, Smith K, Henn P, **Theisen BK**, Shyu S, Shalaby A, Choudry MHA, and Singhi AD. Targeted Next-Generation Sequencing Improves the Prognostication of Patients with Disseminated Appendiceal Mucinous Neoplasms (Pseudomyxoma Peritonei). *Ann Surg Oncol* 2023; Epub ahead of print. PMID: 37314541. Full Text

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BACKGROUND: Appendiceal mucinous neoplasms (AMNs) with disseminated disease (pseudomyxoma peritonei) are heterogeneous tumors with variable clinicopathologic behavior. Despite the development of prognostic systems, objective biomarkers are needed to stratify patients. With the advent of next-generation sequencing (NGS), it remains unclear if molecular testing can improve the evaluation of disseminated AMN patients. METHODS: Targeted NGS was performed for 183 patients and correlated with clinicopathologic features to include American Joint Committee on Cancer/World Health Organization (AJCC/WHO) histologic grade, peritoneal cancer index (PCI), completeness of cytoreduction (CC) score, and overall survival (OS). RESULTS: Genomic alterations were identified for 179 (98%) disseminated AMNs. Excluding mitogen-activated protein kinase genes and GNAS due to their ubiquitous nature, collective genomic alterations in TP53, SMAD4, CDKN2A, and the mTOR genes were associated with older mean age, higher AJCC/WHO histologic grade, lymphovascular invasion, perineural invasion, regional lymph node metastasis, and lower mean PCI ($p < 0.040$). Patients harboring TP53, SMAD4, ATM, CDKN2A, and/or mTOR gene alterations were found to have lower OS rates of 55% at 5 years and 14% at 10 years, compared with 88% at 5 years and 88% at 10 years for patients without the aforementioned alterations ($p < 0.001$). Based on univariate and multivariate analyses, genomic alterations in TP53, SMAD4, ATM, CDKN2A, and/or the mTOR genes in disseminated AMNs were a negative prognostic factor for OS and independent of AJCC/WHO histologic grade, PCI, CC score, and hyperthermic intraperitoneal chemotherapy treatment ($p = 0.006$). CONCLUSIONS: Targeted NGS improves the prognostic assessment of patients with disseminated AMNs and identifies patients who may require increased surveillance and/or aggressive management.

Pathology and Laboratory Medicine
Wald AI, Pingpank JF, Ongchin M, Hall LB, Jones H, Altpeter S, Liebdzinski M, Hamed AB, Derby J, Nikiforova MN, Bell PD, Paniccia A, Zureikat AH, Gorantla VC, Rhee JC, Thomas R, Bartlett DL, Smith K, Henn P, **Theisen BK**, Shyu S, Shalaby A, Choudry MHA, and Singhi AD. ASO Visual Abstract: Targeted Next-Generation Sequencing Improves the Prognostication of Patients with Disseminated Appendiceal Mucinous Neoplasms (Pseudomyxoma Peritonei). *Ann Surg Oncol* 2023; Epub ahead of print. PMID: 37378848. Full Text

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Pharmacy
August BA, Kale-Pradhan PB, Giuliano C, and Johnson LB. Biomarkers in the intensive care setting: A focus on using procalcitonin and C-reactive protein to optimize antimicrobial duration of therapy. *Pharmacotherapy* 2023; Epub ahead of print. PMID: 37300522. Full Text

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Managing the critically ill patient with infection is complex, requiring clinicians to synthesize considerable information relating to antimicrobial efficacy and treatment duration. The use of biomarkers may play an important role in identifying variation in treatment response and providing information about treatment efficacy. Though a vast number of biomarkers for clinical application have been described, procalcitonin and C-reactive protein (CRP) are the most thoroughly investigated in the critically ill. However, the presence of heterogeneous populations, variable end points, and incongruent methodology in the literature complicates the use of such biomarkers to guide antimicrobial therapy. This review focuses on an appraisal of evidence for use of procalcitonin and CRP to optimize antimicrobial duration of therapy (DOT) in critically ill patients. Procalcitonin-guided antimicrobial therapy in mixed critically ill populations with varying degrees of sepsis appears to be safe and might assist in reducing antimicrobial DOT. Compared to procalcitonin, fewer studies exist examining the impact of CRP on antimicrobial DOT and clinical outcomes in the critically ill. Procalcitonin and CRP have been insufficiently studied in many key intensive care unit populations, including surgical patients with concomitant trauma, renally insufficient populations, the immunocompromised, and patients with septic shock. We believe the available evidence is not strong enough to warrant routine use of procalcitonin or CRP to guide antimicrobial DOT in critically ill patients with infection. So long as its limitations are recognized, procalcitonin could be considered to tailor antimicrobial DOT on a case-by-case basis in the critically ill patient.

Pharmacy
DeKoven S, **Naccarato M**, Brumme CJ, and Tan DHS. Treatment-emergent reverse transcriptase resistance during antiretroviral therapy with bictegravir, tenofovir alafenamide, and emtricitabine: A case series. *HIV Med* 2023; Epub ahead of print. PMID: 37317505. Full Text

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OBJECTIVES: Bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) is a complete regimen for the treatment of HIV with a high barrier to resistance and few reported cases of treatment failure. We present three cases of treatment-emergent resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in patients with suboptimal treatment adherence and assess whether the resistance-associated mutations were present before BIC/TAF/FTC initiation or emerged during therapy. METHODS: We used genotypic drug resistance testing by Sanger sequencing to identify emergent resistance mutations in plasma viral load specimens collected after combination antiretroviral therapy initiation in all participants. Additionally, we performed ultra-deep sequencing by Illumina MiSeq on the earliest available plasma HIV-1 viral load specimen and on any available specimens closest in time to the initiation of BIC/TAF/FTC therapy to identify low-abundance resistance mutations present in the viral quasispecies. RESULTS: All three participants developed NRTI resistance after prolonged exposure and incomplete adherence to BIC/TAF/FTC. The T69N, K70E, M184I, and/or T215I mutations identified in clinical samples at the time of virological failure were not present on deep sequencing of either baseline samples or samples collected before BIC/TAF/FTC initiation. CONCLUSIONS: Despite a generally high genetic barrier to resistance, NRTI resistance-associated mutations may emerge during therapy with BIC/TAF/FTC in the setting of suboptimal adherence.

Pharmacy

Johnson JM, Yost RJ, Pangrazzi MH, Golden KA, Soubani AO, and Wahby KA. Azithromycin and Septic Shock Outcomes. *J Pharm Pract* 2023; 36(3):559-565. PMID: 34967253. Full Text

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Introduction: Although there is evidence describing the immunomodulatory effects of macrolide antibiotics, there is little literature exploring the clinical effects these properties may have and their impact on measurable outcomes. Objective: The purpose of this study was to determine if empiric antimicrobial regimens containing azithromycin shorten time to shock resolution. Methods: A retrospective study was performed in adults with septic shock admitted to intensive care units (ICUs) of 3 university-affiliated, urban teaching hospitals between June 2012 and June 2016. Eligible patients with septic shock required treatment with norepinephrine as the first-line vasopressor for a minimum of 4 hours and received at least 48 hours of antimicrobial treatment from the time of shock onset. Propensity scores were utilized to match patients who received azithromycin to those who did not. Results: A total of 3116 patients met initial inclusion criteria. After propensity score matching, 258 patients were included, with 124 and 134 patients in the azithromycin and control groups, respectively. Median shock duration was similar in patients treated with or without azithromycin (45.6 hr vs 59.7 hr, P = .44). In-hospital mortality was also similar (37.9% vs 38.1%, P = .979). There were no significant differences in mechanical ventilation duration, ICU length of stay (LOS), or hospital LOS. Conclusions: In patients admitted to the ICU with septic shock, empiric azithromycin did not have a significant effect on shock duration, mechanical ventilation duration, ICU LOS, hospital LOS, or in-hospital mortality.

Pharmacy

Keinath JJ, Lekura J, **Hauser CD**, **Bajwa MK**, **Bloome ME**, **Kalus JS**, and **Jones MC**. Deterioration free discharge comparison of andexanet-alfa and prothrombin complex concentrates (PCC) for reversal of factor Xa inhibitor associated bleeds. *J Thromb Thrombolysis* 2023; Epub ahead of print. PMID: 37289371. Full Text

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Given the paucity of comparative efficacy data and the difference in cost between andexanet-alfa and prothrombin complex concentrates (PCC), debates continue regarding optimal cost-effective therapy for patients who present with major bleeding associated with oral factor Xa inhibitors. Available literature comparing the cost-effectiveness of the reversal agents is limited, and the large difference in price between therapy options has led many health systems to exclude andexanet-alfa from their formularies. To evaluate the clinical outcomes and cost of PCC compared to andexanet-alfa for patients with factor Xa inhibitor associated bleeds. We performed a quasi-experimental, single health system study of patients treated with PCC or andexanet-alfa from March 2014 to April 2021. Deterioration-free discharge, thrombotic events, length of stay, discharge disposition, and cost were reported. 170 patients were included in the PCC group and 170 patients were included in the andexanet-alfa group. Deterioration-free discharge was achieved in 66.5% of PCC-treated patients compared to 69.4% in the andexanet alfa-treated patients. 31.8% of PCC-treated patients were discharged home compared to 30.6% in the andexanet alfa-treated patients. The cost per deterioration-free discharge was $20,773.62 versus $5230.32 in the andexanet alfa and 4 F-PCC group, respectively. Among patients that experienced a bleed while taking a factor Xa inhibitor, there was no difference in clinical outcomes for patients treated with andexanet-alfa compared to PCC. Although there was no difference in the clinical outcomes, there was a significant difference in cost with andexanet-alfa costing approximately four times as much as PCC per deterioration-free discharge.

Pharmacy

Martirosov AL, **Alex J**, Doane A, Patel R, Aprilliano B, and Kale-Pradhan P. Podcasts and videos and slides…oh my!: Traditional vs. nontraditional teaching methods in remote settings. *Curr Pharm Teach Learn* 2023; Epub ahead of print. PMID: 37357125. Request Article

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INTRODUCTION: Nontraditional teaching methods are student-centered and motivate students to participate in class activities. Some studies have shown benefit in using various teaching activities; however, data are limited regarding students' perspective and performance after implementation of nontraditional learning strategies. The study compared student preference and performance assessment with traditional and nontraditional presentation methods. METHODS: This study included first-year pharmacy students enrolled in a course at a research-intensive, public university. Students in 2020 received traditional lectures while students in 2021 were presented three topics as nontraditional activities, including a podcast, an escape room, a video inspired by Khan Academy, and a traditional asynchronous lecture using slides with voice-over. First-year pharmacy students were surveyed in 2021 regarding their perspective on the nontraditional presentations. Students' performance was compared between 2020 and 2021. RESULTS: Ninety-eight students in 2020 and 89 students in 2021 were enrolled in the course. Sixty-seven students completed the 2021 survey. Most students (71.6%) preferred the traditional lecture; the Khan Academy and escape room activities were the least favored. Most students (86.5%) responded they learned "quite a bit" or a "tremendous amount" with the traditional lecture, and 59.7% of students felt they would perform better on assessments with the traditional lecture compared to nontraditional. Students in 2021 only performed better on all exam questions related to the nontraditional podcast activity. CONCLUSIONS: Students preferred traditional lectures and also seemed to perform

better on assessment, with the exception of the nontraditional presentation podcast style. Further studies are needed to confirm these findings.

Public Health Sciences

Bagher-Ebadian H, **Brown SL**, Ghassemi MM, **Nagaraja TN**, Valadie OG, Acharya PC, **Cabral G**, **Divine G**, **Knight RA**, **Lee IY**, **Xu JH**, **Movsas B**, **Chetty IJ**, and **Ewing JR**. Dynamic contrast enhanced (DCE) MRI estimation of vascular parameters using knowledge-based adaptive models. *Sci Rep* 2023; 13(1):9672. PMID: 37316579. Full Text

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We introduce and validate four adaptive models (AMs) to perform a physiologically based Nested-Model-Selection (NMS) estimation of such microvascular parameters as forward volumetric transfer constant, K(trans), plasma volume fraction, v(p), and extravascular, extracellular space, v(e), directly from Dynamic Contrast-Enhanced (DCE) MRI raw information without the need for an Arterial-Input Function (AIF). In sixty-six immune-compromised-RNU rats implanted with human U-251 cancer cells, DCE-MRI studies estimated pharmacokinetic (PK) parameters using a group-averaged radiological AIF and an extended Patlak-based NMS paradigm. One-hundred-ninety features extracted from raw DCE-MRI information were used to construct and validate (nested-cross-validation, NCV) four AMs for estimation of model-based regions and their three PK parameters. An NMS-based a priori knowledge was used to fine-tune the AMs to improve their performance. Compared to the conventional analysis, AMs produced stable maps of vascular parameters and nested-model regions less impacted by AIF-dispersion. The performance (Correlation coefficient and Adjusted R-squared for NCV test cohorts) of the AMs were: 0.914/0.834, 0.825/0.720, 0.938/0.880, and 0.890/0.792 for predictions of nested model regions, v(p), K(trans), and v(e), respectively. This study demonstrates an application of AMs that quickens and improves DCE-MRI based quantification of microvasculature properties of tumors and normal tissues relative to conventional approaches.

Public Health Sciences

Carroll NM, Eisenstein J, Burnett-Hartman AN, Greenlee RT, Honda SA, **Neslund-Dudas CM**, Rendle KA, Vachani A, and Ritzwoller DP. Uptake of novel systemic therapy: Real world patterns among adults with advanced non-small cell lung cancer. *Cancer Treat Res Commun* 2023; 36:100730. PMID: 37352588. Full Text

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INTRODUCTION/BACKGROUND: Systemic treatment for advanced non-small cell lung cancer (NSCLC) is shifting from platinum-based chemotherapy to immunotherapy and targeted therapies associated with improved survival in clinical trials. As new therapies are approved for use, examining variations in use for treating patients in community practice can generate additional evidence as to the magnitude of their benefit. PATIENTS AND METHODS: We identified 1,442 patients diagnosed with de novo stage IV NSCLC between 3/1/2012 and 12/31/2020. Patient characteristics and treatment patterns are described overall and by type of first- and second-line systemic therapy received. Prevalence ratios estimate the association of patient and tumor characteristics with receipt of first-line therapy. RESULTS: Within 180 days of diagnosis, 949 (66%) patients received first-line systemic therapy, increasing from 53% in 2012 to 71% in 2020 ($p = 0.0004$). The proportion of patients receiving first-line immunotherapy+/-chemotherapy (IMO) increased from 14%-66% ($p<0.0001$). Overall, 380 (26%) patients received both first- and second-line treatment, varying by year between 16%-36% ($p = 0.18$). The proportion of patients receiving second-line IMO increased from 13%-37% ($p<0.0001$). Older age and current smoking status were inversely associated with receipt of first-line therapy. Higher BMI, receipt of radiation, and diagnosis year were positively associated with receipt of first-line therapy. No association was found for race, ethnicity, or socioeconomic status. CONCLUSION: The proportion of advanced NSCLC patients receiving first- and second-line treatment increased over time, particularly for IMO treatments. Additional research is needed to better understand the impact of these therapies on patient outcomes, including short-term, long-term, and financial toxicities. MICROABSTRACT: Systemic treatment for non-small cell lung cancer (NSCLC) is shifting from platinum-based therapies to immunotherapy and targeted therapies. Using de novo stage IV NSCLC patients identified from 4 healthcare systems, we examine trends in systemic therapy. We saw an increase in the portion of patients receiving any systemic therapy and a sharp increase in the proportion of patients receiving immunotherapy.

Public Health Sciences

Choi E, **Leonard KW**, **Jassal JS**, **Levin AM**, **Ramachandra V**, and **Jones LR**. Artificial Intelligence in Facial Plastic Surgery: A Review of Current Applications, Future Applications, and Ethical Considerations. *Facial Plast Surg* 2023; Epub ahead of print. PMID: 37353051. Request Article

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From virtual chat assistants to self-driving cars, artificial intelligence (AI) is often heralded as the technology that has and will continue to transform this generation. Among widely adopted applications in other industries, its potential use in medicine is being increasingly explored, where the vast amounts of data present in electronic health records and need for continuous improvements in patient care and workflow efficiency present many opportunities for AI implementation. Indeed, AI has already demonstrated capabilities for assisting in tasks such as documentation, image classification, and surgical outcome prediction. More specifically, this technology can be harnessed in facial plastic surgery, where the unique characteristics of the field lends itself well to specific applications. AI is not without its limitations, however, and the further adoption of AI in medicine and facial plastic surgery must necessarily be accompanied by discussion on the ethical implications and proper usage of AI in healthcare. In this article, we review current and potential uses of AI in facial plastic surgery, as well as its ethical ramifications.

Public Health Sciences

Darst BF, Shen J, Madduri RK, Rodriguez AA, Xiao Y, Sheng X, Saunders EJ, Dadaev T, Brook MN, Hoffmann TJ, Muir K, Wan P, Le Marchand L, Wilkens L, Wang Y, Schleutker J, MacInnis RJ, Cybulski C, Neal DE, Nordestgaard BG, Nielsen SF, Batra J, Clements JA, Cancer BioResource AP, Grönberg H, Pashayan N, Travis RC, Park JY, Albanes D, Weinstein S, Mucci LA, Hunter DJ, Penney KL, Tangen CM, Hamilton RJ, Parent M, Stanford JL, Koutros S, Wolk A, Sørensen KD, Blot WJ, Yeboah ED, Mensah JE, Lu YJ, Schaid DJ, Thibodeau SN, West CM, Maier C, Kibel AS, Cancel-Tassin G, Menegaux F, John EM, Grindedal EM, Khaw KT, Ingles SA, Vega A, Rosenstein BS, Teixeira MR, Kogevinas M, Cannon-Albright L, Huff C, Multigner L, Kaneva R, Leach RJ, Brenner H, Hsing AW, Kittles RA, Murphy AB, Logothetis CJ, Neuhausen SL, Isaacs WB, Nemesure B, Hennis AJ, Carpten J, Pandha H, De Ruyck K, Xu J, Razack A, Teo SH, Newcomb LF, Fowke JH, **Neslund-Dudas C**, **Rybicki BA**, Gamulin M, Usmani N, Claessens F, Gago-Dominguez M, Castelao JE, Townsend PA, Crawford DC, Petrovics G, Casey G, Roobol MJ, Hu JF, Berndt SI, Van Den Eeden SK, Easton DF, Chanock SJ, Cook MB, Wiklund F, Witte JS, Eeles RA, Kote-Jarai Z, Watya S, Gaziano JM, Justice AC, Conti DV, and Haiman CA. Evaluating approaches for constructing polygenic risk scores for prostate cancer in men of African and European ancestry. *Am J Hum Genet* 2023; Epub ahead of print. PMID: 37311464. Request Article

Genome-wide polygenic risk scores (GW-PRSs) have been reported to have better predictive ability than PRSs based on genome-wide significance thresholds across numerous traits. We compared the predictive ability of several GW-PRS approaches to a recently developed PRS of 269 established prostate cancer-risk variants from multi-ancestry GWASs and fine-mapping studies (PRS(269)). GW-PRS models were trained with a large and diverse prostate cancer GWAS of 107,247 cases and 127,006 controls that we previously used to develop the multi-ancestry PRS(269). Resulting models were independently tested in 1,586 cases and 1,047 controls of African ancestry from the California Uganda Study and 8,046 cases and 191,825 controls of European ancestry from the UK Biobank and further validated in 13,643 cases and 210,214 controls of European ancestry and 6,353 cases and 53,362 controls of African ancestry from the Million Veteran Program. In the testing data, the best performing GW-PRS approach had AUCs of 0.656 (95% CI = 0.635-0.677) in African and 0.844 (95% CI = 0.840-0.848) in European ancestry men and corresponding prostate cancer ORs of 1.83 (95% CI = 1.67-2.00) and 2.19 (95% CI = 2.14-2.25), respectively, for each SD unit increase in the GW-PRS. Compared to the GW-PRS, in African and European ancestry men, the PRS(269) had larger or similar AUCs (AUC = 0.679, 95% CI = 0.659-0.700 and AUC = 0.845, 95% CI = 0.841-0.849, respectively) and comparable prostate cancer ORs (OR = 2.05, 95% CI = 1.87-2.26 and OR = 2.21, 95% CI = 2.16-2.26, respectively). Findings were similar in the validation studies. This investigation suggests that current GW-PRS approaches may not improve the ability to predict prostate cancer risk compared to the PRS(269) developed from multi-ancestry GWASs and fine-mapping.

Public Health Sciences

Garman L, Pezant N, Dawkins BA, Rasmussen A, **Levin AM**, **Rybicki BA**, Iannuzzi MC, Bagavant H, Deshmukh US, and Montgomery CG. Inclusivity in Research Matters: Variants in PVT1 Specific to People of African Descent Are Associated with Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2023; Epub ahead of print. PMID: 37348127. Full Text

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Public Health Sciences

Hamilton T, **Bartlett S**, **Deshpande N**, **Hadi M**, **Reese JC**, **Mansour TR**, **Telemi E**, **Springer K**, **Schultz L**, **Nerenz DR**, **Abdulhak M**, Soo T, **Schwalb J**, Khalil JG, Aleem I, Easton R, Perez-Cruet M, Park P, and **Chang V**. Association of prolonged symptom duration with poor outcomes in lumbar spine surgery: a Michigan Spine Surgery Improvement Collaborative study. *J Neurosurg Spine* 2023; 1-10. Epub ahead of print. PMID: 37347591. Full Text

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OBJECTIVE: There is a scarcity of large multicenter data on how preoperative lumbar symptom duration relates to postoperative patient-reported outcomes (PROs). The objective of this study was to determine the effect of preoperative and baseline symptom duration on PROs at 90 days, 1 year, and 2 years after lumbar spine surgery. METHODS: The Michigan Spine Surgery Improvement Collaborative registry was queried for all lumbar spine operations between January 1, 2017, to December 31, 2021, with a follow-up of 2 years. Patients were stratified into three subgroups based on symptom duration: < 3 months, 3 months to < 1 year, and ≥ 1 year. The primary outcomes were reaching the minimal clinically important difference (MCID) for the PROs (i.e., leg pain, Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF), EQ-5D, North American Spine Society satisfaction, and return to work). The EQ-5D score was also analyzed as a continuous variable to calculate quality-adjusted life years. Multivariable Poisson generalized estimating equation models were used to report adjusted risk ratios, with the < 3-month cohort used as the reference. RESULTS: There were 37,223 patients (4670 with < 3-month duration, 9356 with 3-month to < 1-year duration, and 23,197 with ≥ 1-year duration) available for analysis. Compared with patients with a symptom duration of < 1 year, patients with a symptom duration of ≥ 1 year were significantly less likely to achieve an MCID in PROMIS PF, EQ-5D, back pain relief, and leg pain relief at 90 days, 1 year, and 2 years postoperatively. Similar trends were observed for patient satisfaction and return to work. With the EQ-5D score as a continuous variable, a symptom duration of ≥ 1 year was associated with 0.04, 0.05, and 0.03 ($p < 0.001$) decreases in EQ-5D score at 90 days, 1 year, and 2 years after surgery, respectively. CONCLUSIONS: A symptom duration of ≥ 1 year was associated with poorer outcomes on several outcome metrics. This suggests that timely referral and surgery for degenerative lumbar pathology may optimize patient outcome.

Public Health Sciences

Huang Y, **Chen D**, **Levin AM**, **Ahmedani BK**, **Frank C**, Li M, Wang Q, **Gui H**, and Sham PC. Cross-phenotype relationship between opioid use disorder and suicide attempts: new evidence from polygenic association and Mendelian randomization analyses. *Mol Psychiatry* 2023; Epub ahead of print. PMID: 37340172. Request Article

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Clinical epidemiological studies have found high co-occurrence between suicide attempts (SA) and opioid use disorder (OUD). However, the patterns of correlation and causation between them are still not clear due to psychiatric confounding. To investigate their cross-phenotype relationship, we utilized raw phenotypes and genotypes from >150,000 UK Biobank samples, and genome-wide association summary statistics from >600,000 individuals with European ancestry. Pairwise association and a potential bidirectional relationship between OUD and SA were evaluated with and without controlling for major psychiatric disease status (e.g., schizophrenia, major depressive disorder, and alcohol use disorder). Multiple statistical and genetics tools were used to perform epidemiological association, genetic correlation, polygenic risk score prediction, and Mendelian randomizations (MR) analyses. Strong associations between OUD and SA were observed at both the phenotypic level (overall samples [OR = 2.94, P = 1.59 ×10(-14)]; non-psychiatric subgroup [OR = 2.15, P = 1.07 ×10(-3)]) and the genetic level (genetic correlation rg = 0.38 and 0.5 with or without conditioning on psychiatric traits, respectively). Consistently, increasing polygenic susceptibility to SA is associated with increasing risk of OUD (OR = 1.08, false discovery rate [FDR] =1.71 ×10(-3)), and similarly, increasing polygenic susceptibility to OUD is associated with increasing risk of SA (OR = 1.09, FDR = 1.73 ×10(-6)). However, these polygenic associations were much attenuated after controlling for comorbid psychiatric diseases. A combination of MR analyses suggested a possible causal association from genetic liability for SA to OUD risk (2-sample univariable MR: OR = 1.14, P = 0.001; multivariable MR: OR = 1.08, P = 0.001). This study provided new genetic evidence to explain the observed OUD-SA comorbidity. Future prevention strategies for each phenotype needs to take into consideration of screening for the other one.

Public Health Sciences

Keteyian SJ, **Steenson K**, **Grimshaw C**, **Mandel N**, **Koester-Qualters W**, **Berry R**, **Kerrigan DJ**, **Ehrman JK**, **Peterson EL**, and **Brawner CA**. Among Patients Taking Beta-Adrenergic Blockade Therapy, Use Measured (Not Predicted) Maximal Heart Rate to Calculate a Target Heart Rate for Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev* 2023; Epub ahead of print. PMID: 37311037. Full Text

Division of Cardiovascular Medicine, Henry Ford Health, Detroit, Michigan (Drs Keteyian, Kerrigan, Ehrman, and Brawner, Mss Steenson, Grimshaw, and Koester-Qualters, and Messrs Mandel and Berry); and Department of Public Health Sciences, Henry Ford Health, Detroit, Michigan (Dr Peterson).

PURPOSE: Among patients in cardiac rehabilitation (CR) on beta-adrenergic blockade (βB) therapy, this study describes the frequency for which target heart rate (THR) values computed using a predicted maximal heart rate (HRmax), correspond to a THR computed using a measured HRmax in the guideline-based heart rate reserve (HRreserve) method. METHODS: Before CR, patients completed a cardiopulmonary exercise test to measure HRmax, with the data used to determine THR via the HRreserve method. Additionally, predicted HRmax was computed for all patients using the 220 - age equation and two disease-specific equations, with the predicted values used to calculate THR via the straight percent and HRreserve methods. The THR was also computed using resting heart rate (HR) +20 and +30 bpm. RESULTS: Mean predicted HRmax using the 220 - age equation (161 ± 11 bpm) and the disease-specific equations (123 ± 9 bpm) differed (P < .001) from measured HRmax (133 ± 21 bpm). Also, THR computed using predicted HRmax resulted in values that were infrequently within the guideline-based HRreserve range calculated using measured HRmax. Specifically, 0 to ≤61% of patients

would have had an exercise training HR that fell within the guideline-based range of 50-80% of measured HRreserve. Use of standing resting HR +20 or +30 bpm would have resulted in 100% and 48%, respectively, of patients exercising below 50% of HRreserve. CONCLUSIONS: A THR computed using either predicted HRmax or resting HR +20 or +30 bpm seldom results in a prescribed exercise intensity that is consistent with guideline recommendations for patients in CR.

Public Health Sciences

Martin CL, Ghastine L, **Wegienka G**, Wise LA, Baird DD, and Vines AI. Early Life Disadvantage and the Risk of Depressive Symptoms among Young Black Women. *J Racial Ethn Health Disparities* 2023; Epub ahead of print. PMID: 37380937. Request Article

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OVERVIEW: We examined the association between early-life socioeconomic disadvantage and depressive symptoms in adulthood and assessed whether social factors in adulthood modify the association. METHODS: The 11-item Center for Epidemiologic Studies-Depression Scale (CES-D) assessed adult depressive symptoms among 1612 Black women and other participants with a uterus (hereafter participants) in the Study of Environment, Lifestyle and Fibroids. Baseline self-reported childhood factors (i.e., parents in the household, mother's educational attainment, food insecurity, neighborhood safety, childhood income, and quiet bedroom for sleep) were included in a latent class analysis to derive an early life disadvantage construct. Multivariable log-binomial models estimated the association between early life disadvantage and adult depressive symptoms. Potential effect modifiers included adult educational attainment, social support, and financial difficulty. RESULTS: Participants classified as having high early life disadvantage had 1.34 times (95% CI: 1.20, 1.49) the risk of high depressive symptoms than those in the low early life disadvantage class after adjusting for age, first born status, and childhood health. Adult educational attainment and social support modified the association. CONCLUSION: Early life disadvantage increased the risk of depressive symptoms in adulthood. Participants with at least some college education and with high social support had greater risk than those with less than college education and low social support, respectively. Thus, the mental health of Black women and other participants with a uterus exposed to early life disadvantage do not necessarily benefit from higher education or from social support.

Public Health Sciences

Mason W, **Levin AM**, **Buhl K**, **Ouchi T**, **Parker B**, **Tan J**, Ashammakhi N, and **Jones L**. Translational Research Techniques for the Facial Plastic Surgeon: An Overview. *Facial Plast Surg* 2023; Epub ahead of print. PMID: 37339663. Request Article

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The field of Facial Plastic and Reconstructive Surgery (FPRS) is an incredibly diverse, multi-specialty field that seeks innovative and novel solutions for the management of physical defects on the head and neck. To aid in the advancement of medical and surgical treatments for these defects, there has been a recent

emphasis on the importance of translational research. With recent technological advancements, there are now a myriad of research techniques that are widely accessible for physician and scientist use in translational research. Such techniques include integrated multiomics, advanced cell culture and microfluidic tissue models, established animal models, and emerging computer models generated using bioinformatics. The following article discusses these various research techniques and how they have and can be used for research in the context of various important diseases within the field of FPRS.

Public Health Sciences

Nulty P, **Mason W**, **Peterson EL**, **Cook B**, **Rock J**, **Eide J**, and **Craig JR**. Using Ipratropium Bromide Nasal Spray Response as a Screening Tool in the Diagnostic Workup of Cerebrospinal Fluid Rhinorrhea. *Laryngoscope* 2023; Epub ahead of print. PMID: 37265206. Full Text

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OBJECTIVES: Unilateral clear thin rhinorrhea (UCTR) can be concerning for a nasal cerebrospinal fluid (CSF) leak. Beta-2 transferrin electrophoresis has been the gold standard for initial non-invasive confirmatory testing for CSF rhinorrhea, but there can be issues with fluid collection and testing errors. Ipratropium bromide nasal spray (IBNS) is highly effective at reducing rhinitis-related rhinorrhea, and should presumably not resolve CSF rhinorrhea. This study assessed whether different clinical features and IBNS response helped predict presence or absence of CSF rhinorrhea. METHODS: A prospective cohort study was conducted where all patients with UCTR had nasal fluid tested for beta-2 transferrin, and were prescribed 0.06% IBNS. Patients were diagnosed with CSF rhinorrhea or other rhinologic conditions. Clinical variables like IBNS response (rhinorrhea reduction), positional worsening, salty taste, postoperative state, female gender, and body-mass index were assessed for their ability to predict CSF rhinorrhea. Sensitivity, specificity, and predictive values and odds ratios were calculated for all clinical variables. RESULTS: Twenty patients had CSF rhinorrhea, and 53 had non-CSF etiologies. Amongst clinical variables assessed for predicting CSF absence or presence, significant associations were shown for IBNS response (OR = 844.66, p = 0.001), positional rhinorrhea worsening (OR = 8.22, p = 0.049), and body-mass index ≥30 (OR = 2.92, p = 0.048). IBNS response demonstrated 96% sensitivity and 100% specificity, and 100% positive and 91% negative predictive values for predicting CSF rhinorrhea. CONCLUSIONS: In patients with UCTR, 0.06% IBNS response is an excellent screening tool for excluding CSF rhinorrhea, and should be considered in the diagnostic workup of CSF rhinorrhea. LEVEL OF EVIDENCE: 2 Laryngoscope, 2023.

Public Health Sciences

Obri MS, **Youssef RM**, **Alluri S**, **Vemulapalli K**, **Ichkhanian Y**, **Todter EN**, **Jesse MT**, and **Salgia R**. Disparities in Referrals to End-of-Life Care in Eligible Hepatocellular Carcinoma Patients. *Dig Dis Sci* 2023; Epub ahead of print. PMID: 37289417. Full Text

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BACKGROUND: Hepatocellular Carcinoma (HCC) is a malignancy with increasing incidence and morbidity. For patients with a poor prognosis, engagement with advanced care planning and end-of life (EOL) services (I.e., palliative care, hospice) can address physical, financial, and social complications of a terminal diagnosis. Minimal data exist on the demographics of the patients being referred to and enrolling in EOL services for HCC. AIMS: We aim to report the relationship between demographics and EOL service referral. METHODS: Retrospective review of a prospectively maintained high-volume liver center registry of patients diagnosed with HCC from 2004 to 2022. EOL services eligible patients were defined

as BCLC stage C or D, evidence of metastases, and/or transplant ineligible. RESULTS: Black patients were more likely to be referred than white patients (OR 1.47 (1.03, 2.11)). Once referred, patients were significantly more likely to be enrolled if they had insurance coverage, though no other factors in models were significant. There were no significant differences in survival among those referred who did or did not enroll, after controlling for other factors. CONCLUSION: Black patients were more likely to be referred compared to white patients and patients who were insured were more likely to be enrolled. Whether this is indicative of black patients being appropriately referred at a higher rate, being offered EOL care instead of aggressive treatment, or other unknown factors warrants further study.

Public Health Sciences

Rasmussen A, Dawkins BA, Li C, Pezant N, **Levin AM**, **Rybicki BA**, Iannuzzi MC, and Montgomery CG. Multiple Correspondence Analysis and HLA-Associations of Organ Involvement in a Large Cohort of African-American and European-American Patients with Sarcoidosis. *Lung* 2023; 201(3):297-302. PMID: 37322162. Full Text

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Sarcoidosis is a systemic granulomatous disease with predominant pulmonary involvement and vast heterogeneity of clinical manifestations and disease outcomes. African American (AA) patients suffer greater morbidity and mortality. Using Multiple Correspondence Analysis, we identified seven clusters of organ involvement in European American (EA; n = 385) patients which were similar to those previously described in a Pan-European (GenPhenReSa) and a Spanish cohort (SARCOGEAS). In contrast, AA (n = 987) had six, less well-defined and overlapping clusters with little similarity to the cluster identified in the EA cohort evaluated at the same U.S. institutions. Association of cluster membership with two-digit HLA-DRB1 alleles demonstrated ancestry-specific patterns of association and replicated known HLA effects.These results further support the notion that genetically influenced immune risk profiles, which differ based on ancestry, play a role in phenotypic heterogeneity. Dissecting such risk profiles will move us closer to personalized medicine for this complex disease.

Public Health Sciences

Sitarik AR, **Wegienka G**, **Johnson CC**, and **Joseph CLM**. Impact of spirometry race-correction on pre-adolescent Black and White children. *J Allergy Clin Immunol Pract* 2023; Epub ahead of print. PMID: 37301437. Full Text

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BACKGROUND: Race-correction for Black patients is standard practice in spirometry testing. History suggests that these corrections are at least partially a result of racist assumptions regarding lung anatomy among Black individuals, which can potentially lead to less frequent diagnoses of pulmonary diseases in this population. OBJECTIVE: The purpose of this study was to evaluate the impact of race-correction in spirometry testing among Black and White pre-adolescents, and examine the frequency of current asthma symptoms in Black children who were differentially classified depending on whether race-corrected or uncorrected reference equations were deployed. METHODS: Data from Black and White children who completed a clinical exam at age 10 from a Detroit-based unselected birth cohort were analyzed. Global lung initiative (GLI) 2012 reference equations were applied to spirometry data using both race-corrected and race-uncorrected (i.e., population-average) equations. Abnormal results were defined as values less than the fifth percentile. Asthma symptoms were assessed concurrently using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, while asthma control was assessed using the asthma control test (ACT). RESULTS: The impact of race-correction on FEV1/FVC ratio was minimal, but abnormal classification of FEV1 results more than doubled among

Black children when race-uncorrected equations were used (7% vs. 18.1%) and were almost 8 times greater based on FVC classification (1.5% vs. 11.4%). More than half of Black children differentially classified on FEV1 (whose FEV1 was classified as normal with race-corrected equations but abnormal with race-uncorrected equations) experienced asthma symptoms in the past 12 months (52.6%), which was significantly higher than Black children consistently classified as normal (35.5%, p=0.049), but similar to that of Black children consistently classified as abnormal using both race-corrected and race-uncorrected equations (62.5%, p=0.60). ACT scores were not different based on classification. CONCLUSIONS: Race-correction had an extensive impact on spirometry classification in Black children, and differentially classified children had a higher rate of asthma symptoms than children consistently classified as normal. Spirometry reference equations should be reevaluated to be aligned with current scientific perspectives on the use of race in medicine.

Public Health Sciences

Wang J, **Adrianto I**, **Subedi K**, **Liu T**, **Wu X**, **Yi Q**, **Loveless I**, **Yin C**, **Datta I**, Sant'Angelo DB, Kronenberg M, **Zhou L**, and **Mi QS**. Integrative scATAC-seq and scRNA-seq analyses map thymic iNKT cell development and identify Cbfβ for its commitment. *Cell Discov* 2023; 9(1):61. PMID: 37336875. Full Text

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Unlike conventional αβT cells, invariant natural killer T (iNKT) cells complete their terminal differentiation to functional iNKT1/2/17 cells in the thymus. However, underlying molecular programs that guide iNKT subset differentiation remain unclear. Here, we profiled the transcriptomes of over 17,000 iNKT cells and the chromatin accessibility states of over 39,000 iNKT cells across four thymic iNKT developmental stages using single-cell RNA sequencing (scRNA-seq) and single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) to define their developmental trajectories. Our study discovered novel features for iNKT precursors and different iNKT subsets and indicated that iNKT2 and iNKT17 lineage commitment may occur as early as stage 0 (ST0) by two distinct programs, while iNKT1 commitments may occur post ST0. Both iNKT1 and iNKT2 cells exhibit extensive phenotypic and functional heterogeneity, while iNKT17 cells are relatively homogenous. Furthermore, we identified that a novel transcription factor, Cbfβ, was highly expressed in iNKT progenitor commitment checkpoint, which showed a similar expression trajectory with other known transcription factors for iNKT cells development, Zbtb16 and Egr2, and could direct iNKT cells fate and drive their effector phenotype differentiation. Conditional deletion of Cbfβ blocked early iNKT cell development and led to severe impairment of iNKT1/2/17 cell differentiation. Overall, our findings uncovered distinct iNKT developmental programs as

well as their cellular heterogeneity, and identified a novel transcription factor Cbfβ as a key regulator for early iNKT cell commitment.

Public Health Sciences

Younger JD, Faryami A, Prasad M, Viar D, Menkara A, **Tang A**, and Harris CA. Direct Comparison of Peak Bulk Flow Rate of Programmable Intermittent Epidural Bolus and Manual Epidural Bolus Using a Closed-End Multiorifice Catheter: An Experimental Study. *Anesth Analg* 2023; 136(6):1198-1205. PMID: 36730916. Full Text

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BACKGROUND: The programmable intermittent epidural bolus (PIEB) has been popularized as the optimal delivery technique for labor analgesia. Suggested advantages of this method are less local anesthetic consumption, improved maternal satisfaction, potentially shorter duration of labor, and decreased workload requirements for the anesthesia providers. However, a manual bolus is still routinely used for breakthrough pain when the PIEB is underperforming. METHODS: We conducted a laboratory-based study to quantify the flow through a multiorifice epidural catheter using the PIEB setting on an epidural pump compared to the manual epidural bolus. Four syringe volumes, 3, 5, 10, and 20 mL, were selected for this experiment. The flow in a manual bolus was also studied with and without the presence of an epidural catheter filter. A generalized estimating equation analysis was done to compare data between the groups. RESULTS: Regardless of the syringe size, there was a several-fold increase in flow when a manual bolus was used compared to a pump-administered dose, with the highest difference in the peak flow rate observed in 3-mL boluses with up to a 12-fold difference, while the difference was, at most, 7-fold in 5-mL and 10-mL boluses. Manual boluses without a filter achieve a mean peak flow rate higher than manual boluses with a filter. CONCLUSIONS: Our study found that manual boluses produced a higher flow rate compared to the CADD-Solis epidural pump (Smiths Medical). This study also found that the placement of a particulate filter reduces the flow rates generated while bolusing. Bulk flow rate is directly correlated with induced pressure and solution spread. Because higher bolus pressure has been shown to provide a more efficient distribution of local anesthetic and more efficient pain relief, these results may have impactful clinical significance and will pave the way for future studies.

Pulmonary and Critical Care Medicine

Fadel RA, Scott A, **Parsons A**, **Murskyj I**, **Nasiri N**, **Abu Sayf A**, and **Ouellette D**. Tocilizumab Associated With Survival in Patients Hospitalized for COVID-19 Acute Respiratory Distress Syndrome and Low Urine Output. *J Intensive Care Med* 2023; Epub ahead of print. PMID: 37306148. Full Text

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BACKGROUND: Acute respiratory distress syndrome (ARDS) with oliguria is associated with increased mortality. Interleukin-6 (IL-6) plays an integral role in the pathophysiology of both disease processes. Patients who experience severe COVID-19 have demonstrated higher IL-6 levels compared to baseline, and use of tocilizumab has demonstrated efficacy in such cohorts. We set out to investigate the relationship between tocilizumab use, COVID-19 ARDS, low urine output, and mortality. METHODS: Retrospective cohort review of adult patients aged ≥ 18 years with COVID-19 and moderate or severe ARDS, admitted to the intensive care unit (ICU) of a tertiary referral center in metropolitan Detroit. Patients were analyzed based on presence of oliguria (defined as ≤ 0.7 mL/kg/h) on the day of intubation

and exposure to tocilizumab while inpatient. The primary outcome was inpatient mortality. RESULTS: One hundred and twenty-eight patients were analyzed, 103 (80%) with low urine output, of whom 30 (29%) received tocilizumab. In patients with low urine output, risk factors associated with mortality on univariate analysis included Black race (P = .028), lower static compliance (P = .015), and tocilizumab administration (P = .002). Tocilizumab (odds ratio 0.245, 95% confidence interval 0.079-0.764, P = .015) was the only risk factor independently associated with survival on multivariate logistic regression analysis. CONCLUSION: In this retrospective cohort review of patients hospitalized with COVID-19 and moderate or severe ARDS, tocilizumab administration was independently associated with survival in patients with low urine output ≤ 0.7 mL/kg/h on the day of intubation. Prospective studies are needed to investigate the impact of urine output on efficacy of interleukin-targeted therapies in the management of ARDS.

Radiation Oncology

Bagher-Ebadian H, **Brown SL**, Ghassemi MM, **Nagaraja TN**, Valadie OG, Acharya PC, **Cabral G**, **Divine G**, **Knight RA**, **Lee IY**, **Xu JH**, **Movsas B**, **Chetty IJ**, and **Ewing JR**. Dynamic contrast enhanced (DCE) MRI estimation of vascular parameters using knowledge-based adaptive models. *Sci Rep* 2023; 13(1):9672. PMID: 37316579. Full Text

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We introduce and validate four adaptive models (AMs) to perform a physiologically based Nested-Model-Selection (NMS) estimation of such microvascular parameters as forward volumetric transfer constant, K(trans), plasma volume fraction, v(p), and extravascular, extracellular space, v(e), directly from Dynamic Contrast-Enhanced (DCE) MRI raw information without the need for an Arterial-Input Function (AIF). In sixty-six immune-compromised-RNU rats implanted with human U-251 cancer cells, DCE-MRI studies estimated pharmacokinetic (PK) parameters using a group-averaged radiological AIF and an extended Patlak-based NMS paradigm. One-hundred-ninety features extracted from raw DCE-MRI information were used to construct and validate (nested-cross-validation, NCV) four AMs for estimation of model-based regions and their three PK parameters. An NMS-based a priori knowledge was used to fine-tune the AMs to improve their performance. Compared to the conventional analysis, AMs produced stable maps of vascular parameters and nested-model regions less impacted by AIF-dispersion. The performance (Correlation coefficient and Adjusted R-squared for NCV test cohorts) of the AMs were: 0.914/0.834, 0.825/0.720, 0.938/0.880, and 0.890/0.792 for predictions of nested model regions, v(p), K(trans), and v(e), respectively. This study demonstrates an application of AMs that quickens and improves DCE-MRI based quantification of microvasculature properties of tumors and normal tissues relative to conventional approaches.

Radiation Oncology

Dai Z, Jambor I, Taimen P, **Pantelic M**, **Elshaikh M**, **Dabaja A**, **Rogers C**, Ettala O, Boström PJ, Aronen HJ, Merisaari H, and Wen N. Prostate cancer detection and segmentation on MRI using non-local mask R-CNN with histopathological ground truth. *Med Phys* 2023; Epub ahead of print. PMID: 37358061. Full Text

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BACKGROUND: Automatic detection and segmentation of intraprostatic lesions (ILs) on preoperative multiparametric-magnetic resonance images (mp-MRI) can improve clinical workflow efficiency and enhance the diagnostic accuracy of prostate cancer and is an essential step in dominant intraprostatic lesion boost. PURPOSE: The goal is to improve the detection and segmentation accuracy of 3D ILs in MRI by a proposed a deep learning (DL)-based algorithm with histopathological ground truth. METHODS: This retrospective study included 262 patients with in vivo prostate biparametric MRI (bp-MRI) scans and were divided into three cohorts based on their data analysis and annotation. Histopathological ground truth was established by using histopathology images as delineation reference standard on cohort 1, which consisted of 64 patients and was randomly split into 20 training, 12 validation, and 32 testing patients. Cohort 2 consisted of 158 patients with bp-MRI based lesion delineation, and was randomly split into 104 training, 15 validation, and 39 testing patients. Cohort 3 consisted of 40 unannotated patients, used in semi-supervised learning. We proposed a non-local Mask R-CNN and boosted its performance by applying different training techniques. The performance of non-local Mask R-CNN was compared with baseline Mask R-CNN, 3D U-Net and an experienced radiologist's delineation and was evaluated by detection rate, dice similarity coefficient (DSC), sensitivity, and Hausdorff Distance (HD). RESULTS: The independent testing set consists of 32 patients with histopathological ground truth. With the training technique maximizing detection rate, the non-local Mask R-CNN achieved 80.5% and 94.7% detection rate; 0.548 and 0.604 DSC; 5.72 and 6.36 95 HD (mm); 0.613 and 0.580 sensitivity for ILs of all Gleason Grade groups (GGGs) and clinically significant ILs (GGG > 2), which outperformed baseline Mask R-CNN and 3D U-Net. For clinically significant ILs, the model segmentation accuracy was significantly higher than that of the experienced radiologist involved in the study, who achieved 0.512 DSC ($p = 0.04$), 8.21 ($p = 0.041$) 95 HD (mm), and 0.398 ($p = 0.001$) sensitivity. CONCLUSION: The proposed DL model achieved state-of-art performance and has the potential to help improve radiotherapy treatment planning and noninvasive prostate cancer diagnosis.

Radiation Oncology

Snyder KC, **Mao W**, **Kim JP**, **Cunningham J**, **Chetty IJ**, **Siddiqui SM**, **Parikh P**, and **Dolan J**. Commissioning, clinical implementation, and initial experience with a new brain tumor treatment package on a low-field MR-linac. *J Appl Clin Med Phys* 2023; 24(6):e13919. PMID: 37278646. Full Text

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To evaluate the image quality, dosimetric properties, setup reproducibility, and planar cine motion detection of a high-resolution brain coil and integrated stereotactic brain immobilization system that constitute a new brain treatment package (BTP) on a low-field magnetic resonance imaging (MRI) linear accelerator (MR-linac). Image quality of the high-resolution brain coil was evaluated with the 17 cm diameter spherical phantom and the American College of Radiology (ACR) Large MRI Phantom. Patient imaging studies approved by the institutional review board (IRB) assisted in selecting image acquisition parameters. Radiographic and dosimetric evaluation of the high-resolution brain coil and the associated immobilization devices was performed using dose calculations and ion chamber measurements. End-to-end testing was performed simulating a cranial lesion in a phantom. Inter-fraction setup variability and motion detection tests were evaluated on four healthy volunteers. Inter-fraction variability was assessed

based on three repeat setups for each volunteer. Motion detection was evaluated using three-plane (axial, coronal, and sagittal) MR-cine imaging sessions, where volunteers were asked to perform a set of specific motions. The images were post-processed and evaluated using an in-house program. Contrast resolution of the high-resolution brain coil is superior to the head/neck and torso coils. The BTP receiver coils have an average HU value of 525 HU. The most significant radiation attenuation (3.14%) of the BTP, occurs through the lateral portion of the overlay board where the high-precision lateral-profile mask clips attach to the overlay. The greatest inter-fraction setup variability occurred in the pitch (average 1.08 degree) and translationally in the superior/inferior direction (average 4.88 mm). Three plane cine imaging with the BTP was able to detect large and small motions. Small voluntary motions, sub-millimeter in magnitude (maximum 0.9 mm), from motion of external limbs were detected. Imaging tests, inter-fraction setup variability, attenuation, and end-to-end measurements were quantified and performed for the BTP. Results demonstrate better contrast resolution and low contrast detectability that allows for better visualization of soft tissue anatomical changes relative to head/neck and torso coil systems.

Research Administration

Ghazi N, Aarabi MH, and **Soltanian-Zadeh H**. Deep Learning Methods for Identification of White Matter Fiber Tracts: Review of State-of-the-Art and Future Prospective. *Neuroinformatics* 2023; Epub ahead of print. PMID: 37328715. Full Text

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Quantitative analysis of white matter fiber tracts from diffusion Magnetic Resonance Imaging (dMRI) data is of great significance in health and disease. For example, analysis of fiber tracts related to anatomically meaningful fiber bundles is highly demanded in pre-surgical and treatment planning, and the surgery outcome depends on accurate segmentation of the desired tracts. Currently, this process is mainly done through time-consuming manual identification performed by neuro-anatomical experts. However, there is a broad interest in automating the pipeline such that it is fast, accurate, and easy to apply in clinical settings and also eliminates the intra-reader variabilities. Following the advancements in medical image analysis using deep learning techniques, there has been a growing interest in using these techniques for the task of tract identification as well. Recent reports on this application show that deep learning-based tract identification approaches outperform existing state-of-the-art methods. This paper presents a review of current tract identification approaches based on deep neural networks. First, we review the recent deep learning methods for tract identification. Next, we compare them with respect to their performance, training process, and network properties. Finally, we end with a critical discussion of open challenges and possible directions for future works.

Research Administration

Siadat MR, Elisevich K, **Soltanian-Zadeh H**, Eetemadi A, and Smith B. Curvature analysis of perisylvian epilepsy. *Acta Neurol Belg* 2023; Epub ahead of print. PMID: 37368146. Request Article

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PURPOSE: We assess whether alterations in the convolutional anatomy of the deep perisylvian area (DPSA) might indicate focal epileptogenicity. MATERIALS AND METHODS: The DPSA of each

hemisphere was segmented on MRI and a 3D gray-white matter interface (GWMI) geometrical model was constructed. Comparative visual and quantitative assessment of the convolutional anatomy of both the left and right DPSA models was performed. Both the density of thorn-like contours (peak percentage) and coarse interface curvatures was computed using Gaussian curvature and shape index, respectively. The proposed method was applied to a total of 14 subjects; 7 patients with an epileptogenic DPSA and 7 non-epileptic subjects. RESULTS: A high peak percentage correlated well with the epileptogenic DPSA. It distinguished between patients and non-epileptic subjects (P = 0.029) and identified laterality of the epileptic focus in all but one case. A diminished regional curvature also identified epileptogenicity (P = 0.016) and, moreover, its laterality (P = 0.001). CONCLUSION: An increased peak percentage from a global view of the GWMI of the DPSA provides some indication of a propensity toward a focal or regional DPSA epileptogenicity. A diminished convolutional anatomy (i.e., smoothing effect) appears also to coincide with the epileptogenic site in the DPSA and to distinguish laterality.

Sleep Medicine

Kalmbach DA, **Cheng P**, **Reffi AN**, Ong JC, Swanson LM, Fresco DM, Walch O, **Seymour GM**, **Fellman-Couture C**, **Bayoneto AD**, **Roth T**, and **Drake CL**. Perinatal Understanding of Mindful Awareness for Sleep (PUMAS): A single-arm proof-of-concept clinical trial of a mindfulness-based intervention for DSM-5 insomnia disorder during pregnancy. *Sleep Med* 2023; 108:79-89. PMID: 37343335. Full Text

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OBJECTIVES: Cognitive-behavioral therapy is effective for prenatal insomnia, but unresolved cognitive arousal limits patient outcomes. Therapies aimed at reducing cognitive arousal may benefit pregnant women with insomnia. This proof-of-concept trial evaluated Perinatal Understanding of Mindful Awareness for Sleep (PUMAS, which combines mindfulness with behavioral sleep strategies) on insomnia, depression, and cognitive arousal. METHODS: A single-arm trial of 12 pregnant women with DSM-5 insomnia disorder (n = 5/12 with comorbid depression) who received six sessions of PUMAS delivered individually via telemedicine. Pretreatment and posttreatment outcomes included the insomnia severity index (ISI), Edinburgh postnatal depression scale (EPDS), pre-sleep arousal scale's cognitive factor (PSASC; nocturnal cognitive arousal), perinatal-focused rumination (appended to PSASC), and Glasgow sleep effort scale. RESULTS: Eleven of 12 patients completed all sessions. Intent-to-treat analyses revealed a 10.83-point reduction in ISI (Cohen's dz = 3.05), resulting in 83.3% insomnia remission. PUMAS produced large reductions in EPDS (Cohen's dz = 2.76 in depressed group), resulting in all five baseline depressed patients remitting from depression. PUMAS produced large reductions in nocturnal cognitive arousal, perinatal-focused rumination, and sleep effort (all Cohen's dzs>2.00). Patients were highly satisfied with PUMAS and identified the telemedicine format and meditation app as positive features of its delivery. Patients rated sleep restriction and guided meditations as the most helpful treatment components. CONCLUSION: Prenatal insomnia patients were highly engaged in PUMAS, which produced large acute reductions in insomnia, depression, and cognitive arousal. These findings support the concept and feasibility of PUMAS for pregnant women with insomnia who present with or without comorbid depression. GOV ID: NCT04443959.

Surgery

Intagliata A, Samuel S, **Rountree KM**, Vogel TR, Balasundaram N, and Bath J. Needle fenestration of popliteal artery covered stent graft to salvage inadvertent stent misdeployment. *J Vasc Surg Cases Innov Tech* 2023; 9(2):101207. PMID: 37274434. Full Text

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Endovascular methods have transformed treatment of lower extremity peripheral arterial disease but can still present technical challenges. We report the case of a 69-year-old man with rest pain who underwent superficial femoral artery recanalization with covered stents. During completion angiography, the distal stent was discovered to have been misdeployed into an anterior geniculate branch overlying the behind-the-knee popliteal artery. Subsequently, an endovascular reentry device was used to fenestrate the stent posteriorly to enter the lumen of the popliteal artery. Cutting balloons were used to enlarge the fenestration in the stent fabric, with placement of an additional 6 × 50-mm covered stent bridging from the popliteal artery into the fenestrated misdeployed covered stent. Completion angiography demonstrated no evidence of distal embolization and patent two-vessel runoff. The patient had an uncomplicated recovery and at 2 years of follow-up remained asymptomatic with documented popliteal stent patency.

Surgery

Obri MS, **Youssef RM**, **Alluri S**, **Vemulapalli K**, **Ichkhanian Y**, **Todter EN**, **Jesse MT**, and **Salgia R**. Disparities in Referrals to End-of-Life Care in Eligible Hepatocellular Carcinoma Patients. *Dig Dis Sci* 2023; Epub ahead of print. PMID: 37289417. Full Text

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BACKGROUND: Hepatocellular Carcinoma (HCC) is a malignancy with increasing incidence and morbidity. For patients with a poor prognosis, engagement with advanced care planning and end-of life (EOL) services (I.e., palliative care, hospice) can address physical, financial, and social complications of a terminal diagnosis. Minimal data exist on the demographics of the patients being referred to and enrolling in EOL services for HCC. AIMS: We aim to report the relationship between demographics and EOL service referral. METHODS: Retrospective review of a prospectively maintained high-volume liver center registry of patients diagnosed with HCC from 2004 to 2022. EOL services eligible patients were defined as BCLC stage C or D, evidence of metastases, and/or transplant ineligible. RESULTS: Black patients were more likely to be referred than white patients (OR 1.47 (1.03, 2.11)). Once referred, patients were significantly more likely to be enrolled if they had insurance coverage, though no other factors in models were significant. There were no significant differences in survival among those referred who did or did not enroll, after controlling for other factors. CONCLUSION: Black patients were more likely to be referred compared to white patients and patients who were insured were more likely to be enrolled. Whether this is indicative of black patients being appropriately referred at a higher rate, being offered EOL care instead of aggressive treatment, or other unknown factors warrants further study.

Surgery

Wojack CA, **Marrocco AM**, Enstrom JC, and Casida J. Thromboelastography: A Novel Approach to Hemostasis in Cardiac Surgery. *AACN Adv Crit Care* 2023; 34(2):139-144. PMID: 37289626. Request Article

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Urology

Dai Z, Jambor I, Taimen P, **Pantelic M**, **Elshaikh M**, **Dabaja A**, **Rogers C**, Ettala O, Boström PJ, Aronen HJ, Merisaari H, and Wen N. Prostate cancer detection and segmentation on MRI using non-local mask R-CNN with histopathological ground truth. *Med Phys* 2023; Epub ahead of print. PMID: 37358061. Full Text

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BACKGROUND: Automatic detection and segmentation of intraprostatic lesions (ILs) on preoperative multiparametric-magnetic resonance images (mp-MRI) can improve clinical workflow efficiency and enhance the diagnostic accuracy of prostate cancer and is an essential step in dominant intraprostatic lesion boost. PURPOSE: The goal is to improve the detection and segmentation accuracy of 3D ILs in MRI by a proposed a deep learning (DL)-based algorithm with histopathological ground truth. METHODS: This retrospective study included 262 patients with in vivo prostate biparametric MRI (bp-MRI) scans and were divided into three cohorts based on their data analysis and annotation. Histopathological ground truth was established by using histopathology images as delineation reference standard on cohort 1, which consisted of 64 patients and was randomly split into 20 training, 12 validation, and 32 testing patients. Cohort 2 consisted of 158 patients with bp-MRI based lesion delineation, and was randomly split into 104 training, 15 validation, and 39 testing patients. Cohort 3 consisted of 40 unannotated patients, used in semi-supervised learning. We proposed a non-local Mask R-CNN and boosted its performance by applying different training techniques. The performance of non-local Mask R-CNN was compared with baseline Mask R-CNN, 3D U-Net and an experienced radiologist's delineation and was evaluated by detection rate, dice similarity coefficient (DSC), sensitivity, and Hausdorff Distance (HD). RESULTS: The independent testing set consists of 32 patients with histopathological ground truth. With the training technique maximizing detection rate, the non-local Mask R-CNN achieved 80.5% and 94.7% detection rate; 0.548 and 0.604 DSC; 5.72 and 6.36 95 HD (mm); 0.613 and 0.580 sensitivity for ILs of all Gleason Grade groups (GGGs) and clinically significant ILs (GGG > 2), which outperformed baseline Mask R-CNN and 3D U-Net. For clinically significant ILs, the model segmentation accuracy was significantly higher than that of the experienced radiologist involved in the study, who achieved 0.512 DSC ($p = 0.04$), 8.21 ($p = 0.041$) 95 HD (mm), and 0.398 ($p = 0.001$) sensitivity. CONCLUSION: The proposed DL model achieved state-of-art performance and has the potential to help improve radiotherapy treatment planning and noninvasive prostate cancer diagnosis.

Urology

Dalela D, Malchow T, **Butaney M**, **Majdalany S**, **Corsi N**, **Rakic I**, **Sood A**, **Rogers C**, and **Abdollah F**. Temporal and Racial Trends in Prostate Specific Antigen Screening for US Men With Family History of Prostate Cancer. *Urol Pract* 2023; Epub ahead of print. PMID: 37347799. Full Text

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PURPOSE: Limited data exists on trends in prostate-specific antigen (PSA) screening in men with family history of prostate cancer (PCa). THE AIMS OF OUR STUDY WERE: 1) to study age-stratified temporal

trends in PSA screening from 2000-2018 for men with a family history of PCa and black men with family history of PCa; and 2) identify determinants associated with receipt of PSA screening in aforementioned groups. METHODS: We identified men aged ≥40 without prior history of PCa using data from National Health Institution Survey (NHIS) 2000-2018 who self-reported PSA testing in the last 12 months. Age-stratified temporal trends and weighted multivariable logistic regression analyses were assessed. RESULTS: PSA screening increased for men with a family history of prostate cancer between NHIS 2000 (28.9%) and 2005 (41.9%), with stable rates for the following years. Black men with family history of PCa showed no significant change in PSA screening rates regardless of age. Controlling for socio-demographics and access to healthcare provider, younger age (40-54) and later survey years (2013-2018) were associated with a lower likelihood of PSA screening overall and for black men, but not for those with positive family history. CONCLUSION: Data from nationally representative study of US men indicated that the annual PSA screening rates for men with a family history of PCa was higher than reported for the overall male population. We believe this represents the first study on trends and determinants of PSA screening in US men with a family history of PCa.

Urology
Kachroo N. Editorial Comment. *J Urol* 2023; Epub ahead of print. PMID: 37340901. Full Text

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Urology
Levy A, **Wilder S**, **Butaney M**, **Majdalany S**, **Peabody J**, **Jeong W**, and **Rogers C**. Solving clinical challenges in prostate cancer using the single-port robot system. *Urol Video J* 2023; 18. Full Text

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Objective: Patients who desire or require surgical management for prostate cancer, but are poor candidates for multi-port robotic surgery, can present a clinical challenge. Use of single port (SP) robotic technology may help overcome these challenges. We present our initial experience with robotic-assisted radical prostatectomy (RARP) using the da Vinci SP robot for prostate cancer in patients who would otherwise not be good surgical candidates for conventional multi-port transabdominal robotic surgery. Patients and surgical procedure: Fourteen of 41 patients who underwent SP-RARP from November 2020 to February 2022 for biopsy confirmed, organ-confined prostate adenocarcinoma at a single tertiary care institution qualified for inclusion in our study due to specific considerations posing challenges for conventional multiport transperitoneal RARP. Perioperative metrics, pathologic findings and functional outcomes were collected prospectively. The accompanying video shows two cases demonstrating our transvesical and extraperitoneal approaches to SP-RARP. Results: All patients underwent successful procedures without need to convert to multi-port robotic or open approach. Most patients had prior abdominal surgery (13/14, 93%) including aborted multi-port RARP (2), hernia repairs (5), bowel diversions (3), and peritoneal dialysis catheters (2) among others. Most underwent extraperitoneal (9/14, 64%) followed by transvesical (5/14, 36%) approach. There were no intraoperative complications and one Clavien III post-operative complication. Positive margin rate was 29%, most of which were microscopic (≤3 mm, 3/4, 75%). Eighty-five percent of patients had undetectable nadir PSA. Conclusions: Our initial experience using the SP robot suggests that this technology can facilitate surgery for prostate cancer patients who might otherwise not be considered surgical candidates. Operative outcomes are not compromised despite a smaller incision and working space. We have found the SP system to be a valuable tool for carefully selected patients.

Urology
Majdalany SE, **Yaguchi G**, **Arora S**, **Ray C**, **Atiemo HO**, and **Raza J**. Genital Sparing Robot-Assisted Radical Cystectomy with Intracorporeal Neobladder & Paravaginal Repair. *Urology* 2023; Epub ahead of print. PMID: 37321278. Full Text

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INTRODUCTION: Vaginal prolapse is a known complication after Radical cystectomy (RC), requiring additional procedures in 10% of patients(1). This results from loss of level I and II vaginal support due to removal of pelvic structures. In addition, a neobladder urinary diversion, with Valsalva voiding, predisposes to vaginal prolapse. Genital sparing approach with paravaginal repair can help prevent such complication. METHODS & TECHNIQUE: Genital sparing technique preserves the uterus, fallopian tubes, ovaries, and vagina, while paravaginal repair involves suturing of the lateral vaginal wall to the arcuate fascia located on the medial aspect of the obturator internus muscle. Procedure begins by placing the patient in lithotomy position, with a steep Trendelenburg. Standard 6 port cystectomy configuration is utilized with an additional 15 mm port for bowel anastomosis. Initially the ureters and lateral bladder space is mobilized. Posteriorly a dissection plane is developed separating the bladder from the anterior vaginal wall. Distal dissection is carefully performed in that plane to avoid disrupting urethral-external sphincter complex. Then the bladder is dropped from anterior attachments, the DVC and bladder neck are exposed. Urethra is transected distal to bladder neck, after circumferential mobilization, to complete the cystectomy, again avoiding disruption of continence mechanism and opening the endo-pelvic fascia. Cystectomy and pelvic lymph node dissected are completed in standard fashion. The arcuate fascia is identified bilaterally for level I paravaginal repair. The lateral aspect of the paravaginal tissue is secured to this ligament, using 3 interrupted PDS sutures, bilaterally. An ileal "Hautman's W pouch" neobladder is constructed using 50cm of small intestine, similar to the previously reported technique(2). Bricker-type uretero-ileal anastomosis is performed over a double J stent. Bowel continuity is restored by a side-to-side anastomosis using endo-GIA staplers. RESULTS: No intra- or post-operative complications were noted. Robot dock-time was 8 hours and 23 minutes with EBL of 100mL. Patient was discharged on POD 6 and Foley-catheter with ureteral stents were removed on POD 27 after a cystogram confirming no leaks. At 6-month follow-up, patient reported good continence using a single pad, voiding every 3-4hours. Fluoro-urodynamics demonstrated 651 mL capacity, low-pressure voiding, minimal residual urine, and no reflux. No prolapse was noted on fluoroscopy and pelvic exam with Valsalva maneuver. Patient reported good satisfaction level, regarding her urinary symptoms. CONCLUSIONS: We report satisfactory short-term outcomes of a feasible technique to prevent post-cystectomy prolapse, however long-term follow-up of a larger cohort, can help establish its efficacy.

Urology

Modonutti D, **Majdalany SE**, **Butaney M**, **Davis MJ**, **Corsi N**, **Sood A**, Trinh QD, Cole AP, **Rogers CG**, Novara G, and **Abdollah F**. Conditional survival does not improve over time in metastatic castration-resistant prostate cancer patients undergoing docetaxel. *Prostate* 2023; Epub ahead of print. PMID: 37290911. Full Text

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PURPOSE: To investigate the conditional overall survival (OS) of metastatic castration-resistant prostate cancer (mCRPC) patients receiving docetaxel chemotherapy. METHODS: We used deidentified patient-level data from the Prostate Cancer DREAM Challenge database and the control arm of the ENTHUSE 14 trial. We identified 2158 chemonaïve mCRPC patients undergoing docetaxel chemotherapy in the five randomized clinical trials. The 6-month conditional OS was calculated at times 0, 6, 12, 18, and 24 months from randomization. Survival curves of each group were compared using the log-rank test. Patients were then stratified into low- and high-risk groups based on the median predicted value of our recently published nomogram predicting OS in mCRPC patients. RESULTS: Nearly half (45%) of the study population was aged between 65 and 74 years. Median interquartile range prostate-specific antigen

for the overall cohort was 83.2 (29.6-243) ng/mL, and 59% of patients had bone metastasis with or without lymph node involvement. The 6-month conditional survival rates at 0, 6, 12, 18, and 24 months for the entire cohort were 93% (95% confidence interval [CI]: 92-94), 82% (95% CI: 81-84), 76% (95% CI: 73-78), 75% (95% CI: 71-78), and 71% (95% CI: 65-76). These rates were, respectively, 96% (95% CI: 95-97), 92% (95% CI: 90-93), 84% (95% CI: 81-87), 81% (95% CI: 77-85), and 79% (95% CI: 72-84) in the low-risk group and 89% (95% CI: 87-91), 73% (95% CI: 70-76), 65% (95% CI: 60-69), 64% (95% CI: 58-70), and 58% (95% CI: 47-67) in the high-risk group. CONCLUSION: The conditional OS for patients undergoing docetaxel chemotherapy tends to plateau over time, with the main drop in conditional OS happening during the first year from initiating docetaxel treatment. That is the longer a patient survives, the more likely they are to survive further. This prognostic information could be a useful tool for a more accurate tailoring of both follow-up and therapies. PATIENT SUMMARY: In this report, we looked at the future survival in months of patients with metastatic castration resistant prostate cancer on chemotherapy who have already survived a certain period. We found that the longer time that a patient survives, the more likely they will continue to survive. We conclude that this information will help physicians tailor follow-ups and treatments for patients for a more accurate personalized medicine.

Urology

Patel AK, **Butaney M**, Lane BR, **Wilder S**, Johnson A, Qi J, **Wang Y**, DiBianco J, Herrel L, Maatman T, **Peabody J**, Rosenberg B, Seifman B, Semerjian A, Shetty S, Schervish E, Collins J, Tandogdu Z, and **Rogers CG**. Building a Roadmap for Surveillance of Renal Masses using a modified Delphi Method to help Achieve Consensus. *Urology* 2023; Epub ahead of print. PMID: 37353086. Full Text

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OBJECTIVE: To establish a consensus for initial evaluation and follow-up of patients on active surveillance (AS) for T1 renal masses (T1RM). METHODS: A modified Delphi method was used to gather information about AS of T1RM, with a focus on patient selection, timing/type of imaging modality, and triggers for intervention. A consensus panel of MUSIC-affiliated urologists who routinely manage renal masses was formed. Areas of consensus (defined >80% agreement) about T1RM AS were established iteratively via three rounds of online questionnaires. RESULTS: Twenty-six MUSIC urologists formed the panel. Consensus was achieved for 321/587 scenarios (54.7%) administered through 124 questions. Life expectancy (LE), age, comorbidity, and renal function were most important for patient selection, with LE ranking first. All tumors<3cm and all patients with LE<1 year were considered appropriate for AS. Appropriateness also increased with elevated perioperative risk, increasing tumor complexity, and/or declining renal function. Consensus was for multiphasic axial imaging initially (contrast CT for GFR>60 or MRI for GFR>30) with first repeat imaging at 3-6 months and subsequent imaging timing determined by tumor size. Consensus was for chest imaging for tumors >3 cm initially and >5 cm at follow up. Renal biopsy was not felt to be a requirement for entering AS, but useful in several scenarios. Consensus indicated rapid tumor growth as an appropriate trigger for intervention. CONCLUSIONS: Our consensus panel was able to achieve areas of consensus to help define a clinically useful and specific roadmap for AS of T1RM and areas for further discussion where consensus was not achieved.

Urology

Salkowski M, Checcucci E, Chow AK, **Rogers C**, **Adbollah F**, Liatsikos E, Dasgupta P, Guimaraes GC, Rassweiler J, Mottrie A, Breda A, Crivellaro S, Kaouk J, Porpiglia F, and Autorino R. New multiport robotic surgical systems: a comprehensive literature review of clinical outcomes in urology. *Ther Adv Urol* 2023; 15. PMID: 37325289. Full Text

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Over the past 20 years, the field of robotic surgery has largely been dominated by the da Vinci robotic platform. Nevertheless, numerous novel multiport robotic surgical systems have been developed over the past decade, and some have recently been introduced into clinical practice. This nonsystematic review aims to describe novel surgical robotic systems, their individual designs, and their reported uses and clinical outcomes within the field of urologic surgery. Specifically, we performed a comprehensive review of the literature regarding the use of the Senhance robotic system, the CMR-Versius robotic system, and the Hugo RAS in urologic procedures. Systems with fewer published uses are also described, including the Avatera, Hintori, and Dexter. Notable features of each system are compared, with a particular emphasis on factors differentiating each system from the da Vinci robotic system.

Urology

Schuler N, Shepard L, Holler T, **Rogers C**, Autorino R, Elsamra S, Crivellaro S, Joseph J, and Ghazi A. Pilot evaluation of a perfused robot-assisted partial nephrectomy procedural simulation platform for single port robotic retroperitoneal approaches. *Urol Video J* 2023; 18. Full Text

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Objective: In this study our objective was to develop a simulation platform for use cases in Laparoendoscopic Single Site (LESS) Surgery intended for patient-specific rehearsal prior to Robot-assisted Partial nephrectomy procedures. Patients and Surgical Procedure: This represents a simulation platform requiring no patients, although the fabrication process allows for the platform to be patient-specific. Tissue phantom 3D models were developed from de-identified CT imaging fulfilling the criteria of tumors located in the posterior lower pole of the kidney. Results: Respondents completed surveys on platform novelty and effectiveness. Agreement on simulator novelty was unanimously positive (100% agree or better). Performance evaluations reached a minimum of 80% agreement for all categories, with zero respondents Conclusions: We have developed a highly realistic simulation platform for use in single-port robot-assisted partial nephrectomy that can be produced in a patient specific manner, which we believe will be highly useful for trainees as well as experts attempting to transfer skills to the newer platform.

Conference Abstracts

Dermatology
Eichenfield LF, Hebert AA, **Stein Gold L**, Cartwright M, Moro L, Han J, Squittieri N, and Mazzetti A. Efficacy and Safety of Clascoterone Cream 1% in Patients with Acne vulgaris across Subgroups Defined By Demographic Characteristics. *Value Health* 2023; 26(6):S29. Full Text

Objectives: Clascoterone cream 1% is approved for the treatment of acne vulgaris in patients aged ≥12 years. Pooled efficacy and safety data stratified by age and sex from two randomized, double-blind, vehicle-controlled Phase 3 studies (CB-03-01/25 and CB-03-01/26) and an open-label long-term extension study (CB-03-01/27) are presented. Methods: Patients with moderate-to-severe acne were randomized 1:1 to twice-daily treatment of the face with clascoterone or vehicle for 12 weeks (W); all patients continuing into the open-label extension study applied clascoterone for up to 9 additional months. Efficacy was assessed in the intention-to-treat (ITT) population for proportion of randomized patients achieving an Investigator's Global Assessment score of 0 or 1 (IGA 0/1) with a ≥2-point reduction from baseline. Safety was assessed from treatment-emergent adverse events (TEAEs) in all treated patients. Results: Of 709/712 patients aged ≥12 years originally randomized to clascoterone/vehicle, 63.9%/60.4% were female, and the mean ± standard deviation (SD) age was 19.8 ± 6.1/19.5 ± 6.1 years; there were only 11/13 male patients aged ≥25 years, and no data are shown for this subgroup. Among patients in the ITT population randomized to clascoterone/vehicle, 17.2%/3.9% (12–17 years; P <0.0001), 24.4%/9.8% (≥18 years; P <0.0001), and 31.5%/10.8% (females ≥25 years; P = 0.002) achieved IGA 0/1 by W12; 45.6%, 54.0%, and 44.4% of extension study patients aged 12–17, ≥18, and females ≥25 years, respectively, achieved IGA 0/1 after 12 months applying clascoterone. Frequency of TEAEs through W12 in clascoterone/vehicle-treated patients was 10.8%/14.2%, 11.5%/11.6%, and 9.6%/12.9% for ages 12–17, ≥18, and females ≥25 years, respectively. Conclusions: Clascoterone efficacy and safety were maintained in adolescent and adult patients, including female patients aged ≥25 years.

Dermatology
Eichenfield LF, Hebert AA, **Stein Gold L**, Cartwright M, Moro L, Han J, Squittieri N, and Mazzetti A. CO125 Efficacy of Clascoterone Cream 1% for up to 12 Months in Patients ≥9 Years of Age with Acne vulgaris: Results from a Long-Term Extension Study. *Value Health* 2023; 26(6):S38. Full Text

Objectives: Clascoterone cream 1% is approved for the treatment of acne vulgaris in patients aged ≥12 years. Efficacy data from an open-label extension study are presented. Methods: The open-label, multicenter extension study (CB-03-01/27) enrolled male and female patients aged ≥9 years who completed one of the 12-week Phase 3 trials (CB-03-01/25 and CB-03-01/26) in patients with moderate-to-severe acne vulgaris. All patients applied 1% clascoterone cream twice daily to the face for 9 months; in the extension study, patients with truncal acne could also treat affected areas of the shoulders, chest, and/or back. Total time on clascoterone was up to 12 months for patients originally randomized to clascoterone in the Phase 3 trials. A 5-point Investigator's Global Assessment (IGA; 0, clear; 4, severe) was performed at extension Days 29, 85, 183, and 274; clascoterone treatment could be discontinued if IGA was 0 or 1 (IGA 0/1) and reinstated if/when acne worsened. Efficacy was analyzed in the intention-to-treat (ITT) population. Results: The ITT population included 609 patients, of whom 251 patients were treated for truncal acne. At baseline/Day 29/85/183/274, the proportion of ITT patients achieving facial IGA 0/1 was 9.9%/8.5%/10.1%/17.3%/29.8% and the proportion of ITT patients achieving truncal IGA 0/1 was 4.8%/17.1%/20.7%/25.9%/31.5%. In the ITT population, 539/417/304/123 patients used clascoterone for a total of 3/6/9/12 months. By total time on clascoterone, 13.1%/18.9%/39.2%/56.1% of ITT patients achieved facial IGA 0/1 and 13.6%/37.6%/43.4%/59.2% of ITT patients achieved truncal IGA 0/1 after 3/6/9/12 months on clascoterone treatment. Conclusions: Clascoterone cream 1% maintained a favorable efficacy profile for up to 12 months in patients aged ≥9 years with acne vulgaris.

Dermatology
Kirby J, **Hamzavi I**, Villani AP, Warren RB, Keal A, Hernandez-Daly AC, Jha R, Song H, and Kimball AB. PCR234 Impact of Draining Tunnels on Patient- and Physician-Reported Burden in Patients with Hidradenitis Suppurativa (HS). *Value Health* 2023; 26(6):S356. Full Text

Objectives: Hidradenitis suppurativa (HS) has one of the greatest impacts on quality of life (QoL) of any dermatological disease. This study explored the patient- and physician-reported burden of HS with and without draining tunnels (dT). Methods: This study used real-world data collected (November 2020–April 2021) from physician surveys, patient surveys, and medical records as part of the Adelphi HS Disease Specific Programme (DSP™). Validated patient-reported outcomes used were the HS QoL (HiSQOL) score, the work productivity and activity impairment questionnaire, and the EQ5D-visual analog scale (EQ5D-VAS). Results are presented descriptively. Patients with missing values for a variable were removed from all analyses involving that variable. Results: Of 580 moderate-to-severe HS patients included in this study, 46% (n=264) had dT. For patients with and without dT, mean age of 38.9 and 33.3 years, and 55.3% and 57.6% were female, respectively. From physician-reported data, patients with dT were more likely to experience a great impact on their lives than patients without dT (51.1% vs. 31.3%). Physicians agreed (agreement of 7–10 on a 1–10 scale) that patients with dT were more likely to experience a negative impact on their mental health (66.3% vs. 48.7%) and sexual function (65.5% vs. 50.3%). Patients with dT reported higher ratings on a pain scale from 7–10 (10 indicating worst pain, 28.9% vs. 11.0%), and were more likely to experience worse mood, reduced ability to work, negative feelings about the futures, and a deteriorated financial situation. Overall, patients with dT reported worse QoL (HiSQOL, 22.3 vs. 16.2), greater work impairment (34.0% vs. 25.9%), and worse general health (EQ5D-VAS, 62.9 vs. 72.0). Conclusions: In this group, patients with dT experienced a more substantial disease burden than patients without dT; this provides insight into the impact of dT and highlights the need for effective treatment strategies.

Neurology

LeWitt P, Klepitskaya O, Serbin M, Jen E, Rattana S, Trotter J, and Liang G. CO109 Patient-Reported Improvements in “Off”-Time Quality, Non-Motor Fluctuation Severity, and Medication Satisfaction in the Real-World Opti-on Study of Opicapone in Parkinson's Disease. *Value Health* 2023; 26(6):S35. Full Text

Objectives: Opicapone is an oral, once-daily, selective catechol-O-methyltransferase (COMT) inhibitor, approved as an adjunctive treatment to levodopa/carbidopa (LD/CD) in patients with Parkinson’s disease (PD) experiencing “OFF” episodes. OPTI-ON (OPicapone Treatment Initiation OpeN-Label Study) was a “real-world” study of opicapone use in the US that evaluated the characteristics, treatment patterns, and safety/tolerability of patients initiating opicapone treatment. Methods: OPTI-ON was a 6-month, prospective, single-arm, multicenter, observational, longitudinal study that included patients with PD experiencing “OFF” episodes who were newly prescribed opicapone adjunctive to LD/CD. Patient-reported outcomes including the Patient Global Impression of Severity in the “OFF” state (PGI-S OFF), Patient Global Impression of Change (PGI-C), Non-Motor Fluctuations PGI-S (NMFs PGI-S), and Medication Satisfaction Questionnaire (MSQ) were obtained at baseline and throughout follow-up. Results: Overall, 164 participants completed the study. On the PGI-S OFF, more participants rated their “OFF”-time symptom severity as “none” or “very mild” at 6 months versus baseline (20.4% vs. 10.3%). Fewer rated their “OFF”-time as “moderately severe” to “extremely severe” at 6 months versus baseline (17.3% vs. 26.5%). For the PGI-C, 23.5% of patients were “much improved” or “very much improved” at 6 months. On the NMFs PGI-S, fewer participants self-rated themselves as “markedly affected” to “most extremely affected” with non-motor fluctuations at 6 months versus baseline (3.2% vs. 11.9%). On the MSQ, 42.3% of participants were “very satisfied” or “extremely satisfied” with opicapone at 6 months; in contrast, only 14.1% were very or extremely satisfied with their LD/CD-only regimen at baseline. Conclusions: Results from the OPTI-ON study, along with the efficacy demonstrated in Phase 3 studies, demonstrated that once-daily opicapone may improve the quality of “OFF”-time, more effectively manage motor and non-motor fluctuations, and increase patients’ satisfaction with their PD treatment regimen.

Surgery

Intagliata A, Samuel S, **Rountree KM**, Vogel TR, Balasundaram N, and Bath J. Needle fenestration of popliteal artery covered stent graft to salvage inadvertent stent misdeployment. *J Vasc Surg Cases Innov Tech* 2023; 9(2). Full Text

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Endovascular methods have transformed treatment of lower extremity peripheral arterial disease but can still present technical challenges. We report the case of a 69-year-old man with rest pain who underwent superficial femoral artery recanalization with covered stents. During completion angiography, the distal stent was discovered to have been misdeployed into an anterior geniculate branch overlying the behind-the-knee popliteal artery. Subsequently, an endovascular reentry device was used to fenestrate the stent posteriorly to enter the lumen of the popliteal artery. Cutting balloons were used to enlarge the fenestration in the stent fabric, with placement of an additional 6 × 50-mm covered stent bridging from the popliteal artery into the fenestrated misdeployed covered stent. Completion angiography demonstrated no evidence of distal embolization and patent two-vessel runoff. The patient had an uncomplicated recovery and at 2 years of follow-up remained asymptomatic with documented popliteal stent patency.

Urology

Butaney M, **Wilder S**, **Tinsley S**, **Ugolini A**, **Al-Mohammed A**, Cool C, Haislip I, and **Rogers C**. Efficiency and User Satisfaction of Single-Use Vs Reusable Cystoscopes in a High-Volume Urology Clinic. *Value Health* 2023; 26(6):S300. Full Text

Objectives: Cystoscopy is the most common procedure performed by urologists in clinic. Efficiency improvements are essential for the delivery of high-quality patient care. Single-use cystoscopes have emerged as an alternative to reusable cystoscopes with the potential for in-clinic time savings and reduction of cross-contamination. We evaluated differences in efficiency and user satisfaction for reusable and single-use cystoscopes in the outpatient setting. Methods: Cystoscopies at a high-volume clinic were randomized into single-use or reusable cystoscopy. Times were recorded starting from set up to in-room cleanup for 60 single-use and 55 reusable cystoscopies. A survey was conducted among providers, nurses, and medical assistants who routinely perform or assist in outpatient cystoscopy to assess utility and satisfaction. Participants were asked to rank both cystoscopes on a 5-point Likert scale (1 = very poor, 5 = excellent) regarding efficiency, performance, and satisfaction. Results: When compared to reusable, single-use cystoscopes were associated with significant reductions in time spent on pre-patient set up (5:47 vs. 6:50 min, p=0.03), time providers spent in room (7:29 vs. 9:25 min, p=0.02), and time spent on in-room clean up (3:44 vs. 10:02; p<0.005) (Table). Procedure time was not significantly different. When examining total handling time (set up, procedure, and clean up), single-use saved 7:40 min in staff time when compared to reusable cystoscopes (P<0.005). Among survey respondents, 100% ranked single-use cystoscopes 5 for all qualities assessed, compared to reusable cystoscopes which averaged at or below 3.8 for each quality. Conclusions: Single-use cystoscopes can increase efficiency in the clinic in addition to time saved for reprocessing and transport. Additionally, single-use cystoscopes are preferred over reusable cystoscopes by physicians and staff involved in outpatient cystoscopy, and overall satisfaction and perception of benefit to clinic flow is high. Further investigations into cost and sustainability can help clarify the role of single use-cystoscopy when efficiency is of priority.